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Copper-catalyzed dehydrogenative reaction: synthesis of amide from aldehydes and aminopyridine

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ABSTRACT

We have developed a highly efficient method in the presence of copper catalyst to form amides from aminopyridines and aldehydes. This method is simple, environmental benign and has practical advantages in the amide synthesis.

1. Introduction

The amide bond is a key functional group in organic chemistry. It plays an important role in the composition of polymers, proteins, natural products, and pharmaceuticals.[1] The most common synthetic route to these nitrogen-containing compounds relies heavily on the reactions of activated carboxylic acids and their derivatives with amines.[2] However, this method has the innate drawbacks, for instance, a large amount of byproducts are generated and the activated carboxylic acid derivatives are not stable. Over the past few years, alternative procedures of amide synthesis have been developed, including an azide based modified Staudinger reaction,[3] hydrative reactions between alkynes and azides,[4] carbonylation of aryl chlorides to the corresponding amides,[5] and oxidative coupling of an *R*-bromonitroalkane.[6] Recently, direct aldehyde amidation with amines has drawn attention owing to its economical and the abundant nature of starting materials, for example, the radical-mediated oxidative amidation with radical initiators[7] and light,[8] the amidation via Cannizzaro reactions using lithium diisopropylamide (LDA)[9] or lanthanide reagents,[10] and the NHC catalyst amidation[11] were reported. However, most catalytic amidation processes need transition-metal complexes (such as Cu,[12a–c] Rh,[12d] Ru,[12e] Pd,[12f] Ni,[12g] Au,[12h] Fe[12i]) and extra oxidant. Besides, metal-free oxidative amidation from aldehydes[13] and the direct oxidative amidation from alcohols have also been reported.[14] Noteworthy all these reactions require relatively harsh conditions such as light, expensive oxidant, strong bases or high temperature, so there is still a need for easy and efficient methods to construct amide bond.

N-(Pyridin-2-yl)benzamide as an important pharmacophore is widely found in many bioactive compounds, such as the compounds shown in Fig. 1, compound **a** is a luciferase inhibitor and the same structure of **a** has been patented for osteoporosis treatment;[15] compound **b** can be accommodated in the luciferin binding site;[16] a series of compound **c** showed antiulcer activity.[17] Recently, we have developed a simple amidation of this kind of compounds with copper salts as the catalyst, no other extra oxidant and strong base are used.

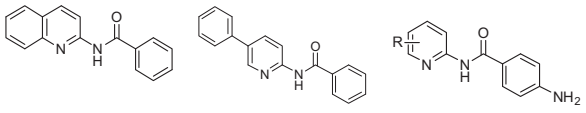

Fig. 1. Examples illustrating the importance of aminopyridine amide.

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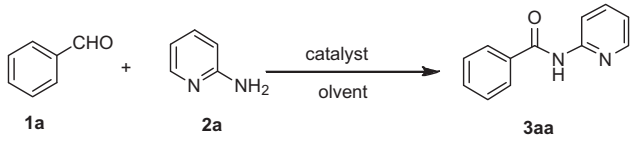
2. Results and discussions

Initially, benzaldehyde **1a** and pyridine-2-amine **2a** were chosen as model substrates for surveying the reaction parameters. Firstly, the reaction was carried out with CuI at 80 °C in *N*,*N*-dimethylformamide (DMF). Gratifyingly, the desired *N*-(pyridin-2-yl) benzamide **3aa** was obtained in 45% after 6 h (Table 1, entry 1). Then we tried other copper salts and some iron salts to improve the yield, but no satisfied result was achieved (Table 1, entries 2–5). When we prolonged the reaction time from 6 h to 12 h, the yield increased to 73%, and after 24 h, we got a yield of 92% (Table 1, entries 6 and 7). A reduced amount of CuI gave lower yield (Table 1, entry 10). As expected, no target product was obtained in the absence of catalyst (Table 1, entry 11). Furthermore, when O_2 was employed as the oxidant, 85% of desired product was isolated (Table 1, entry 12). Thus, air was chosen as oxidant for its abundance, low cost, and convenience. Switching the reaction solvent like DMA, DMSO, CH_3CN or NMP didn't further improve the yield (Table 1, entries 13–16), and the yield decreased either raised or lowered the temperature (Table 1, entries 8 and 9). Ultimately, the optimized conditions were identified (Table 1, entry 7).

