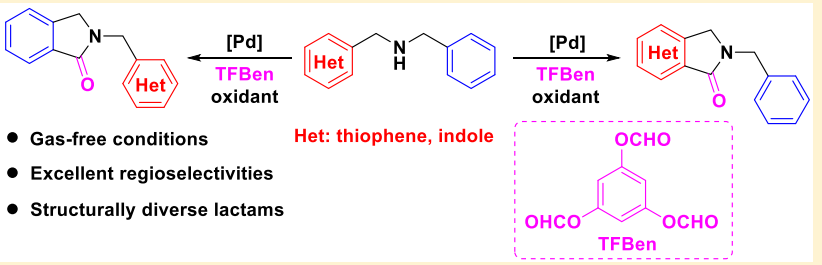
JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX
Note
pubs.acs.org/joc

Site-Selective Carbonylative Synthesis of Structurally Diverse Lactams from Heterocyclic Amines with TFBen as the CO Source

Jun Ying,[†] Qian Gao,[†] and Xiao-Feng Wu*[,†,‡]

[†]Department of Chemistry, Zhejiang Sci-Tech University, Xiasha Campus, Hangzhou 310018, People's Republic of China
[‡]Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Straβe 29a, Rostock 18059, Germany

Supporting Information



ABSTRACT: A palladium-catalyzed site-selective C−H carbonylation of heterocyclic amines for the synthesis of lactam motifs has been developed. The reaction of 3-thiophene methylamines, 2-thiophene methylamines, and tryptamines with benzene-1,3,5-triyl triformate (TFBen) as the CO source provides a series of structurally diverse lactams in moderate to high yields with excellent regioselectivities.

Transition-metal-catalyzed C−H carbonylation with carbon monoxide or its surrogates has become one of the most powerful methods for the construction of various carbonyl compounds and has received more attention over the past decades.[1,2] Recently, the direct C−H carbonylation of amine derivatives has been well developed to access key lactam motifs that are ubiquitous in drug molecules and natural products.[3−9] For instance, Orito and co-workers developed a useful synthetic protocol toward isoindolinone ring systems via C−H carbonylation of benzylamines using $Pd(OAc)_2$ and $Cu(OAc)_2$ as the catalyst system under an atmosphere of CO gas containing air.[3] In 2018, Li and co-workers realized an efficient method for the synthesis of *N*-unprotected benzolactams via palladium-catalyzed *ortho*-C−H carbonylation of free benzylamines using NH_2 as the directing group.[4] Wang and Li developed an interesting palladium-catalyzed carbonylation of *α*,*α*-disubstituted benzylamines to synthesize the corresponding sterically hindered benzolactams under atmospheric pressure of CO.[5] Zhao and Shi disclosed a Ru(II)-catalyzed C−H carbonylation of benzylamines with isocyanate as the CO source.[6] Very recently, our group developed a facile approach for the synthesis of isoindolinone skeleton via palladium-catalyzed C−H carbonylation of benzylamines.[7] TFBen, used in this reaction, is a solid, safe, and convenient CO surrogate.[2a,7,10] However, these synthetic protocols are only suitable for simple benzylamine derivatives. It may encounter selectivity issues when complicated heterocyclic amines containing more than one possible carbonylation sites are employed. Herein, we report a palladium-catalyzed C−H carbonylation of 3-thiophene methylamines, 2-thiophene methylamines, and tryptamines with TFBen as the CO source, producing a variety of structurally diverse lactams in moderate to good yields with excellent regioselectivities (Scheme 1).

At the outset, 3-thiophene methylamine **1a** was selected as the model substrate for the C−H carbonylation (Table 1). We used **1a** to react with TFBen (2.0 equiv) in the presence of $Pd(TFA)_2$ (10 mol %) as the catalyst and $Cu(OAc)_2$ (1.5 equiv) as the oxidant at 110 °C for 20 h. Fortunately, the reaction occurred at the 2-position of the thiophene ring with an excellent regioselectivity to give the desired product **2a** in 49% yield (Table 1, entry 1). Replacing the catalyst with $Pd(OAc)_2$ slightly improved the yield to 52% (Table 1, entry 2). Increasing the amount of TFBen did not affect the yield of **2a** (Table 1, entry 3). Finally, it was found that the reaction yield was enhanced remarkably to 73% when 2.0 equiv of $Cu(OAc)_2$ was employed (Table 1, entry 4). Further increasing the amount of $Cu(OAc)_2$ added could not continue to promote the reaction outcome (Table 1, entry 5). It is important to mention that other oxidants such as BQ, *t*BuOOH, $K_2S_2O_8$, and TEMPO were also tested but failed.

Then, the optimal reaction conditions (Table 1, entry 4) were applied to a series of 3-thiophene methylamines **1**, and the results are summarized in Scheme 2. It was shown that 3-thiophene methylamines bearing electron-donating groups could undergo the reaction smoothly to give the corresponding products **2b−d** in 55−75% yields. The reaction of compounds with electron-withdrawing substituents led to the expected products **2e−f** in moderate yields. The substrate with *ortho*-methyl substituted on the phenyl ring can be transformed as

Received: August 1, 2019
Published: October 7, 2019

DOI: 10.1021/acs.joc.9b02114
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. C−H Carbonylative Synthesis of Lactam Motifs

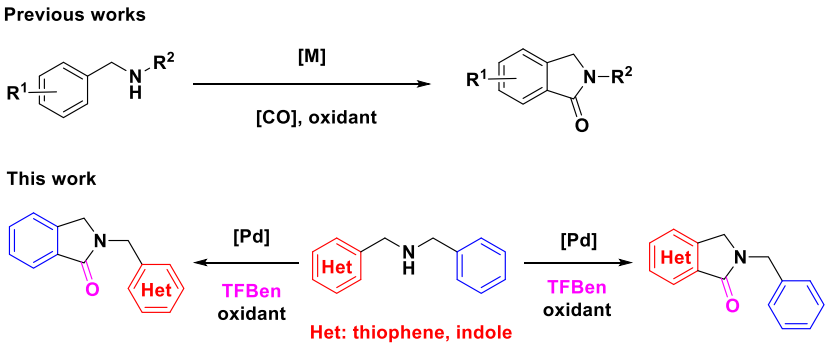
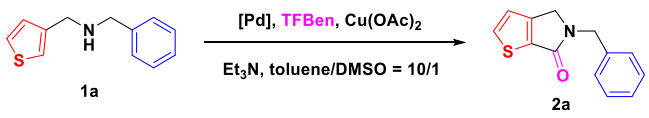


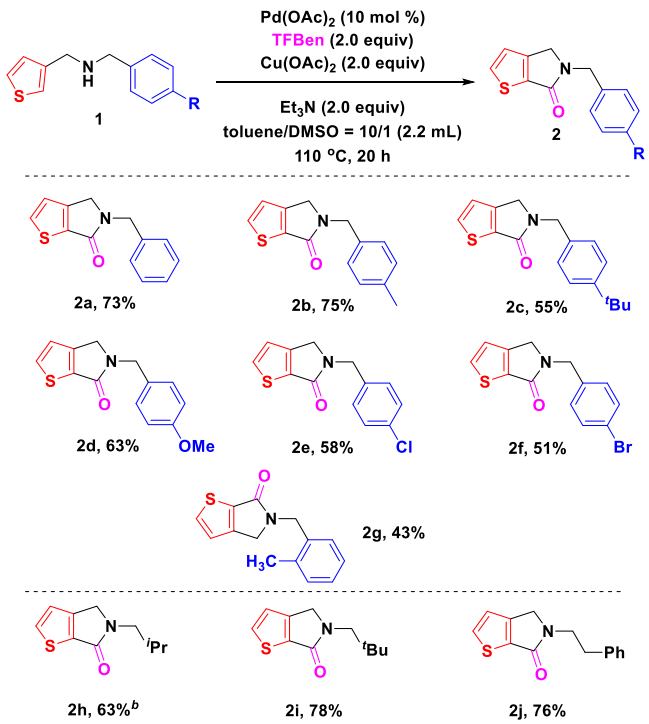
Table 1. Screening of the Reaction Conditions with 1a[a]



entry	[Pd]	oxidant	[CO]	yield (%)
1	$Pd(TFA)_2$	$Cu(OAc)_2$	TFBen	49
2	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	52
3[b]	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	48
4[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	73
5[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	72

[a]Reaction condition: **1a** (0.5 mmol), Pd catalyst (10 mol %), $Cu(OAc)_2$ (1.5 equiv), TFBen (2.0 equiv), Et_3N (2.0 equiv), toluene/DMSO = 10:1 (2.2 mL), 110 °C, 20 h, isolated yield. [b]TFBen (4.0 equiv). [c]$Cu(OAc)_2$ (2.0 equiv). [d]$Cu(OAc)_2$ (3.0 equiv).

