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Transition-Metal-Free Oxidative α-C−H Amination of Ketones via a Radical Mechanism: Mild Synthesis of α-Amino Ketones

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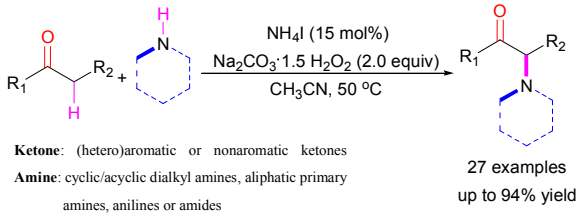


ABSTRACT: A transition-metal-free direct α-C−H amination of ketones has been developed using commercially available ammonium iodide as the catalyst and sodium percarbonate as the co-oxidant. A wide range of ketone ((hetero)aromatic or nonaromatic ketones) and amine (primary/secondary amines, anilines or amides) substrates undergo cross-coupling to generate synthetically useful α-amino ketones. The mechanistic studies indicated that a radical pathway might be involved in the reaction process. The utility of the method is highlighted through a concise one-step synthesis of the pharmaceutical agent amfepramone.

INTRODUCTION

Direct functionalization of C−H bonds to build C−C and C−heteroatom bonds is of great significance and a fundamental challenge in organic chemistry and it offers substantial benefits owing to their remarkable potential for atom-economy and environmental sustainability.[1] Over the past decade, construction of carbon−carbon (C−C) bonds via the oxidative cross-dehydrogenative couplings between two C−H centers has become a field of intense interest because such couplings avoid the tedious and time-consuming prefunctionalization of both substrates, and a plethora of new synthetic methods have been developed toward the synthesis of complex structures.[2] In parallel, the development of C−N bond formation reactions has recently also captured the attention of organic chemists since a wide array of important compounds (such as pharmaceuticals, natural

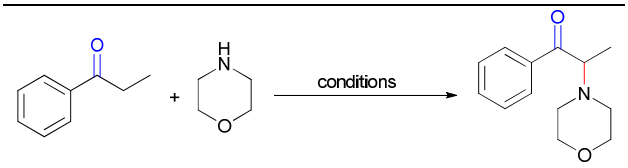
products, and functional polymers/materials) contain nitrogen.[3] However, despite the success of C−H amination methods based on tandem C(sp^2)−H/N−H functionalization,[4] C(sp^3)−H/N−H coupling reactions is more limited; existing reports suffered from one or more limitations such as use of expensive and/or toxic transition metal or reagents, harsh reaction conditions, and/or narrow substrate scope.[5] Consequently, the development of new and improved methods for C(sp^3)−H amination with N−H bonds is a worthwhile objective and remains an important challenge in organic synthesis. As part of our continuous interest in transition-metal-free transformations,[6] we herein disclose a transition-metal-free oxidative α-C−H amination of ketones with amines using NH_4I as the catalyst in the presence of sodium percarbonate as the oxidant. This transition-metal-free oxidative amination method extends amine compounds to cyclic or acyclic dialkyl amines, aliphatic primary amines, anilines and amides, thus allowing introduction of an amino group into the α-position of ketone. Most importantly, α-amino ketones are common structural motifs in pharmaceutical agents and natural products[7] as well as versatile intermediates in organic synthesis.[8]

RESULTS AND DISCUSSION

We started our investigations with propiophenone (**1a**) and morpholine (**2a**) as the model substrates. By optimizing various reaction parameters, the combination of NH_4I (15 mol%) and sodium percarbonate (2.0 equiv) in CH_3CN at 50 ^oC was found to be the best reaction conditions for this transformation, which provided the desired product **3a** in 97% yield along with byproduct 2-iodo-1-phenylpropan-1-one **4a** in 2% yield (Table 1, entry 1). Control reactions confirmed that no reaction occurred in the absence of NH_4I or sodium percarbonate (Table 1, entries 2 and 3). When NH_4I was replaced by NaI or KI, a relatively low yield of corresponding product was obtained (Table 1, entries 4 and 5), while using a catalytic amount of NH_4Br led to no conversion (Table 1, entry 6). Moreover, using I_2 as catalyst provided the desired **3a** in 94% yield (Table 1, entry 7). Further optimization with sodium percarbonate showed that only a trace amount of desired amination product was detected at room temperature (Table 1, entry 8). Increasing the temperature to 80 ^oC resulted in a significantly lower yield (54 %; Table 1, entry 9). Thus, the optimal temperature was established to be 50 ^oC. A screening of solvents revealed that essentially no conversion was observed in DMSO (Table 1, entry 10), while CH_3CN, DMF and DCE

performed with comparable efficiency (Table 1, entries 1, 11 and 12). Various oxidants such as TBHP, PIDA, $K_2S_2O_8$ and DTBP were then screened in the presence of NH_4I (Table 1, entries 13-16). TBHP was found to be as effective as sodium percarbonate. Using slightly lower amount of sodium percarbonate resulted in a decrease in the yield (Table 1, entry 17). To our delight, the reaction could be carried out at a relatively lower loading of NH_4I (2 mol%) which furnished the desired product **3a** in 62% yield (Table 1, entry 18).

Table 1. Optimization of the reaction conditions[a]