Table 1
Optimization of the reaction conditions[a]



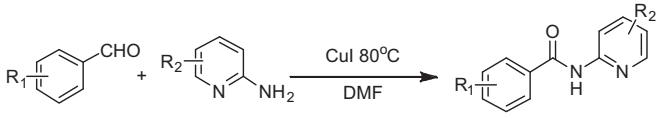
1a 2a 3aa

Entry	Catalyst	Oxidant	Solvent	Time (h)	Yield (%)
1	CuI	Air	DMF	6	45
2	CuBr	Air	DMF	6	20
3	CuCl	Air	DMF	6	17
4	$Cu(OAc)_2$	Air	DMF	6	5
5	$FeCl_2$	Air	DMF	6	32
6	CuI	Air	DMF	12	73
7	CuI	Air	DMF	24	92
8	CuI	Air	DMF	24	63[b]
9	CuI	Air	DMF	24	80[c]
10	CuI	Air	DMF	24	35[d]
11	—	Air	DMF	24	0
12	CuI	O_2	DMF	24	85
13	CuI	Air	DMA	24	87
14	CuI	Air	DMSO	24	42
15	CuI	Air	CH_3CN	24	0
16	CuI	Air	NMP	24	Trace

[a] Reaction condition: The reaction was carried out using **1a** (0.47 mmol), **2a** (0.34 mmol), and catalyst (0.03 mmol) in 2 mL DMF for 24 h at 80 °C.
[b] Reaction condition: The reaction was carried out using **1a** (0.47 mmol), **2a** (0.34 mmol), and catalyst (0.03 mmol) in 2 mL DMF for 24 h at 60 °C.
[c] Reaction condition: The reaction was carried out using **1a** (0.47 mmol), **2a** (0.34 mmol), and catalyst (0.03 mmol) in 2 mL DMF for 24 h at 100 °C.
[d] The reaction was carried out using **1a** (0.47 mmol), **2a** (0.34 mmol), and catalyst (0.015 mmol) in 2 mL DMF for 24 h at 80 °C.

Under the optimized reaction conditions, we examined a series of benzaldehydes and aminopyridines to establish the scope and limitation of the process, and the results are illustrated in Table 2. To our delight, a wide range of substituted groups attached to benzaldehydes or aminopyridines all give a good yield although the nature of the substituent in pyridine ring had some influence on the yield. Generally, benzaldehydes substituted with electron-donating groups showed better reactivity and a higher yield (Table 2, entries 2–12). Interestingly, electron-deficient substituent on position-2 of the benzaldehyde seems have a bad impact, such as chloro and bromo groups, but the electron-rich ones still give a high yield, such as methyl and methoxy groups (Table 2, entries 6–10). As a result of the steric effects from the substituent, the 2-substituted aldehydes show

Table 2
Copper-catalyzed oxidative amidation of aldehydes[a]



1a-n 2a-j 3

Entry	R_1	R_2	Product	Yield (%)
1	H	H	**3aa**	92
2	4-Cl	H	**3ba**	82
3	4-Br	H	**3ca**	71
4	4-CH_3	H	**3da**	90
5	4-OCH_3	H	**3ea**	85
6	2-Br	H	**3fa**	30
7	2-OCH_3	H	**3ga**	94
8	2-F	H	**3ha**	58
9	2-Cl	H	**3ia**	56
10	2,4-Di-Cl	H	**3ja**	66
11	3,4-Di-CH_3	H	**3ka**	82
12	3,4-Di-OCH_3	H	**3la**	87
13	Piperonyl	H	**3ma**	83
14	Furyl	H	**3na**	45
15	H	4-CH_3	**3ab**	89
16	H	4-Cl	**3ac**	48
17	H	5-CH_3	**3ad**	74
18	H	5-F	**3ae**	50
19	H	6-CH_3	**3af**	28
20	H	6-Cl	**3ag**	Trace
21	4-OCH_3	4-CH_3	**3ah**	86
22	4-OCH_3	4-Cl	**3ai**	53
23	H	4-COOEt	**3aj**	55

[a] Reaction condition: The reaction was carried out using **1a**–**n** (0.47 mmol), **2a**–**j** (0.34 mmol), and catalyst (0.03 mmol) in 2 mL DMF for 24 h at 80 °C.

lower yields (Table 2, entries 6, 8, and 9). To our disappointment, when other electron-withdrawing groups such as *o*-NO_2, *p*-NO_2 were tested, only a trace amount of product was detected on the silica gel. Furthermore, the reaction of the heteroatom-containing aromatic aldehydes also proceeded efficiently (Table 2, entries 13 and 14).

Subsequently, the substrate scope of aminopyridines was further investigated. With the comparison of electron-withdrawing and electron-donating groups in positions 4, 5, and 6 of amino (Table 2, entries 15–22), the reaction exhibited the similar activities, the results indicated that electron-donating 2-aminopyridines were successfully employed and gave higher yields (Table 2, entries 15 and 17) than those with electron-deficient substituent (Table 2, entries 16 and 18). However **1a** reacted with **2f** to produce **3af** in only 28% yield, and nearly trace desired product **3ag** could get. This may be due to the steric hindrance on the pyridine ring, especially on the electron-deficient functional group. Moreover, different 2-amino heterocycles were also tested (Table 2, entry 23). When 2-aminopyrimidine was subjected to the reaction system, no reaction was observed, and 2-aminobenzimidazole also didn't react as the desired product was not detected.

