Catalysis Science & Technology

Accepted Manuscript

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Combination of gold and iridium catalysts for the synthesis of *N*-alkylated amides from nitriles and alcohols†

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

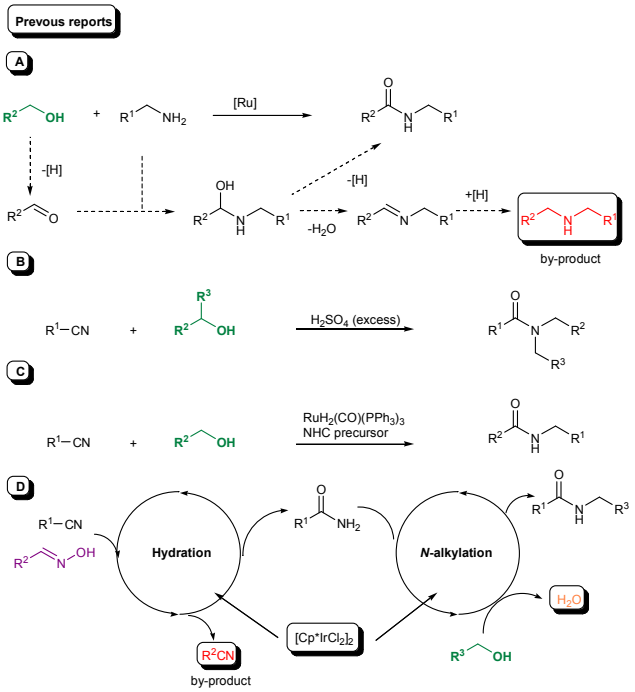
DOI: 10.1039/b000000x

An alternative and efficient approach for the synthesis of *N*-alkylated amides from nitriles and alcohols was proposed and accomplished. By the combination of [(IPr)AuNTf] (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) and $[Cp^*IrCl_2]_2$ (Cp^* = η^5-pentamethylcyclopentadienyl), a series of nitriles are first hydrated to give amides, followed by the resulting amides were further *N*-alkylated with a variety of alcohols as alkylating agents to afford *N*-alkylated amides with good to excellent yields. Compared with previous methods for the synthesis of *N*-alkylated amides from nitriles and alcohols as starting materials, this protocol could be accomplished with high atom economy under more environmentally benign conditions.

Introduction

The *N*-alkylated amides constitute one of the most important classes of nitrogen-containing compounds because they occurred widely in natural products, pharmaceuticals, agrochemicals, polymers, peptides and polymers.[1] Traditionally, *N*-alkylated amides were synthesized *via* the coupling of activated carboxylic acid derivatives, such as acid chlorides, anhydrides and esters, with *N*-alkylated amines.[2] However, these procedures are suffering from the use of the stoichiometric amount of hazardous and/or expensive reagents, low tolerance to sensitive functional groups, and the generation of a large amount of harmful by-products. In recent years, the synthesis of *N*-alkylated amides *via* transition metal-catalyzed dehydrogenative coupling of amines and alcohols has been developed and attracted much attention due to the low toxicity of alcohols and high atom economy of reaction (Scheme 1, **A**).[3] Although significant advances have been made, *N*-alkylated amines would be generated inevitably as by-products (even with high proportion) in above process.

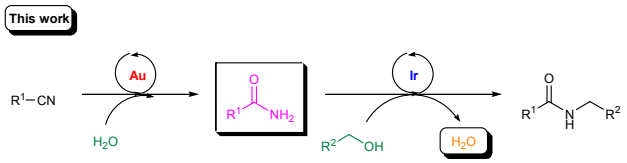
The classical Ritter reaction possesses a long history and provides a powerful method for the synthesis of *N*-alkylated amides from easily available nitriles and alcohols as starting materials (Scheme 1, **B**).[4] However, this reaction was carried out in the presence of an excess amount of concentrated sulfuric acid, and thus its application were seriously restricted. In 2013, Hong and co-workers reported a catalytic strategy available for the synthesis of *N*-alkylated amides from nitriles and alcohols based on "hydrogen transfer" using $[RuH_2(CO)(PPh_3)_3]$ as the catalyst (Scheme 1, **C**).[5] Despite complete atom efficiency, this procedure has still obvious limitations and it requires 10 mol% catalyst loading, 10 mol% ligand (NHC precursor) and 20 mol% inorganic strong base (NaH). More recently, we demonstrated the synthesis of *N*-alkylated amides *via* iridium-catalyzed tandem hydration/*N*-alkylation reaction from nitriles, *n*-butylaldoxime and alcohols (Scheme 1, **D**).[6] This procedure is attractive due to the use of low catalyst loading, high yields and operational convenience. However, 1.1-1.3 equiv of *n*-butylaldoxime was used as the water surrogate, and thus it resulted in the generation of large amount of *n*-butyronitrile as by-products and low atom economy. From the standpoint of sustainable chemistry, it is necessary to develop a new catalytic system for the synthesis of *N*-alkylated amides from nitriles and alcohols with high atom economy under more



Scheme 1 Strategies for the synthesis of *N*-alkylated amides from alcohols.

environmentally benign conditions.