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

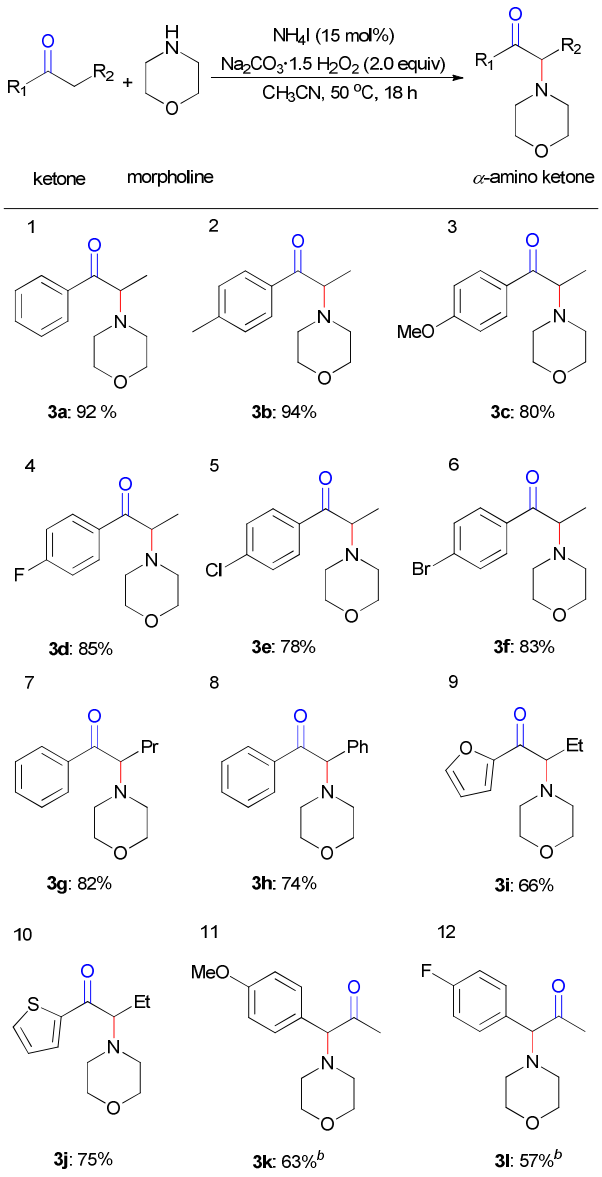
Entry	Catalyst (mol %)	Oxidant (equiv)	Solvent	*T* (°C)	Yield[b] (%)
1	**NH_4I (15)**	**$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)**	**CH_3CN**	**50**	**97**
2	none	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	CH_3CN	50	0
3	NH_4I (15)	none	CH_3CN	50	0
4	NaI (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	CH_3CN	50	92
5	KI (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	CH_3CN	50	90
6	NH_4Br (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	CH_3CN	50	0
7	I_2 (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	CH_3CN	50	94
8	NH_4I (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	CH_3CN	25	trace
9	NH_4I (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	CH_3CN	80	54
10	NH_4I (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	DMSO	50	trace
11	NH_4I (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	DMF	50	93
12	NH_4I (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	DCE	50	95
13	NH_4I (15)	TBHP (2.0)	CH_3CN	50	92
14	NH_4I (15)	PIDA (2.0)	CH_3CN	50	trace
15	NH_4I (15)	$K_2S_2O_8$ (2.0)	CH_3CN	50	trace
16	NH_4I (15)	DTBP (2.0)	CH_3CN	50	trace
17	NH_4I (15)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (1.5)	CH_3CN	50	84
18	NH_4I (2.0)	$Na_2CO_3{\cdot}1.5\ H_2O_2$ (2.0)	CH_3CN	50	62

[a] Reaction conditions: propiophenone (1.0 mmol), morpholine (3.0 mmol), solvent (1.0 mL), 18h. [b] GC yields. The entry hightlighted in bold marks optimized reaction conditions.

With the establishment of the optimal conditions, the scope and limitation of the reaction of different ketones with morpholine was next examined. As shown in Table 2, electron-rich, -neutral and -poor aryl propiophenones could all be coupled with morpholine in good to excellent yields (entries 1-6, 78%-94% yield). Notably, halo substituents including Br, Cl and F are compatible with the reaction conditions, providing more chance for further functionalization or modification of these molecules.[9] Moreover, Substituents at the carbonyl *β*-position did not hinder the reaction, providing the corresponding amination products in high yields (entries 7 and 8, 82% and 74%

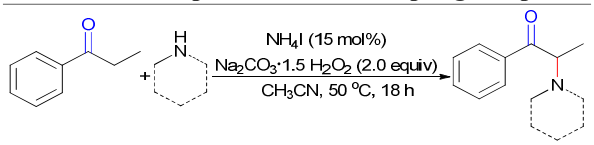
yield). Heteroaromatic ketones are also suitable reaction substrates, which delivered the desired α-amination products in good yield (entries 9 and 10, 66% and 75% yield). In addition, the methodology could be extended to nonaromatic ketones as well, although in moderate yield (entries 11 and 12, 63% and 57% yield). However, dialkyl-substituted ketone such as 3-pentanone did not afford the desired amination product and almost all of the 3-pentanone remained intact.

Table 2. α-Amination of ketones: Scope of the ketone coupling component[a,c]



[a] Reaction conditions: ketone (1.0 mmol), morpholine (3.0 mmol), NH_4I (15 mol%), sodium percarbonate (2.0 equiv), CH_3CN (1.0 mL), 50 °C, 18 h. [b] TBHP was used as oxidant. [c] The cited yields are of material isolated by column chromatography.

Table 3. α-Amination of ketones: Scope of the amine coupling component[a,e]



propiophenone amine α-amino ketone

1 **3a**: 92 %

2 **3m**: 83%[b]

3 **3n**: 82%[b]

4 **3o**: 65%

5 **3p**: 64%

6 **3q**: 87%

7 **3r**: 85%

8 **3s**: 74%

9 **3t**: 62%[d]

10 **3u**: 32%[d]

11 **3v**: 56%[c]

12 **3w**: 36%[c,d]

13 **3x**: 35%[d]

14 **3y**: 42%[d]

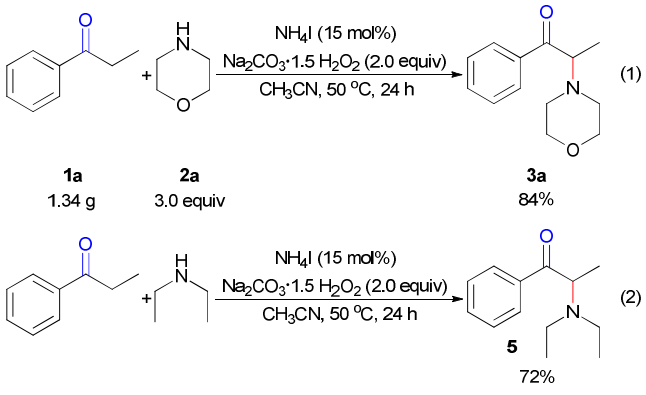
15 **3z**: 24%[d]

[a] Reaction conditions: propiophenone (1.0 mmol), amine (3.0 mmol), NH_4I (15 mol%), sodium percarbonate (2.0 equiv), CH_3CN (1.0 mL), 50 °C, 18 h. [b] TBHP was used as oxidant. [c] DMF was employed as solvent. [d] 28 h. [e] The cited yields are of material isolated by column chromatography.

Considering the great importance of direct functionalization of different amines, we further investigated the applicability of propiophenone with various simple amine derivatives in this transformation. As demonstrated in Table 3, a range of amines is viable in this transformation.

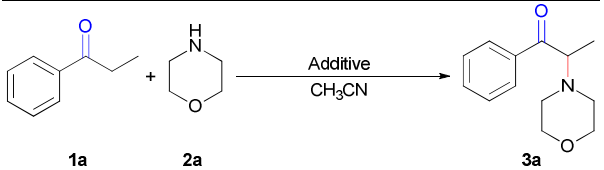
Cyclic amines coupled smoothly with propiophenone **1a**, affording the corresponding *α*–amination products in 64–92% yield (entries 1–5). Differentially protected acyclic dialkyl amines such as *N*-methylbenzylamine and *N*-ethylbenzylamine were also compatible reaction partners in this protocol, thus affording the corresponding desired products **3q** and **3r** in 87% and 85% yield, respectively (entries 6 and 7). Moreover, *N*-methylallylamine was allowed to react with propiophenone to give the corresponding product **3s** in 74% yield, wherein carbon-carbon double bond could be well tolerated in the reaction process (entry 8). In addition, the present protocol could be further extended to primary amines. For instance, *tert*-butylamine and 4-bromobenzylamine could afford the corresponding amination products **3t** and **3u** in 62% and 32% yield, respectively (entries 9 and 10). To our delight, amides such as phthalimide and benzamide also coupled with **1a**, but in moderate or low yield (entries 11 and 12, 56% and 36% yield). Notably, anilines are also applicable, albeit with relatively low conversion and yield (entries 13-15, 24%-42% yield).

