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Palladium-Catalyzed Carbonylative Synthesis of Isoindolinones from Benzylamines with TFBen as the CO Source

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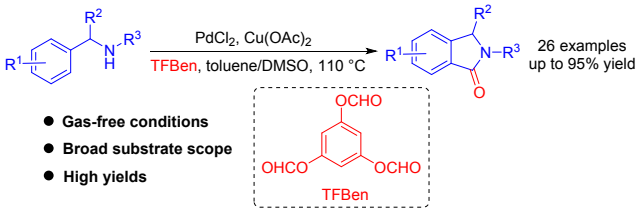
Supporting Information Placeholder



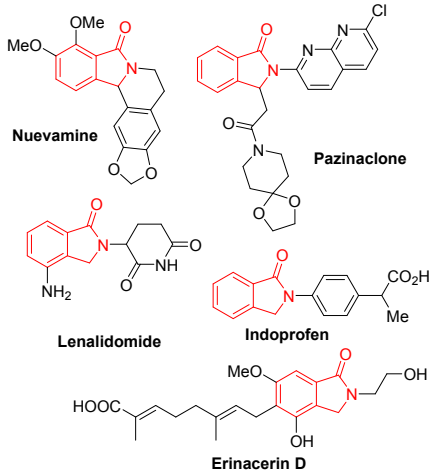
ABSTRACT: A palladium-catalyzed C-H carbonylation of benzylamines for the synthesis of isoindolinone scaffolds has been developed. This protocol is conducted under gas-free conditions by using benzene-1,3,5-triyl triformate (TFBen) as a convenient CO surrogate, furnishing a variety of isoindolinone derivatives in moderate to high yields (up to 95%).

Introduction

Isoindolinone scaffold is a class of important motif frequently found in pharmaceuticals and bioactive natural products (Scheme 1).[1] For instance, Lenalidomide is one of the novel drug agents used to treat multiple myeloma.[2] Pazinaclone shows excellent sedative and anxiolytic properties by acting as a partial agonist at GABA-A benzodiazepine receptors.[3] Nuevamine, a representative example of natural isoindolinone alkaloids, whose analogues possess potential and promising biological activities such as anti-inflammatory, anti-microbial, anti-tumoral and so on.[4] Due to the potent applications, many procedures have been developed for their construction. The achieved methods include lactamization of *o*-(aminomethyl)benzoic acids,[5] monoreduction of phthalimides,[6] Bischler-Napieralski-type cyclization of carbamates from benzylamines,[7] and metal-catalyzed carbonylation of benzylamine derivatives.[8-15]

Benzylamine is an attractive precursor to the establishment of the isoindolinone core *via* carbonylation with carbon monoxide (CO) or its surrogates in the presence of metal catalysts (Scheme 2). Over the past decades, tremendous work on metal-catalyzed carbonylation of 2-aminomethylaryl halides or 2-aminomethylaryl tosylates have been reported (Scheme 2, eq a).[8-10] Recently, metal-catalyzed direct C-H carbonylation of benzylamines have been realized as well.[11-15] Zhao and Shi disclosed a Ru(II)-catalyzed C-H carbonylation of benzylamines with isocyanate as a CO source (Scheme 2, eq b).[11] In this reaction, oxalyl amide as a directing group was required in the coordination of the Ru center and activation of *ortho*-C-H of a benzylamine. Orito and co-workers developed a synthetic protocol to the isoindolinone ring systems *via* C-H carbonylation of benzylamines using $Pd(OAc)_2$ and $Cu(OAc)_2$ in an atmosphere of CO gas containing air (Scheme 2, eq c).[12] Very recently, Wang, Li and their co-workers developed a palladium-catalyzed carbonylation of α,α-disubstituted benzylamine to synthesis the corresponding sterically hindered benzolactams under atmospheric pressure of CO.[13b].

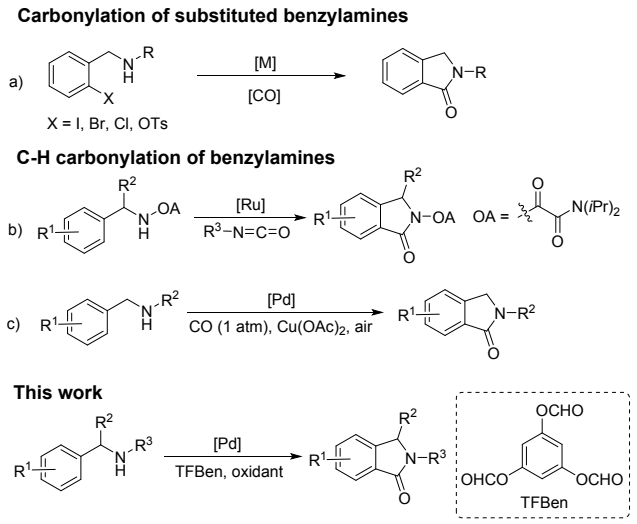
Scheme 1. Representative Pharmaceuticals and Natural Products of Isoindolinones.



To avoid the use of flammable CO gas in carbonylative reactions, various CO surrogates have been developed.[16] Among them, TFBen, developed by our group,[17] is a solid, safe and

convenient CO source. Herein, we report a Pd-catalyzed C-H carbonylation of benzylamines with TFBen as the CO source, producing a series of isoindolinones.

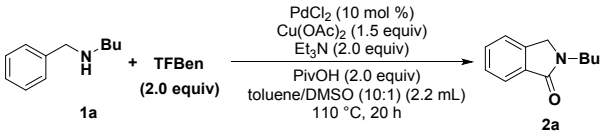
Scheme 2. Carbonylative Synthesis of Isoindolinones from Benzylamines.



Results and Discussion

Initially, benzylamine **1a** was chosen as a substrate for the model reaction.[13] After extensive study of the reaction conditions, the desired isoindolinone product **2a** was obtained in 83% yield in the presence of $PdCl_2$. The reaction employed TFBen as the CO source and $Cu(OAc)_2$ as the oxidant (Table 1, entry 1). The use of other Pd catalysts instead of $PdCl_2$ gave similar results (Table 1, entries 2-5). Et_3N and PivOH were likely to tune the acidity of the reaction system and promote the activation of C-H bond. Without the addition of Et_3N and PivOH, the yield was remarkably decreased to 47% (Table 1, entry 6). When toluene or DMSO was used instead of their mixed solvent system, reduced yields of the product **2a** were achieved (Table 1, entry 7 and 8). Moreover, a series of other oxidants were examined and the reaction gave much lower yields or no product (Table 1, entries 9-12). Finally, using other CO surrogates instead of TFBen decreased the reaction yield (Table 1, entry 13 and 14). Here 2 equivalents of TFBen is needed to maintain the CO concentration in the reaction media.