Scheme 2. Scope of 3-Thiophene Methylamines 1[a]

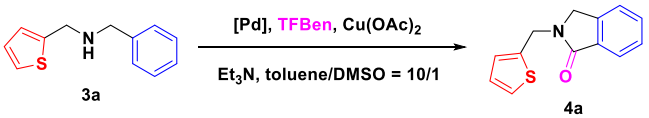


[a]Reaction condition: **1** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2.0 equiv), TFBen (2.0 equiv), Et_3N (2.0 equiv), toluene/DMSO = 10:1 (2.2 mL), 110 °C, 20 h, isolated yield. [b]**1g** (0.25 mmol).

well and give the corresponding product in 43% yield, **2g**. Additionally, compounds with alkyl substituents were tolerated as well to access the products **2h−j** in high yields.

Next, we screened the reaction conditions of C−H carbonylation with 2-thiophene methylamine **3a** (Table 2).

Table 2. Screening of the Reaction Conditions with 3a[a]



entry	[Pd]	oxidant	[CO]	yield (%)
1	$PdCl_2$	$Cu(OAc)_2$	TFBen	30
2	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	43
3[b]	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	35
4[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	34
5[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	50
6[d,e]	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	60
7[d,f]	$Pd(OAc)_2$	$Cu(OAc)_2$	TFBen	55

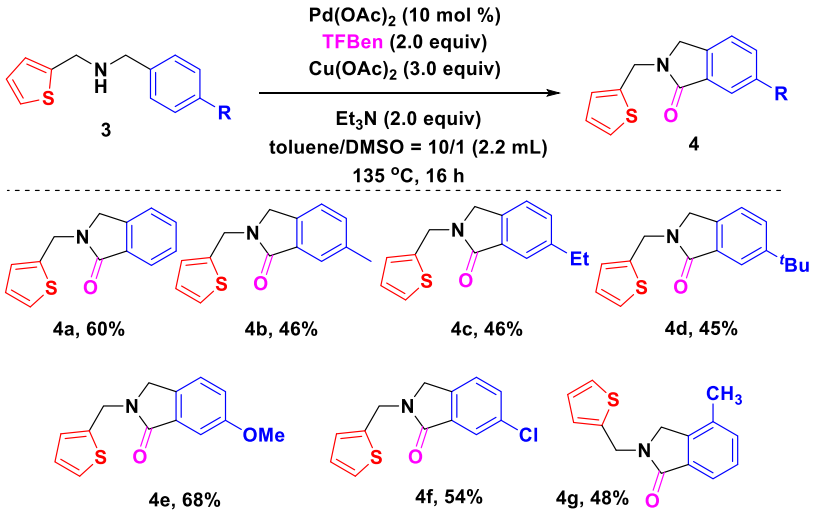
[a]Reaction condition: **3a** (0.5 mmol), Pd catalyst (10 mol %), $Cu(OAc)_2$ (3.0 equiv), TFBen (2.0 equiv), Et_3N (2.0 equiv), toluene/DMSO = 10:1 (2.2 mL), 110 °C, 20 h, isolated yield. [b]TFBen (1.0 equiv). [c]TFBen (3.0 equiv). [d]135 °C. [e]16 h. [f]12 h.

When **3a** was treated with TFBen (2.0 equiv) and $Cu(OAc)_2$ (3.0 equiv) in the presence of $PdCl_2$ (10 mol %) as the catalyst at 110 °C for 20 h, the carbonylation selectively occurred at the *ortho*-position of the benzene ring to give the desired product **4a** as a single regiomer in 30% yield (Table 2, entry 1). Using $Pd(OAc)_2$ instead of $PdCl_2$ as the catalyst enhanced the yield to 43% (Table 2, entry 2). Moreover, increasing or reducing the amount of TFBen hampered the reaction (Table 2, entries 3 and 4). Gratifyingly, the reaction yield was improved to 50% when the temperature was raised (Table 2, entry 5). Finally, shortening the reaction time to 16 h increased the yield to 60% (Table 2, entry 6). Further reduction of the reaction time slightly decreased the yield of **4a** (Table 2, entry 7).

Subsequently, the scope of 2-thiophene methylamines **3** was investigated under optimal reaction conditions (Table 2, entry 6) as shown in Scheme 3. The reaction of substrates bearing electron-donating groups gave the expected products **4b−e** in 45−68% yields. It should be noted that the strong electron-donating group such as −OMe facilitates the carbonylation reaction. Furthermore, the chloro-substituted compound **3f** was successfully converted to product **4f** in a 54% yield as well. As we expected, *ortho*-methyl substituted substrate can be transformed into the desired product in 48% yield **4g**.

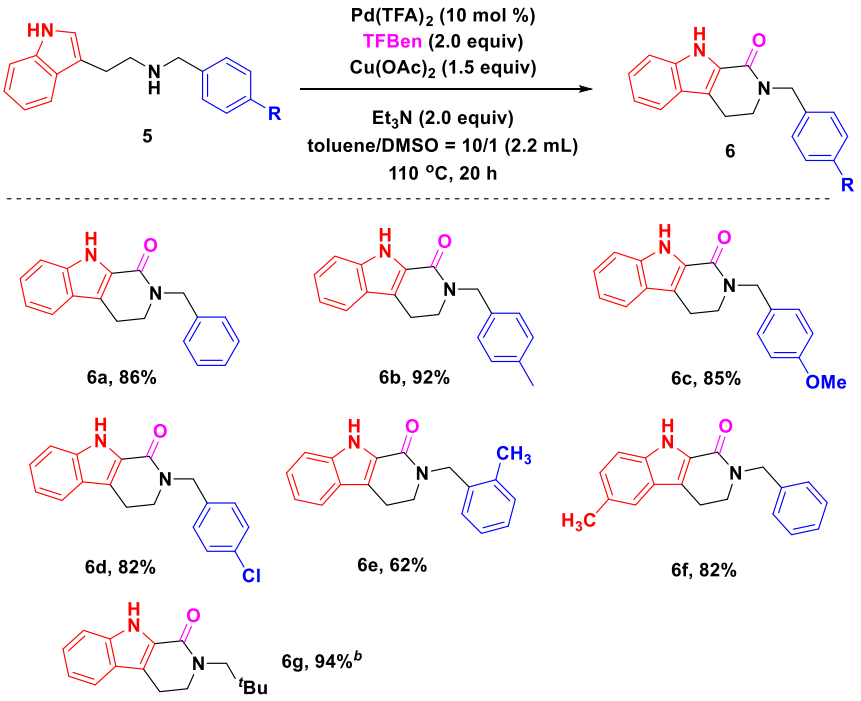
DOI: 10.1021/acs.joc.9b02114
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Scope of 2-Thiophene Methylamines 3[a]



[a]Reaction condition: **3** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (3.0 equiv), TFBen (2.0 equiv), Et_3N (2.0 equiv), toluene/DMSO = 10:1 (2.2 mL), 135 °C, 16 h, isolated yield.

Scheme 4. Scope of Tryptamines 5[a]



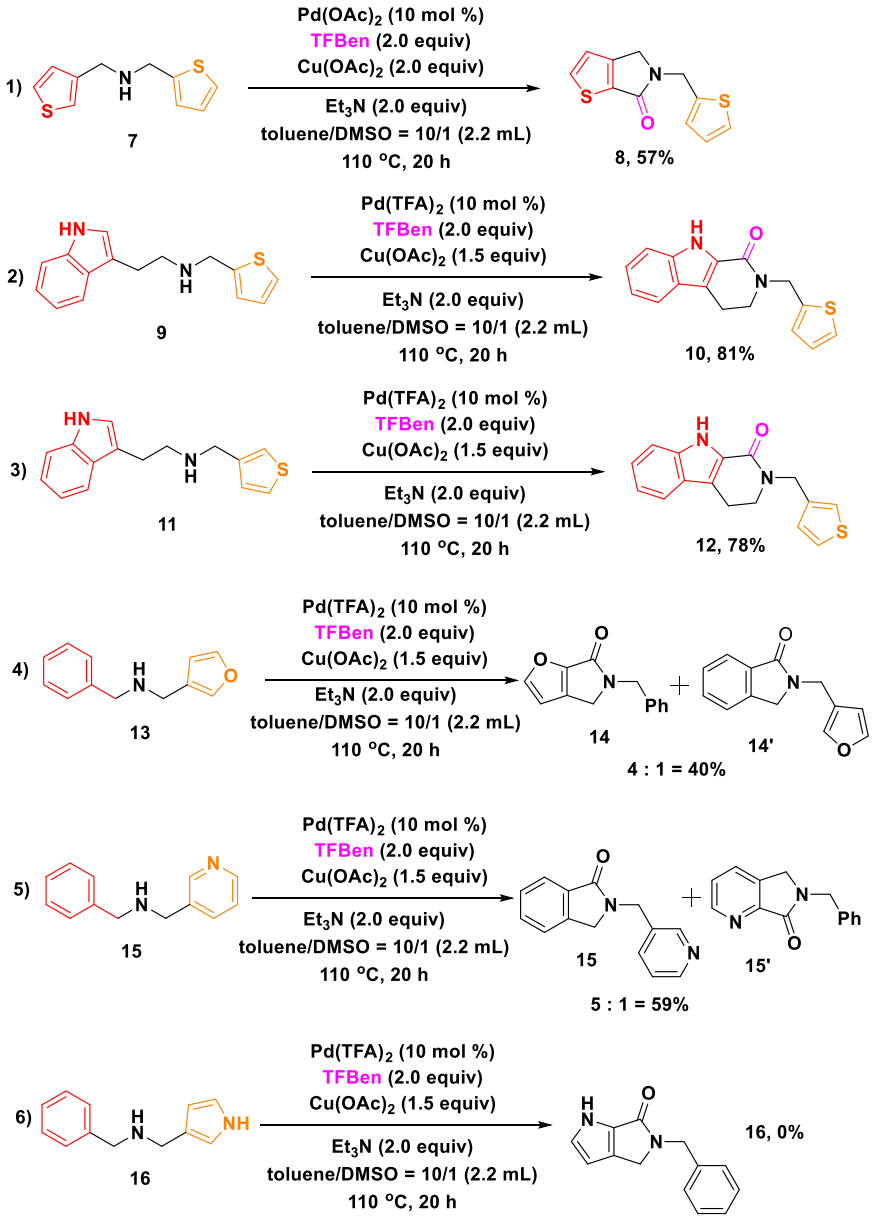
[a]Reaction condition: **5** (0.5 mmol), $Pd(TFA)_2$ (10 mol %), $Cu(OAc)_2$ (1.5 equiv), TFBen (2.0 equiv), Et_3N (2.0 equiv), toluene/DMSO = 10:1 (2.2 mL), 110 °C, 20 h, isolated yield. [b]**5e** (0.25 mmol).

