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# Mild and Efficient Cobalt-Catalyzed Cross-Coupling of Aliphatic Amides and Aryl Iodides in Water

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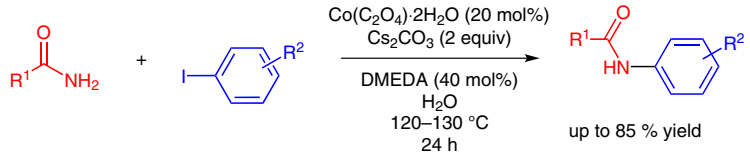


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**Abstract** A convenient protocol for the C–N cross-coupling of aliphatic amides and iodobenzene is demonstrated using a simple and inexpensive $Co(C_2O_4)\cdot 2H_2O$/*N*,*N*′-dimethylethylenediamine (DMEDA) catalytic system in water. Good yields of N-arylated products were isolated (up to 85%) and the protocol has been successfully applied to the synthesis of the anticancer drug, flutamide.

**Key words** cobalt, *N*-arylation, cross-coupling, aliphatic amide, water

*N*-Aryl aliphatic amides are valuable moieties that are frequently found in pharmaceutical and natural products. They feature prominently in compounds used for the treatment of hypertension,[1] cancer,[2] and for anaesthesia.[3] This class of organic molecules is readily synthesized through the reaction of acyl chlorides with anilines. Although generally effective, this acylation approach is considered to be less than desirable due to the possible genotoxicity of aniline and its impurities,[4] while the lachrymatory property of acyl chlorides also poses potential safety issues.[5]

Presented with these concerns, a straightforward and appealing alternative for the synthesis of this moiety is the metal-mediated C–N cross-coupling reaction between aliphatic amides and aryl halides. In this regard, protocols involving the use of palladium[6,7] and copper[8,9] salts to catalyze this class of transformation have emerged recently, supplanting the classical Goldberg coupling reaction. However, in spite of the improvements made, one limitation still persists; aromatic amides, which are typically more reactive,[10,11] are commonly employed as the nucleophile. There is a consequent and associated lack in the substrate scope of the less reactive aliphatic amides in these reported protocols.[7,8,12] Therefore, the development of an alternative protocol that provides access to a broader scope of *N*-aryl aliphatic amides would represent a welcome advance in this class of transformation.

The application of cobalt salts to carbon–heteroatom bond-formation reactions has recently attracted keen interest and has provided a new synthetic methodology.[13] Benefits of using this alternative metal catalyst include its low cost, stability, sustainability and environmentally benign nature.[14] In this aspect, we have recently demonstrated a cobalt-catalyzed C–N arylation of benzamide and iodobenzene in aqueous medium.[15] Given that excellent yields of up to 92% were achieved for most substituted benzamides, we envisaged the application of such a cobalt/ligand catalytic system towards the more challenging cross-coupling of aliphatic amides and aryl halides. Herein, we report a versatile, mild and practical cross-coupling of a wide range of non-aromatic amides with iodobenzene in water. It is noteworthy that the reaction does not require stringent inert conditions and it proceeds efficiently in air.

Our initial study began with the application of the previously reported conditions for the cobalt-catalyzed N-arylation[15] towards the cross-coupling of iodobenzene and 2-pyrrolidinone. To our delight, a modest yield of 50% of N-arylated product was obtained (Table 1, entry 1). To improve the yield, we hypothesized that a higher catalyst loading could be utilized due to the lower reactivity of 2-pyrrolidinone relative to benzamide. Indeed, a good yield of 75% was obtained through a slight increase of catalyst and ligand loadings to 20 mol% and 40 mol% respectively (entry 2). Inspired by this result, we proceeded to examine the effects that different combinations of Co salts, base, ligands and solvent had on the reaction. The results of this preliminary investigation are summarized in Table 1. Firstly, amongst the Co(II) salts, $Co(C_2O_4)\cdot 2H_2O$ was found to be the most effective at promoting the arylation process, affording a good yield of 75%. All the other Co salts gave significantly