Table 1. Study on Reaction Conditions.[a]

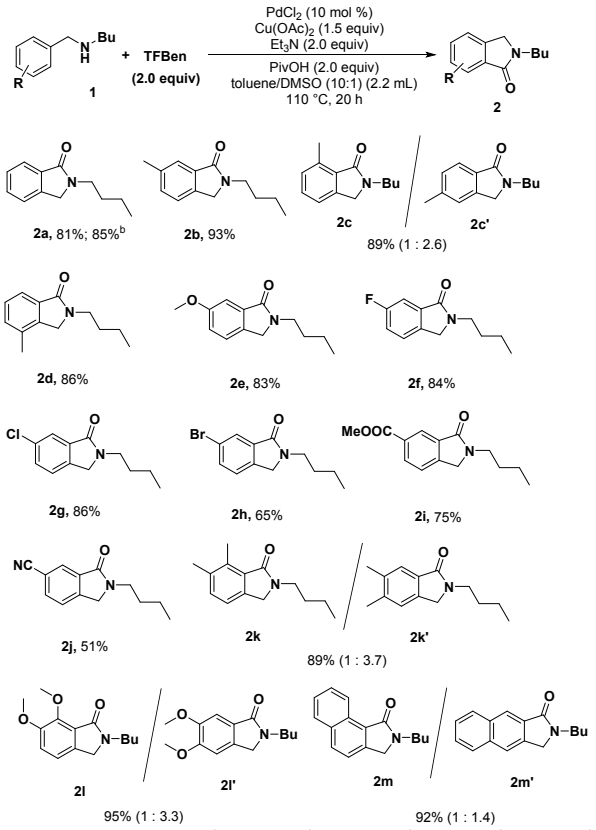


entry	variations from the standard conditions	yield (%)[b]
1	none	83 (81[c])
2	$Pd(PPh_3)_2Cl_2$ as catalyst	63
3	$Pd(OAc)_2$ as catalyst	78
4	Pd(cinnamyl)Cl_2 as catalyst	68
5	$PdBr_2$ as catalyst	81
6	without Et_3N and PivOH	47
7	toluene instead of mixed solvent	75
8	DMSO instead of mixed solvent	71
9	CuO as oxidant	25
10	Ag_2O as oxidant	16
11	BQ as oxidant	10
12	$K_2S_2O_8$ as oxidant	0
13[d]	$Mo(CO)_6$ as CO source	57
14[e]	$HCOOH/Ac_2O$ as CO source	67

[a]Reaction conditions: **1a** (0.5 mmol), TFBen (2.0 equiv), catalyst (10 mol %), oxidant (1.5 equiv), Et_3N (2.0 equiv), PivOH (2.0 equiv), solvent (2.2 mL), 110 °C, 20 h. [b]Yields were determined by GC with dodecane as an internal standard. [c]Isolated yield. [d]$Mo(CO)_6$ (1.0 equiv), DBU (2.0 equiv). [e]HCOOH (2.0 equiv), Ac_2O (2.0 equiv), Et_3N (2.0 equiv).

With the optimal reaction conditions in hand, we began exploring the scope of C-H carbonylation of benzylamines. First, various substituted benzylamines were tested and the results were summarized in Scheme 3. Benzylamines with electron-donating substituents could undergo the reaction smoothly to give the desired products **2b**-**2d** in excellent yields (86-93%). It was found that *para*-Me substituted benzylamine **1c** gave the products **2c** and **2c'** with a ratio of 1:2.6. The observed regioselectivity could be attributed to the steric hindrance of C-H activation site. Other tested functional groups including methoxy, fluoro and chloro can be well tolerated as well and gave the corresponding products in good yields **2e**-**2g**. The reaction with electron-withdrawing substituted benzylamines also afforded moderate to good yields (51-86%) of products **2h**-**2j**. Similar to **1c**, the reaction with di-substituted benzylamines provided two regiomers. A ratio of 1:3.7 in 89% yield was observed for the products **2k** and **2k'** in the reaction with di-Me substituted benzylamine. Di-OMe substituted benzylamine gave the expected products **2l** and **2l'** in 95% yield with a ratio of 1:3.3. For compound **1m**, the reaction proceeded well to produce the regiomers **2m** and **2m'** with 1:1.4 ratio in 92% yield. Additionally, thiophene and pyridine analogue of amines were tested as well, but very low yield of the desired products were obtained. In the case of free benzylamine, mainly *N*-benzylformamide was formed.

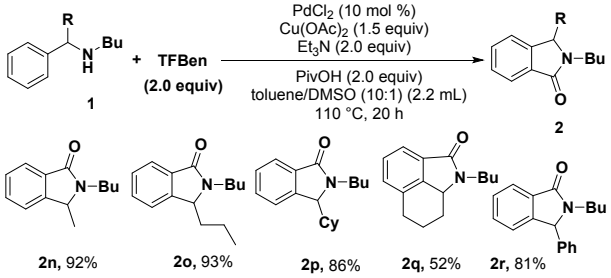
Scheme 3. Scope of Substituted Benzylamines.[a]



[a]Reaction conditions: **1** (0.5 mmol), TFBen (2.0 equiv), $PdCl_2$ (10 mol %), $Cu(OAc)_2$ (1.5 equiv), Et_3N (2.0 equiv), PivOH (2.0 equiv), toluene/DMSO (10:1) (2.2 mL), 110 °C, 20 h, isolated yield. [b] 2 mmol scale.

Next, we turned our attention to the scope of *a*-substituted benzylamines (Scheme 4). These compounds were prepared *via* the condensation of ketones and amines and subsequent reduction with $NaBH_4$. For compounds bearing linear alkyl *a*-substituents, the reaction afforded the corresponding products **2n** and **2o** in excellent yields. The reaction with a compound having the carbocycle unit gave the desired product **2p** in 86% yield. Interestingly, the substrate containing a tetrahydronaphthalene system could undergo the C-H carbonylation to generate the polycyclic product **2q** in 52% yield. Additionally, a high yield of the product **2r** was obtained when benzylamines with aryl *a*-substituent was subjected to the same condition.

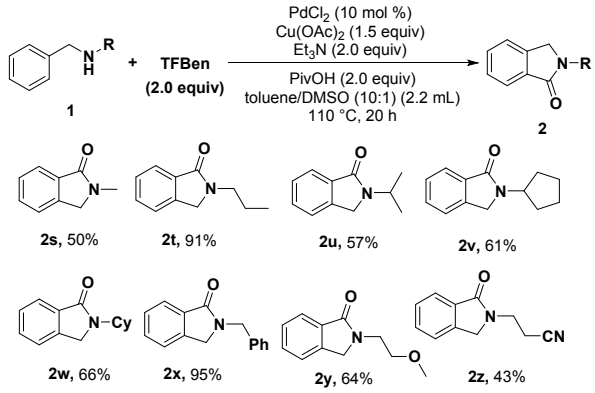
Scheme 4. Scope of *a*-Substituted Benzylamines.[a]



[a]Reaction conditions: **1** (0.5 mmol), TFBen (2.0 equiv), $PdCl_2$ (10 mol %), $Cu(OAc)_2$ (1.5 equiv), Et_3N (2.0 equiv), PivOH (2.0 equiv), toluene/DMSO (10:1) (2.2 mL), 110 °C, 20 h, isolated yield.

Then, a couple of *N*-substituted benzylamines were investigated (Scheme 5). The reaction with *N*-linear alkyl substituents gave moderate to good yields of products **2s** and **2t**. *N*-^{i}Pr substituted benzylamine was converted to the isoindolinone product **2u** in 57% yield. Compounds with the carbocycle unit were successfully transformed to the expected products **2v** and **2w** in high yields. Also, the reaction with *N*-benzyl substituted benzylamine proceeded well in an excellent yield (**2x**, 95%). For substrates containing functional groups such as methoxyl and cyano, 64% and 43% yield of products **2y** and **2z** were achieved, respectively.