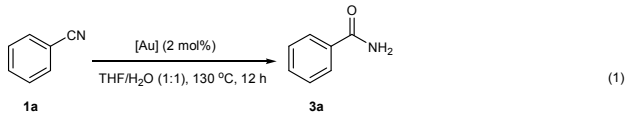
In the past decade, homogeneous gold complexes have emerged as one of the most promising catalysts for the activation of multiple bonds in organic synthesis.[7] Especially, Nolan and co-workers have demonstrated that cationic gold complexes [(IPr)Au(NTf$_2$)] [IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, NTf = bis(trifluoromethanesulfonyl)imidate)] is highly effective catalysts for the hydration of nitriles to amides under microwave irradiation.[8] Encouraged by their research and as part of our continuing interest in the development of catalytic transformations with the activation of alcohols as electrophiles,[6,9] we herein wish to report an alternative and efficient protocol for the synthesis of *N*-alkylaed amides from nitriles and alcohols by the combination of gold and iridum catalysts. The proposed reaction pathway is shown in Scheme 2. Nitriles are first hydrated to form amides catalyzed by a gold complex, and the resulting amides are further *N*-alkylated with alcohols to afford *N*-alkylated amides catalyzed by an iridium complex.

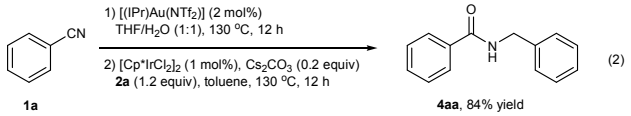


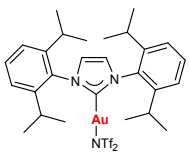
Scheme 2 The alternative protocol for the synthesis of *N*-alkylated amides from nitriles and alcohols.

Results and discussion

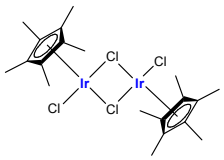
Our initial investigation focused on the synthesis of *N*-benzylbenzamide from benzonitrile **1a** and benzyl alcohol **2a**. When [(IPr)Au(NTf$_2$)] was used as the catalyst, the hydration of **1a** proceeded in THF/H$_2$O (1:1) at 130 ^{o}C for 12 h to give benzamide **3a** in 90% yield [Equation (1)]. Using [(IPr)Au(OTf)] (OTf = triflate) as the alternative catalyst, the product **3a** could be obtained in 83% yield. However, only 10% yield was found when [(Ph$_3$P)Au(NTf$_2$)] was used as a





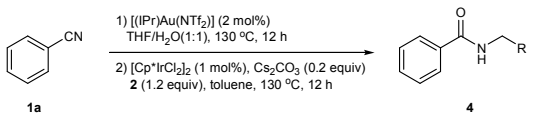


[(IPr)Au(NTf$_2$)]



[Cp*IrCl$_2$]$_2$

Table 1 Synthesis of *N*-alkylated amides from benzonitrile **1a** and a variety of alcohols **2** [a,b]



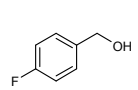
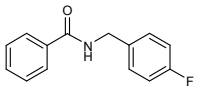
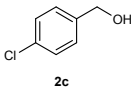
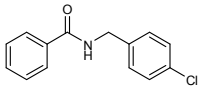
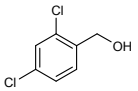
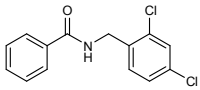
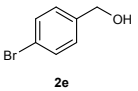
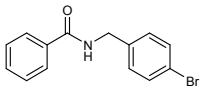
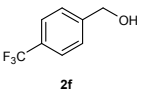
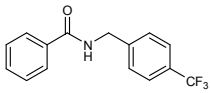
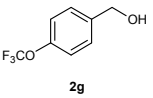
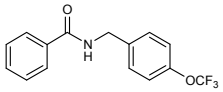
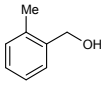
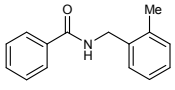
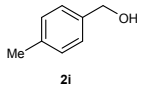
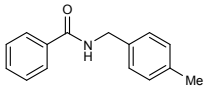
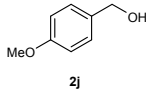
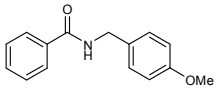
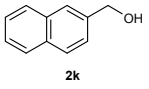
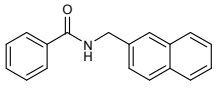
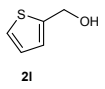
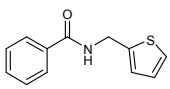
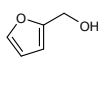
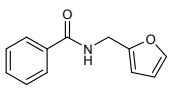
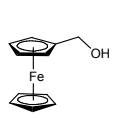
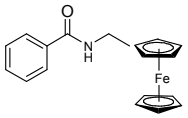
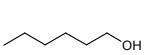
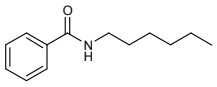
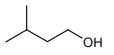
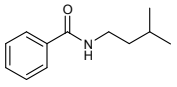
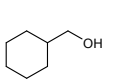
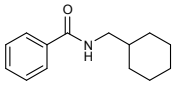
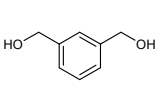
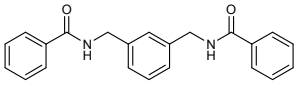
Entry	Alcohol	Product	Yield (%)[b]
1	 **2b**	 **4ab**	85
2	 **2c**	 **4ac**	84
3	 **2d**	 **4ad**	82
4	 **2e**	 **4ae**	80
5	 **2f**	 **4af**	81
6	 **2g**	 **4ag**	84
7	 **2h**	 **4ah**	81
8	 **2i**	 **4ai**	83
9	 **2j**	 **4aj**	85
10	 **2k**	 **4ak**	86
11	 **2l**	 **4al**	84
12	 **2m**	 **4am**	80