It is noteworthy that when benzaldehyde was replaced with corresponding benzoic acid, the expected amide was not achieved under the optimized reaction conditions. Therefore, the possibility that amide formation may arise from a transamidation reaction with a carboxylic acid origin from the direct oxidation of the aldehyde should be excluded. Based on the above results, a plausible mechanism for the direct oxidative amidation of aldehydes for amide formation is shown in Scheme 1. Intermediate **C** can be obtained through complexation under the influence of the Cu(I) salt. After that the nucleophilic attack of amino to the carbonyl functional group and the further proton transfer gave a hemiaminal **E**, which then may be oxidized by oxygen to produce the target product **F**. However, imines couldn't be employed as the starting substrates to accomplish the amidation reaction to generate the target products directly.

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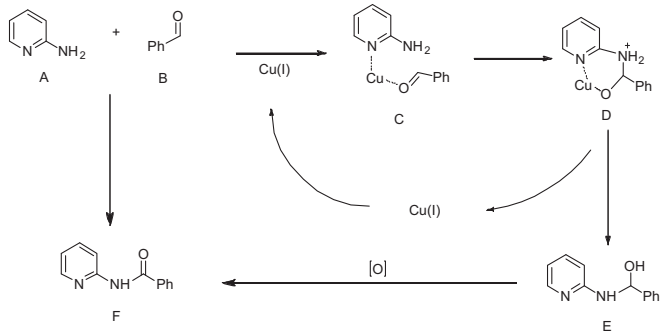

Scheme 1. Proposed mechanism of the reaction.

3. Conclusion

We have demonstrated a one-pot, efficient copper-catalyst dehydrogenative cross-coupling to form amides from aminopyridines and aldehydes. Using a simple catalyst and air as the oxidant, the protocol can achieve excellent yields. This current development makes the environmentally benign and economical acylation of amines directly with aldehydes come true, which has wide range of applications in organic synthesis.

4. Experimental

4.1. General

Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm^{-1}. All new compounds were further characterized by HRMS; copies of their ^{1}H NMR and C NMR spectra are provided. All melting points were determined without correction. Commercially available reagents and solvents were used without further purification.

4.2. Reactions of benzaldehyde 1a–n with pyridine-2-amine 2a–i

*4.2.1. Typical procedure for the preparation of N-(pyridin-2-yl)benzamide (**3aa**).* A test tube was charged with **1a** (0.47 mmol), **2a** (0.34 mmol), and CuI (5.73 mg, 0.03 mmol). Then 2 mL DMF was added to the reaction system. The reaction mixture was stirred at 80 °C for 24 h. After cooling to room temperature, the solvent was diluted with 10 mL ethyl acetate and washed with 5 mL brine and dried over anhydrous Na_2SO_4. After the solvent was evaporated in vacuo, the residue was purified by column chromatography, eluting with petroleum ether/EtOAc (5:1) to afford *N*-(pyridin-2-yl)benzamide **3aa** (62 mg, 92% yield) as yellow solid. Mp 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (br s, 1H), 8.40 (d, J=8.4 Hz, 1H), 8.23 (d, J=4 Hz, 1H), 7.93 (d, J=7.2 Hz, 1H), 7.918 (s, 1H), 7.78–7.74 (m, 1H), 7.59–7.55 (m, 1H), 7.51–7.48 (m, 2H), 7.06 (dd, J=6.8, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 151.6, 147.9, 138.5, 134.3, 132.2, 128.8, 127.2, 119.9, 114.2; IR (neat, cm^{-1}) 3412, 3110, 3030, 2241, 1665, 1595, 1458, 1301, 1260, 773, 753, 700; HRMS (ESI) calcd for $C_{12}H_{11}N_2O$ $[M+H]^+$: 199.0875; found: 199.0871.

*4.2.2. 4-Chloro-N-(pyridin-2-yl)benzamide(**3ba**).* Compound **3ba** was prepared from **1b** and **2a** according to the typical experimental procedure shown in Section4.2.1. White solid (64 mg, 82%). Mp 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (br s, 1H), 8.38 (d, J=8.4 Hz, 1H), 8.08–8.07 (m, 1H), 7.87 (d, J=8.4 Hz, 2H), 7.76–7.72 (m, 1H), 7.42 (d, J=8.4 Hz, 2H), 7.04–7.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 151.6, 147.7, 138.5, 138.4, 132.7, 128.9, 128.7, 120.0, 114.5; IR (neat, cm^{-1}) 3415, 3197, 3045, 2245, 1673, 1601, 1452, 1308, 1245, 1010, 836, 743, 733; HRMS (ESI) calcd for $C_{12}H_{10}ClN_2O$ $[M+H]^+$: 233.0487; found: 233.0482.