We also employed the modified reaction conditions in the carbonylation of various tryptamines **5**, and the results are illustrated in Scheme 4. The carbonylation of substrates with either electron-donating or electron-withdrawing groups occurred at the 2-position of the indole ring to give the corresponding products **6a−f** with excellent regioselectivities and yields (62−92%). Additionally, the alkyl-substituted tryptamine **5g** could be transformed into product **6g** in a 94% yield.

Interestingly, when the amine **7** containing 2-thiophene and 3-thiophene units was subjected to the $Pd(OAc)_2$ catalytic system, the selective carbonylation at the 2-position of the 3-thiophene ring afforded the lactam **8** in 57% yield (Scheme 5, eq 1). Moreover, it was found that the treatment of the amine **9** bearing indole and 2-thiophene units with the $Pd(TFA)_2$ catalytic system promoted the selective carbonylation at the 2-position of the indole ring, accessing to the lactam **10** in 81% yield (Scheme 5, eq 2). Finally, the amine **11** having indole and 3-thiophene units selectively carbonylated at the 2-position of the indole ring to give the lactam **12** in 78% yield (Scheme 5, eq 3). Furan and pyridine related substrates were prepared and tested; however, a mixture of isomers was obtained and not separable (Scheme 5, eqs 4 and 5). In the

DOI: 10.1021/acs.joc.9b02114
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 5. Selective Carbonylation of Heterocyclic Amines



case of pyrrole related substrate, no desired product could be detected (Scheme 5, eq 6).

In conclusion, we have developed an efficient approach for the synthesis of lactam motifs via palladium-catalyzed site-selective C−H carbonylation of heterocyclic amines using TFBen as the CO source. The reaction proceeds smoothly with 3-thiophene methylamines, 2-thiophene methylamines, and tryptamines, affording structurally diverse lactams in moderate to high yields and with excellent regioselectivities.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere. All reagents were obtained from commercial sources and used as received without further purification. Column chromatography was performed on silica gel (200−300 mesh) using petroleum ether (bp 60−90 °C) and ethyl acetate as an eluent. ^{1}H and ^{13}C NMR spectra were taken on 400 MHz instruments, and spectral data were reported in ppm relative to tetramethylsilane (TMS) as an internal standard and $CDCl_3$ or DMSO-d_6 as a solvent.

Preparation of TFBen. Formic acid (8.4 mL, 222.8 mmol, 5.0 equiv) was added to acetic anhydride (16.8 mL, 178.2 mmol, 4.0 equiv) at rt. The mixture was stirred at 60 °C in an oil bath for 1 h and cooled to rt. The resulting solution was poured into a flask containing 1,3,5-trihydroxybenzene (5.62 g, 44.6 mmol, 1.0 equiv) and AcONa (1.83 g, 22.3 mmol, 0.5 equiv). The mixture was stirred for 4 h in a water bath and then diluted with toluene (100 mL) and washed with H_2O (50 mL) two times. The organic phase was kept in a fridge (2−8 °C) overnight and then filtered and dried in vacuo to afford the desired product benzene-1,3,5-triyl triformate (TFBen) (5.1 g, 55%) as a white solid.

General Procedure for the Syntheses of the Secondary Amines. In a round-bottomed flask fitted with a magnetic stirring bar, primary amine (3 mmol, 1.0 equiv) and aldehyde (3.3 mmol, 1.1 equiv) were dissolved in MeOH (8 mL). The reaction mixture was added with molecular sieves (4 Å) and stirred at rt. The reaction was monitored by TLC, and upon full conversion of benzaldehyde (24 h), solid $NaBH_4$ (147.5 mg, 3.9 mmol, 1.3 equiv) was added. After a further 16 h of stirring, the reaction mixture was filtered through a pad of Celite, which was washed with MeOH. The filtrate was evaporated in vacuo. The residue was taken up in sat. $NaHCO_3$ (10 mL), H_2O

DOI: 10.1021/acs.joc.9b02114
J. Org. Chem. XXXX, XXX, XXX−XXX

(10 mL), and EtOAc (30 mL) and transferred to a separatory funnel. The organic layer was separated and washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4. The crude mixture was purified by flash column chromatography on silica gel eluted with petroleum ether/ethyl acetate (3:1) or pure DCM to give the secondary amine products.

Characterization of TFBen and the Secondary Amines. *Benzene-1,3,5-triyltriformate (TFBen):*[10] 5.1 g, 55% yield, white solid, mp 53.2−55.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 3H), 6.95 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 158.0, 150.5, 112.8.

*N-Benzyl-1-(thiophen-3-yl)methanamine (**1a**):*[11] 339.8 mg, 55% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 4.4 Hz, 4H), 7.27−7.21 (m, 2H), 7.11 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 4.9, 1.1 Hz, 1H), 3.79 (d, J = 2.8 Hz, 4H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 141.4, 140.2, 128.5, 128.2, 127.7, 127.0, 125.8, 121.6, 53.2, 48.2.

*N-(4-Methylbenzyl)-1-(thiophen-3-yl)methanamine (**1b**):* 361.8 mg, 55% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.18 (m, 1H), 7.17−7.12 (m, 2H), 7.06 (d, J = 5.0 Hz, 3H), 6.98 (t, J = 3.9 Hz, 1H), 3.73 (d, J = 3.4 Hz, 2H), 3.70 (d, J = 3.4 Hz, 2H), 2.26 (d, J = 3.4 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 141.5, 137.2, 136.6, 129.1, 128.2, 127.7, 125.7, 121.5, 53.0, 48.1, 21.1; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{13}H_{16}NS^+$ 218.0998, found 218.1004.

*N-(4-(tert-Butyl)benzyl)-1-(thiophen-3-yl)methanamine (**1c**):* 467.0 mg, 60% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.2 Hz, 2H), 7.25 (dd, J = 9.9, 6.1 Hz, 3H), 7.14 (dd, J = 1.7, 0.8 Hz, 1H), 7.06 (d, J = 5.0 Hz, 1H), 3.82 (s, 2H), 3.78 (s, 2H), 2.14 (s, 1H), 1.31 (s, 9H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 149.9, 137.0, 129.2, 127.9, 127.7, 125.7, 125.3, 121.6, 52.8, 48.1, 34.5, 31.4; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{16}H_{22}NS^+$ 260.1467, found 260.1483.

*N-(4-Methoxybenzyl)-1-(thiophen-3-yl)methanamine (**1d**):* 427.1 mg, 61% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 4.9, 3.0 Hz, 2H), 7.24 (s, 1H), 7.14 (s, 1H), 7.06 (d, J = 4.9 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 3.81 (d, J = 3.4 Hz, 5H), 3.75 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 158.7, 141.5, 132.3, 129.3, 127.6, 125.7, 121.5, 113.8, 55.3, 52.6, 48.0; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{13}H_{16}NOS^+$ 234.0947, found 234.0958.

*N-(4-Chlorobenzyl)-1-(thiophen-3-yl)methanamine (**1e**):* 369.8 mg,52% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.23 (m, 5H), 7.12 (s, 1H), 7.04 (d, J = 4.9 Hz, 1H), 3.78 (s, 2H), 3.75 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 141.2, 138.7, 132.7, 129.5, 128.5, 127.6, 125.9, 121.7, 52.4, 48.1; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{12}H_{13}ClNS^+$ 238.0452, found 238.0464.