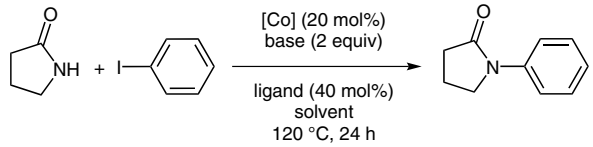
lower yields (entries 3–6). The choice of $Cs_2CO_3$ as base was found to be essential for efficient reaction; whereas other bases such as $K_3PO_4$, $K_2CO_3$, $Na_2CO_3$ and $C_2H_3O_2Cs$ only afforded the N-arylated product in yields of less than 38% (entries 7–10). Next, the efficiency of different diamine ligands on the reaction was examined (entries 11–14). *N*,*N*′-Dimethylethylenediamine (DMEDA) was shown to be the best ligand to form the active species with the cobalt catalyst, when the desired product was isolated in 75% yield. The solvent effect was subsequently probed through the screening of a range of organic solvents and water proved to be superior to all the organic solvents tested (entries 15–20). Even polar organic solvents such as methanol and ethanol proved to be ineffective for this protocol. This result points to the potential of this conversion in large-scale industrial applications.[16]

Next, control reactions were carried out in the absence of Co salt or DMEDA (entries 22 and 23). Unsurprisingly, traces of product and no reaction were observed, respectively, verifying that both components are essential for the success of the protocol. To conclude our optimization studies, a control reaction was carried out by applying Bolm's protocol of ppm copper-catalyzed N-arylation[17] with our Co salt. In his report, yields of 33–57% product were obtained for the cross-coupling of iodobenzene and butanamide using ppm amounts of Cu salt. To our satisfaction, only a trace amount of product was obtained when $Co(C_2O_4)\cdot 2H_2O$ was applied to the same protocol, effectively ruling out the possibility of catalysis due to Cu contaminants in our Co salt. In summary, the optimized conditions for the C–N cross-coupling of iodobenzene and 2-pyrrolidinone involve $Co(C_2O_4)\cdot 2H_2O$/DMEDA at 20 mol% and 40 mol%, respectively, $Cs_2CO_3$ as the base, at 120 °C for 24 hours in air.

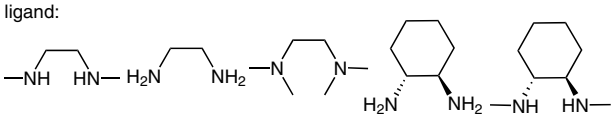
In order to evaluate the generality of the protocol with respect to the aryl halide, a range of substituted aryl and heteroaryl iodides were reacted with 2-pyrrolidinone under the optimized conditions. The results of this study are shown in Table 2. In general, good yields of the corresponding *N*-aryl amide derivatives were obtained (up to 85%). Steric effects were significant, where bulky *ortho* substituents such as Cl and OMe groups tend to hamper the reaction. However, encouraging yields of up to 52% could still be obtained, albeit at slightly elevated temperature of 130 °C (entries 3 and 4).

Interestingly, this trend was not observed for 2-fluoroiodobenzene, where a good yield of 73% was obtained (entry 2). This is possibly due to the less bulky nature and inductive effect of the fluoro substituent. The reaction can tolerate substituents of different electronic effects at the *meta* and *para* positions, affording good yields (entries 5–15). However, certain functional groups such as CN, OH and $NH_2$ groups were not tolerated in the protocol. It is noteworthy that C–N cross-coupling reaction can also be carried out smoothly using heteroaryl iodides to afford good yields of up to 60% (entries 16 and 17). Unfortunately, bromobenzene derivatives proved to be unsuitable electrophilic partners for the reaction, where only 15% and trace amounts of the desired product were isolated when the reaction was

**Table 1** Optimization Studies on the Co-Catalyzed Cross-Coupling of Pyrrolidinone and Iodobenzene[a]




ligand:

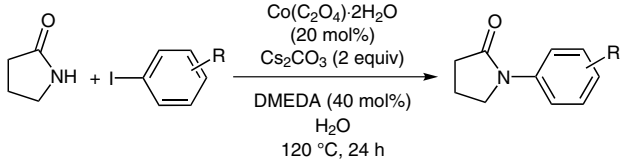


L1 L2 L3 L4 L5

| Entry | Catalyst | Base | Ligand | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L1 | $H_2O$ | 50[c] |
| 2 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L1 | $H_2O$ | 75 |
| 3 | $Co(OAc)_2$ | $Cs_2CO_3$ | L1 | $H_2O$ | 20 |
| 4 | $Co(ClO_4)_2\cdot 6H_2O$ | $Cs_2CO_3$ | L1 | $H_2O$ | 42 |
| 5 | $CoCl_2$ | $Cs_2CO_3$ | L1 | $H_2O$ | 50 |
| 6 | $Co(C_5H_7O_2)_2$ | $Cs_2CO_3$ | L1 | $H_2O$ | 37 |
| 7 | $Co(C_2O_4)\cdot 2H_2O$ | $K_3PO_4$ | L1 | $H_2O$ | 38 |
| 8 | $Co(C_2O_4)\cdot 2H_2O$ | $K_2CO_3$ | L1 | $H_2O$ | 30 |
| 9 | $Co(C_2O_4)\cdot 2H_2O$ | $Na_2CO_3$ | L1 | $H_2O$ | trace |
| 10 | $Co(C_2O_4)\cdot 2H_2O$ | $C_2H_3O_2Cs$ | L1 | $H_2O$ | trace |
| 11 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L2 | $H_2O$ | 15 |
| 12 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L3 | $H_2O$ | 0 |
| 13 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L4 | $H_2O$ | 30 |
| 14 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L5 | $H_2O$ | 41 |
| 15 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L1 | MeOH | trace |
| 16 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L1 | EtOH | trace |
| 17 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L1 | DMF | trace |
| 18 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L1 | DMSO | trace |
| 19 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L1 | THF | trace |
| 20 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L1 | toluene | trace |
| 21 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | L1 | $H_2O$ | 25[d] |
| 22 | - | $Cs_2CO_3$ | L1 | $H_2O$ | trace |
| 23 | $Co(C_2O_4)\cdot 2H_2O$ | $Cs_2CO_3$ | - | $H_2O$ | 0 |

[a] Reaction conditions: Co catalyst (20 mol%), base (2.94 mmol), pyrrolidinone (1.47 mmol), ligand (40 mol%), $H_2O$ (0.3 mL), iodobenzene (2.21 mmol), at 120 °C for 24 h in air.
[b] Isolated yield.
[c] The reaction was carried out using 10 mol% Co catalyst and 20 mol% ligand.
[d] The reaction was carried out at 110 °C.

**Table 2** N-Arylation of Pyrrolidinone with Various Substituted Aryl Halides[a]



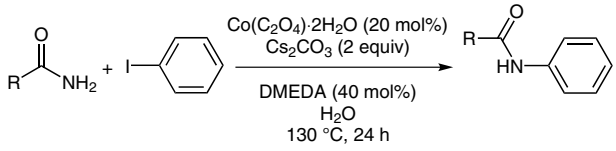

| Entry | ArX | Product | Yield (%)[b] |
|---|---|---|---|
| 1 | PhI | **2a** | 75 |
| 2 | 2-$FC_6H_4I$ | **2b** | 73 |
| 3 | 2-$ClC_6H_4I$ | **2c** | 40[c] |
| 4 | 2-$OMeC_6H_4I$ | **2d** | 50[c] |
| 5 | 3-$FC_6H_4I$ | **2e** | 72 |
| 6 | 3-$ClC_6H_4I$ | **2f** | 80 |
| 7 | 3-$BrC_6H_4I$ | **2g** | 85 |
| 8 | 3-$CF_3C_6H_4I$ | **2h** | 72 |
| 9 | 3-$OMeC_6H_4I$ | **2i** | 60 |
| 10 | 3-$NO_2C_6H_4I$ | **2j** | 50 |
| 11 | 4-$FC_6H_4I$ | **2k** | 82 |
| 12 | 4-$ClC_6H_4I$ | **2l** | 60 |
| 13 | 4-$CF_3C_6H_4I$ | **2m** | 71 |
| 14 | 4-$OMeC_6H_4I$ | **2n** | 60 |
| 15 | 4-$MeC_6H_4I$ | **2o** | 60 |
| 16 | 2-I-thiophene | **2p** | 60 |
| 17 | 3-I-thiophene | **2q** | 50 |
| 18 | PhBr | **2a** | 20[c] |
| 19 | 4-$FC_6H_4Br$ | **2r** | trace[c] |