*4.2.3. 4-Bromo-N-(pyridin-2-yl)benzamide (**3ca**).* Compound **3ca** was prepared from **1c** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (66 mg, 71%). Mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (br s, 1H), 8.37 (d, J=8.4 Hz, 1H), 8.13 (s, 1H), 7.80 (d, J=8.4 Hz, 2H), 7.75 (t, J=0.8 Hz, 1H), 7.62–7.59 (m, 2H), 7.05 (d, J=4.8 Hz, 1H); IR (neat, cm^{-1}) 3410, 3185, 3042, 2240, 1678, 1597, 1432, 1354, 1245, 1006, 909, 832, 731; HRMS (ESI) calcd for $C_{12}H_{10}BrN_2O$ $[M+H]^+$: 276.9979; found: 276.9977.

*4.2.4. 4-Methyl-N-(pyridin-2-yl)benzamide (**3da**).* Compound **3da** was prepared from **1d** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (65 mg, 90%). Mp 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (br s, 1H), 8.40 (t, J=6.8 Hz, 1H), 8.20 (s, 1H), 7.84–7.80 (m, 2H), 7.74 (d, J=6.8 Hz, 1H), 7.27 (s, 2H), 7.03 (d, J=4.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 151.7, 147.8, 142.8, 138.4, 131.4, 129.4, 127.3, 119.7, 114.2, 21.5; IR (neat, cm^{-1}) 3414, 3080, 3028, 2918, 2240, 1673, 1600, 1430, 1323, 1259, 825, 749, 730; HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1024; found: 213.1028.

*4.2.5. 4-Methoxy-N-(pyridin-2-yl)benzamide (**3ea**).* Compound **3ea** was prepared from **1e** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (66 mg, 85%). Mp 99–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (br s, 1H), 8.40 (d, J=8.4 Hz, 1H), 8.16–8.15 (m, 1H), 7.91 (d, J=8.8 Hz, 2H), 7.72 (dd, J=8, 7.2 Hz, 1H), 7.02–6.99 (m, 1H), 6.94 (d, J=7.6 Hz, 1H), 6.93 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 162.6, 151.9, 147.6, 138.3, 129.2, 126.4, 119.5, 114.3, 113.8, 55.3; IR (neat, cm^{-1}) 3365, 3084, 3006, 2944, 2231, 1701, 1583, 1436, 1342, 1248, 1165, 838, 780, 734; HRMS (ESI) calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$: 229.0978; found: 229.0977.

*4.2.6. 2-Bromo-N-(pyridin-2-yl)benzamide (**3fa**).* Compound **3fa** was prepared from **1f** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (28 mg, 30%). Mp 82–84 °C; ^{1}H NMR (400 MHz, CDCl^3): δ 9.13 (d, J=12.8 Hz, 1H), 8.39 (d, J=8.4 Hz, 1H), 8.32 (dd, J=4.8, 0.8 Hz, 1H), 8.17–8.13 (m, 1H), 7.78–7.74 (m, 1H), 7.57–7.52 (m, 1H), 7.34–7.30 (m, 1H), 7.22–7.17 (m, 1H), 7.10–7.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 159.2, 151.3, 148.0, 138.4, 134.1, 132.0, 125.0, 121.2, 120.1, 116.5, 114.6; IR (neat, cm^{-1}) 3385, 3067, 2248, 1732, 1597, 1503, 1462, 1320, 1248, 788, 731; HRMS (ESI) calcd for $C_{12}H_{10}BrN_2O$ $[M+H]^+$: 276.9981; found: 276.9977.

*4.2.7. 2-Methoxy-N-(pyridin-2-yl)benzamide (**3ga**).* Compound **3ga** was prepared from **1g** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (73 mg, 94%). Mp 70–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.36 (br s, 1H), 8.44 (d, J=8.4 Hz, 1H), 8.32–8.31 (m, 1H), 8.27 (dd, J=7.6, 1.6 Hz, 1H), 7.74–7.70 (m, 1H), 7.52–7.47 (m, 1H), 7.12 (t, J=7.2 Hz, 1H), 7.05–7.01 (m, 2H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 157.4, 151.9, 147.9, 138.1, 133.5, 132.3, 121.3, 121.2, 119.5, 114.6, 111.4, 56.1; IR (neat, cm^{-1}) 3345, 3069, 2975, 2840, 1670, 1600, 1463, 1435, 1310, 1240, 1020, 777, 755, 681; HRMS (ESI) calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$: 229.0974; found: 229.0977.