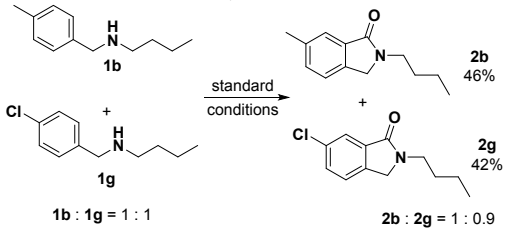
Scheme 5. Scope of *N*-Substituted Benzylamines.[a]



[a]Reaction conditions: **1** (0.5 mmol), TFBen (2.0 equiv), $PdCl_2$ (10 mol %), $Cu(OAc)_2$ (1.5 equiv.), Et_3N (2.0 equiv), PivOH (2.0 equiv), toluene/DMSO (10:1) (2.2 mL), 110 °C, 20 h, isolated yield.

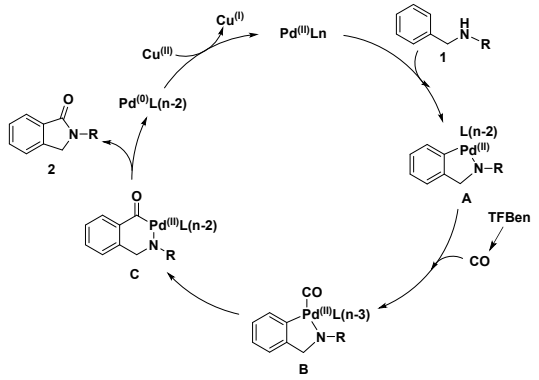
In order to study the reaction rate of different substrates, electron donating group and electron withdrawing group substituted substrates **1b** and **1g** were selected and combined as 1:1 ratio. Under our standard reaction conditions, the corresponding products were obtained in almost the same ratio (Scheme 6).

Scheme 6. Reaction rate study.



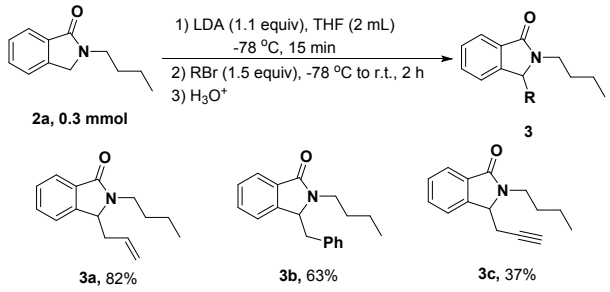
On the basis of previous reports,[12-14] a plausible mechanism is proposed to account for the C-H carbonylation of benzylamines (Scheme 7). Initially, the Pd(II) catalyst coordinates with benzylamine **1** and activates *ortho*-C-H bond to generate the five-palladacycle **A**. Then, coordination of CO, generated *in-situ* from TFBen, leads to the formation of the intermediate **B**. Subsequently, CO insertion of **B** forms the acyl Pd(II) complex **C**, which can undergo reductive elimination to give the final product **2** and a Pd(0) species. Finally, oxidation of the Pd(0) species by Cu(II) salt regenerates the active Pd(II) catalyst.

Scheme 7. Plausible Mechanism.



Finally, a few functionalizations of the isoindolinone **2a** have been demonstrated as well (Scheme 8).[18] Treatment of **2a** with lithium diisopropylamide (LDA) at -78 °C followed by the addition of alkyl bromide can give the 3-substituted isoindolinones **3**, an important skeleton in biologically active compounds exhibiting antipsychotic, antihypertensive, antiulcer and anxiolytic properties.[18a] The reaction of **2a** with allyl bromide and phenyl bromide provided good yields of **3a** (82%) and **3b** (63%), respectively. When **2a** was treated with propargyl bromide, a lower yield (37%) of **3c** was obtained. Moreover, the alkyl group can be removed easily as well.[18b]

Scheme 8. Functionalizations of the Isoindolinone 2a.



In conclusion, we have developed a facile approach for the synthesis of the isoindolinone skeleton *via* Pd-catalyzed C-H carbonylation of benzylamines using TFBen as a convenient CO source. The reaction proceeds smoothly with a wide range of benzylamine substrates, affording various isoindolinone derivatives in 43-95% yields.

EXPERIMENTAL SECTION

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere. All reagents and **1s** 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 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 internal standard and $CDCl_3$ as solvent.

Preparation of Benzene-1,3,5-triyl triformate (TFBen)[17]. 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 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), washed with H_2O (50 mL) two times. Keep the organic phase in fridge (2-8 °C) for overnight. 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. mp 53.2-55.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 3H), 6.97 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 158.1, 150.3, 112.6.

General Procedure for the Syntheses of the Secondary Amines 1a-1m' and 1t-1z[19]. To a solution of aldehyde (3 mmol, 1.0 equiv.) in MeOH (15 mL) at 0 °C was added primary amine (3.6 mmol, 1.2 equiv.) slowly, and the reaction mixture was stirred at 0 °C for 0.5 h, then at rt for 5 h. The reaction mixture was again cooled to 0 °C, and $NaBH_4$ (4.5 mmol, 1.5 equiv.) was added every 10 min in three portions. Then it was stirred at rt for 1h. The reaction was quenched by the addition of H_2O (10 mL) and Na_2CO_3 (0.252 g). The reaction mixture was washed with CH_2Cl_2 (20 mL), then the organic phase was separated and aqueous phase was further extracted with CH_2Cl_2 (20 mL × 2). Combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash column chromatography on silica gel eluted with petroleum ether / ethyl acetate (2 / 1) to give the secondary amine products **1a-1m'** and **1t-1z**.

General Procedure for the Syntheses of the Secondary Amines 1n-1r[20]. Titanium(IV) isopropoxide (4 mmol, 1.3 equiv.) was added to a solution of *n*-butylamine in MeOH (2 M, 4.5 mL, 3 equiv.) followed by the addition of the ketone (3 mmol, 1.0 equiv.). The reaction mixture was stirred at rt for 5 h, after was cooled to 0 °C and $NaBH_4$ (3 mmol, 1.0 equiv.) was added and the resulting mixture was further stirred for 2 h. The reaction was then quenched by the addition of water (1 mL), the resulting inorganic precipitate was filtered and washed with CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous phase was further extracted with CH_2Cl_2 (20 mL × 2). The combined CH_2Cl_2 extracts were washed with HCl (2 M, 10 mL × 2). The acidic aqueous solution was made alkaline (pH = 10) by slow addition of (10%, w / v) aqueous NaOH and extracted with CH_2Cl_2 (20 mL × 2). Combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash column chromatography on silica gel eluted with petroleum ether / ethyl acetate (10 / 1) to give the secondary amine products **1n-1r**.

N-benzylbutan-1-amine, ***1a***[21]. 455.1 mg, 93%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 4.3 Hz, 4H), 7.24 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.78 (s, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.54 (s, 1H), 1.48 (dd, *J* = 14.8, 7.5 Hz, 2H), 1.40 – 1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.4, 128.2, 127.9, 126.7, 53.9, 49.1, 32.1, 20.4, 13.9.

N-(4-methylbenzyl)butan-1-amine, ***1b***[21]. 488.4 mg, 92%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 3.74 (s, 2H), 2.68 – 2.56 (m, 2H), 2.32 (s, 3H), 1.62 (s, 1H), 1.49 (dt, *J* = 14.5, 7.1 Hz, 2H), 1.34 (dq, *J* = 14.5, 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.4, 136.3, 128.9, 128.0, 53.7, 49.0, 32.1, 20.9, 20.4, 13.9.