*N-(4-Bromobenzyl)-1-(thiophen-3-yl)methanamine (**1f**):* 379.3 mg, 45% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.43 (m, 2H), 7.30 (dd, J = 4.9, 3.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.15−7.13 (m, 1H), 7.06 (dd, J = 5.0, 1.1 Hz, 1H), 3.81 (s, 2H), 3.77 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 141.1, 139.1, 131.5, 129.9, 127.6, 125.8, 121.7, 120.8, 52.4, 48.0; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{12}H_{13}BrNS^+$ 281.9947, found 281.9959.

*N-(2-Methylbenzyl)-1-(thiophen-3-yl)methanamine (**1g**):* 434.4 mg, 66.7% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 2H), 7.18−7.12 (m, 4H), 7.07 (dd, J = 4.9, 1.0 Hz, 1H), 3.86 (s, 2H), 3.78 (s, 2H), 2.32 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 141.5, 138.1, 136.4, 130.3, 128.5, 127.7, 127.0, 125.9, 125.7, 121.6, 51.0, 48.6, 18.9; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{13}H_{16}NS^+$ 218.0998, found 218.0996.

*2-Methyl-N-(thiophen-3-ylmethyl)propan-1-amine (**1h**):* 169.4 mg, 33% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.27 (m, 1H), 7.14 (s, 1H), 7.06 (d, J = 4.7 Hz, 1H), 3.81 (s, 2H), 2.46 (d, J = 6.3 Hz, 2H), 1.79 (dt, J = 13.3, 6.6 Hz, 1H), 0.92 (dd, J = 6.6, 1.5 Hz, 6H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 141.5, 127.6, 125.6, 121.5, 57.4, 49.0, 28.2, 20.7; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_9H_{16}NS^+$ 170.0998, found 170.1007.

*2,2-Dimethyl-N-(thiophen-3-ylmethyl)propan-1-amine (**1i**):* 222.5 mg, 40% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.26 (m, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.05 (d, J = 4.9 Hz, 1H), 3.82 (s, 2H), 2.37 (s, 2H), 0.92 (s, 9H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 142.1, 127.6, 125.5, 121.1, 61.7, 49.8, 31.5, 27.8; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{10}H_{18}NS^+$ 184.1154, found 184.1165.

*2-Phenyl-N-(thiophen-3-ylmethyl)ethan-1-amine (**1j**):* 261.1 mg, 40% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.24 (m, 3H), 7.20 (t, J = 5.6 Hz, 3H), 7.08 (dd, J = 1.8, 0.9 Hz, 1H), 7.00 (d, J = 4.9 Hz, 1H), 3.81 (s, 2H), 2.91 (t, J = 6.9 Hz, 2H), 2.82 (t, J = 7.0 Hz, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 140.8, 139.8, 128.7, 128.5, 127.6, 126.2, 125.8, 121.8, 50.4, 48.6, 36.1; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{13}H_{16}NS^+$ 218.0998, found 218.1008.

*N-Benzyl-1-(thiophen-2-yl)methanamine (**3a**):*[12] 330.2 mg, 54% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (m, 4H), 7.26−7.20 (m, 1H), 7.19−7.15 (m, 1H), 6.91 (ddd, J = 7.0, 3.5, 2.3 Hz, 2H), 3.95 (s, 2H), 3.79 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 144.3, 140.1, 128.5, 128.3, 127.1, 126.7, 125.0, 124.5, 52.8, 47.6.

*N-(4-Methylbenzyl)-1-(thiophen-2-yl)methanamine (**3b**):* 342.6 mg, 52% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 5.4 Hz, 3H), 7.13 (d, J = 7.2 Hz, 2H), 6.96−6.89 (m, 2H), 3.97 (s, 2H), 3.78 (s, 2H), 2.33 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 144.3, 137.0, 136.6, 129.1, 128.2, 126.6, 124.9, 124.4, 52.5, 47.5, 21.1; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{13}H_{16}NS^+$ 218.0998, found 218.1013.

*N-(4-Ethylbenzyl)-1-(thiophen-2-yl)methanamine (**3c**):* 352.2 mg, 50% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 5.0 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.93 (d, J = 5.3 Hz, 2H), 3.98 (s, 2H), 3.79 (s, 2H), 2.63 (q, J = 7.6 Hz, 2H), 2.10 (s, 1H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 144.0, 143.1, 137.0, 128.3, 128.0, 126.7, 125.0, 124.4, 52.5, 47.5, 28.6, 15.7; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{14}H_{18}NS^+$ 232.1154, found 232.1169.

*N-(4-(tert-Butyl)benzyl)-1-(thiophen-2-yl)methanamine (**3d**):* 415.1 mg, 53% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.22−7.18 (m, 1H), 6.93 (dd, J = 8.5, 3.6 Hz, 2H), 3.99 (s, 2H), 3.80 (s, 2H), 1.31 (s, 9H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 149.9, 144.4, 137.0, 127.9, 126.6, 125.3, 124.8, 124.3, 52.5, 47.7, 34.5, 31.4; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{16}H_{22}NS^+$ 260.1467, found 260.1482.

*N-(4-Methoxybenzyl)-1-(thiophen-2-yl)methanamine (**3e**):* 327.3 mg, 47% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.23 (s, 1H), 7.20 (dd, J = 5.0, 1.2 Hz, 1H), 6.94 (dd, J = 5.0, 3.5 Hz, 1H), 6.92−6.89 (m, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 1.9 Hz, 1H), 3.96 (d, J = 0.5 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 158.7, 144.3, 132.2, 129.4, 126.6, 124.9, 124.3, 113.9, 55.3, 52.2, 47.5; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{13}H_{16}NOS^+$ 234.0947, found 234.0957.

*N-(4-Chlorobenzyl)-1-(thiophen-2-yl)methanamine (**3f**):* 346.3 mg, 49% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 3H), 7.27−7.20 (m, 2H), 6.97−6.89 (m, 2H), 3.97 (s, 2H), 3.79 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 144.0, 138.5, 132.7, 129.5, 128.5, 126.7, 125.0, 124.5, 52.0, 47.5; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{12}H_{13}ClNS^+$ 238.0452, found 238.0465.

*N-(2-Methylbenzyl)-1-(thiophen-2-yl)methanamine (**3g**):* 456.3 mg, 70.1% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 3.2 Hz, 1H), 7.15−7.12 (m, 1H), 7.10−7.05 (m, 3H), 6.89−6.85 (m, 2H), 3.95 (s, 2H), 3.73 (s, 2H), 2.25 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 144.4, 138.0, 136.5, 130.3, 128.6, 127.1, 126.6, 125.9, 124.8, 124.4, 50.7, 48.1, 19.0; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{13}H_{16}NS^+$ 218.0998, found 218.0996.

*N-Benzyl-2-(1H-indol-3-yl)ethan-1-amine (**5a**):*[13] 526.1 mg, 70% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.39−7.06 (m, 8H), 6.94 (s, 1H), 3.80 (s, 2H), 2.99 (s, 4H), 2.04 (s, 1H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 140.1, 136.5, 128.4, 128.2, 127.5, 127.0, 122.1, 122.0, 119.2, 118.9, 113.8, 111.2, 53.8, 49.3, 25.7.

DOI: 10.1021/acs.joc.9b02114
J. Org. Chem. XXXX, XXX, XXX−XXX

2-(1H-Indol-3-yl)-N-(4-methylbenzyl)ethan-1-amine (**5b**): 545.3 mg, 69% yield, white solid, mp 260.3−265.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.15 (ddd, J = 24.8, 17.4, 10.4 Hz, 6H), 6.95 (s, 1H), 3.76 (s, 2H), 2.98 (s, 4H), 2.31 (s, 3H), 2.15 (s, 1H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 137.0, 136.5, 136.4, 129.1, 128.2, 127.5, 122.1, 122.0, 119.2, 118.9, 113.8, 111.2, 53.5, 49.2, 25.7, 21.1; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{18}H_{21}N_2^+$ 265.1699, found 265.1714.

2-(1H-Indol-3-yl)-N-(4-methoxybenzyl)ethan-1-amine (**5c**):[14] 550.5 mg, 66% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.20−7.16 (m, 3H), 7.12−7.08 (m, 1H), 6.98 (d, J = 1.7 Hz, 1H), 6.84−6.80 (m, 2H), 3.77 (s, 3H), 3.75 (s, 2H), 2.98 (s, 4H), 2.00 (s, 1H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 158.6, 136.4, 132.3, 129.3, 127.5, 122.0, 119.2, 118.9, 113.9, 113.8, 111.1, 55.3, 53.2, 49.2, 25.7.