*4.2.8. 2-Fluoro-N-(pyridin-2-yl)benzamide (**3ha**).* Compound **3ha** was prepared from **1h** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (43 mg, 58%). Mp

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162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (br s, 1H), 8.39 (d, *J*=8.4 Hz, 1H), 7.75–7.69 (m, 1H), 7.68 (d, *J*=4.4 Hz, 1H), 7.61–7.57 (m, 2H), 7.39 (dd, *J*=7.6, 1.2 Hz, 1H), 7.36–7.27 (m, 1H), 6.94–6.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 151.5, 147.4, 138.6, 137.9, 133.5, 131.6, 129.3, 127.6, 120.0, 119.5, 114.6; IR (neat, cm^{-1}) 3357, 3080, 1735, 1650, 1576, 1423, 1202, 1034, 898, 778, 752; HRMS (ESI) calcd for $C_{12}H_{10}FN_2O$ $[M+H]^+$: 217.0775; found: 217.0777.

*4.2.9. 2-Chloro-N-(pyridin-2-yl)benzamide (**3ia**).* Compound **3ia** was prepared from **1i** and **2a** according to the typical experimental procedure shown in Section 4.2.1. White solid (44 mg, 56%). Mp 134–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.37 (br s, 1H), 8.40 (d, *J*=8.4 Hz, 1H), 7.73–7.69 (m, 1H), 7.62 (d, *J*=7.6 Hz, 1H), 7.53 (dd, *J*=4.8, 1.2 Hz, 1H), 7.39–7.38 (m, 2H), 7.35–7.30 (m, 1H), 6.89–6.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 151.6, 147.2, 138.5, 135.6, 131.4, 131.0, 130.2, 129.4, 127.0, 119.8, 114.6; IR (neat, cm^{-1}) 3450, 3233, 3076, 2236, 1674, 1502, 1456, 1438, 1352, 1244, 1124, 1009, 756, 737; HRMS (ESI) calcd for $C_{12}H_{10}ClN_2O$ $[M+H]^+$: 233.0486; found: 233.0482.

*4.2.10. 2,4-Dichloro-N-(pyridin-2-yl)benzamide (**3ja**).* Compound **3ja** was prepared from **1j** and **2a** according to the typical experimental procedure shown in Section 4.2.1. White solid (60 mg, 66%). Mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.16 (br s, 1H), 8.37 (d, *J*=8.4 Hz, 1H), 7.77–7.72 (m, 1H), 7.69 (d, *J*=4.8, 1H), 7.58 (d, *J*=8 Hz, 1H), 7.40 (d, *J*=2 Hz, 1H), 7.31 (dd, *J*=8.4, 2 Hz, 1H), 6.96 (dd, *J*=6.8, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 151.4, 147.2, 138.7, 137.0, 133.9, 132.0, 130.5, 130.1, 127.4, 120.1, 114.7; IR (neat, cm^{-1}) 3405, 3081, 3016, 1673, 1599, 1500, 1432, 1357, 1280, 1101, 828, 777, 733; HRMS (ESI) calcd for $C_{12}H_9Cl_2N_2O$ $[M+H]^+$: 267.0095; found: 267.0092.

*4.2.11. 3,4-Dimethyl-N-(pyridin-2-yl)benzamide (**3ka**).* Compound **3ka** was prepared from **1k** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (63 mg, 82%). Mp 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (br s, 1H), 8.41 (d, *J*=8.4 Hz, 1H), 8.14 (d, *J*=4.4 Hz, 1H), 7.73 (d, *J*=8 Hz, 2H), 7.70 (s, 1H), 7.65 (d, *J*=8 Hz, 1H), 7.00 (t, *J*=5.6 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 151.8, 147.7, 141.3, 138.3, 137.0, 131.7, 129.8, 128.5, 124.7, 119.5, 114.2, 19.7, 19.6; IR (neat, cm^{-1}) 3240, 3054, 3024, 2973, 2943, 2246, 1676, 1611, 1594, 1500, 1432, 1384, 1263, 1149, 1108, 811, 778, 752, 733; HRMS (ESI) calcd for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1188; found: 227.1184.