To demonstrate the practicality of this transition-metal-free reaction, we carried out the *α*-amination reaction of propiophenone with morpholine on a gram scale (Eq. 1). Reaction of 1.34 g (10 mmol) of propiophenone with 3.0 equiv morpholine in the presence of 15 mol% NH_4I in acetonitrile gave **2a** (1.84 g) in 84% isolated yield. Finally, given the generality and operational simplicity of this transformation, the synthetic utility of this new catalytic protocol has been demonstrated. As shown in eq 2, the reaction of propiophenone **1a** with diethylamine using our catalysis protocol yielded the desired amfepramone **5** in 72% yield, which is a high-profile appetite suppressant.[10]



In order to better understand the reaction mechanism and to determine the active intermediates involved, several control experiments were conducted. The reaction of **1a** and **2a** was studied in CH_3CN at 50 °C using iodized salts of different oxidation states (Table 4). The use of a mixture of molecular iodine (I_2) and two equivalents of potassium hydroxide or sodium iodate ($NaIO_4$) only resulted in trace formation of the desired product **3a** (Table 4, entries 2 and 4). No product was detected when sodium periodate ($NaIO_3$) was used (Table 4, entry 3). In contrast, when molecular iodine was employed in this reaction, the desired product was obtained in a good yield of 72 % (Table 4, entry 1). As a result, an in situ generated molecular iodine (I_2) was suggested to be the active intermediate. This proposal was also supported by the result obtained from entry 7 in Table 1. When radical inhibitors, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), were employed in the standard reaction, and the reaction was obviously inhibited (Scheme 1a). This observation implied that the reaction presumably underwent a radical pathway, and also indicated that the present reaction mechanism is different from those developed by Prabhu[5b] and MacMillan.[5a] Moreover, the 2-iodo-1-phenylpropan-1-one **4a** was utilized for this reaction, which provided only a trace amount of the desired product **3a** (Schemes 1b, 1c and 1d). These results suggested that the **4a** is not possible intermediate in this transformation, and that a nucleophilic substitution might not be involved in the reaction process. Subsequently we wanted to verify whether in situ generation of an activated *N*-iodamine is likely. Thus *N*-iodomorpholine hydroiodide **6** was synthesized and further investigated. The reaction of **6** with propiophenone **1a** only gave a trace amount of **3a** no matter the existence of the NH_4I (Schemes 1e), which suggested that **6** as intermediate is also unlikely.

Table 4. Control experiments: use of iodized salts at different oxidations states[a]

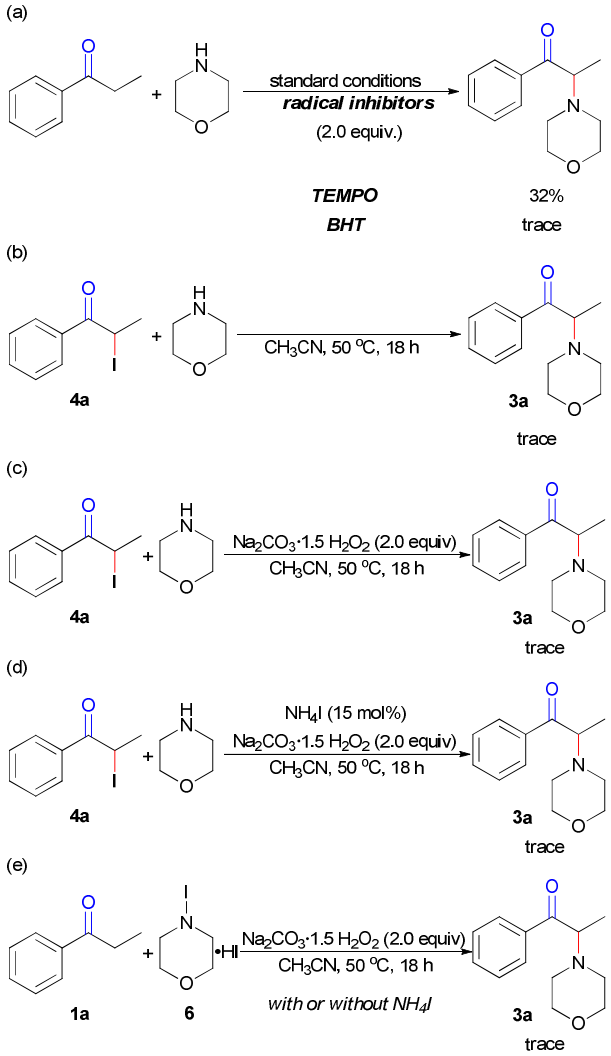


1a **2a** **3a**

Entry	Additive (equiv)	Yield[b] (%)
1	I_2 (1.0)	72
2	I_2 (1.0) + KOH (2.0)	trace
3	$NaIO_3$ (1.0)	0
4	$NaIO_4$ (1.0)	trace

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), additive (1.0 equiv), CH_3CN (1.0 mL), 50 °C, 18 h. [b] GC yields.

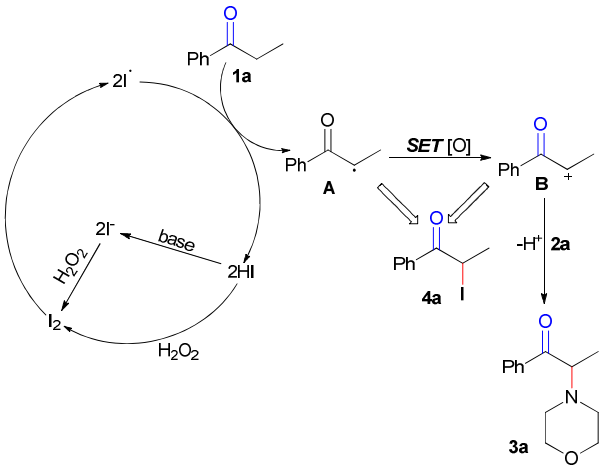
Scheme 1. Mechanistic studies and control experiments



On the basis of the above results and previous reports,[11] a tentative mechanism for this transition-metal-free oxidative amination is proposed and shown in Scheme 2 (using propiophenone **1a** and morpholine **2a** as the model). Initially, oxidation of iodide (I^-) by hydrogen peroxide generates molecular iodine, which is further decomposed into iodine radical. Then, the iodine radical abstracts the α-hydrogen of the propiophenone to form a carbon radical intermediate **A**, accompanied by the liberation of one molecule of HI, which is trapped by the base to regenerate iodide (I^-). Moreover, the HI can also be reoxidized into molecular iodide by hydrogen peroxide. Through further single electron oxidation, this carbon radical **A** would be converted to intermediate cation **B**. This proposal is supported by the isolation of byproduct 2-iodo-1-

phenylpropan-1-one **4a**. Finally, the nucleophilic substitution of **2a** to **B** gives the desired product **3a**. Moreover, under the standard conditions, the possibility of a nitrogen-centered radical process can not be completely ruled out at present.