N-(4-Chlorobenzyl)-2-(1H-indol-3-yl)ethan-1-amine (**5d**): 475.6 mg, 56% yield, white solid, mp 254.2−259.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.3 Hz, 2H), 7.17 (t, J = 8.0 Hz, 3H), 7.10 (t, J = 7.3 Hz, 1H), 6.93 (s, 1H), 3.74 (s, 2H), 3.01−2.90 (m, 4H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 138.8, 136.5, 132.6, 129.5, 128.5, 127.5, 122.1, 119.3, 118.9, 113.8, 111.2, 53.1, 49.3, 25.8; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{17}H_{18}ClN_2^+$ 285.1153, found 285.1171.

2-(1H-Indol-3-yl)-N-(2-methylbenzyl)ethan-1-amine (**5e**): 590.1 mg, 74.5% yield, pale yellow solid, mp 88.1−91.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.22−7.16 (m, 2H), 7.09 (tt, J = 14.0, 7.2 Hz, 5H), 6.80 (s, 1H), 3.74 (s, 2H), 2.98 (t, J = 5.0 Hz, 4H), 2.19 (s, 3H), 1.80 (s, 1H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 138.2, 136.6, 136.3 130.4, 128.4, 127.5, 127.1, 126.0, 122.2, 122.0, 119.2, 118.9, 113.7, 111.3, 51.4, 49.8, 25.8, 19.0; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{18}H_{21}N_2^+$ 265,1699, found 265,1702.

N-Benzyl-2-(5-methyl-1H-indol-3-yl)ethan-1-amine (**5f**): 317.0 mg, 40.1% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.37 (s, 1H), 7.30−7.25 (m, 4H), 7.22 (dd, J = 6.4, 2.1 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 1.3 Hz, 1H), 3.80 (s, 2H), 2.97 (s, 4H), 2.44 (s, 3H), 1.64 (s, 1H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 140.4, 134.8, 128.4, 128.2, 127.8, 126.9, 123.6, 122.2, 118.6, 113.4, 110.9, 53.9, 49.4, 25.8, 21.5; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{18}H_{21}N_2^+$ 265.1699, found 265.1702.

N-(2-(1H-Indol-3-yl)ethyl)-2,2-dimethylpropan-1-amine (**5g**): 314.4 mg, 46% yield, white solid, mp 98.3−103.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 6.97 (d, J = 1.6 Hz, 1H), 2.94 (s, 4H), 2.38 (s, 2H), 0.85 (s, 9H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 136.4, 127.6, 121.9, 121.9, 119.2, 119.0, 114.2, 111.1, 62.3, 51.1, 31.5, 27.9, 25.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{15}H_{23}N_2^+$ 231.1856, found 231.1869.

1-(Thiophen-2-yl)-N-(thiophen-3-ylmethyl)methanamine (**7**): 383.1 mg, 61% yield, pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 4.9, 3.0 Hz, 1H), 7.20 (dd, J = 5.0, 1.1 Hz, 1H), 7.13 (dd, J = 1.8, 0.8 Hz, 1H), 7.05 (d, J = 4.9 Hz, 1H), 6.96−6.93 (m, 1H), 6.91 (d, J = 3.3 Hz, 1H), 3.99 (s, 2H), 3.84 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 144.1, 141.1, 127.7, 126.7, 125.8, 125.0, 124.4, 121.7, 47.8, 47.6; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{10}H_{12}NS_2^+$ 210.0406, found 210.0412.

2-(1H-Indol-3-yl)-N-(thiophen-2-ylmethyl)ethan-1-amine (**9**):[15] 500.93 mg, 65% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 7.13 (ddd, J = 28.4, 12.5, 7.8 Hz, 3H), 6.89 (dd, J = 12.5, 7.6 Hz, 3H), 3.97 (s, 2H), 2.99 (s, 4H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 144.0, 136.5, 127.5, 126.7, 125.0, 124.4, 122.2, 122.0, 119.3, 118.9, 113.7, 111.3, 49.2, 48.3, 25.7.

2-(1H-Indol-3-yl)-N-(thiophen-3-ylmethyl)ethan-1-amine (**11**): 459.4 mg, 60% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.20−7.03 (m, 4H), 6.94 (d, J = 1.8 Hz, 1H), 6.89 (d, J = 4.9 Hz, 1H), 6.74 (s, 1H), 3.72 (s, 2H), 2.93 (s, 4H), 2.07 (s, 1H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 141.1, 136.7, 127.9, 127.6, 126.0, 122.6, 122.0, 122.0, 119.3, 119.0, 113.3, 111.6, 49.5, 48.8, 25.8; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{15}H_{17}N_2S^+$ 257.1107, found 257.1122.

General Procedure for C−H Carbonylation of 3-Thiophene Methylamines. To the ex-tube (15 mL) of an oven-dried in−ex tube were added amine **1** (0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol %), $Cu(OAc)_2$ (181 mg, 1.0 mmol, 2.0 equiv), and a stirring bar. In the in-tube (2.5 mL), TFBen (210 mg, 1.0 mmol, 2.0 equiv) was added. Then the in−ex tube was placed under a vacuum and refilled with nitrogen three times. Et_3N (102 mg, 1.0 mmol, 2.0 equiv), toluene (2.0 mL), and DMSO (0.2 mL) were added into the ex-tube via syringe. The in−ex tube was sealed and stirred at 110 °C in an oil bath for 20 h. Upon reaction completion, the mixture was diluted with CH_2Cl_2 and washed with water three times. The crude mixture was purified by silica gel column chromatography (PE/EtOAc = 5:1 to 3:1) to obtain the desired products **2**.

General Procedure for C−H Carbonylation of 2-Thiophene Methylamines. To the ex-tube (15 mL) of an oven-dried in−ex tube were added amine **3** (0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol %), $Cu(OAc)_2$ (279 mg, 1.5 mmol, 3.0 equiv), and a stirring bar. In the in-tube (2.5 mL), TFBen (210 mg, 1.0 mmol, 2.0 equiv) was added. Then the in−ex tube was placed under a vacuum and refilled with nitrogen three times. Et_3N (102 mg, 1.0 mmol, 2.0 equiv), toluene (2.0 mL), and DMSO (0.2 mL) were added into the ex-tube via syringe. The in−ex tube was sealed and stirred at 135 °C in an oil bath for 16 h. Upon reaction completion, the mixture was diluted with CH_2Cl_2 and washed with water three times. The crude mixture was purified by silica gel column chromatography (PE/EtOAc = 5:1 to 3:1) to obtain the desired products **4**.

General Procedure for C−H Carbonylation of Tryptamines. To the ex-tube (15 mL) of an oven-dried in−ex tube were added amine **5** (0.5 mmol, 1.0 equiv), $Pd(TFA)_2$ (15.0 mg, 0.05 mmol, 10 mol %), $Cu(OAc)_2$ (136 mg, 0.75 mmol, 1.5 equiv), and a stirring bar. To the in-tube (2.5 mL) was added TFBen (210 mg, 1.0 mmol, 2.0 equiv). Then the in−ex tube was placed under a vacuum and refilled with nitrogen three times. Et_3N (102 mg, 1.0 mmol, 2.0 equiv), toluene (2.0 mL), and DMSO (0.2 mL) were added into the ex-tube via syringe. The in−ex tube was sealed and stirred at 110 °C in an oil bath for 20 h. Upon reaction completion, the mixture was diluted with CH_2Cl_2 and washed with water three times. The crude mixture was purified by alumina column chromatography (EtOAc) to obtain the desired products **6**.

Procedure for C−H Carbonylation of the Amine. To the ex-tube (15 mL) of an oven-dried in−ex tube were added amine **7** (0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol %), $Cu(OAc)_2$ (181 mg, 1.0 mmol, 2.0 equiv), and a stirring bar. In the in-tube (2.5 mL), TFBen (210 mg, 1.0 mmol, 2.0 equiv) was added. Then the in−ex tube was placed under a vacuum and refilled with nitrogen three times. Et_3N (102 mg, 1.0 mmol, 2.0 equiv), toluene (2.0 mL), and DMSO (0.2 mL) were added into the ex-tube via syringe. The in−ex tube was sealed and stirred at 110 °C in an oil bath for 20 h. Upon reaction completion, the mixture was diluted with CH_2Cl_2 and washed with water three times. The crude mixture was purified by silica gel column chromatography (PE/EtOAc = 5:1 to 3:1) to obtain the desired product **8**.

Procedure for C−H Carbonylation of the Amine **9**. To the ex-tube (15 mL) of an oven-dried in−ex tube were added amine **9** (0.5 mmol, 1.0 equiv), $Pd(TFA)_2$ (15.0 mg, 0.05 mmol, 10 mol %), $Cu(OAc)_2$ (136 mg, 0.75 mmol, 1.5 equiv), and a stirring bar. In the in-tube (2.5 mL), TFBen (210 mg, 1.0 mmol, 2.0 equiv) was added. Then the in−ex tube was placed under a vacuum and refilled with nitrogen three times. Et_3N (102 mg, 1.0 mmol, 2.0 equiv), toluene (2.0 mL), and DMSO (0.2 mL) were added into the ex-tube via syringe. The in−ex tube was sealed and stirred at 110 °C in an oil bath for 20 h. Upon reaction completion, the mixture was diluted with CH_2Cl_2 and washed with water three times. The crude mixture was purified by alumina column chromatography (EtOAc) to obtain the desired product **10**.