[a] Unless otherwise stated, the reaction was carried out with $Co(C_2O_4)·2H_2O$ (20 mol%), $Cs_2CO_3$ (2.94 mmol), 2-pyrrolidinone (1.47 mmol), DMEDA (40 mol%), $H_2O$ (0.3 mL), substituted iodobenzene (2.21 mmol), at 120 °C for 24 h in air.
[b] Isolated yield.
[c] The reaction was carried out at 130 °C.

carried out at slightly elevated temperature (entries 18 and 19).

Next, the substrate scope of the protocol was tested with a range of aliphatic amides. As shown in Table 3, moderate to good yields of up to 70% were obtained when the reactions were conducted at 130 °C. To the best of our knowledge, this protocol demonstrates the widest scope of alkyl and cyclic amides as the N-nucleophile for a cross-coupling reaction of this type. Of the amides screened, reactions using ethanamide and propanamide proved to be unsuccessful (Table 3, entries 1 and 2). Nevertheless, good yields of up to 65% were obtained for amides with alkyl substituents of more than two carbons (entries 4–6). Similarly, this trend was observed when amides with cycloalkyl rings as substituents were employed. An increase in the yield from 40% to 68% could be observed when cyclopropanecarboxamide was replaced with cyclohexanecarboxamide as the nucleophilic partner (entries 7–9).

**Table 3** N-Arylation of Aliphatic Amides with Iodobenzene[a]

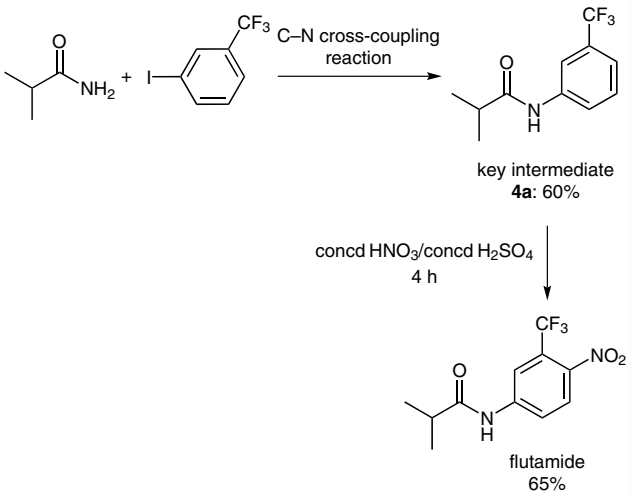



| Entry | R | Product | Yield (%)[b] |
|---|---|---|---|
| 1 | Me | **3a** | trace |
| 2 | Et | **3b** | trace |
| 3 | Pr | **3c** | 60 |
| 4 | *i*-Pr | **3d** | 60 |
| 5 | Bu | **3e** | 64 |
| 6 | pentyl | **3f** | 65 |
| 7 | cyclopropyl | **3g** | 40 |
| 8 | cyclopentyl | **3h** | 68 |
| 9 | cyclohexyl | **3i** | 62 |
| 10 | Bn | **3j** | 70 |

[a] Unless otherwise stated, the reaction was carried out with $Co(C_2O_4)·2H_2O$ (20 mol%), $Cs_2CO_3$ (2.94 mmol), aliphatic amides (1.47 mmol), DMEDA (40 mol%), $H_2O$ (0.3 mL), iodobenzene (2.21 mmol), at 130 °C for 24 h in air.
[b] Isolated yield.