Table 1 (Continued)

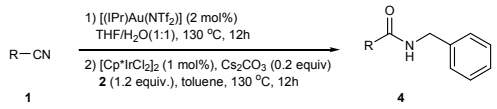
Entry	Alcohol	Product	Yield (%)[b]
13	 **2n**	 **4an**	82
14	 **2o**	 **4ao**	81[c]
15	 **2p**	 **4ap**	79[c]
16	 **2q**	 **4aq**	81[c]
17	 **2r**	 **4ar**	77[d]

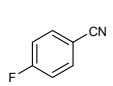
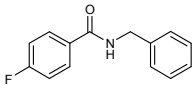
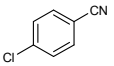
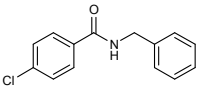
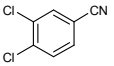
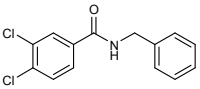
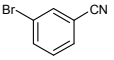
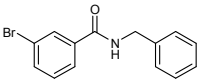
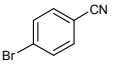
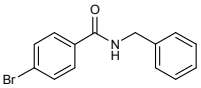
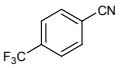
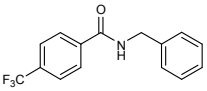
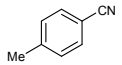
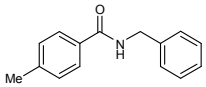
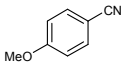
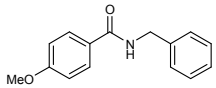
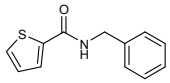
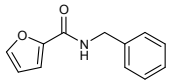
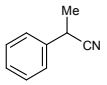
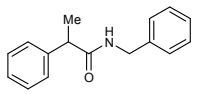
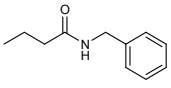
[a] Reaction conditions: 1) **1a** (1 mmol), [(IPr)Au(NTf$_2$)] (2 mol%), THF (0.5 mL), H_2O (0.5 mL), 130 °C, 12 h; 2) [Cp*IrCl$_2$]$_2$ (1 mol%), **2** (1.2 mmol), Cs_2CO_3 (0.2 equiv), toluene (1 mL), 130 °C, 12 h. [b] Isolated yield. [c] In the step of *N*-alkylation, **2** (2 mmol), KOH (0.2 equiv). [d] **2r** (0.5 mmol), the yield is based on **2r**.

catalyst under same reaction conditions. Apparently, the gold complex bearing a NHC ligand exhibited higher activity than one bearing a phosphine ligand under current conditions, and thus [(IPr)Au(NTf$_2$)] was selected as the catalyst in the step of the hydration of nitrile. In our previous work,[9g] [Cp*IrCl$_2$]$_2$ (Cp* = pentamethylcyclopentadienyl) was proven to be the most effective catalyst for the *N*-alkylation of benzamide with benzyl alcohol over other commercially available transition metal complexes, including [Ir(cod)Cl]$_2$ (cod = 1,5-cyclooctadienyl), [Cp*RhCl$_2$]$_2$, [Rh(cod)Cl]$_2$ and [Ru(*p*-cymene)Cl$_2$]$_2$. As a result of it, [Cp*IrCl$_2$]$_2$ was selected as the catalyst in the step of *N*-alkylation with alcohol. The sequential hydration/*N*-alkylation catalyzed by the combination of [(IPr)Au(NTf$_2$)] and [Cp*IrCl$_2$]$_2$ was then examined. In the presence of [Cp*IrCl$_2$]$_2$ (1 mol%), Cs_2CO_3 (0.2 equiv) and benzyl alcohol **2a** (1.2 equiv), the resulting intermediate **3a** in the step of hydration could be further converted to the *N*-alkylated product **4aa** in 84% yield [Equation (2)].