N-(3-methylbenzyl)butan-1-amine, ***1c***. 504.5 mg, 95%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (td, *J* = 7.5, 2.8 Hz, 1H), 7.17 – 7.08 (m, 2H), 7.05 (d, *J* = 7.2 Hz, 1H), 3.75 (s, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 2.34 (d, *J* = 2.5 Hz, 3H), 1.77 (s, 1H), 1.57 – 1.43 (m, 2H), 1.42 – 1.27 (m, 2H), 0.91 (td, *J* = 7.3, 2.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.2, 137.9, 128.9, 128.2,

127.6, 125.1, 53.9, 49.1, 32.1, 21.3, 20.4, 13.9. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{12}H_{20}N^+$, 178.1590; found, 178.1595.

N-(2-methylbenzyl)butan-1-amine, ***1d***[21]. 472.6 mg, 89%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 1H), 7.20 – 7.08 (m, 3H), 3.75 (s, 2H), 2.75 – 2.58 (m, 2H), 2.34 (s, 3H), 1.51 (dt, *J* = 14.6, 7.1 Hz, 2H), 1.36 (dq, *J* = 14.4, 7.2 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.5, 136.1, 130.2, 128.2, 126.8, 125.8, 51.6, 49.5, 32.3, 20.5, 18.9, 13.9.

N-(4-methoxybenzyl)butan-1-amine, ***1e***[21]. 526.8 mg, 91%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.8, 6.1 Hz, 2H), 6.88 – 6.82 (m, 2H), 3.78 (s, 3H), 3.72 (s, 2H), 2.66 – 2.56 (m, 2H), 1.78 (s, 1H), 1.49 (dt, *J* = 20.2, 7.1 Hz, 2H), 1.34 (dq, *J* = 14.3, 7.2 Hz, 2H), 0.94 – 0.84 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.6, 132.5, 129.2, 113.7, 55.2, 53.3, 48.9, 32.1, 20.4, 13.9.

N-(4-fluorobenzyl)butan-1-amine, ***1f***[21]. 445.3 mg, 82%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.2, 5.6 Hz, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 3.74 (s, 2H), 2.61 (t, *J* = 7.2 Hz, 2H), 1.49 (dt, *J* = 14.5, 7.1 Hz, 3H), 1.34 (dq, *J* = 14.3, 7.2 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 245.2 Hz), 136.3, 129.6 (d, *J* = 7.9 Hz), 115.1 (d, *J* = 20.8 Hz), 53.3, 49.1, 32.2, 20.4, 13.9.

N-(4-Chlorobenzyl)butan-1-amine, ***1g***[22]. 520.0 mg, 88%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.14 (m, 1H), 3.74 (s, 1H), 2.73 – 2.44 (m, 1H), 1.48 (dt, *J* = 14.5, 7.1 Hz, 2H), 1.42 (s, 1H), 1.34 (dq, *J* = 14.3, 7.2 Hz, 1H), 0.91 (t, *J* = 7.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 139.1, 132.4, 129.3, 128.4, 53.3, 49.1, 32.2, 20.4, 13.9.

N-(4-Bromobenzyl)butan-1-amine, ***1h***[21]. 643.4 mg, 89%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 3.73 (s, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.57 (s, 1H), 1.53 – 1.42 (m, 2H), 1.34 (dq, *J* = 14.3, 7.2 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 139.5, 131.3, 129.8, 120.6, 53.3, 49.0, 32.1, 20.4, 13.9.

Methyl 4-((butylamino)methyl)benzoate, ***1i***[23]. 590.1 mg, 89, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 2H), 2.62 (t, *J* = 7.1 Hz, 2H), 1.55 – 1.44 (m, 3H), 1.35 (dq, *J* = 14.3, 7.2 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9, 145.9, 129.6, 128.7, 127.8, 53.6, 51.9, 49.2, 32.2, 20.4, 13.9.

4-((Butylamino)methyl)benzonitrile, ***1j***[23]. 423.0 mg, 75%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 3.85 (s, 2H), 2.61 (t, *J* = 7.1 Hz, 2H), 1.54 – 1.45 (m, 2H), 1.44 (s, 1H), 1.36 (dq, *J* = 14.3, 7.2 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.3, 132.1, 128.5, 118.9, 110.6, 53.5, 49.2, 32.2, 20.3, 13.9.

N-(3,4-dimethylbenzyl)butan-1-amine, ***1k***. 504.2 mg, 88%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 1H), 3.71 (s, 2H), 2.67 – 2.56 (m, 2H), 2.25 (s, 3H), 2.24 (s, 3H), 1.49 (dt, *J* = 20.1, 7.2 Hz, 3H), 1.34 (dq, *J* = 14.3, 7.2 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.9, 136.4, 134.9, 129.5, 129.5, 125.5, 53.8, 49.2, 32.2, 20.5, 19.6, 19.3, 13.9. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{13}H_{22}N^+$, 192.1747; found, 192.1753.

N-(3,4-dimethoxybenzyl)butan-1-amine, ***1l***[24]. 568.6 mg, 85%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.87 – 6.79 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.73 (s, 2H), 2.63 (t, *J* = 7.2 Hz, 2H), 1.50 (dt, *J* = 14.6, 7.1 Hz, 3H), 1.40 – 1.30 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.8, 147.8, 133.2, 120.0, 111.3, 110.9, 55.8, 55.7, 53.7, 49.0, 32.1, 20.3, 13.8.

N-(naphthalen-2-ylmethyl)butan-1-amine, ***1m***[25]. 517.6 mg, 81%, Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.75 (m, 3H), 7.73 (s, 1H), 7.46 – 7.37 (m, 3H), 3.91 (s, 2H), 2.68 – 2.59 (m, 2H), 1.50 (dt, *J* = 14.7, 7.2 Hz, 3H), 1.39 – 1.29 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.0, 133.4, 132.5, 127.9, 127.6, 127.5, 126.5, 126.3, 125.8, 125.3, 54.1, 49.1, 32.2, 20.4, 13.9.

N-(1-phenylethyl)butan-1-amine, ***1n***[20]. 456.7 mg, 86%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H), 7.23 (ddd, *J* = 11.3, 5.4, 2.8 Hz, 1H), 3.75 (q, *J* = 6.6 Hz, 1H), 2.57 – 2.36 (m, 2H), 1.52 – 1.39 (m, 3H), 1.36 – 1.33 (m, 3H), 1.29 (tdd, *J* = 9.8, 7.4, 2.1 Hz, 2H), 0.87 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.9, 128.3, 126.7, 126.5, 58.4, 47.5, 32.4, 24.3, 20.5, 13.9.

N-butyl-1-phenylbutan-1-amine, ***1o***. 516.6 mg, 84%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 5H), 3.55 (dd, *J* = 7.7, 6.2 Hz, 1H), 2.47 – 2.33 (m, 2H), 1.69 (ddt, *J* = 11.9, 10.3, 5.9 Hz, 1H), 1.64 – 1.53 (m, 1H), 1.41 (tdd, *J* = 9.2, 7.6, 3.5 Hz, 2H), 1.33 – 1.20 (m, 3H), 1.21 – 1.09 (m, 1H), 0.86 (td, *J* = 7.3, 2.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.7, 128.2, 127.1, 126.7, 63.3, 47.4, 40.5, 32.4, 20.4, 19.5, 14.0, 13.9. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{14}H_{24}N^+$, 206.1903; found, 206.1910.