Scheme 2. Proposed mechanism



CONCLUSION

In conclusion, we have discovered a highly efficient α-amination of various ketones catalyzed by in situ generated molecular iodine. This process offers an expedient approaches to the introduction of an amine functionality at the carbonyl α-position of ketones. This reaction has apparent advantages, such as mild reaction conditions, non-toxicity, broad substrate scope, and easy handling, and sodium percarbonate is used as an environmentally benign co-oxidant. Furthermore, this simple method, which exhibits a broad substrate scope and good functional group tolerance, has been applied to concise one-step synthesis of one prominent pharmaceutical agent. Further studies on the synthetic applications and relevant transition-metal-free transformations are currently ongoing in our laboratory.

EXPERIMENTAL SECTION

General Comments. All reagents and solvents used were purchased from commercial suppliers and used without further purification unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz in $CDCl_3$ using TMS as internal standard. Column chromatography was performed on silica gel. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet), and coupling constants (J) are reported in Hertz. Mass spectra were obtained on

a mass instrument using the EI technique.

General procedure for the transition-metal-free oxidative *α*-amination of ketones with amines. NH_4I (21.7 mg, 0.15 mmol, 0.15 equiv) was added to a mixture of sodium percarbonate or TBHP (2 mmol, 2 equiv), ketones (1 mmol, 1 equiv), and amines (3 mmol, 3 equiv) in acetonitrile or DMF(1 mL) at room temperature. The reaction was stirred at 50 ^oC for the time indicated. The reaction mixture was then allowed to cool to room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the desired *α*-amino ketones.

2-Morpholino-1-phenylpropan-1-one (3a). Following the general procedure, the product was isolated as a yellow oil, 201.5 mg (92%); Flash chromatography (petroleum ether/ ethyl acetate, 3/1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (d, J = 6.8 Hz, 3 H), 2.56-2.66 (m, 4 H), 3.66-3.73 (m, 4 H), 4.08 (q, J = 6.8 Hz, 1 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.57 (t, J = 7.2 Hz, 1 H), 8.09 (d, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 11.7, 50.1, 64.8, 67.2, 128.5, 128.8, 133.1, 136.2, 208.2 ppm; LRMS: m/z calcd for $C_{13}H_{17}NO_2$ (M+H): 219, found: 219.

2-Morpholino-1-(4-(methyl)phenyl)propan-1-one (3b). Following the general procedure, the product was isolated as a colorless solid, 219.0 mg (94%), mp = 83.2-85.5 ^oC; Flash chromatography (petroleum ether/ ethyl acetate, 2/1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, J = 6.4 Hz, 3 H), 2.42 (s, 3 H), 2.57-2.62 (m, 4 H), 3.69 (m, 4 H), 4.04 (q, J = 6.4 Hz, 1 H), 7.25 (d, J = 7.6 Hz, 2 H), 8.00 (d, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.0, 21.7, 50.2, 64.7, 67.1, 129.0, 129.2, 133.6, 143.9, 199.9 ppm; Anal.Calcd for $C_{14}H_{19}NO_2$ Elemental Analysis: C, 72.07; H, 8.21; N, 6.00; Found: C, 72.01; H, 8.28; N, 5.91.

2-Morpholino-1-(4-(methoxyl)phenyl)propan-1-one (3c). Following the general procedure, the product was isolated as a pale yellow solid, 199.2 mg (80%), mp = 66.4-68.5 ^oC; Flash chromatography (petroleum ether/ ethyl acetate, 1/1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, J = 5.6 Hz, 3 H), 2.47-2.52 (m, 4 H), 3.60-3.64 (m, 4 H), 3.78 (s, 3 H), 3.92 (q, J = 5.6 Hz, 1 H), 6.84 (d, J = 8.0 Hz, 2 H), 8.02 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.1, 50.2, 55.4, 64.8, 67.1, 113.6, 129.0, 131.2, 163.4, 198.8 ppm; Anal.Calcd for $C_{14}H_{19}NO_3$ Elemental Analysis: C, 67.45; H, 7.68; N, 5.62; Found: C, 67.38; H, 7.78; N, 5.54.

2-Morpholino-1-(4-(fluoro)phenyl)propan-1-one (3d). Following the general procedure, the product was isolated as a colorless solid, 201.5 mg (85%), mp = 68.6-70.8 ^{o}C; Flash chromatography (petroleum ether/ ethyl acetate, 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, J = 6.8 Hz, 3 H), 2.49-2.60 (m, 4 H), 3.61-3.68 (m, 4 H), 3.97 (q, J = 6.8 Hz, 1 H), 7.08 (t, J = 8.8 Hz, 2 H), 8.11-8.15 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 11.1, 49.9, 65.1, 67.0, 115.3 (d, J_{C-F} = 22.0 Hz), 131.5 (d, J_{C-F} = 29.0 Hz), 132.2 (d, J_{C-F} = 3.0 Hz), 165.5 (d, J_{C-F} = 253.0 Hz), 198.5 ppm; Anal.Calcd for $C_{13}H_{16}FNO_2$ Elemental Analysis: C, 65.81; H, 6.80; N, 5.90; Found: C, 65.72; H, 6.88; N, 5.78.

2-Morpholino-1-(4-(chloro)phenyl)propan-1-one (3e). Following the general procedure, the product was isolated as a pale yellow solid, 197.3 mg (78%), mp = 84.2-86.1 ^{o}C; Flash chromatography (petroleum ether/ ethyl acetate, 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, J = 6.0 Hz, 3 H), 2.56-2.59 (m, 4 H), 3.68 (m, 4 H), 4.10 (q, J = 6.0 Hz, 1 H), 7.42 (d, J = 7.6 Hz, 2 H), 8.07 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 11.0, 49.9, 65.2, 67.1, 128.7, 130.4, 134.2, 139.4, 199.0 ppm; Anal.Calcd for $C_{13}H_{16}ClNO_2$ Elemental Analysis: C, 61.54; H, 6.36; N, 5.52; Found: C, 61.46; H, 6.42; N, 5.43.