With the identified catalytic system in hand, the scope of reaction with respect to alcohols was investigated and these results are summarized in Table 1. Transformations of benzylic alcohols bearing one or two halogen atoms, such as fluorine **2b**, chlorine **2c**, dichloride **2d** and bromine **2e**, gave the corresponding products **4ab-4ae** in 80-85% yields (Table 1, entries 1-4). When benzylic alcohols bearing a more strong electron-withdrawing substituent, such as trifluoromethyl **2f** and trifluoromethoxy **2g**, were used as substrates, the desired products **4af** and **4ag** were obtained in 81% and 84% yields, respectively (Table 1, entries 5-6). Benzylic alcohols bearing

Table 2 Synthesis of *N*-alkylated amides from a series of nitriles **1** and benzyl alcohol **2a** [a,b]



Entry	Nitrile	Product	Yield (%)[b]
1	 **1b**	 **4ba**	85
2	 **1c**	 **4ca**	88
3	 **1d**	 **4da**	86
4	 **1e**	 **4ea**	80
5	 **1f**	 **4fa**	84
6	 **1g**	 **4ga**	82
7	 **1h**	 **4ha**	80[c]
8	 **1i**	 **4ia**	82[c]
9	 **1j**	 **4ja**	81
10	 **1k**	 **4ka**	82[d]
11	 **1l**	 **4la**	79[e]
12	 **1m**	 **4ma**	77[e]

[a] Reaction conditions: 1) **1a** (1 mmol), [(IPr)Au(NTf$_2$)] (2 mol%), THF (0.5 mL), H_2O (0.5 mL), 130 °C, 12 h; 2) [Cp*IrCl$_2$]$_2$ (1 mol%), **2a** (1.2 mmol), Cs_2CO_3 (0.2 equiv), toluene (1 mL), 130 °C, 12 h. [b] Isolated yield. [c] In the step of hydration, 140 °C. [d] In the step of *N*-alkylation, the use of KOH (0.2 equiv) instead of Cs_2CO_3. [e] In the step of hydration, [(IPr)Au(NTf$_2$)] (5 mol%), MW, 140 °C, 6 h; In the step of *N*-alkylation, [Cp*IrCl$_2$]$_2$ (2 mol%), **2a** (2 equiv), Cs_2CO_3 (0.4 equiv), MW, 130 °C, 3 h.

an electron-donating substituent, such as methyl **2h-i** and methoxy **2j**, proceeded smoothly as well, giving the corresponding products **4ah-4aj** in 81-85% yields (Table 1, entries 7-9). Furthermore, 2-naphthalenemethanol **2k**, thiophen-2-ylmethanol **2l**, 2-furanylmethanol **2m** and ferrocenemethanol **2n** were also proven to be suitable substrates and the desired products **4ak-4an** were obtained in 80-86% yield (Table 1, entries 10-13). Aliphatic alcohols, such as *n*-hexanol **2o**, 3-methyl-1-butanol **2p** and cyclohexylmethanol **2q**, could be also converted to the *N*-alkylated products **4ao-4aq** in 79-81% yields, although 2 equiv of alcohols were required (Table 1, entries 14-16). When 1,3-benzenedimethanol **2r** was used as the substrate, the *N,N'*-dialkylated product **4ar** was obtained in 77% yield (Table 1, entry 17).

As shown in Table 2, the scope of reaction with respect to nitriles was then examined. Reactions of benzonitriles bearing one or two electron-withdrawing substituents, such as halogen atoms **1b-f** and trifluoromethyl **1g**, provided the corresponding products **4ba-4ga** in 80-88% yields (Table 2, entries 1-6). Transformations of benzonitriles bearing an electron-donating substituent, such as methyl **1h** and methoxy **1i**, afforded also the desired products **4ha** and **4ia** in 80% and 82% yields, respectively (Table 2, entries 7-8). In the case of heteroaryl nitriles **1j** and **1k**, the corresponding products **4ja** and **4ka** could be also obtained in 81% and 82% yields, respectively (Table 2, entries 9-10). Under microwave irradiation at 140 ^{o}C (a focused single-mode microwave synthesizer, Discover CEM, USA, 300W), hydrations of aliphatic nitriles **1l** and **1m** proceeded for 6 h at 140 ^{o}C to afford the corresponding amides, which underwent the *N*-alkylation to give the desired products **4la** and **4ma** in 79% and 77% yields, respectively (Table 2, entries 11-12).[10]

Conclusion

We have established an alternative and efficient approach for the synthesis of *N*-alkylated amides from nitriles and alcohols by the combination of [(IPr)Au(NTf$_2$)] and [Cp*IrCl$_2$]$_2$. Compared with previous methods for the synthesis of *N*-alkylated amides from nitriles and alcohols as starting materials, this protocol could be accomplished with high atom economy under more environmentally benign conditions and thus it exhibited the significant application potential.