Procedure for C−H Carbonylation of the Amine **11**. To the ex-tube (15 mL) of an oven-dried in−ex tube were added amine **11** (0.5 mmol, 1.0 equiv), $Pd(TFA)_2$ (15.0 mg, 0.05 mmol, 10 mol %),

DOI: 10.1021/acs.joc.9b02114
J. Org. Chem. XXXX, XXX, XXX−XXX

$Cu(OAc)_2$ (136 mg, 0.75 mmol, 1.5 equiv), and a stirring bar. In the in-tube (2.5 mL), TFBen (210 mg, 1.0 mmol, 2.0 equiv) was added. Then the in−ex tube was placed under a vacuum and refilled with nitrogen three times. Et_3N (102 mg, 1.0 mmol, 2.0 equiv), toluene (2.0 mL), and DMSO (0.2 mL) were added into the ex-tube via syringe. The in−ex tube was sealed and stirred at 110 °C in an oil bath for 20 h. Upon reaction completion, the mixture was diluted with CH_2Cl_2 and washed with water three times. The crude mixture was purified by alumina column chromatography (EtOAc) to obtain the desired product **12**.

Characterization of Products. *5-Benzyl-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2a**):*[16] 83.6 mg, 73% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 4.6 Hz, 1H), 7.35−7.26 (m, 5H), 6.99 (d, J = 4.5 Hz, 1H), 4.75 (s, 2H), 4.19 (d, J = 3.0 Hz, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.6, 150.9, 137.3, 135.7, 134.6, 128.8, 128.1, 127.7, 120.9, 48.2, 47.0.

*5-(4-Methylbenzyl)-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2b**):* 91.2 mg, 75% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 4.8 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 6.97 (d, J = 4.8 Hz, 1H), 4.71 (s, 2H), 4.17 (s, 2H), 2.33 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.6, 150.9, 137.4, 135.8, 134.4, 134.2, 129.4, 128.1, 120.8, 48.1, 46.7, 21.1; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{14}H_{14}NOS^+$ 244.0791, found 244.0809.

*5-(4-(tert-Butyl)benzyl)-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2c**):* 78.4 mg, 55% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 4.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 6.97 (d, J = 4.6 Hz, 1H), 4.72 (s, 2H), 4.18 (s, 2H), 1.30 (s, 9H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.5, 150.9, 150.6, 135.8, 134.4, 134.2, 127.9, 125.7, 120.9, 48.2, 46.6, 34.5, 31.3; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{17}H_{20}NOS^+$ 286.1260, found 286.1276.

*5-(4-Methoxybenzyl)-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2d**):* 81.6 mg, 63% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 4.7 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 4.7 Hz, 1H), 6.89−6.82 (m, 2H), 4.68 (s, 2H), 4.16 (s, 2H), 3.79 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.5, 159.1, 150.9, 135.8, 134.4, 129.4, 120.9, 114.1, 55.3, 48.1, 46.4; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{14}H_{14}NO_2S^+$ 260.0740, found 260.0754.

*5-(4-Chlorobenzyl)-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2e**):* 76.3 mg, 58% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 4.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 4.8 Hz, 1H), 4.72 (s, 2H), 4.19 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.6, 150.9, 135.8, 135.5, 134.8, 133.5, 129.4, 129.0, 120.9, 48.2, 46.3; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{13}H_{11}ClNOS^+$ 264.0244, found 264.0257.

*5-(4-Bromobenzyl)-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2f**):* 78.3 mg, 51% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 4.7 Hz, 1H), 4.70 (s, 2H), 4.19 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.6, 150.9, 136.4, 134.8, 131.9, 129.7, 121.6, 120.9, 48.2, 46.4; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{13}H_{10}BrNNaOS^+$ 329.9559, found 329.9565.

*5-(2-Methylbenzyl)-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2g**):* 52.3 mg, 43.2% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 4.8 Hz, 1H), 7.18 (t, J = 6.0 Hz, 4H), 6.97 (d, J = 4.8 Hz, 1H), 4.77 (s, 2H), 4.11 (s, 2H), 2.35 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.3, 150.9, 136.7, 134.9, 134.5, 130.7, 128.9, 127.9, 126.2, 120.8, 48.2, 45.1, 19.1; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{14}H_{13}NNaOS^+$, 266.0610, found 266.0611.

*5-Isobutyl-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2h**):* 30.8 mg, 63% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 4.7 Hz, 1H), 7.03 (d, J = 4.7 Hz, 1H), 4.30 (s, 2H), 3.38 (d, J = 7.6 Hz, 2H), 2.09−1.96 (m, 1H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.8, 150.5, 136.2, 134.2, 120.7, 50.7, 49.3, 28.1, 20.1; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{10}H_{13}NOS^+$ 196.0791, found 196.0806.

*5-Neopentyl-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2i**):* 81.5 mg, 78% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 4.7 Hz, 1H), 7.02 (d, J = 4.8 Hz, 1H), 4.43 (s, 2H), 3.34 (s, 2H), 1.02 (s, 9H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 165.5, 150.8, 136.0, 134.3, 120.6, 55.8, 52.0, 33.9, 28.2; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{11}H_{16}NOS^+$ 210.0947, found 210.0964.

*5-Phenethyl-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**2j**):* 92.3 mg, 76% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 4.8 Hz, 1H), 7.31−7.27 (m, 2H), 7.25−7.19 (m, 3H), 6.97 (d, J = 4.7 Hz, 1H), 4.10 (s, 2H), 3.82 (t, J = 7.3 Hz, 2H), 2.98 (t, J = 7.3 Hz, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.6, 150.7, 138.9, 136.0, 134.2, 128.7, 128.6, 126.5, 120.7, 49.4, 44.8, 35.2; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{14}H_{14}NOS^+$, 244.0791, found 244.0804.

*2-(Thiophen-2-ylmethyl)isoindolin-1-one (**4a**):*[17] 68.7 mg, 60% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.5 Hz, 1H), 7.51 (dt, J = 7.4, 3.7 Hz, 1H), 7.45 (t, J = 7.3 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.25−7.22 (m, 1H), 7.04 (d, J = 3.2 Hz, 1H), 6.96 (dd, J = 5.0, 3.5 Hz, 1H), 4.97 (s, 2H), 4.35 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 168.1, 141.2, 139.4, 132.5, 131.5, 128.1, 127.0, 126.8, 125.7, 123.9, 122.8, 49.3, 40.8.

*6-Methyl-2-(thiophen-2-ylmethyl)isoindolin-1-one (**4b**):* 55.9 mg, 46% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.22 (dd, J = 5.1, 1.2 Hz, 1H), 7.04−7.01 (m, 1H), 6.95 (dd, J = 5.1, 3.5 Hz, 1H), 4.95 (s, 2H), 4.30 (s, 2H), 2.43 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 168.2, 139.5, 138.4, 138.0, 132.6, 132.4, 126.9, 126.6, 125.5, 124.1, 122.4, 49.1, 40.8, 21.3; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{14}H_{13}NNaOS^+$ 266.0610, found 266.0627.

*6-Ethyl-2-(thiophen-2-ylmethyl)isoindolin-1-one (**4c**):* 59.1 mg, 46% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.36−7.32 (m, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.22 (dd, J = 5.1, 1.1 Hz, 1H), 7.03 (d, J = 3.0 Hz, 1H), 6.95 (dd, J = 5.0, 3.5 Hz, 1H), 4.96 (s, 2H), 4.30 (s, 2H), 2.73 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 168.3, 144.5, 139.5, 138.7, 132.6, 131.5, 127.0, 126.7, 125.6, 122.9, 122.6, 49.1, 40.8, 28.8, 15.7; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{15}H_{15}NNaOS^+$ 280.0767, found 280.0780.

*6-(tert-Butyl)-2-(thiophen-2-ylmethyl)isoindolin-1-one (**4d**):* 64.2 mg, 45% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 1.7 Hz, 1H), 7.57 (dd, J = 8.0, 1.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.24−7.20 (m, 1H), 7.03 (d, J = 3.0 Hz, 1H), 6.95 (dd, J = 5.0, 3.5 Hz, 1H), 4.97 (s, 2H), 4.31 (s, 2H), 1.36 (s, 9H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 168.5, 151.7, 139.5, 138.5, 132.3, 128.9, 126.9, 126.7, 125.5, 122.4, 120.6, 49.0, 40.9, 35.0, 31.4; HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{17}H_{20}NOS^+$ 286.1260, found 286.1271.

*6-Methoxy-2-(thiophen-2-ylmethyl)isoindolin-1-one (**4e**):* 88.1 mg, 68% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 2.4 Hz, 1H), 7.28 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 7.08 (dd, J = 8.3, 2.4 Hz, 1H), 7.03 (d, J = 3.3 Hz, 1H), 6.96 (dd, J = 4.9, 3.6 Hz, 1H), 4.96 (s, 2H), 4.28 (s, 2H), 3.86 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 168.1, 160.0, 139.4, 133.8, 133.4, 127.0, 126.7, 125.6, 123.6, 119.9, 106.7, 55.7, 48.9, 40.9; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{14}H_{13}NNaO_2S^+$ 282.0559, found 282.0577.