2-Morpholino-1-(4-(bromo)phenyl)propan-1-one (3f). Following the general procedure, the product was isolated as a colorless solid, 247.3 mg (83%), mp = 98.2-100.5 ^{o}C; Flash chromatography (petroleum ether/ ethyl acetate, 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, J = 6.8 Hz, 3 H), 2.50-2.61 (m, 4 H), 3.62-3.70 (m, 4 H), 3.98 (q, J = 6.8 Hz, 1 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.97 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.9, 49.8, 65.1, 67.0, 128.1, 130.4, 131.6, 134.5, 199.0 ppm; Anal.Calcd for $C_{13}H_{16}BrNO_2$ Elemental Analysis: C, 52.36; H, 5.41; N, 4.70; Found: C, 52.25; H, 5.50; N, 4.58.

1-Phenyl-2-morpholinopentan-1-one (3g). Following the general procedure, the product was isolated as a yellow oil, 202.5 mg (82%); Flash chromatography (petroleum ether/ ethyl acetate, 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (d, J = 8.0 Hz, 3 H), 1.21-1.27 (m, 2 H), 1.64-1.66 (m, 1 H), 1.82-1.87 (m, 1 H), 2.53-2.58 (m, 2 H), 2.62-2.67 (m, 2 H), 3.62-3.64 (m, 4 H), 3.98 (dd, J = 8.0, 4.0 Hz, 1 H), 7.42-7.52 (m, 2 H), 7.52-7.56 (m, 1 H), 8.02-8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.2, 19.8, 28.5, 50.2, 67.3, 68.4, 128.4, 128.5, 133.0, 137.2, 199.8 ppm; LRMS: m/z calcd for $C_{15}H_{24}NO_2$ (M+H): 247, found: 247.

1,2-Diphenyl-2-morpholinoethan-1-one (3h). Following the general procedure, the product was isolated as a yellow oil, 207.9 mg (74%); Flash chromatography (petroleum ether/ ethyl acetate, 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46-2.53 (m, 4 H), 3.70-3.80 (m, 4 H), 4.93 (s, 1 H), 7.23-7.49 (m, 8 H), 8.00 (d, J = 8.0, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 52.2, 66.8, 76.4, 128.4, 128.5, 128.7, 128.9, 129.7, 133.2, 134.6, 136.3, 197.2 ppm; LRMS: m/z calcd for $C_{18}H_{19}NO_2$ (M+H): 281, found: 281.

1-(Furan-2-yl)-2-morpholinobutan-1-one (3i). Following the general procedure, the product was isolated as a yellow oil, 147.2 mg (66%); Flash chromatography (petroleum ether/ ethyl acetate, 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 8.0 Hz, 3 H), 1.73-1.90 (m, 2 H), 2.58-2.69 (m, 4 H), 3.67 (m, 4 H), 3.76 (t, J = 8.0, 1 H), 6.57 (m, 1 H), 7.34 (s, 1 H), 7.85 (s, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.6, 20.6, 50.4, 67.3, 70.1, 112.3, 118.1, 146.8, 152.9, 189.3 ppm; LRMS: m/z calcd for $C_{12}H_{17}NO_3$ (M+H): 223, found: 223.

1-(Thiophen-2-yl)-2-morpholinobutan-1-one (3j). Following the general procedure, the product was isolated as a yellow oil, 179.3 mg (75%); Flash chromatography (petroleum ether/ ethyl acetate, 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 8.0 Hz, 3 H), 1.73-1.85 (m, 2 H), 2.50-2.56 (m, 2 H), 2.61-2.67 (m, 2 H), 2.53 (dd, J = 8.0, 4.0 Hz, 1 H), 3.65-3.67 (m, 4 H), 7.08-7.10 (m, 1 H), 7.57-7.60 (m, 1 H), 7.89-7.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.9, 20.5, 50.6, 67.1, 73.1, 127.8, 132.9, 134.0, 142.7, 193.3 ppm; LRMS: m/z calcd for $C_{12}H_{17}NO_2S$ (M+H): 239, found: 239.

3-Morpholino-3-(4-(methoxyl)phenyl)propan-2-one (3k). Following the general procedure, the product was isolated as a pale yellow oil, 156.9 mg (63%); Flash chromatography (petroleum ether/ ethyl acetate, 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3 H), 2.39 (m, 4 H), 3.74 (m, 4 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 6.89 (d, J = 7.6 Hz, 2 H), 7.30 (d, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 26.5, 52.0, 55.3, 66.8, 81.4, 114.3, 126.4, 130.2, 159.8, 206.7 ppm; LRMS: m/z calcd for $C_{14}H_{19}NO_3$ (M+H): 249, found: 249.

3-Morpholino-3-(4-(fluoro)phenyl)propan-2-one (3l). Following the general procedure, the product was isolated as a yellow oil, 135.1 mg (57%); Flash chromatography (n-hexane/ acetone, 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (s, 3 H), 2.32-2.34 (m, 4 H), 3.67-3.69 (m, 4 H), 3.85 (s, 1 H), 7.00 (t, J = 8.0 Hz, 2 H), 7.31-7.34 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 26.4, 51.9, 66.7,

81.2, 115.9 (d, J_{C-F} = 21.0 Hz), 130.3 (d, J_{C-F} = 3.0 Hz), 130.5 (d, J_{C-F} = 8.0 Hz), 162.7 (d, J_{C-F} = 246.0 Hz), 206.4 ppm; LRMS: m/z calcd for $C_{13}H_{16}FNO_2$ (M+H): 237, found: 237.

1-Phenyl-2-(piperidin-1-yl)propan-1-one (3m). Following the general procedure, the product was isolated as a brown oil, 180.1 mg (83%); Flash chromatography (petroleum ether/ ethyl acetate, 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, J = 8.0 Hz, 3 H), 1.28-1.34 (m, 2 H), 1.39-1.48 (m, 4 H), 2.39-2.50 (m, 4 H), 4.00 (q, J = 8.0 Hz, 1 H), 7.33-7.43 (m, 2 H), 7.44-7.47 (m, 1 H), 8.01-8.03 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 11.1, 24.5, 26.2, 50.6, 64.9, 128.1, 128.8, 132.6, 136.4, 201.0 ppm; LRMS: m/z calcd for $C_{14}H_{19}NO$ (M+H): 217, found: 217.

1-Phenyl-2-(4-methylpiperidin-1-yl)propan-1-one (3n). Following the general procedure, the product was isolated as a yellow oil, 189.4 mg (82%); Flash chromatography (petroleum ether/ ethyl acetate, 5/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (d, J = 6.8 Hz, 3 H), 1.01-1.20 (m, 6 H), 1.46-1.55 (m, 2 H), 2.06 (t, J = 12.0 Hz, 1 H), 2.33 (t, J = 12.0 Hz, 1 H), 2.68 (d, J = 8.0 Hz, 1 H), 2.83 (d, J = 8.0 Hz, 1 H),4.03 (q, J = 8.0 Hz, 1 H), 7.36 (t, J = 8.0 Hz, 2 H), 7.46 (t, J = 8.0 Hz, 1 H), 8.03 (d, J = 8.0, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 11.5, 21.9, 30.8, 34.4, 34.8, 48.7, 51.7, 64.8, 128.3, 128.9, 132.8, 136.5, 201.1 ppm; LRMS: m/z calcd for $C_{15}H_{21}NO$ (M+H): 231, found: 231.