Experimental Section

General Experimental Details. High-resolution mass spectra (HRMS) were obtained on a HPLC-Q-Tof MS(Micro) spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion [M+Na].$^{+}$ Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 500 MHz using a Bruker Avance 500 spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for $CDCl_3$ and 2.50 ppm for DMSO-d_6. Coupling constants *J* values are reported in Hertz (Hz), and the splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 125 MHz using a Bruker Avance 500 spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for $CDCl_3$ and 39.5 ppm for DMSO-d_6. ^{13}C NMR spectra were routinely run with broadband decoupling. [(IPr)Au(NTf$_2$)][11] and [Cp*IrCl$_2$]$_2$[12] were synthesized according to previous reports.

General procedure for the synthesis of *N*-alkylated amines from nitriles and alcohols. To a 25 ml oven-dried Schlenk tube were added nitrile **1** (1 mmol), [(IPr)Au(NTf$_2$)] (0.02 mmol, 2 mol%), THF (0.5 mL), H_2O (0.5 mL), and the mixture was heated at 130 ^{o}C for 12 h. The reaction mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Alcohol **2** (1.2 mmol), [Cp*IrCl$_2$]$_2$ (0.01 mmol, 1 mol%), Cs_2CO_3 (0.2 mmol, 0.2 equiv) and toluene (1 mL) were added. The mixture was further heated at 130 ^{o}C for 12h. The reaction mixture was cooled to ambient temperature, concentrated in *vacuo* and purified by flash column chromatography with hexanes/ethyl acetate to afford the corresponding product.

***N*-benzylbenzamide (4aa).**[6] mp 96-97 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.4 Hz, 2H, ArH), 7.50 (t, *J* = 7.0 Hz, 1H, ArH), 7.43 (t, *J* = 7.3 Hz, 2H, ArH), 7.39-7.27 (m, 5H, ArH), 6.45 (br s, 1H, NH), 4.65 (d, *J* = 5.4 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 138.2, 134.3, 131.5, 128.7, 128.5, 127.8, 127.5, 126.9, 44.0.

***N*-(4-fluorobenzyl)benzamide (4ab).**[6] mp 107-108 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.4Hz, 2H, ArH), 7.51 (t, *J* = 7.4 Hz, 2H, ArH), 7.43 (t, *J* = 7.6 Hz, 2H, ArH), 7.36-7.29 (m, 2H, ArH), 7.03 (t, *J* = 8.6 Hz, 2H, ArH), 6.46 (br s, 1H, NH), 4.61 (d, *J* = 5.7 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 162.2 (d, J_{C-F} = 244.1 Hz), 134.2, 134.0, 131.6, 129.5 (d, J_{C-F} = 8.0 Hz), 128.6, 126.9, 115.5 (d, J_{C-F} = 21.5 Hz), 43.3.

***N*-(4-chlorobenzyl)benzamide (4ac).**[6] mp 139-140 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$).δ 7.78 (d, *J* = 7.4 Hz, 2H, ArH), 7.51 (t, *J* = 7.3 Hz, 1H, ArH), 7.43 (t, *J* = 7.5 Hz, 2H, ArH), 7.34-7.27 (m, 4H, ArH), 6.51 (br s, 1H, NH), 4.61 (d, *J* = 5.8 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 136.8, 134.1, 133.2, 131.6, 129.1, 128.8, 128.5, 126.9, 43.3.

***N*-(2,4-dichlorobenzyl)benzamide (4ad).**[6] mp 93-94 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 2H, ArH), 7.51 (t, *J* = 7.3 Hz, 1H, ArH), 7.47-7.37 (m, 4H, ArH), 7.23 (dd, *J* = 8.2 Hz and 1.3 Hz, 1H, ArH), 6.66 (br s, 1H, NH), 4.68 (d, *J* = 6.0 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 134.2, 134.1, 133.99, 133.95, 131.7, 131.0, 129.3, 128.6, 127.3, 126.9, 41.4.

***N*-(4-bromobenzyl)benzamide (4ae).**[6] mp 134-135 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 2H, ArH), 7.51 (t, *J* = 7.3 Hz, 1H, ArH), 7.48-7.41 (m, 4H, ArH), 7.23 (d, *J* = 8.2 Hz, 2H, ArH), 6.50 (br s, 1H, NH), 4.59 (d, *J* = 5.8 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 137.3, 134.1, 131.8, 131.6, 129.5, 128.6, 126.9, 121.4, 43.4.

***N*-(4-(trifluoromethyl)benzyl)benzamide (4af).**[6] mp 140-141 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 6.2 Hz, 2H, ArH), 7.60 (t, *J* = 7.2 Hz, 2H, ArH), 7.55-7.49 (m, 1H, ArH), 7.49-7.38 (m, 4H, ArH), 6.74-6.47 (m, 1H, NH), 4.75-4.64 (m, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 142.4, 134.0, 131.7, 129.8

(q, J_{C-F} = 32.2 Hz), 128.6, 127.9, 127.0, 125.6 (q, J_{C-F} = 3.5 Hz), 124.0 (q, J_{C-F} = 270.4 Hz), 43.5.