*4.2.12. 3,4-Dimethoxy-N-(pyridin-2-yl)benzamide (**3la**).* Compound **3la** was prepared from **1l** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (76 mg, 87%). Mp 122–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (d, *J*=20.4 Hz, 1H), 8.39 (d, *J*=8.4 Hz, 1H), 8.20 (d, *J*=4.4 Hz, 1H), 7.74–7.72 (m, 1H), 7.53–7.50 (m, 2H), 7.05–7.02 (m, 1H), 6.89 (d, *J*=7.6 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 152.3, 151.8, 149.0, 147.7, 138.4, 126.7, 120.2, 120.2, 119.6, 114.2, 110.3, 55.9, 55.9; IR (neat, cm^{-1}) 3255, 3077, 3023, 2903, 1500, 1450, 1230, 915, 838, 754; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_3$ $[M+H]^+$: 259.1086; found: 259.1083.

*4.2.13. N-(Pyridin-2-yl)benzo[d][1,3]dioxole-5-carboxamide (**3ma**).* Compound **3ma** was prepared from **1m** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (68 mg, 83%). Mp 112–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (br s, 1H), 8.36 (d, *J*=8.4 Hz, 1H), 8.18 (d, *J*=4.4 Hz, 1H), 7.74–7.71 (m, 1H), 7.46 (d, *J*=8.4 Hz, 1H), 7.42 (d, *J*=0.4 Hz, 1H), 7.04–7.01 (m, 1H), 6.85–6.82 (m, 1H), 6.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 151.8, 150.9, 148.1, 147.7, 138.3, 128.4, 122.1, 119.7, 114.2, 108.0, 107.9, 101.8; IR (neat, cm^{-1}) 3224, 3052, 3020, 2916, 2251, 1668, 1502, 1486, 1433, 1257, 1241, 1038, 910, 777, 735; HRMS (ESI) calcd for $C_{13}H_{10}N_2O_3$ $[M+H]^+$: 242.0693; found: 242.0691.

*4.2.14. N-(Pyridin-2-yl)furan-2-carboxamide (**3na**).* Compound **3na** was prepared from **1n** and **2a** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (29 mg, 45%). Mp 70–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (br s, 1H), 8.33 (d, *J*=8.4 Hz, 2H), 7.76–7.72 (m, 1H), 7.53 (s, 1H), 7.28 (d, *J*=3.6 Hz, 1H), 7.07 (dd, *J*=7.2, 5.2 Hz, 1H), 6.57 (dd, *J*=4.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 151.0, 148.0, 147.3, 144.7, 138.4, 119.9, 115.8, 114.1, 112.6; IR (neat, cm^{-1}) 3400, 3231, 3118, 3065, 2247, 1678, 1595, 1578, 1522, 1434, 1310, 1269, 1228, 1166, 776, 758; HRMS (ESI) calcd for $C_{10}H_9N_2O_2$ $[M+H]^+$: 189.0667; found: 189.0664.

*4.2.15. N-(4-Methylpyridin-2-yl)benzamide (**3ab**).* Compound **3ab** was prepared from **1a** and **2b** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (64 mg, 89%). Mp 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (br s, 1H), 8.26 (s, 1H), 7.97 (d, *J*=5.2 Hz, 1H), 7.93 (s, 1H), 7.91 (s, 1H), 7.55 (t, *J*=7.2 Hz, 1H), 7.48–7.45 (m, 2H), 6.84 (d, *J*=4.8 Hz, 1H), 2.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 151.7, 150.0, 147.3, 134.4, 132.0, 128.7, 127.3, 121.0, 114.8, 21.4; IR (neat, cm^{-1}) 3412, 3180, 3053, 2915, 2243, 1693, 1605, 1512, 1492, 1380, 798, 772, 731, 700; HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1031; found: 213.1028.

*4.2.16. N-(4-Chloropyridin-2-yl)benzamide (**3ac**).* Compound **3ac** was prepared from **1a** and **2b** according to the typical experimental procedure shown in Section 4.2.1. White solid (38 mg, 48%). Mp 115–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (br s, 1H), 8.50 (d, *J*=2 Hz, 1H), 8.10 (d, *J*=5.2 Hz, 1H), 7.92–7.90 (m, 1H), 7.60–7.57 (m, 1H), 7.52–7.48 (m, 2H), 7.06 (dd, *J*=5.6, 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 152.5, 148.5, 146.0, 133.9, 132.5, 128.9, 127.2, 120.3, 114.3; IR (neat, cm^{-1}) 3415, 3230, 3104, 3064, 3030, 2873, 2251, 1681, 1566, 1518, 1492, 1403, 1285, 1095, 879, 818, 796, 710; HRMS (ESI) calcd for $C_{12}H_{10}ClN_2O$ $[M+H]^+$: 233.0487; found: 233.0482.