*6-Chloro-2-(thiophen-2-ylmethyl)isoindolin-1-one (**4f**):* 71.1 mg, 54% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 1.8 Hz, 1H), 7.48 (dd, J = 8.1, 1.9 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.24 (dd, J = 5.0, 1.1 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 6.97 (dd, J = 5.0, 3.4 Hz, 1H), 4.96 (s, 2H), 4.32 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 166.8, 139.3, 138.9, 134.4, 134.3, 131.6, 128.9, 127.0, 126.9, 125.8, 124.0, 49.0, 40.9; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{13}H_{10}ClNNaOS^+$ 286.0064, found 286.0077.

*4-Methyl-2-(thiophen-2-ylmethyl)isoindolin-1-one (**4g**):* 58.3 mg, 48.1% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.4 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.23 (dd, J = 5.1, 1.1 Hz, 1H), 7.04 (d, J = 2.7 Hz, 1H), 6.96 (dd, J = 5.1, 3.5 Hz, 1H), 4.97 (s, 2H), 4.25 (s, 2H), 2.29 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 168.5, 140.1, 139.5, 132.5, 132.3, 132.2, 128.3, 127.0, 126.7, 125.6, 121.4, 48.5, 40.8, 17.5; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{14}H_{13}NNaOS^+$ 266.0610, found 266.0610.

*2-Benzyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (**6a**):*[18] 119.3 mg, 86% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.41−7.38 (m, 2H), 7.37−7.33 (m, 2H), 7.32−7.28 (m, 1H), 7.25−7.23 (m, 1H), 7.14−7.09 (m, 1H), 4.86 (s, 2H), 3.66 (t, J = 7.1 Hz,

DOI: 10.1021/acs.joc.9b02114
J. Org. Chem. XXXX, XXX, XXX−XXX

2H), 3.03 (t, J = 7.1 Hz, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 161.8, 137.8, 137.6, 128.7, 128.0, 127.5, 126.9, 125.2, 124.8, 120.0, 118.2, 112.7, 49.6, 47.5, 20.7.

*2-(4-Methylbenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (**6b**):* 133.5 mg, 92% yield, white solid, mp 260.9−265.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 7.2 Hz, 3H), 7.16 (d, J = 7.4 Hz, 2H), 7.05 (t, J = 7.4 Hz, 1H), 4.66 (s, 2H), 3.57 (s, 2H), 2.96 (t, J = 6.7 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6) δ 161.0, 137.9, 136.7, 135.4, 129.6, 128.1, 127.4, 125.2, 124.5, 120.6, 119.9, 117.9, 113.0, 48.9, 47.6, 21.2, 20.5; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{19}H_{18}N_2NaO^+$ 313.1311, found 313.1299.

*2-(4-Methoxybenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (**6c**):* 130.6 mg, 85% yield, white solid, mp 230.2−235.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 8.7 Hz, 2H), 7.29−7.23 (m, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 4.67 (s, 2H), 3.77 (s, 3H), 3.59 (d, J = 7.1 Hz, 2H), 2.99 (t, J = 7.0 Hz, 2H); ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6) δ 161.0, 158.9, 137.9, 130.3, 129.5, 127.5, 125.2, 124.5, 120.5, 119.9, 117.8, 114.4, 113.0, 55.5, 48.5, 47.5, 20.5; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{19}H_{19}N_2O_2^+$ 307.1441, found 307.1451.

*2-(4-Chlorobenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (**6d**):* 127.4 mg, 82% yield, white solid, mp 254.5−259.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.40 (dt, J = 18.2, 5.8 Hz, 5H), 7.22 (dd, J = 11.3, 3.9 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 4.69 (s, 2H), 3.60 (t, J = 7.0 Hz, 2H), 2.98 (t, J = 7.0 Hz, 2H); ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6) δ 161.1, 137.9, 137.5, 132.2, 130.0, 129.0, 127.2, 125.2, 124.6, 120.6, 120.0, 118.1, 113.0, 48.6, 47.8, 20.5; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{18}H_{16}ClN_2O^+$ 311.0946, found 311.0957.

*2-(2-Methylbenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (**6e**):* 90 mg, 62.2% yield, pale yellow solid, mp 164.5−168.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.27−7.16 (m, 5H), 7.06 (t, J = 7.3 Hz, 1H), 4.70 (s, 2H), 3.58 (t, J = 7.0 Hz, 2H), 2.97 (t, J = 7.0 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6) δ 160.9, 137.9, 136.5, 136.0, 130.7, 127.8, 127.5, 127.4, 126.4, 125.2, 124.5, 120.5, 119.9, 117.9, 113.0, 47.5, 47.1, 20.5, 19.2; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{19}H_{18}N_2NaO^+$ 313.1311, found 313.1309.

*2-Benzyl-6-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (**6f**):* 118.9 mg, 82.3% yield, white solid, mp 170.3−175.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 7.35−7.32 (m, 5H), 7.30 (s, 1H), 7.29−7.25 (m, 1H), 7.05 (d, J = 8.4 Hz, 1H), 4.69 (s, 2H), 3.56 (t, J = 7.0 Hz, 2H), 2.93 (t, J = 7.0 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6) δ 161.1, 138.5, 136.4, 129.0, 128.6, 128.0, 127.6, 127.4, 126.4, 125.4, 119.8, 117.4, 112.7, 49.2, 47.8, 21.6, 20.5; HRMS (ESI-TOF) [M + Na]$^+$ calcd for $C_{19}H_{18}N_2NaO^+$ 313.1311, found 313.1309.

*2-Neopentyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (**6g**):* 60.2 mg, 94% yield, white solid, mp 275.4−277.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.29 (dd, J = 7.1, 1.0 Hz, 1H), 7.14 (dd, J = 11.1, 3.9 Hz, 1H), 3.76 (t, J = 6.9 Hz, 2H), 3.39 (s, 2H), 3.06 (t, J = 6.9 Hz, 2H), 1.05 (s, 9H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 162.5, 137.6, 127.6, 125.3, 124.6, 120.0, 118.4, 112.6, 57.8, 50.9, 33.9, 28.2, 21.0; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{16}H_{21}N_2O^+$ 257.1648, found 257.1662.

*5-(Thiophen-2-ylmethyl)-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (**8**):* 70.0 mg, 57% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 4.8 Hz, 1H), 7.24 (dd, J = 5.0, 0.9 Hz, 1H), 7.03 (d, J = 2.9 Hz, 1H), 7.00 (d, J = 4.8 Hz, 1H), 6.96 (dd, J = 5.0, 3.6 Hz, 1H), 4.91 (s, 2H), 4.27 (s, 2H); ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 164.3, 151.0, 139.6, 135.5, 134.7, 127.0, 126.6, 125.6, 120.9, 48.1, 41.4; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{11}H_{10}NOS_2^+$ 236.0198, found 236.0207.

*2-(Thiophen-2-ylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (**10**):* 114.2 mg, 81% yield, white solid, mp 248.3−252.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 5.0, 0.8 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 2.9 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.99 (dd, J = 5.0, 3.5 Hz, 1H), 4.86 (s, 2H), 3.64 (t, J = 7.0 Hz, 2H), 2.99 (t, J = 7.0 Hz, 2H); ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6) δ 160.9, 140.9, 137.9, 127.2, 127.1, 126.2, 125.2, 124.6, 120.6, 120.0, 119.0, 113.0, 47.6, 44.3, 20.5; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{16}H_{15}N_2OS^+$ 283.0900, found 283.0907.

*2-(Thiophen-3-ylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (**12**):* 110.0 mg, 78% yield, pale yellow solid, mp 220.1−225.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.52 (dd, J = 4.9, 2.9 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.06 (dd, J = 12.6, 5.9 Hz, 2H), 4.68 (s, 2H), 3.61 (t, J = 7.0 Hz, 2H), 2.98 (t, J = 7.0 Hz, 2H); ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6) δ 160.9, 139.2, 137.9, 128.0, 127.4, 127.1, 125.2, 124.5, 123.1, 120.6, 119.9, 118.0, 113.0, 47.7, 44.8, 20.5; HRMS (ESI-TOF) [M + H]$^+$ calcd for $C_{16}H_{15}N_2OS^+$ 283.0900, found 283.0911.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02114.

NMR spectra of substrates and products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xiao-feng.wu@catalysis.de.

ORCID

Xiao-Feng Wu: 0000-0001-6622-3328

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Zhejiang Natural Science Fund for Young Scholars (LQ18B020008), Zhejiang Sci-Tech University (17062078-Y), and National Natural Science Foundation of China (21772177).