N-(cyclohexyl(phenyl)methyl)butan-1-amine, ***1p***. 551.2 mg, 75%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.24 – 7.19 (m, 3H), 3.31 (d, *J* = 7.1 Hz, 1H), 2.35 (td, *J* = 7.4, 1.9 Hz, 2H), 1.99 – 1.88 (m, 1H), 1.77 – 1.69 (m, 1H), 1.61 (dt, *J* = 8.8, 7.9 Hz, 2H), 1.55 – 1.46 (m, 2H), 1.44 – 1.35 (m, 3H), 1.34 – 1.18 (m, 3H), 1.17 – 1.04 (m, 2H), 1.01 – 0.90 (m, 1H), 0.87 – 0.79 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.4, 128.0, 127.8, 126.5, 69.0, 47.7, 44.3, 32.4, 30.4, 29.9, 26.6, 26.4, 26.3, 20.4, 13.9. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{17}H_{28}N^+$, 246.2216; found, 246.2222.

N-butyl-1,2,3,4-tetrahydronaphthalen-1-amine, ***1q***. 444.6 mg, 73%, Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 1H), 7.19 – 7.09 (m, 2H), 7.09 – 7.03 (m, 1H), 3.74 (t, *J* = 4.9 Hz, 1H), 2.85 – 2.60 (m, 4H), 2.02 – 1.89 (m, 1H), 1.85 (dt, *J* = 3.5, 3.1 Hz, 2H), 1.78 – 1.66 (m, 1H), 1.54 – 1.44 (m, 2H), 1.44 – 1.31 (m, 2H), 1.23 (s, 1H), 0.92 (dd, *J* = 7.8, 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 139.5, 137.3, 128.9, 128.6, 126.5, 125.6, 55.4, 47.1, 32.7, 29.3, 28.4, 20.5, 18.9, 13.9. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{14}H_{22}N^+$, 204.1747; found, 204.1754.

N-benzhydrylbutan-1-amine, ***1r***[20]. 473.2 mg, 66%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.6 Hz, 4H), 7.27 (t, *J* = 7.6 Hz, 4H), 7.17 (t, *J* = 7.3 Hz, 2H), 4.80 (s, 1H), 2.56 (t, *J* = 7.1 Hz, 2H), 1.49 (dq, *J* = 14.5, 7.1 Hz, 3H), 1.39 – 1.28 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.4, 128.4, 127.2, 126.8, 67.6, 47.9, 32.4, 20.4, 13.9.

N-benzylpropan-1-amine, ***1t***[12b]. 421.8 mg, 95%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 10.1, 2.8 Hz, 4H), 7.27 – 7.20 (m, 1H), 3.78 (s, 2H), 2.65 – 2.52 (m, 2H), 1.58 – 1.48 (m, 2H), 1.44 (s, 1H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.5, 128.3, 128.0, 126.7, 53.9, 51.3, 23.1, 11.7.

N-benzylpropan-2-amine, ***1u***[26]. 388.8 mg, 87%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 4.5 Hz, 4H), 7.27 – 7.20 (m, 1H), 3.78 (s, 2H), 2.85 (hept, *J* = 6.2 Hz, 1H), 1.42 (s, 1H), 1.09 (d, *J* = 6.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.8, 128.3, 128.0, 126.8, 51.6, 48.0, 22.9.

N-benzylcyclopentanamine, ***1v***[27]. 435.7 mg, 83%, Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 7.26 – 7.20

(m, 1H), 3.76 (s, 2H), 3.11 (p, *J* = 6.7 Hz, 1H), 1.90 – 1.78 (m, 2H), 1.75 – 1.64 (m, 2H), 1.63 – 1.44 (m, 3H), 1.37 (qd, *J* = 8.0, 1.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.7, 128.3, 128.1, 126.7, 59.1, 52.7, 33.1, 24.0.

N-benzylcyclohexanamine, ***1w***[27]. 504.6 mg, 89%, Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 4.4 Hz, 4H), 7.27 – 7.20 (m, 1H), 3.80 (s, 2H), 2.48 (tt, *J* = 10.1, 3.7 Hz, 1H), 1.99 – 1.85 (m, 2H), 1.78 – 1.68 (m, 2H), 1.66 – 1.55 (m, 1H), 1.42 (s, 1H), 1.32 – 1.06 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.9, 128.3, 128.0, 126.7, 56.2, 51.0, 33.5, 26.2, 24.9.

Dibenzylamine, ***1x***[27]. 531.9 mg, 90%, Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.9, 5.2 Hz, 7H), 7.27 – 7.19 (m, 2H), 3.79 (s, 4H), 1.71 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.3, 128.3, 128.1, 126.9, 53.1.

N-benzyl-2-methoxyethan-1-amine, ***1y***[28]. 351.4 mg, 71%, Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H), 7.27 – 7.21 (m, 1H), 3.81 (s, 2H), 3.53 – 3.48 (m, 2H), 3.35 (s, 3H), 2.83 – 2.77 (m, 2H), 1.80 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.2, 128.3, 128.1, 126.9, 72.0, 58.7, 53.9, 48.7.

3-(benzylamino)propanenitrile, ***1z***[29]. 297.6 mg, 62%, Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 4H), 7.27 – 7.19 (m, 1H), 3.79 (s, 2H), 2.86 (td, *J* = 6.6, 2.6 Hz, 2H), 2.44 (td, *J* = 6.6, 2.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.3, 128.3, 127.8, 126.9, 118.6, 52.8, 44.1, 18.5.

General Procedure for Carbonylative Synthesis of Isoindolinone from Benzylamines. $PdCl_2$ (0.05 mmol, 10 mol%), $Cu(OAc)_2$ (0.75 mmol, 1.5 equiv.), and a 2.5 mL vial containing TFBen (1.0 mmol, 2.0 equiv.) were added to an oven-dried tube (15 mL) which was then placed under vacuum and refilled with nitrogen three times. An amine **1** (0.5 mmol, 1.0 equiv.), PivOH (1.0 mmol, 2.0 equiv.), Et_3N (1.0 mmol, 2.0 equiv.), toluene (2.0 mL) and DMSO (0.2 mL) were added into the tube via syringe. The tube was sealed and stirred at 110 °C for 20 h. Upon the reaction was completed, the mixture was diluted with EtOAc and washed with water three times. The crude mixture was purified by silica gel column chromatography (PE/EtOAc = 5/1 to 2/1) to obtain the desired products **2**.

Procedure for 2 mmol scale: $PdCl_2$ (10 mol%), $Cu(OAc)_2$ (1.5 equiv.), and a 5 mL vial containing TFBen (2.0 equiv.) were added to an oven-dried tube (25 mL) which was then placed under vacuum and refilled with nitrogen three times. An amine **1** (2 mmol, 1.0 equiv.), PivOH (2.0 equiv.), Et_3N (2.0 equiv.), toluene (8.0 mL) and DMSO (0.8 mL) were added into the tube via syringe. The tube was sealed and stirred at 110 °C for 20 h. Upon the reaction was completed, the mixture was diluted with EtOAc and washed with water three times. The crude mixture was purified by silica gel column chromatography (PE/EtOAc = 5/1 to 2/1) to obtain the desired products **2**.

2-butylisoindolin-1-one, ***2a***[12b]. 76.6 mg, 81% yield (2 mmol scale, 85% yield, 321.3 mg), colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 4.37 (s, 2H), 3.62 (t, *J* = 7.4 Hz, 2H), 1.72 – 1.59 (m, 2H), 1.45 – 1.32 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.3, 141.0, 133.0, 130.9, 127.8, 123.5, 122.5, 49.8, 42.0, 30.4, 19.9, 13.7.