***N*-(4-(trifluoromethoxy)benzyl)benzamide (4ag).**[6] mp 134-135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6Hz, 2H, ArH), 7.52 (t, *J* = 7.3 Hz, 1H, ArH), 7.44 (t, *J* = 7.5 Hz, 2H, ArH), 7.38 (d, *J* = 8.4 Hz, 2H, ArH), 7.19 (d, *J* = 8.2 Hz, 2H, ArH), 6.50 (br s, 1H, NH), 4.65 (d, *J* = 5.8 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 148.6, 137.1, 134.1, 131.7, 129.2, 128.6, 127.0, 121.2, 120.4 (q, J_{C-F} = 255.6 Hz), 43.2.

***N*-(2-methylbenzyl)benzamide (4ah).**[13] mp 113-114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H, ArH), 7.50 (t, *J* = 7.2 Hz, 1H, ArH), 7.42(t, *J* = 7.6 Hz, 2H, ArH), 7.30 (d, *J* = 7.0 Hz, 1H, ArH), 7.25-7.17 (m, 3H, ArH), 6.22 (br s, 1H, NH), 4.65 (d, *J* = 5.3 Hz, 2H, NCH_2), 2.38 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 136.6, 135.7, 134.3, 131.5, 130.6, 128.6, 128.5, 127.9, 126.9, 126.2, 42.3, 19.0.

***N*-(4-methylbenzyl)benzamide (4ai).**[6] mp 140-141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 2H, ArH), 7.49 (t, *J* = 7.3 Hz, 1H, ArH), 7.42 (t, *J* = 7.6 Hz, 2H, ArH), 7.25 (d, *J* = 7.9 Hz, 2H, ArH), 7.16 (d, *J* = 7.7 Hz, 2H, ArH), 6.38 (br s, 1H, NH), 4.60 (d, *J* = 5.5 Hz, 2H, NCH_2), 2.34 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 137.3, 135.1, 134.4, 131.4, 129.4, 128.5, 127.9, 126.9, 43.8, 21.0.

***N*-(4-methoxybenzyl)benzamide (4aj).**[6] mp 97-98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H, ArH), 7.49 (t, *J* = 7.2 Hz, 1H, ArH), 7.42 (t, *J* = 7.4 Hz, 2H, ArH), 7.29 (d, *J* = 8.2 Hz, 2H, ArH), 6.88 (d, *J* = 8.3 Hz, 2H, ArH), 6.36 (br s, 1H, NH), 4.58 (d, *J* = 5.4 Hz, 2H, NCH_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 159.0, 134.4, 131.4, 130.3, 129.2, 128.5, 126.9, 114.1, 55.2, 43.5.

***N*-(naphthalen-2-ylmethyl)benzamide (4ak).**[6] mp 141-142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88-7.76 (m, 6H, ArH), 7.52-7.39 (m, 6H, ArH), 6.54 (br s, 1H,NH), 4.80 (d, *J* = 5.0 Hz, 2H, NCH_2); ^{13}CNMR (125 MHz, $CDCl_3$) δ 167.4, 135.6, 134.3, 133.3, 132.8, 131.5, 128.6, 127.7, 127.6, 127.0, 126.5, 126.3, 125.94, 125.91, 44.2.

***N*-(thiophen-2-ylmethyl)benzamide (4al).**[6] mp 119-120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H, ArH), 7.50 (t, *J* = 7.4 Hz, 1H, ArH), 7.43 (t, *J* = 7.6 Hz, 2H, ArH), 7.25 (d, *J* = 5.3 Hz, 1H, ArH), 7.05 (d, *J* = 3.0 Hz, 1H, ArH), 6.98 (dd, *J* = 4.8 Hz and 3.7 Hz, 1H, ArH), 6.45 (br s, 1H, NH), 4.82 (d, *J* = 5.6 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 140.8, 134.1, 131.6, 128.5, 127.0, 126.9, 126.2, 125.3, 38.8.

***N*-(furan-2-ylmethyl)benzamide (4am).**[6] mp 98-99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 2H, ArH), 7.50 (t, *J* = 7.3 Hz, 1H, ArH), 7.43 (t, *J* = 7.5 Hz, 2H, ArH), 7.38 (s, 1H, ArH), 6.44 (br s, 1H, NH), 6.34 (m, 1H, ArH), 6.30 (m, 1H, ArH), 4.65 (d, *J* = 5.4 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 151.2, 142.2, 134.1, 131.6, 128.5, 127.0, 110.5, 107.6, 37.0.