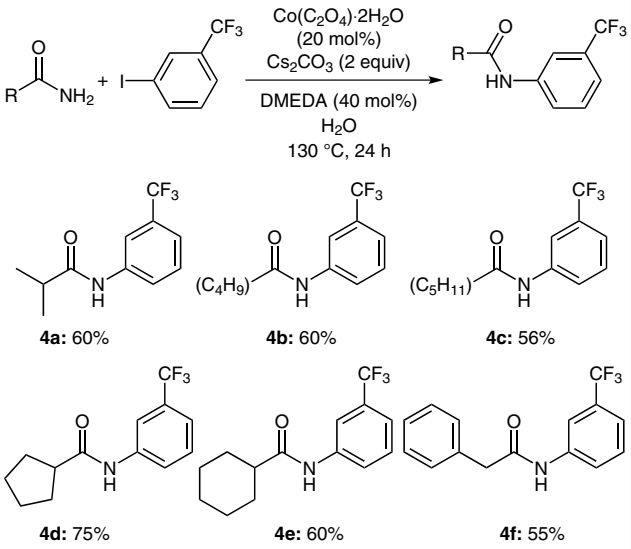
This observation could possibly be due to the extra steric stability offered by substituents with bulkier alkyl groups.[10,18] 2-Phenylethanamide, a substrate which contained α-acidic protons, was well tolerated by the protocol, affording the corresponding N-arylated amide in a good yield of 70% (entry 10).

To demonstrate the synthetic utility of this procedure, we attempted to synthesize flutamide, a non-steroidal antiandrogen used primarily to treat prostate cancer. Traditionally, flutamide is synthesized through the reaction of 4-nitro-3-(trifluoromethyl)aniline and isobutyryl chloride.[19] Recently, Bandgar and Sawant described a green, recyclable method through the use of 2,4,6-trichloro-1,3,5-triazine and *N*-methylmorpholine,[20] while Ghaffarzadeh and Rahbar demonstrated the assembly of the C–N using 3-trifluoronitrobenzene, in the presence of an Fe catalyst under reflux conditions.[21] However, both protocols proved to be more complex than the traditional method. In light of this, we were able to synthesize flutamide using the Co-catalyzed C–N cross-coupling of isobutyramide and 1-iodo-3-(trifluoromethyl)benzene, followed by nitration[20] of the resultant 3-trifluoroisobutyranilide (Scheme 1). Through this practical two-step synthesis, we were able to obtain flutamide in good yield.




**Scheme 1** Synthesis of flutamide via a C–N cross-coupling

The utility of our approach was further illustrated with the synthesis of a range of intermediates that could be nitrated to yield flutamide derivatives (Scheme 2, compounds **4a**–**f**). In general, good yields of up to 75% were obtained using the optimized conditions. Given that certain flutamide analogues with modifications of the aliphatic side chain showed antiandrogen and antiprogestin properties,[22] this cross-coupling method could potentially be a mild and convenient method of accessing such structures.




**Scheme 2** Synthesis of intermediates of flutamide derivatives. Isolated yields are given for reactions carried out with $Co(C_2O_4)\cdot 2H_2O$ (20 mol%), $Cs_2CO_3$ (2.94 mmol), aliphatic amide (1.47 mmol), DMEDA (40 mol%), $H_2O$ (0.3 mL), 1-iodo-3-(trifluoromethyl)benzene (2.21 mmol), at 130 °C for 24 h in air.

In summary, a mild, simple and efficient method for the preparation of *N*-aryl aliphatic amides via Co-catalyzed cross-coupling reaction in water has been developed.[23] Furthermore, a good range of substrates can be used in the protocol, complementing previously reported cross-coupling reactions. We also succeeded in applying our optimized conditions to the synthesis of flutamide. Studies to expand the scope of cobalt-catalyzed cross-coupling reactions are currently ongoing.

## Acknowledgment

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## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380724.