2-Thiomorpholino-1-phenylpropan-1-one (3o). Following the general procedure, the product was isolated as a brown oil, 152.8 mg (65%); Flash chromatography (petroleum ether/ ethyl acetate, 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, J = 8.0 Hz, 3 H), 2.55-2.65 (m, 4 H), 2.87 (m, 4 H), 4.15 (q, J = 8.0 Hz, 1 H), 7.44 (t, J = 8.0 Hz, 2 H), 7.55 (t, J = 8.0 Hz, 1 H), 8.05 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 9.9, 28.4, 51.6, 65.2, 128.3, 128.9, 133.0, 136.2, 200.1 ppm; LRMS: m/z calcd for $C_{13}H_{17}NOS$ (M+H): 235, found: 235.

2-(3,4-Dihydroisoquinolin-2(1H)-yl)-1-phenylpropan-1-one (3p). Following the general procedure, the product was isolated as a yellow oil, 169.6 mg (64%); Flash chromatography (petroleum ether/ ethyl acetate, 10/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (d, J = 6.8 Hz, 3 H), 2.83-2.89 (m, 4 H), 3.83 (d, J = 16.0 Hz, 1 H), 3.92 (d, J = 12.0 Hz, 1 H), 4.35 (q, J = 8.0 Hz, 1 H),7.02-7.14 (m, 4 H), 7.42-7.46 (m, 2 H), 7.52-7.56 (m, 1 H), 8.14-8.16 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 11.3, 29.5, 47.0, 51.9, 64.0, 125.5, 125.9, 126.5, 128.3, 128.6, 128.8, 132.9, 134.3, 134.7, 136.1, 200.5 ppm; LRMS: m/z calcd for $C_{18}H_{19}NO$ (M+H): 265, found: 265.

2-(Benzylmethylamino)-1-phenylpropan-1-one (3q). Following the general procedure, the product was isolated as a yellow oil, 220.1 mg (87%); Flash chromatography (petroleum ether/ ethyl acetate, 10/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (d, J = 8.0 Hz, 3 H), 2.23 (s, 3 H), 3.65 (s, 2 H), 4.31 (q, J = 8.0 Hz, 1 H),7.21-7.27 (m, 5 H), 7.43 (t, J = 8.0 Hz, 2 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 9.8, 37.6, 58.4, 62.2, 127.1, 128.2, 128.3, 128.9, 129.0, 132.8, 136.5, 139.0, 200.9 ppm; LRMS: m/z calcd for $C_{17}H_{19}NO$ (M+H): 253, found: 253.

2-(Benzylethylamino)-1-phenylpropan-1-one (3r). Following the general procedure, the product was isolated as a yellow oil, 226.9 mg (85%); Flash chromatography (petroleum ether/ ethyl acetate, 15/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, J = 8.0 Hz, 3 H), 1.29 (d, J = 8.0 Hz, 3 H), 2.53-2.60 (m, 2 H), 3.53 (d, J = 16.0 Hz, 1 H), 3.71 (d, J = 12.0 Hz, 1 H), 4.41 (q, J = 8.0 Hz, 1 H),7.16-7.18 (m, 2 H), 7.21-7.274 (m, 3 H), 7.38-7.42 (m, 2 H), 7.50-7.54 (m, 1 H), 7.90-7.92 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 8.7, 13.5, 41.2, 54.5, 58.6, 126.8, 127.9, 128.0 128.8, 128.9, 132.4, 136.7, 139.6, 201.8 ppm; LRMS: m/z calcd for $C_{18}H_{21}NO$ (M+H): 267, found: 267.

2-(Allylmethylamino)-1-phenylpropan-1-one (3s). Following the general procedure, the product was isolated as a yellow oil, 150.2 mg (74%); Flash chromatography (petroleum ether/ ethyl acetate, 8/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, J = 8.0 Hz, 3 H), 2.25 (s, 3 H), 3.15 (d, J = 6.8 Hz, 3 H), 4.30 (q, J = 8.0 Hz, 1 H), 5.11-5.19 (m, 2 H), 5.80-5.90 (m, 1 H), 7.44 (t, J = 8.0, 2 H), 7.53 (t, J = 8.0, 1 H), 8.05 (d, J = 8.0, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 9.9, 37.6, 57.6, 61.9, 117.6, 128.4, 128.8, 132.8, 135.9, 136.5, 201.0 ppm; LRMS: m/z calcd for $C_{13}H_{17}NO$ (M+H): 203, found: 203.

2-*Tert*-butylamino-1-phenylpropan-1-one (3t). Following the general procedure, the product was isolated as a yellow oil, 127.1 mg (62%); Flash chromatography (petroleum ether/ ethyl acetate, 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9 H), 1.28 (d, J = 8.0 Hz, 3 H), 2.74 (brs, 1 H), 4.39 (q, J = 8.0 Hz, 1 H), 7.50 (t, J = 8.0 Hz, 2 H), 7.60 (t, J = 8.0 Hz, 1 H), 8.00 (d, J = 8.0, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 22.6, 29.7, 50.9, 51.9, 128.3, 128.8, 133.3, 134.9, 204.9 ppm; LRMS: m/z calcd for $C_{13}H_{19}NO$ (M+H): 205, found: 205.

2-((4-Bromobenzyl)amino)-1-phenylpropan-1-one (3u). Following the general procedure, the product was isolated as a pale yellow solid, 101.8 mg (32%), mp = 50.3-52.4 ^{o}C; Flash

chromatography (hexane/acetone, 8/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (d, J = 8.0 Hz, 3 H), 3.60 (d, J = 16.0 Hz, 1 H), 3.79 (d, J = 12.0 Hz, 1 H), 4.32 (q, J = 8.0 Hz, 1 H), 7.24 (t, J = 8.0 Hz, 2 H), 7.43-7.50 (m, 4 H), 7.60 (t, J = 8.0 Hz, 1 H), 7.92 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.0, 51.2, 57.0, 120.9, 128.3, 128.8, 130.1, 131.5, 133.5, 135.5, 138.8, 203.4 ppm; Anal.Calcd for $C_{16}H_{16}BrNO$ Elemental Analysis: C, 60.39; H, 5.07; N, 4.40; Found: C, 60.28; H, 5.16; N, 4.29.