*4.2.17. N-(5-Methylpyridin-2-yl)benzamide (**3ad**).* Compound **3ad** was prepared from **1a** and **2d** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (53 mg, 74%). Mp 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (br s, 1H), 8.30 (d, *J*=8.4 Hz, 1H), 7.96 (s, 1H), 7.92 (t, *J*=7.6 Hz, 2H), 7.55 (t, *J*=2 Hz, 1H), 7.54–7.53 (m, 1H), 7.49–7.45 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 157.0, 15.8, 138.7, 134.4, 132.2, 128.8, 127.2, 119.4, 110.9, 24.0; IR (neat, cm^{-1}) 3407, 3196, 3051, 2937, 1688, 1526, 1430, 1245, 1072, 835, 773, 736, 700; HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1032; found: 213.1028.

*4.2.18. N-(5-Fluoropyridin-2-yl)benzamide (**3ae**).* Compound **3ae** was prepared from **1a** and **2e** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (37 mg, 50%). Mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (br s, 1H), 8.43 (dd, *J*=9.2, 4.4 Hz, 1H), 8.09 (d, *J*=2.8 Hz, 1H), 7.91 (d, *J*=7.2 Hz, 1H), 7.90 (s, 1H), 7.60–7.56 (m, 1H), 7.52–7.50 (m, 1H), 7.49 (t, *J*=1.6 Hz, 1H), 7.47 (d, *J*=2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 157.7, 155.2, 147.8, 135.5, 135.3, 134.0, 132.3, 128.9, 127.2, 125.4, 125.2, 114.9; IR (neat, cm^{-1}) 3455, 3284, 3086, 3055, 1651, 1532, 1508, 1368, 1203, 1120, 808, 771, 698; HRMS (ESI) calcd for $C_{12}H_{10}FN_2O$ $[M+H]^+$: 217.0775; found: 217.0777.

*4.2.19. N-(6-Methylpyridin-2-yl)benzamide (**3af**).* Compound **3af** was prepared from **1a** and **2f** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (20 mg, 28%). Mp 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 8.19 (d, *J*=8.4 Hz, 1H), 7.93 (d, *J*=7.2 Hz, 2H), 7.65 (t, *J*=8 Hz, 1H), 7.59–7.55 (m, 1H), 7.52–7.48 (m, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 157.0, 150.8, 138.7, 134.4, 132.2, 128.8, 127.2, 119.4, 110.9,

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24.0; IR (neat, cm^{-1}) 3439, 3346, 3247, 3084, 3042, 1705, 1630, 1469, 1260, 1103, 811, 775, 700; HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1025; found: 213.1028.

*4.2.20. 4-Methoxy-N-(4-methylpyridin-2-yl)benzamide (**3ah**).* Compound **3ah** was prepared from **1a** and **2h** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (44 mg, 53%). Mp 133–135 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.18 (br s, 1H), 8.25 (s, 1H), 8.00 (d, J=4.8 Hz, 1H), 7.91 (d, J=8.8 Hz, 2H), 6.94 (d, J=8.8 Hz, 2H), 6.84 (d, J=4.8 Hz, 1H), 3.85 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 162.6, 151.9, 149.8, 147.3, 129.2, 126.5, 120.7, 114.7, 113.8, 55.4, 21.3; IR (neat, cm^{-1}) 3386, 3230, 3029, 2972, 2896, 2251, 1669, 1610, 1500, 1433, 1258, 910, 875, 733; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_2$ $[M+H]^+$: 243.1138; found: 243.1134.

*4.2.21. N-(4-Chloropyridin-2-yl)-4-methoxybenzamide (**3ai**).* Compound **3ai** was prepared from **1a** and **2i** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (77 mg, 86%). Mp 142–144 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.83 (br s, 1H), 8.49 (d, J=1.6 Hz, 1H), 8.13 (d, J=5.2 Hz, 1H), 7.89 (d, J=8.4 Hz, 2H), 7.05 (dd, J=5.6, 1.6 Hz, 1H), 6.98 (d, J=8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 163.0, 152.7, 148.4, 145.9, 129.2, 125.9, 120.1, 114.3, 114.1, 55.5; IR (neat, cm^{-1}) 3415, 3285, 3226, 3072, 3031, 2948, 2874, 2251, 1675, 1530, 1458, 1322, 1218, 1067, 916, 873, 734; HRMS (ESI) calcd for $C_{13}H_{12}ClN_2O_2$ $[M+H]^+$: 263.0588; found: 263.0587.

*4.2.22. Ethyl 2-benzamidoisonicotinate (**3aj**).* Compound **3aj** was prepared from **1a** and **2j** according to the typical experimental procedure shown in Section 4.2.1. Yellow solid (50 mg, 55%). Mp 94–96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.86 (br d, J=12.8 Hz, 1H), 8.38 (t, J=4.4 Hz, 1H), 7.96 (s, 1H), 7.94 (d, J=1.2 Hz, 1H), 7.64 (dd, J=4.8, 1.2 Hz, 1H), 7.59 (d, J=7.2 Hz, 1H), 7.52 (t, J=7.6 Hz, 2H), 4.44 (q, J=7.2 Hz, 2H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 164.9, 152.4, 148.5, 140.3, 133.9, 132.5, 128.9, 127.2, 119.4, 113.7, 61.9, 14.2; IR (neat, cm^{-1}) 3416, 3058, 2976, 1650, 1443, 1226, 754, 736, 704; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_3$ $[M+H]^+$: 271.1085; found: 271.1083.