***N*-(ferrocenemethyl)benzamide (4an).** mp 165-166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 2H, ArH), 7.51 (t, *J* = 7.3 Hz, 1H, ArH), 7.44 (t, *J* = 7.4 Hz, 2H, ArH), 6.30 (br s, 1H, NH), 4.34 (d, *J* = 5.2 Hz, 2H, NCH_2), 4.27 (s, 2H, Ferrocene H), 4.21 (s, 5H, Ferrocene H), 4.18 (s, 2H, Ferrocene H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 134.5, 131.4, 128.6, 126.8, 84.7, 68.5, 68.3, 68.2, 39.3. HRMS-EI (70 eV) *m/z* calcd for $C_{18}H_{17}NOFeNa$ $[M + Na]^+$ 342.0557, found 342.0567.

***N*-hexylbenzamide (4ao).**[6] mp 41-42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2H, ArH), 7.49 (t, *J* = 7.2 Hz, 1H, ArH), 7.42 (t, *J* = 7.5 Hz, 2H, ArH), 6.14 (br s, 1H, NH), 3.45 (q, *J* = 6.7 Hz, 2H, NCH_2), 1.61 (quint, *J* = 7.3 Hz, 2H, CH_2), 1.42-1.29 (m, 6H, 3xCH_2), 0.89 (t, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 134.9, 131.2, 128.4, 126.8, 40.1, 31.5, 29.6, 26.6, 22.5, 14.0.

***N*-isopentylbenzamide (4ap).**[9g] oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H, ArH), 7.49 (t, *J* = 7.3 Hz, 1H, ArH), 7.42 (t, *J* = 7.5 Hz, 2H, ArH), 6.10 (br s, 1H, NH), 3.48 (quart, *J* = 6.8 Hz, 2H, NCH_2), 1.69 (sept, *J* = 6.6 Hz, 1H, CH), 1.51 (quart, *J* = 7.3 Hz, 2H, CH_2), 0.96 (d, *J* = 6.6 Hz, 6H, 2xCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 134.8, 131.2, 128.4, 126.8, 38.5, 38.3, 25.9, 22.4.

***N*-(cyclohexylmethyl)benzamide (4aq).**[6] mp 103-104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.3 Hz, 2H, ArH), 7.49 (t, *J* = 7.1 Hz, 1H, ArH), 7.43 (t, *J* = 7.3 Hz, 2H, ArH), 6.21 (br s, 1H, NH), 3.30 (t, *J* = 6.3 Hz, 2H, NCH_2), 1.82-1.71 (m, 4H, 2xCH_2), 1.70-1.64 (m, 1H, CH), 1.63-1.54 (m, 1H, CH), 1.30-1.12 (m, 3H, CH and CH_2), 1.00 (q, *J* = 11.7 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 134.9, 131.2, 128.5, 126.8, 46.2, 38.0, 30.9, 26.3, 25.8.

***N,N'*-m-xylylene-bis-benzamide (4ar).**[14] mp 170-171 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (t, *J* = 5.3 Hz, 2H, ArH), 7.86 (d, *J* = 7.4 Hz, 4H, ArH), 7.52 (t, *J* = 7.0 Hz, 2H, ArH), 7.45 (t, *J* = 7.4 Hz, 4H, ArH), 7.32-7.25 (m, 2H, ArH), 7.23-7.17 (m, 2H, ArH), 4.47 (d, *J* = 5.4 Hz, 4H, NCH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.2, 139.8, 134.4, 131.1, 128.2, 127.2, 125.8, 125.6, 42.5.

***N*-benzyl-4-fluorobenzamide (4ba).**[6] mp 141-142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.76 (m, 2H, ArH), 7.40-7.27 (m, 5H, ArH), 7.10 (t, *J* = 8.6 Hz, 2H, ArH), 6.38 (br s, 1H, NH), 4.63 (d, *J* = 5.6 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 164.7 (d, J_{C-F} = 251.0 Hz), 138.0, 130.5,129.3 (d, J_{C-F} = 9.0 Hz), 128.8, 127.8, 127.6, 115.5 (d, J_{C-F} = 21.7 Hz), 44.1.

***N*-benzyl-4-chlorobenzamide (4ca).**[6] mp 162-163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H, ArH), 7.40 (d, J = 8.2 Hz, 2H, ArH), 7.38-7.28 (m, 5H, ArH), 6.40 (br s, 1H, NH), 4.63 (d, *J* = 5.6 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 137.9, 137.7, 132.7, 128.8, 128.4, 127.9, 127.7, 44.2.

***N*-benzyl-3,4-dichlorobenzamide (4da).**[6] mp 105-106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H, ArH), 7.60 (d, *J* = 7.8 Hz, 1H, ArH), 7.50 (d, *J* = 8.2 Hz, 1H, ArH), 7.41-7.29 (m, 5H, ArH), 6.45 (br s, 1H, NH), 4.62 (d, *J* = 5.3 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 137.6, 135.9, 134.1, 133.0, 130.6, 129.2, 128.8, 127.9, 127.7, 126.1, 44.2.