2-butyl-6-methylisoindolin-1-one, ***2b***. 94.5 mg, 93% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.31 (s, 2H), 4.32 (s, 2H), 3.60 (t, *J* = 7.3 Hz, 2H), 2.43 (s, 3H), 1.68 – 1.58 (m, 2H), 1.44 – 1.32 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.5, 138.2, 137.8, 133.2, 131.9, 123.8, 122.2, 49.6, 42.0, 30.5, 21.2, 19.9, 13.7. HRMS (ESI-TOF): $[M+Na^+]$ calcd. for $C_{13}H_{17}NNaO^+$, 226.1202; found, 226.1205.

2-butyl-7-methylisoindolin-1-one, ***2c***. 25.4 mg, 25% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 4.31 (s, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 2.73 (s, 3H), 1.63 (dd, *J* = 14.8, 7.6 Hz, 2H), 1.45 – 1.32 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 141.6, 137.5, 130.5, 130.1, 129.9, 119.9, 49.3, 41.9, 30.5, 20.1, 17.1, 13.7. HRMS (ESI-TOF): $[M+Na^+]$ calcd. for $C_{13}H_{17}NNaO^+$, 226.1202; found, 226.1205.

2-butyl-5-methylisoindolin-1-one, ***2c'***. 65.0 mg, 64% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 9.6 Hz, 2H), 4.32 (s, 2H), 3.60 (t, *J* = 7.4 Hz, 2H), 2.44 (s, 3H), 1.69 – 1.58 (m, 2H), 1.44 – 1.32 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.5, 141.5, 141.5, 130.5, 128.9, 123.3, 123.0, 49.6, 41.9, 30.5, 21.7, 19.9, 13.7. HRMS (ESI-TOF): $[M+Na^+]$ calcd. for $C_{13}H_{17}NNaO^+$, 226.1202; found, 226.1207.

2-butyl-4-methylisoindolin-1-one, ***2d***. 87.3 mg, 86% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 4.27 (s, 2H), 3.63 (t, *J* = 7.3 Hz, 2H), 2.34 (s, 3H), 1.70 – 1.62 (m, 2H), 1.44 – 1.33 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.8, 139.9, 132.7, 132.2, 131.8, 128.1, 121.0, 49.0, 42.0, 30.5, 20.0, 17.4, 13.7. HRMS (ESI-TOF): $[M+Na^+]$ calcd. for $C_{13}H_{17}NNaO^+$, 226.1202; found, 226.1209.

2-butyl-6-methoxyisoindolin-1-one, ***2e***. 90.9 mg, 83% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.4 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.30 (s, 2H), 3.86 (s, 3H), 3.61 (t, *J* = 7.3 Hz, 2H), 1.69 – 1.60 (m, 2H), 1.43 – 1.33 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 159.9, 134.4, 133.2, 123.3, 119.4, 106.4, 55.6, 49.4, 42.2, 30.5, 19.9, 13.7. HRMS (ESI-TOF): $[M+H^+]$ calcd. for $C_{13}H_{18}NO_2^+$, 220.1332; found, 220.1341.

2-butyl-6-fluoroisoindolin-1-one, ***2f***. 86.9 mg, 84% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.7, 2.4 Hz, 1H), 7.40 (dd, *J* = 8.2, 4.5 Hz, 1H), 7.22 (td, *J* = 8.7, 2.4 Hz, 1H), 4.35 (s, 2H), 3.61 (t, *J* = 7.4 Hz, 2H), 1.72 – 1.57 (m, 2H), 1.46 – 1.30 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.4 (d, *J* = 3.4 Hz), 162.9 (d, *J* = 244.7 Hz), 136.4 (d, *J* = 2.3 Hz), 135.2 (d, *J* = 9.4 Hz), 124.1 (d, *J* = 8.3 Hz), 118.6 (d, *J* = 23.6 Hz), 110.3 (d, *J* = 23.5 Hz), 49.4, 42.2, 30.4, 19.9, 13.6. HRMS (ESI-TOF): $[M+Na^+]$ calcd. for $C_{12}H_{14}FNNaO^+$, 230.0952; found, 230.0958.

2-butyl-6-chloroisoindolin-1-one, ***2g***. 95.9 mg, 86% yield, white solid, mp 59.5-61.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.4 Hz, 1H), 7.47 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 4.35 (s, 2H), 3.60 (t, *J* = 7.4 Hz, 2H), 1.70 – 1.58 (m, 2H), 1.43 – 1.31 (m, 2H), 1.01 – 0.91 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.9, 139.1, 134.8, 134.1, 131.1, 123.8, 123.6, 49.4, 42.1, 30.3, 19.9, 13.6. HRMS (ESI-TOF): $[M+Na^+]$ calcd. for $C_{12}H_{14}ClNNaO^+$, 246.0656; found, 246.0660.

6-bromo-2-butylisoindolin-1-one, ***2h***. 86.8 mg, 65% yield, white solid, mp 60.3-64.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.6 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 4.33 (s, 2H), 3.60 (t, *J* = 7.4 Hz, 2H), 1.69 – 1.60 (m, 2H), 1.43 – 1.32 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.9, 139.6, 135.1, 133.9, 126.7, 124.2, 121.9, 49.5, 42.2, 30.3, 19.9, 13.6. HRMS (ESI-TOF): $[M+Na^+]$ calcd. for $C_{12}H_{14}BrNNaO^+$, 290.0151; found, 290.0157.

methyl 2-butyl-3-oxoisoindoline-5-carboxylate, ***2i***. 92.7 mg, 75% yield, white solid, mp 59.3-62.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.22 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 4.44 (s, 2H), 3.95 (s, 3H), 3.63 (t, *J* = 7.4 Hz, 2H), 1.72 – 1.59 (m, 2H), 1.45 – 1.33 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.4, 166.3, 145.5, 133.5, 132.3, 130.4, 124.9, 122.7, 52.2, 49.9, 42.1, 30.4, 20.0, 13.7. HRMS (ESI-TOF): [M+Na$^+$] calcd. for $C_{14}H_{17}NNaO_3^+$, 270.1101; found, 270.1106.

2-butyl-3-oxoisoindoline-5-carbonitrile, ***2j***. 54.6 mg, 51% yield, white solid, mp 102.6-105.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.80 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 4.47 (s, 2H), 3.64 (t, *J* = 7.4 Hz, 2H), 1.71 – 1.56 (m, 2H), 1.49 – 1.31 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.2, 145.3, 134.4, 134.2, 127.6, 123.8, 118.1, 112.3, 49.9, 42.2, 30.3, 19.9, 13.6. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{13}H_{15}N_2O^+$, 215.1179; found, 215.1187.

2-butyl-6,7-dimethylisoindolin-1-one, ***2k***. 20.6 mg, 19% yield, white solid, mp 44.6-46.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 4.25 (s, 2H), 3.58 (t, *J* = 7.3 Hz, 2H), 2.69 (s, 3H), 2.32 (s, 3H), 1.68 – 1.56 (m, 2H), 1.38 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.6, 139.3, 137.1, 136.3, 132.1, 129.9, 119.5, 48.7, 42.0, 30.5, 20.1, 19.2, 13.8, 12.8. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{14}H_{20}NO^+$, 218.1539; found, 218.1552.