■ REFERENCES

(1) For selected reviews on oxidative carbonylation, see: (a) Wu, X.-F.; Neumann, H.; Beller, M. Palladium-catalyzed oxidative carbonylation reactions. *ChemSusChem* **2013**, *6*, 229−241. (b) Gabriele, B.; Mancuso, R.; Salerno, G. Oxidative carbonylation as a powerful tool for the direct synthesis of carbonylated heterocycles. *Eur. J. Org. Chem.* **2012**, *2012*, 6825−6839. (c) Liu, Q.; Zhang, H.; Lei, A. Oxidative carbonylation reactions: organometallic compounds (R-M) or hydrocarbons (R-H) as nucleophiles. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788−10799.

(2) For selected examples of carbonylative C−H activation, see: (a) Ying, J.; Fu, L.-Y.; Zhong, G.; Wu, X.-F. Cobalt-catalyzed direct carbonylative synthesis of free (*NH*)-benzo[*cd*]indol-2(1*H*)-ones from naphthylamides. *Org. Lett.* **2019**, *21*, 5694−5698. (b) Cabrera-Pardo, J. R.; Trowbridge, A.; Nappi, M.; Ozaki, K.; Gaunt, M. J. Selective palladium(II)-catalyzed carbonylation of methylene β-C-H bonds in aliphatic amines. *Angew. Chem., Int. Ed.* **2017**, *56*, 11958−11962. (c) Wen, J.; Tang, S.; Zhang, F.; Shi, R.; Lei, A. Palladium/Copper co-catalyzed oxidative C-H/C-H carbonylation of diphenylamines: a way to access acridones. *Org. Lett.* **2017**, *19*, 94−97. (d) Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. A general catalytic β-C-H carbonylation of aliphatic amines to β-lactams. *Science* **2016**, *354*, 851−857. (e) Shi, B. F.; Maugel, N.; Zhang, Y. H.; Yu, J. Q. Pd^{II}-catalyzed enantioselective activation of C(sp^2)-H and C(sp^3)-H bonds using monoprotected amino acids as chiral ligands. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882−4886. (f) Chen, M.; Ren, Z.-H.; Guan, Z.-H. Palladium-catalyzed regioselective carbonylation of C−H bonds of *N*-alkyl anilines for synthesis of isatoic anhydrides. *J. Am. Chem. Soc.* **2012**, *134*, 17490−

DOI: 10.1021/acs.joc.9b02114
J. Org. Chem. XXXX, XXX, XXX−XXX

17493. (g) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. Palladium-catalyzed oxidative carbonylation of the alkenyl C-H bonds of enamides: synthesis of 1,3-oxazin-6-ones. *Angew. Chem., Int. Ed.* **2013**, *52*, 14196−14199. (h) Bai, X. F.; Mu, Q.-C.; Xu, Z.; Yang, K.-F.; Li, L.; Zheng, Z.-J.; Xia, C. G.; Xu, L.-W. Catalytic Asymmetric Carbonylation of Prochiral Sulfonamides via C-H Desymmetrization. *ACS Catal.* **2019**, *9*, 1431−1436.

(3) (a) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. $Pd(OAc)_2$-catalyzed carbonylation of amines. *J. Org. Chem.* **2006**, *71*, 5951−5958. (b) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. Preparation of benzolactams by $Pd(OAc)_2$-catalyzed direct aromatic carbonylation. *J. Am. Chem. Soc.* **2004**, *126*, 14342−14343.

(4) Zhang, C.; Ding, Y.; Gao, Y.; Li, S.; Li, G. Palladium-catalyzed direct C-H carbonylation of free primary benzylamines: a synthesis of benzolactams. *Org. Lett.* **2018**, *20*, 2595−2598.

(5) Cheng, X.-F.; Wang, T.; Li, Y.; Wu, Y.; Sheng, J.; Wang, R.; Li, C.; Bian, K.-J.; Wang, X.-S. Palladium(II)-catalyzed $C(sp^2)$-H carbonylation of sterically hindered amines with carbon monoxide. *Org. Lett.* **2018**, *20*, 6530−6533.

(6) Han, J.; Wang, N.; Huang, Z.-B.; Zhao, Y.; Shi, D.-Q. Ruthenium-catalyzed carbonylation of oxalyl amide-protected benzylamines with isocyanate as the carbonyl source. *J. Org. Chem.* **2017**, *82*, 6831−6839.

(7) Fu, L.-Y.; Ying, J.; Qi, X.; Peng, J.-B.; Wu, X.-F. Palladium-catalyzed carbonylative synthesis of isoindolinones from benzylamines with TFBen as the CO source. *J. Org. Chem.* **2019**, *84*, 1421−1429.

(8) Wada, Y.; Nagasaki, H.; Tokuda, M.; Orito, K. Synthesis of *N*-protected staurosporinones. *J. Org. Chem.* **2007**, *72*, 2008−2014.

(9) Ling, F.; Ai, C.; Lv, Y.; Zhong, W. Traceless directing group assisted cobalt-catalyzed C-H carbonylation of benzylamines. *Adv. Synth. Catal.* **2017**, *359*, 3707−3712.

(10) (a) Jiang, L.-B.; Qi, X.; Wu, X.-F. Benzene-1,3,5-triyl triformate (TFBen): a convenient, efficient, and non-reacting CO source in carbonylation reactions. *Tetrahedron Lett.* **2016**, *57*, 3368−3370. (b) Wang, H.; Ying, J.; Lai, M.; Qi, X.; Peng, J.-B.; Wu, X.-F. Base promoted carbonylative cyclization of propargylic amines with selenium under CO gas-free conditions. *Adv. Synth. Catal.* **2018**, *360*, 1693−1703. (c) Ying, J.; Zhou, C.; Wu, X.-F. DBU-promoted carbonylative synthesis of 1,3-oxathiolan-2-ones from propargylic alcohols with TFBen as the CO source. *Org. Biomol. Chem.* **2018**, *16*, 1065−1067. (d) Ying, J.; Wang, H.; Qi, X.; Peng, J.-B.; Wu, X.-F. Base-promoted sulfur-mediated carbonylative cyclization of propargylic amines. *Eur. J. Org. Chem.* **2018**, *2018*, 688−692. (e) Zhou, C.; Liu, Y.; Ying, J.; Qi, X.; Peng, J.-B.; Wu, X.-F. Cobalt catalyzed carbonylative cyclization of allyl propargyl ethers with benzene-1,3,5-triyl triformate as the CO source. *Asian J. Org. Chem.* **2019**, *8*, 238−241. (f) Le, Z.; Ying, J.; Wu, X.-F. More than a CO source: palladium-catalyzed carbonylative synthesis of butenolides from propargyl alcohols and TFBen. *Org. Chem. Front.* **2019**, *6*, 3158.

(11) Brice, H.; Clayden, J. Doubly Dearomatising Intramolecular Coupling of a Nucleophilic and an Electrophilicheterocycle. *Chem. Commun.* **2009**, *15*, 1964−1966.

(12) Regnier, R.; Lavastre, O. General and Environmentally Friendly Synthesis of Heterocyclic Multidentate Molecules Based on Microwave-assisted Heating Protocol. *Tetrahedron* **2006**, *62*, 155−159.

(13) Fuente, M. C.; Domínguez, D. Normal Electron Demand Diels-Alder Cycloaddition of Indoles to 2,3-Dimethyl-1,3-butadiene. *Tetrahedron* **2011**, *67*, 3997−4001.

(14) Martin, D. B. C.; Vanderwal, C. D. Efficient Access to the Core of the Strychnos, Aspidosperma and Iboga Alkaloids. A Short Synthesis of Norfluorocurarine. *J. Am. Chem. Soc.* **2009**, *131*, 3472−3473.

(15) Hanna-Elias, A.; T. Manallack, D.; Levit, A.; Nguyen, W.; Ayad, F.; Perera, G.; Shapiro, M.; R. Irving, H.; M. Coupar, I.; N. Iskander, M. Synthesis, testing and structure-activity studies on a library of 5-HT 4 ligands. *Med. Chem.* **2010**, *6*, 344−354.

(16) Benachenhou, F.; Mesli, M. A.; Borai, M. E.; Hanquet, B.; Guilard, R. Synthesis and Structure Elucidation of the Condensation Products between Thiophene Dicarbaldehydes and Aromatic Amines. Potential Analgesic and Anti-inflammatory Agents. *J. Heterocycl. Chem.* **1988**, *25*, 1531−1534.

(17) Aubert, T.; Farnier, M.; Guilard, R. Nouvelle voie de Synthèse d'isoindolones et d'isoquinoléines par condensation d'iminophosphoranes avec l'ortho-phtalaldéhyde: réactions, mécanismes et étude structural. *Can. J. Chem.* **1990**, *68*, 842−851.

(18) Chern, M. S.; Shih, Y. K.; Dewang, P. M.; Li, W. R. Traceless Solid-Phase Synthesis of Carbolinones. *J. Comb. Chem.* **2004**, *6*, 855−858.

DOI: 10.1021/acs.joc.9b02114
J. Org. Chem. XXXX, XXX, XXX−XXX