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Supplementary data

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References and notes

1. (a) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471–479; (b) Bode, J. W. *Curr. Opin. Drug Discov. Dev.* **2006**, *9*, 765–775; (c) Cupido, T.; Tulla-Puche, J.; Spengler, J.; Albericio, F. *Curr. Opin. Drug Discov. Dev.* **2007**, *10*, 768–783; (d) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243–2266.
2. (a) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852; (b) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606–631; (c) Londregan, A. T.; Storer, G.; Wooten, C.; Yang, X.; Warmus, J. *Tetrahedron Lett.* **2009**, *50*, 1986–1988.
3. (a) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007–2010; (b) Damkaci, F.; DeShong, P. *J. Am. Chem. Soc.* **2003**, *125*, 4408–4409; (c) Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406.
4. (a) Cho, S.; Yoo, E.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046–16047; (b) Chen, Z.-W.; Jiang, H.-F.; Pan, X.-Y.; He, Z.-J. *Tetrahedron* **2011**, *67*, 5920–5927.
5. Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460–8463.
6. Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027–1032.
7. Marko, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1990**, *31*, 7237–7240.
8. Davidson, R. S.; Edwards, J.; Warburton, S. K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1511–1514.
9. Ishihara, K.; Yano, T. *Org. Lett.* **2004**, *6*, 1983–1986.
10. (a) Zhang, L.; Wang, S.; Zhou, S.; Yang, G.; Sheng, E. *J. Org. Chem.* **2006**, *71*, 3149–3153; (b) Seo, S. Y.; Marks, T. J. *Org. Lett.* **2008**, *10*, 317–319.
11. (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797; (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799.
12. (a) Yoo, W.; Li, C. *J. Am. Chem. Soc.* **2006**, *128*, 13064–13065; (b) Roberta, C.; Andrea, P.; Giampaolo, G.; Lidia De, L. *Org. Lett.* **2012**, *14*, 5014–5017; (c) Wang, L.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Chem.—Eur. J.* **2008**, *14*, 10722–10726; (d) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523–528; (e) Naota, T.; Murahashi, S. *Synlett* **1991**, 693–694; (f) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* **1983**, 474–476; (g) Nakagawa, K.; Onoue, H.; Minami, K. *J. Chem. Soc., Chem. Commun.* **1966**, 17–18; (h) Kegnaes, S.; Mielby, J.; Mentzel, U. V.; Jensen, T.; Fristrup, P.; Riisager, A. *Chem. Commun.* **2012**, 2427–2429; (i) Porcheddu, A.; De Luca, L. *Adv. Synth. Catal.* **2012**, *354*, 2949–2953.
13. (a) Ekoue-Kovi, K.; Wolf, C. *Org. Lett.* **2007**, *9*, 3429–3432; (b) Gao, J.; Wang, G.-W. *J. Org. Chem.* **2008**, *73*, 2955–2958.
14. (a) Nordstom, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672–17673; (b) Zweifel, T.; Naubron, J. V.; Grutzmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559–563; (c) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Homg, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643–2649; (d) Cheng, C.; Hong, S. H. *Org. Biomol. Chem.* **2011**, *9*, 20–26; (e) Owston, N. A.; Parker, A. J.; Williams, J. M. *J. Org. Lett.* **2007**, *9*, 73–75; (f) Beller, M.; Cornils, B.; Frohning, C. D. *J. Mol. Catal. A: Chem.* **1995**, *104*, 17–85; (h) Ghosh, S. C.; Hong, S. H. *Eur. J. Org. Chem.* **2010**, 4266–4270.
15. Heitman, L. H.; Veldhoven, J. D.; Zweemer, A.; Ye, K.; Brussee, J.; IJzerman, A. P. *J. Med. Chem.* **2008**, *51*, 4724–4729.
16. Nakatsu, T.; Ichiyama, S.; Hiratake, J.; Saldanha, A.; Kobashi, N.; Sakata, K.; Kato, H. *Nature* **2006**, *440*, 372–376.
17. (a) Robert, A; Skaletzky, L. L. U. S. Patent 3,418,325, 1968; (b) Moffett, R. B.; Robert, A.; Skaletzky, L. L. *J. Med. Chem.* **1971**, *14*, 963–968.