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(23) **General Procedure for N-Arylation of Pyrrolidinone/Aliphatic Amides**: A mixture of cobalt(II) oxalate dihydrate (Sigma-Aldrich, 0.294 mmol), $Cs_2CO_3$ (2.94 mmol), pyrrolidinone or aliphatic amide (1.47 mmol), DMEDA (0.588 mmol), distilled $H_2O$ (0.3 mL) and aryl halide (2.205 mmol) were added to an 8.0-mL reaction vial fitted with a Teflon-sealed screw cap. The reaction mixture was stirred under air in a closed system at 120 °C and 130 °C, respectively for 24 h. The heterogeneous mixture was subsequently cooled to r.t. and diluted with $CH_2Cl_2$. The combined organic extracts were dried over anhyd $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. The crude product was loaded into the column using minimal amounts of $CH_2Cl_2$ and was purified by silica gel column chromatography to afford the N-arylated product. The identity and purity of products were confirmed by $^1$H NMR and $^{13}$C NMR spectroscopic analysis.

**1-Phenylpyrrolidin-2-one (2a)**: off-white solid; 176 mg (75% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.7 Hz, 2 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 3.88 (t, *J* = 7.0 Hz, 2 H), 2.62 (t, *J* = 8.0 Hz, 2 H), 2.17 (quin, *J* = 8.2 Hz, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 182.0, 136.5, 128.9, 124.5, 120.0, 48.8, 32.8, 18.1. HRMS: *m*/*z* [M$^+$] calcd for $C_{10}H_{11}NO$: 162.0917; found: 162.0914.

**1-(2-Fluorophenyl)pyrrolidin-2-one (2b)**: off-white solid; 192 mg (73% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.43 (m, 1 H), 7.21–7.28 (m, 1 H), 7.10–7.18 (m, 2 H), 3.83 (t, *J* = 6.8 Hz, 2 H), 2.57 (t, *J* = 8.4 Hz, 2 H), 2.21 (qn, *J* = 7.6 Hz, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 174.7, 157.0 (d, *J* = 248.4 Hz), 128.2 (d, *J* = 7.6 Hz), 127.8 (d, *J* = 2.3 Hz), 126.3 (d, *J* = 11.4 Hz), 124.4 (d, *J* = 3.8 Hz), 116.5 (d, *J* = 19.8 Hz), 49.9, 31.0, 18.9. HRMS: *m*/*z* [M$^+$] calcd for $C_{10}H_{10}NOF$: 180.0822.; found: 180.0806.

**1-(3-Methoxyphenyl)pyrrolidin-2-one (2i)**: pale yellow solid; 169 mg (60% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 2.8 Hz, 1 H), 7.24 (t, *J* = 8.0 Hz, 1 H), 7.10 (dd, *J* = 8.0 Hz, 1 H), 6.70 (dd, *J* = 8.0 Hz, 1 H), 3.82 (t, *J* = 8.0 Hz, 2 H), 3.80 (s, 3 H), 2.58 (t, *J* = 8.0 Hz, 2 H), 2.12 (qn, *J* = 7.2 Hz, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 174.2, 159.9, 140.6, 129.4, 111.9, 110.0, 105.9, 55.2, 48.8, 32.8, 17.9. HRMS: *m*/*z* [M$^+$] calcd for $C_{11}H_{13}NO_2$: 192.1022; found: 192.1011.

***N*-[3-(Trifluoromethyl)phenyl]pentanamide (4b)**: off-white solid; 216 mg (60% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 7.72 (d, *J* = 9.2 Hz, 1 H), 7.66 (br s, 1 H), 7.40 (t, *J* = 8.8 Hz, 1 H), 7.34 (d, *J* = 8.8 Hz, 1 H), 2.38 (t, *J* = 8.0 Hz, 2 H), 1.70 (qn, *J* = 8.0 Hz, 2 H), 1.34–1.44 (m, 2 H), 0.93 (t, *J* = 7.6 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 172.0, 138.5, 131.3 (q, *J* = 32.8 Hz), 129.5, 123.9 (q, *J* = 270.6 Hz), 122.9, 120.7 (q, *J* = 3.4 Hz), 116.6 (q, *J* = 3.5 Hz), 47.4, 37.6, 22.3, 13.8. HRMS: *m*/*z* [M$^+$] calcd for $C_{12}H_{14}NOF_3$: 246.1103; found: 246.1117.