2-butyl-5,6-dimethylisoindolin-1-one, ***2k'***. 76.0 mg, 70% yield, white solid, mp 57.5-60.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.19 (s, 1H), 4.29 (s, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 2.33 (d, *J* = 4.5 Hz, 6H), 1.71 – 1.58 (m, 2H), 1.42 – 1.31 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.7, 140.34, 138.9, 136.6, 130.9, 124.2, 123.5, 49.51, 42.0, 30.5, 20.3, 20.0, 19.8, 13.7. HRMS (ESI-TOF): [M+Na$^+$] calcd. for $C_{14}H_{19}NNaO^+$, 240.1359; found, 240.1369.

2-butyl-6,7-dimethoxyisoindolin-1-one, ***2l***. 27.4 mg, 22% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 7.03 (m, 2H), 4.27 (s, 2H), 4.08 (s, 3H), 3.89 (s, 3H), 3.56 (t, *J* = 7.3 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.43 – 1.32 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.6, 152.3, 147.3, 134.5, 125.3, 117.5, 116.3, 62.5, 56.8, 48.9, 42.1, 30.4, 20.0, 13.7. HRMS (ESI-TOF): [M+Na$^+$] calcd. for $C_{14}H_{19}NNaO_3^+$, 272.1257; found, 272.1265.

2-butyl-5,6-dimethoxyisoindolin-1-one, ***2l'***[7]. 90.9 mg, 73% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.92 (s, 1H), 4.28 (s, 2H), 3.94 (d, *J* = 1.3 Hz, 6H), 3.59 (t, *J* = 7.3 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.38 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.6, 152.2, 149.6, 134.5, 125.3, 105.3, 104.9, 56.1, 49.4, 42.0, 30.5, 19.9, 13.6. HRMS (ESI-TOF): [M+Na$^+$] calcd. for $C_{14}H_{19}NNaO_3^+$, 272.1257; found, 272.1263.

2-butyl-2,3-dihydro-1H-benzo[e]isoindol-1-one, ***2m***. 45.4 mg, 38% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.67 – 7.59 (m, 1H), 7.57 – 7.50 (m, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 4.39 (s, 2H), 3.66 (t, *J* = 7.3 Hz, 2H), 1.77 – 1.59 (m, 2H), 1.50 – 1.31 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.4, 141.5, 133.0, 131.8, 129.4, 127.9, 127.6, 126.8, 126.3, 123.8, 119.9, 49.7, 41.9, 30.7, 20.1, 13.7. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{16}H_{18}NO^+$, 240.1383; found, 240.1390.

2-butyl-2,3-dihydro-1H-benzo[f]isoindol-1-one, ***2m'***. 64.6 mg, 54% yield, white solid, mp 82.8-85.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.59 – 7.48 (m, 2H), 4.49 (s, 2H), 3.66 (t, *J* = 7.4 Hz, 2H), 1.73 – 1.64 (m, 2H), 1.46 – 1.35 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.2, 136.1, 135.0, 132.9, 131.0, 129.5, 127.9, 127.4, 126.2, 123.7, 121.4, 49.6, 42.4, 30.3, 20.1, 13.8. HRMS (ESI-TOF): [M+Na$^+$] calcd. for $C_{16}H_{17}NNaO^+$, 262.1202; found, 262.1208.

2-butyl-3-methylisoindolin-1-one, ***2n***[30]. 93.4 mg, 92% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.43 (dd, *J* = 12.2, 7.5 Hz, 2H), 4.55 (q, *J* = 6.7 Hz, 1H), 3.96 (dt, *J* = 14.1, 8.1 Hz, 1H), 3.21 (ddd, *J* = 10.6, 8.5, 5.2 Hz, 1H), 1.70 – 1.52 (m, 2H), 1.46 (dd, *J* = 6.7, 3.2 Hz, 3H), 1.43 – 1.32 (m, 2H), 0.95 (td, *J* = 7.3, 3.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.8, 146.8, 132.0, 131.1, 127.9, 123.4, 121.7, 55.2, 39.4, 30.4, 20.1, 18.0, 13.7.

2-butyl-3-propylisoindolin-1-one, ***2o***[31]. 107.5 mg, 93% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.3 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 4.60 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.02 (dt, *J* = 13.9, 8.0 Hz, 1H), 3.09 (ddd, *J* = 13.8, 8.4, 5.2 Hz, 1H), 2.08 – 1.82 (m, 2H), 1.76 – 1.47 (m, 2H), 1.46 – 1.31 (m, 2H), 1.16 – 1.01 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.90 – 0.73 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.2, 145.1, 132.7, 130.9, 127.7, 123.3, 121.8, 58.8, 39.3, 32.5, 30.3, 20.0, 15.6, 13.8, 13.6.

2-butyl-3-cyclohexylisoindolin-1-one, ***2p***. 116.6 mg, 86% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.4 Hz, 1H), 7.53 – 7.39 (m, 3H), 4.42 (d, *J* = 3.1 Hz, 1H), 4.11 – 3.99 (m, 1H), 3.12 (ddd, *J* = 13.8, 8.6, 5.0 Hz, 1H), 2.01 (tq, *J* = 12.1, 2.9 Hz, 1H), 1.84 (t, *J* = 12.9 Hz, 2H), 1.70 – 1.48 (m, 5H), 1.42 – 1.24 (m, 4H), 1.23 – 1.01 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.42 (qd, *J* = 12.6, 3.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.4, 143.8, 133.2, 130.5, 127.7, 123.4, 123.0, 63.8, 39.7, 39.5, 30.2, 29.7, 26.8, 26.3, 25.9, 25.7, 20.1, 13.7. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{18}H_{26}NO^+$, 272.2009; found, 272.2022.

1-butyl-6,7,8,8a-tetrahydrobenzo[cd]indol-2(1H)-one, ***2q***. 59.6 mg, 52% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 4.25 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.72 – 3.62 (m, 1H), 3.55 – 3.40 (m, 1H), 3.04 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.74 (dt, *J* = 17.6, 8.8 Hz, 1H), 2.39 (dq, *J* = 11.9, 4.0 Hz, 1H), 2.18 (dddd, *J* = 14.2, 7.7, 6.3, 3.7 Hz, 1H), 1.99 (dtd, *J* = 13.8, 9.4, 4.2 Hz, 1H), 1.69 – 1.60 (m, 2H), 1.45 – 1.34 (m, 2H), 1.15 (qd, *J* = 12.0, 4.1 Hz, 1H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.1, 144.2, 133.5, 130.9, 129.9, 128.6, 120.6, 58.2, 40.9, 31.1, 26.4, 25.1, 20.8, 20.2, 13.8. HRMS (ESI-TOF): [M+H$^+$] calcd. for $C_{15}H_{20}NO^+$, 230.1539; found, 230.1549.

2-butyl-3-phenylisoindolin-1-one, ***2r***[32]. 107.4 mg, 81% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 1H), 7.48 – 7.39 (m, 2H), 7.38 – 7.29 (m, 3H), 7.21 – 7.06 (m, 3H), 5.45 (s, 1H), 3.95 (dt, *J* = 14.0, 7.9 Hz, 1H), 2.92 – 2.81 (m, 1H), 1.59 – 1.46 (m, 2H), 1.35 – 1.26 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.4, 146.1, 137.0, 131.6, 131.5, 128.9, 128.5, 128.1, 127.4, 123.3, 122.9, 64.3, 39.8, 30.2, 19.9, 13.6.

2-methylisoindolin-1-one, ***2s***[7a]. 36.8 mg, 50% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.5 Hz, 1H), 7.52 (td, *J* = 7.4, 1.1 Hz, 1H), 7.48 – 7.39 (m, 2H), 4.37 (s, 2H), 3.20 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.6, 140.9, 132.9, 131.1, 127.9, 123.6, 122.5, 51.9, 29.4.