2-(1-Oxo-1-phenylpropan-2-yl)isoindoline-1,3-dione (3v). Following the general procedure, the product was isolated as a pale yellow solid, 156.2 mg (56%), mp = 84.1-86.2 ^{o}C; Flash chromatography (petroleum ether/ ethyl acetate, 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (d, J = 8.0 Hz, 3 H), 5.67 (q, J = 8.0 Hz, 1 H), 7.40 (t, J = 8.0 Hz, 2 H), 7.49 (t, J = 8.0 Hz, 1 H), 7.69-7.71 (m, 2 H), 7.80-7.83 (m, 4 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.9, 50.9, 123.5, 128.0, 128.7, 131.8, 133.1, 134.2, 135.2, 167.5, 196.2 ppm; Anal.Calcd for $C_{17}H_{13}NO_3$ Elemental Analysis: C, 73.11; H, 4.69; N, 5.02; Found: C, 73.01; H, 4.80; N, 4.90.

***N*-(1-Oxo-1-phenylpropan-2-yl)benzamide (3w).** Following the general procedure, the product was isolated as a colorless solid, 91.1 mg (36%), mp = 108.2-110.4 ^{o}C; Flash chromatography (petroleum ether/ ethyl acetate, 10/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (d, J = 8.0 Hz, 3 H), 6.21 (q, J = 8.0 Hz, 1 H), 7.43-7.50 (m, 4 H), 7.55-7.61 (m, 2 H), 8.00 (d, J = 8.0 Hz, 2 H), 8.09 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 17.2, 71.9, 128.4, 128.6, 128.8, 129.5, 129.9, 133.3, 133.6, 134.5, 166.0, 196.8 ppm; Anal.Calcd for $C_{16}H_{15}NO_2$ Elemental Analysis: C, 75.87; H, 5.97; N, 5.53; Found: C, 75.77; H, 6.04; N, 5.42.

2-(*p*-Tolylamino)-1-phenylpropan-1-one (3x). Following the general procedure, the product was isolated as a violet black solid, 83.7 mg (35%), mp = 86.6-88.9 ^{o}C; Flash chromatography (petroleum ether/ ethyl acetate, 10/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (d, J = 8.0 Hz, 3 H), 2.22 (s, 3 H), 4.55 (brs, 1 H), 5.11 (q, J = 8.0 Hz, 1 H), 6.61 (d, J = 6.8 Hz, 2 H), 6.98 (d, J = 8.0 Hz, 2 H), 7.50 (t, J = 8.0 Hz, 2 H), 7.60 (t, J = 8.0 Hz, 1 H), 8.01 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.6, 20.4, 53.8, 113.8, 127.2, 128.5, 128.9, 129.9, 133.6, 134.8, 144.3, 201.0 ppm; Anal.Calcd for $C_{16}H_{17}NO$ Elemental Analysis: C, 80.30; H,7.16; N, 5.85; Found: C, 80.22; H, 7.28; N, 5.75.

2-((4-Methoxyphenyl)amino)-1-phenylpropan-1-one (3y). Following the general procedure, the product was isolated as a red oil, 107.1 mg (42%); Flash chromatography (petroleum ether/ ethyl acetate, 10/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (d, J = 6.8 Hz, 3 H), 3.73 (s, 3 H), 5.06 (q, J = 8.0 Hz, 1 H), 6.67 (d, J = 6.8 Hz, 2 H), 6.77 (d, J = 8.0 Hz, 2 H), 7.50 (t, J = 8.0 Hz, 2 H), 7.61 (t, J = 8.0 Hz, 1 H), 8.01 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.7, 54.6, 55.8, 115.0, 115.4, 128.4, 128.9, 133.6, 134.8, 140.7, 152.6, 201.2 ppm; LRMS: m/z calcd for $C_{16}H_{17}NO_2$ (M+H): 255, found: 255.

2-((4-Chlorophenyl)amino)-1-phenylpropan-1-one (3z). Following the general procedure, the product was isolated as a red oil, 62.2 mg (24%); Flash chromatography (petroleum ether/ ethyl acetate, 10/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (d, J = 6.8 Hz, 3 H), 4.75 (brs, 1 H), 5.08 (q, J = 8.0 Hz, 1 H), 6.59 (d, J = 8.0 Hz, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 7.52 (t, J = 8.0 Hz, 2 H), 7.63 (t, J = 8.0 Hz, 1 H), 8.00 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.5, 53.5, 114.6, 122.5, 128.5, 129.0, 129.2, 133.8, 134.5, 145.1, 200.3 ppm; LRMS: m/z calcd for $C_{15}H_{14}ClNO_2$ (M+H): 259, found: 259.

2-Diethylamino-1-phenylpropan-1-one (5). Following the general procedure, the product was isolated as a brown oil, 147.6 mg (72%); Flash chromatography (petroleum ether/ ethyl acetate, 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, J = 8.0 Hz, 6 H), 1.16 (d, J = 8.0 Hz, 3 H), 2.44-2.61 (m, 4 H), 4.31 (q, J = 8.0 Hz, 1 H), 7.35 (t, J = 8.0 Hz, 2 H), 7.45 (t, J = 8.0 Hz, 1 H), 8.02 (d, J = 8.0, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.1, 13.6, 44.3, 128.1, 128.9, 132.6, 136.8, 202.0 ppm; LRMS: m/z calcd for $C_{13}H_{19}NO$ (M+H): 205, found: 205.

2-Iodo-1-phenylpropan-1-one (4a). Following the general procedure, the product was isolated as a yellow oil, 5.2 mg (2% GC yield); Flash chromatography (petroleum ether/ ethyl acetate, 3/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (d, J = 8.0 Hz, 3 H), 5.18 (q, J = 8.0 Hz, 1 H), 7.51 (t, J = 8.0 Hz, 2 H), 7.63 (t, J = 8.0 Hz, 1 H), 7.94 (d, J = 6.8, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 22.3, 69.3, 128.7, 128.9, 133.3, 134.0, 202.4 ppm; LRMS: m/z calcd for C_9H_9IO (M+H): 260, found: 260.

General procedure for the gram-scale reaction of propiophenone with morpholine (Eq. 1). NH_4I (217 mg, 1.5 mmol, 0.15 equiv) was added to a mixture of sodium percarbonate (3.14 g, 20 mmol, 2 equiv), propiophenone (1.34 g, 10 mmol, 1 equiv), and morpholine (2.61 g, 30 mmol, 3

equiv) in acetonitrile (10 mL) at room temperature. The reaction was stirred at 50 ^{o}C for 24 h. The reaction mixture was then allowed to cool to room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine **3a** (1.84 g, 84%).