***N*-benzyl-3-bromobenzamide (4ea).**[13] mp 87-88 °C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.93 (s, 1H, ArH), 7.70 (d, *J* = 7.7 Hz, 1H, ArH), 7.64-7.62 (m, 1H, ArH), 7.38-7.29 (m, 6H, ArH), 6.40 (s,

br, 1H, NH), 4.63 (d, J = 5.6 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 137.8, 136.3, 134.5, 130.2, 130.1, 128.8, 127.9, 127.7, 125.5, 122.7, 44.2.

***N*-benzyl-4-bromobenzamide (4fa).[15]** mp 169-170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.4 Hz, 2H, ArH), 7.56 (d, J = 8.4 Hz, 2H, ArH), 7.39-7.28 (m, 5H, ArH), 6.38 (br s, 1H, NH), 4.63 (d, J = 5.6 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 137.9, 133.2, 131.8, 128.8, 128.6, 127.9, 127.7, 126.2, 44.2.

***N*-benzyl-4-(trifluoromethyl)benzamide (4ga).[6]** mp 170-171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 2H, ArH), 7.69 (d, J = 8.0 Hz, 2H, ArH), 7.41-7.29 (m, 5H, ArH), 6.48 (br s, 1H, NH), 4.66 (d, J = 5.6 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 137.8, 137.7, 133.3 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.8, 127.9, 127.8, 127.4, 125.6, 123.6 (q, $J_{C\text{-}F}$ = 271.1 Hz), 44.3.

***N*-benzyl-4-methylbenzamide (4ha).[6]** mp 132-133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 2H, ArH), 7.38-7.27 (m, 5H, ArH), 7.22 (d, J = 6.8 Hz, 2H, ArH), 6.50-6.30 (m, 1H, NH), 4.64 (dd, J = 5.3 Hz and 3.4 Hz, NCH_2), 2.39 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 141.9, 138.3, 131.5, 129.2, 128.7, 127.8, 127.5, 126.9, 44.0, 21.4.

***N*-benzyl-4-methoxybenzamide (4ia).[6]** mp 121-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.6 Hz, 2H, ArH), 7.39-7.27 (m, 5H, ArH), 6.91 (d, J = 8.6 Hz, 2H, ArH), 6.36 (br s, 1H, NH), 4.63 (d, J = 5.6 Hz, 2H, NCH_2), 3.84 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 162.2, 138.4, 128.8, 128.7, 127.8, 127.4, 126.6, 113.7 , 55.3, 44.0.

***N*-benzylthiophene-2-carboxamide (4ja).[6]** mp 117-118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 3.8 Hz, 1H, ArH), 7.47 (d, J = 5.0 Hz, 1H, ArH), 7.38-7.33 (m, 4H, ArH), 7.33-7.27 (m, 1H, ArH), 7.06 (t, J = 4.3 Hz, 1H, ArH), 6.30 (br s, 1H, NH), 4.62 (d, J = 5.7 Hz, 2H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 138.8, 138.0, 130.0, 128.7, 128.1, 127.8, 127.6, 127.5, 43.9.

***N*-benzylfuran-2-carboxamide (4ka).[6]** mp 105-106 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.41(m, 1H, ArH), 7.36-7.35 (m, 4H, ArH), 7.32-7.28 (m, 1H, ArH), 7.15 (dd, J= 3.5 Hz and 0.6 Hz, 1H, ArH), 6.64 (s, br, 1H, NH), 6.64 (dd, J= 3.5 Hz and 1.8 Hz, 1H, ArH), 4.62 (d, J = 5.9 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2, 147.9, 143.8, 138.0, 128.7, 127.9, 127.6, 114.3, 112.1, 43.1.

***N*-benzyl-2-phenylpropanamide (4la).[6]** mp 76-77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.20 (m, 8H, ArH), 7.14 (d, J = 7.0 Hz, 2H, ArH), 5.65 (br s, 1H, NH), 4.45-4.33 (m, 2H, NCH_2), 3.60 (q, J = 6.9 Hz, 2H, CH), 1.56 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 141.3, 138.3, 128.9, 128.5, 127.6, 127.4, 127.3, 127.2, 47.1, 43.5, 18.5.

***N*-benzylbutyramide (4ma).[6]** mp 47-48 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 2H, ArH), 7.31-7.24 (m, 3H, ArH), 5.74 (br s, 1H, NH), 4.45 (d, J = 4.7 Hz, 2H, NCH_2), 2.19 (t, J = 7.4 Hz, 2H, CH_2), 1.70 (sext, J = 7.2 Hz, 2H, CH_2), 0.96 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 138.4, 128.6, 127.7, 127.4, 43.5, 38.6, 19.1, 13.7.

Acknowledgements

Financial support by National Natural Science Foundation of China (No. 21272115) and Fundamental Research Funds for the Central Universities (No. 30920130111005) is greatly appreciated.

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† Electronic Supplementary Information (ESI) available: Experimental procedures and analytical data for products. See DOI: 10.1039/b000000x/

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