2-propylisoindolin-1-one, ***2t***[12b]. 79.7 mg, 91% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.44 (t, *J* = 7.0 Hz, 2H), 4.37 (s, 2H), 3.71 – 3.46

(m, 2H), 1.78 – 1.56 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.4, 141.0, 133.0, 131.0, 127.8, 123.5, 122.5, 49.8, 43.9, 21.6, 11.2.

2-isopropylisoindolin-1-one, ***2u***[12a]. 49.4 mg, 57% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.48 – 7.41 (m, 2H), 4.68 (hept, *J* = 6.8 Hz, 1H), 4.34 (s, 2H), 1.29 (d, *J* = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.8, 141.1, 133.3, 130.9, 127.8, 123.5, 122.6, 44.9, 42.5, 20.7.

2-cyclopentylisoindolin-1-one, ***2v***[30]. 61.3 mg, 61% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.79 (m, 1H), 7.55 – 7.47 (m, 1H), 7.47 – 7.41 (m, 2H), 4.83 – 4.71 (m, 1H), 4.35 (s, 2H), 2.07 – 1.94 (m, 2H), 1.87 – 1.74 (m, 2H), 1.73 – 1.58 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.3, 141.0, 133.2, 130.9, 127.8, 123.4, 122.6, 77.3, 77.0, 76.7, 52.5, 46.0, 30.0, 24.0.

2-cyclohexylisoindolin-1-one, ***2w***[33]. 70.9 mg, 66% yield, white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 1H), 7.54 – 7.47 (m, 1H), 7.48 – 7.41 (m, 2H), 4.34 (s, 2H), 4.24 (dt, *J* = 11.4, 5.5 Hz, 1H), 1.86 (t, *J* = 9.8 Hz, 4H), 1.72 (d, *J* = 12.6 Hz, 1H), 1.57 – 1.37 (m, 4H), 1.17 (tdd, *J* = 12.8, 6.2, 3.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.7, 141.2, 133.3, 130.8, 127.7, 123.4, 122.5, 50.4, 45.9, 31.3, 25.5, 25.4.

2-benzylisoindolin-1-one, ***2x***[34]. 105.9 mg, 95% yield, white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.3 Hz, 1H), 7.46 (dt, *J* = 20.8, 7.4 Hz, 2H), 7.37 – 7.25 (m, 6H), 4.78 (s, 2H), 4.22 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.3, 141.1, 136.9, 132.4, 131.2, 128.6, 127.9, 127.8, 127.5, 123.6, 122.6, 49.2, 46.2.

2-(2-methoxyethyl)isoindolin-1-one, ***2y***. 61.1 mg, 64% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 4.52 (s, 2H), 3.80 (t, *J* = 5.1 Hz, 2H), 3.64 (t, *J* = 5.1 Hz, 2H), 3.36 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.5, 141.6, 132.7, 131.1, 127.8, 123.5, 122.5, 71.6, 58.6, 51.5, 42.3. HRMS (ESI-TOF): $[M+H^+]$ calcd. for $C_{11}H_{14}NO_2^+$, 192.1019; found, 192.1027.

3-(1-oxoisoindolin-2-yl)propanenitrile, ***2z***. 40.0 mg, 43% yield, yellow solid, mp 90.8-94.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.58 (td, *J* = 7.4, 1.0 Hz, 1H), 7.48 (t, *J* = 8.2 Hz, 2H), 4.61 (s, 2H), 3.91 (t, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 6.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.8, 141.2, 131.8, 128.2, 123.8, 122.8, 118.2, 50.9, 39.1, 17.5. HRMS (ESI-TOF): $[M+H^+]$ calcd. for $C_{11}H_{11}N_2O^+$, 187.0866; found, 187.0872.

Functionalizations of the Isoindolinone 2a. To a solution of **2a** (0.3 mmol, 1.0 equiv.) in THF (2 mL) at -78 °C was added LDA (0.33 mmol, 1.1 equiv.) slowly, and the reaction mixture was stirred for 15 min. Then an alkyl bromide (0.45 mmol, 1.5 equiv.) in THF (1mL) was added slowly via syringe and the reaction continued at rt for 2h. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (10 mL × 3). The organic layer was combined, dried over anhydrous Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography (PE/EtOAc = 10/1) to obtain the desired products **3**.

3-allyl-2-butylisoindolin-1-one, ***3a***. 56.3 mg, 82% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 1H), 7.55 – 7.48 (m, 1H), 7.48 – 7.41 (m, 2H), 5.48 – 5.28 (m, 1H), 5.09 – 4.95 (m, 2H), 4.61 (dd, *J* = 5.9, 3.7 Hz, 1H), 4.08 – 3.99 (m, 1H), 3.15 (ddd, *J* = 13.8, 8.4, 5.2 Hz, 1H), 2.78 (dddd, *J* = 6.2, 5.0, 3.7, 2.1 Hz, 1H), 2.69 – 2.60 (m, 1H), 1.74 – 1.51 (m, 2H), 1.43 – 1.30 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.3, 144.7, 132.7, 131.3, 131.0, 128.1, 123.5, 122.2, 119.1, 58.4, 39.5, 35.3, 30.4, 20.1, 13.7. HRMS (ESI-TOF): $[M+Na^+]$ calcd. for $C_{15}H_{19}NNaO^+$, 252.1359; found, 252.1359.

3-benzyl-2-butylisoindolin-1-one, ***3b***. 51.9 mg, 63% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.4, 3.3 Hz, 1H), 7.42 (dd, *J* = 6.2, 2.4 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 3H), 7.14 – 7.10 (m, 2H), 6.95 (dd, *J* = 8.0, 4.5 Hz, 1H), 4.83 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.13 (dt, *J* = 14.2, 8.1 Hz, 1H), 3.42 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.25 (ddd, *J* = 13.8, 8.4, 5.2 Hz, 1H), 2.86 (dd, *J* = 13.8, 8.0 Hz, 1H), 1.77 – 1.57 (m, 2H), 1.45 – 1.31 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.1, 144.7, 135.9, 132.4, 130.7, 129.4, 128.4, 128.0, 126.9, 123.4, 122.8, 59.9, 39.8, 38.3, 30.4, 20.1, 13.7. HRMS (ESI-TOF): $[M+H^+]$ calcd. for $C_{19}H_{21}NNaO^+$, 302.1515; found, 302.1532.

2-butyl-3-(prop-2-yn-1-yl)isoindolin-1-one, ***3c***. 25.2 mg, 37% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.55 (td, *J* = 7.4, 1.1 Hz, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 4.63 (dd, *J* = 6.5, 4.3 Hz, 1H), 4.07 – 3.92 (m, 1H), 3.25 (ddd, *J* = 13.9, 8.6, 5.1 Hz, 1H), 2.86 (ddd, *J* = 16.9, 4.2, 2.7 Hz, 1H), 2.66 (ddd, *J* = 16.9, 6.7, 2.6 Hz, 1H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.73 – 1.55 (m, 2H), 1.44 – 1.30 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.2, 144.2, 132.5, 131.3, 128.5, 123.5, 122.3, 78.5, 71.6, 57.5, 39.7, 30.4, 22.6, 20.1, 13.7. HRMS (ESI-TOF): $[M+H^+]$ calcd. for $C_{15}H_{17}NNaO^+$, 250.1202; found, 250.1212.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra for substrates and products (PDF)

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Notes

The authors declare no competing financial interest.

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