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

REFERENCES

(1) For recent reviews on functionalization of C−H bonds, see: (a) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* 2013, 42, 5744. (b) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, 5, 369. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, 51, 8960. (d) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, 39, 712. (e) Ackermann, L. *Chem. Commun.* 2010, 46, 4866. (f) Ackermann, L. *Chem. Rev.* **2011**, 111, 1315. (g) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, 110, 624. (h) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, 110, 824. (i) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, 40, 1885. (j) Baudoin, O. *Chem. Soc. Rev.* 2011, 40, 4902. (k) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, 41, 5588. (l) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, 110, 1147. (m) Chen, D. Y.-K.; Youn, S. W. *Chem. Eur. J.* **2012**, 18, 9452. (n) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, 16, 2654. (o) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* 2010, 110, 890. (p) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, 110, 1147. (q) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, 48, 5094. (r) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, 40, 4740.

(2) For selected reviews: (a) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, 41, 3464. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, 40, 5068. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, 111, 1215. (d) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, 38, 2447. (e) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, 39, 540. (f) Li, C.-J. *Acc. Chem. Res.* **2009**, 42, 335.

(3) (a) *The Alkaloids: Chemistry and Biology* (Ed.: Knölker, H.-J.), Elsevier: San Diego, CA, **2011**; Vol. 70. (b) Ciric-Marjanovic, G. *Synth. Met.* **2013**, 177, 1.

(4) For some recent selected examples on tandem C(sp^2)−H/N−H activation, see: (a) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem. Int. Ed.* **2011**, 50, 8605. (b) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, 133, 16382. (c) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, 133, 19960. (d) Shrestha, R.; Mukherjee, P.; Tan,Y.; Litman, Z. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, 135, 8480. (e) Alla, S. K.; Kumar, R. K.; Sadhu, P.; Punniyamurthy, T.; *Org. Lett.* **2013**, 15, 1334. (f) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem. Int. Ed.* **2013**, 52, 6043. (g) Samanta, R.; Bauer, J. O.; Strohmann, C.; Antonchick, A. P. *Org. Lett.* **2012**, 14, 5518. (h) Huang, J.; He, Y.; Wang, Y.; Zhu, Q. *Chem. Eur. J.* **2012**, 18, 13964. (i) Oda, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2012**, 14, 664. (j) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, 133, 5996. (k) Lamani, M.; Prabhu, K. R. *J. Org. Chem.* **2011**, 76, 7938. (l) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem. Int. Ed.* **2010**, 49, 9899. (m) Wang, J.; Hou, J.-T.; Wen, J.; Zhang, J.; Yu, X.-Q. *Chem. Commun.* **2011**, 47, 3652. (n) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, 76, 4158. (o) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, 133, 1466. (p) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhan, Q. *J. Am. Chem. Soc.* **2011**, 133, 1694. (q) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, 133, 7652.

(5) For some selected examples on tandem C(sp^3)−H/N−H activation, see: (a) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, 135, 16074. (b) Lamani, M.; Prabhu, K. R. *Chem. Eur. J.* **2012**, 18, 14638. (c) Tian, J.-S.; Ng,K. W. J.; Wong, J.-R.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2012**, 51, 9105. (d) Mao, L.; Li, Y.; Xiong, T.; Sun, K.; Zhang, Q. *J. Org. Chem.* **2013**, 78, 733. (e) Souto, J. A.; Zian, D.; Muniz, K. *J. Am. Chem.*

Soc. **2012**, 134, 7242. (f) Lv, Y.; Li, Y.; Xiong, T.; Lu, Y.; Liu, Q.; Zhang, Q. *Chem. Commun.* **2014**, 50, 2367.

(6) (a) Xu, J.-H.; Jiang, Q.; Guo, C.-C. *J. Org. Chem.* **2013**, 78, 11881. (b) Jiang, Q.; Zhao, A.; Xu, B.; Jia, J.; Liu, X.; Guo, C. *J. Org. Chem.* **2014**, 79, 2709. (c) Jiang, Q.; Sheng, W.; Guo, C. *Green Chem.* **2013**, 15, 2175. (d) Wang, J.-Y.; Jiang, Q.; Guo, C.-C. *Synth. Commun.* **2014**, DOI:10.1080/00397911.2014.928938.

(7) (a) Meltzer, P. C.; Butler, D.; Deschamps, J. R.; Madras, B. K. *J. Med. Chem.* **2006**, 49, 1420. (b) Carrol, F. I.; Blough, B. E.; Abraham, P.; Mills, A. C.; Holleman, J. A.; Wolchenhauer, S. A.; Decker, A. M.; Landavazo, A. K.; McElroy, T.; Navarro, H. A.; Gatch, M. B.; Forster, M. J. *J. Med. Chem.* **2009**, 52 , 6768. (c) Bouteiller, C.; Becerril-Ortega, J.; Marchand, P.; Nicole, O.; Barre, L.; Buisson, A.; Perrio, C. *Org. Biomol. Chem.* **2010**, 8, 1111. (d) Meyers, M. C.; Wang, J.-L.; Iera, J. A.; Bang, J.-K.; Hara, T.; Saito, S.; Zambetti, G. P.; Appella, D. H. *J. Am. Chem. Soc.* **2005**, 127, 6152.

(8) (a) Paleo, M. R.; Calaza, M. I.; Sardina, F. J. *J. Org. Chem.* **1997**, 62, 6862. (b) Hill, R. K.; Nugara, P. N.; Holt, E. M.; Holland, K. P. *J. Org.Chem.* **1992**, 57, 1045. (c) Belot, S.; Sulzer-Moss, S.; Kehrli, S.; Alexakis, A. *Chem. Commun.* **2008**, 4694.

(9) (a) E. Negishi in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: Negishi, E.), Wiley-Interscience: New York, **2002**, Vol. I, pp 213−1119. (b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: de Meijere, A.; Diederich, F.), Wiley-VCH: New York, **2004** and references therein. (c) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, 43, 1486.

(10) Silverstone, T. *Drugs*, **1992**, 43, 820.

(11) For selected reviews and examples on I_2-catalyzed reactions, see: (a) Zhang, J.; Zhu, D.; Yu, C.; Wan, C.; Wang, Z. *Org. Lett.* **2010**, 12, 2841. (b) Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, 133, 13577. (c) Uyanik, M.; Ishihara, K. *ChemCatChem* **2012**, 4, 177. (d) Wei, W.; Shao, Y.; Hu, H. Y.; Zhang, F.; Zhang, C.; Xu, Y.; Wan, X. B. *J. Org. Chem.* **2012**, 77, 7157. (e) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Chem. Eur. J.* **2012**, 18, 5460. (f) Zhu, Y. P.; Liu, M. C.; Jia, F. C.; Yuan, J. J.; Gao, Q. H.; Lian, M.; Wu, A. X. *Org. Lett.* **2012**, 14, 3392. (g) Gao, M.; Yang, Y.; Wu, Y. D.; Deng, C.; Cao, L. P.; Meng, X. G.; Wu, A. X. *Org.*

Lett. **2010**, 12, 1856. (*h*) Yin, G. D.; Zhou, B. H.; Meng, X. G.; Wu, A. X.; Pan, Y. J. *Org. Lett.* **2006**, 8, 2245.