JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo5027723 • Publication Date (Web): 28 Jan 2015

Copper-Catalyzed Oxidative Amination of sp^3 C−H Bonds under Air: Synthesis of 1,3-diarylated Imidazo[1,5-a]pyridines

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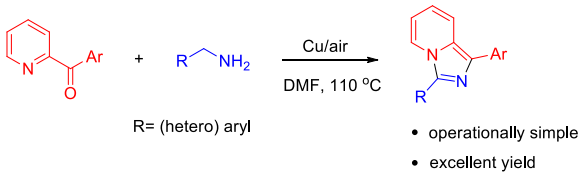
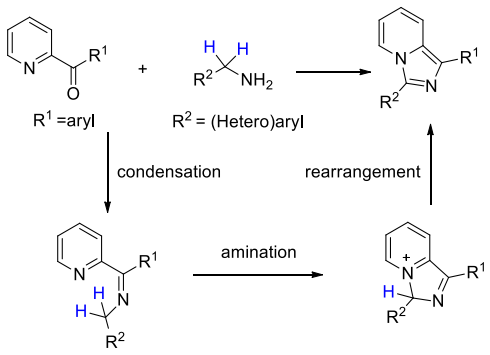


Abstract: A copper (II)-catalyzed tandem reaction between pyridine ketone and benzylamine was developed by using clean O_2 as an oxidant. This transformation proceeded via an efficient condensation-amination-oxidative dehydrogenation process, affording 1,3-diarylated imidazo[1,5-a]pyridines in excellent yields.

Imidazo[1,5-a]pyridines exist widely in both natural products and synthetic compounds of high utility in pharmaceutical and materials chemistry.[1] However, only a few synthetic routes mainly relied on traditional Vilsmeier-type cyclizations[2] and other alternative methods[3] are available so far. Therefore, more straightforward method for the preparation of imidazo[1,5-a] pyridines from easily available substrates is highly desirable.

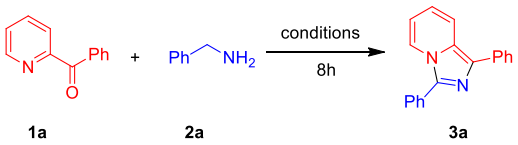
Transition-metal-catalyzed direct aminations of C-H bonds have emerged as important approaches for C-N bond formations. As a result, recent years have witnessed a rapid growth in the development of amination procedures. While synthetic methods enabling sp^2 C−N bond formation have been well-established[4], facile intramolecular amination at sp^3 C−H bonds under aerobic oxidative conditions still remains a great challenge in synthetic chemistry.[5, 6] As a continuous study on constructing C-C/C-N bonds more environmentally friendly[7], we hypothesized that 1,3-diarylated imidazo[1,5-a]pyridine could be synthesized from pyridine ketone and benzylamine via a sp^3 C-H amination process under aerobic conditions (Scheme 1). We herein report our efforts to develop a new tandem reaction for the synthesis of 1,3-diarylated imidazo[1,5-a]pyridine by using clean O_2 as an oxidant.[8]



Scheme 1. Initial hypothesis pathway for sp^3 C-H amination

In order to explore aerobic oxidative amination of sp^3 C−H bonds, 2-benzoylpyridine **1a** was chosen as a model substrate to react with benzylamine **2a** under air (Table 1). First, the reactions were performed with different transition metal catalysts under air atmosphere, it was found that $Cu(OAc)_2$ was the most efficient catalyst for this reaction, which gave the desired product **3a** in 87% yield (Table 1, entry 2); while other Lewis acids, such as CuI, $Cu(OTf)_2$ and $FeCl_3$ gave the desired product in lower yields (Table 1, entries 1, 3-4). However, the reaction didn't work when $Zn(OAc)_2$ was employed as a catalyst (Table 1, entry 5). In the absence of the metal catalyst, the reaction didn't work at all (Table 1, entry 6), which indicated that copper salt played an essential role in this transformation. Subsequently, the influence of oxidants on this reaction was investigated. The results showed that air would be the best choice with the respect of chemical yields (Table 1, entries 2 *vs* 7-9). Further assessment of the reaction conditions indicated that DMF was the optimal solvent; while other solvents gave lower yields (Table 1, entries 2 *vs* 10-14). The temperature had an obvious effect on the reaction, for example, increasing the reaction temperature to 110 °C, the yield was improved to 93% (Table 1, entry 16).

Table 1 Optimization of the reaction conditions[a]



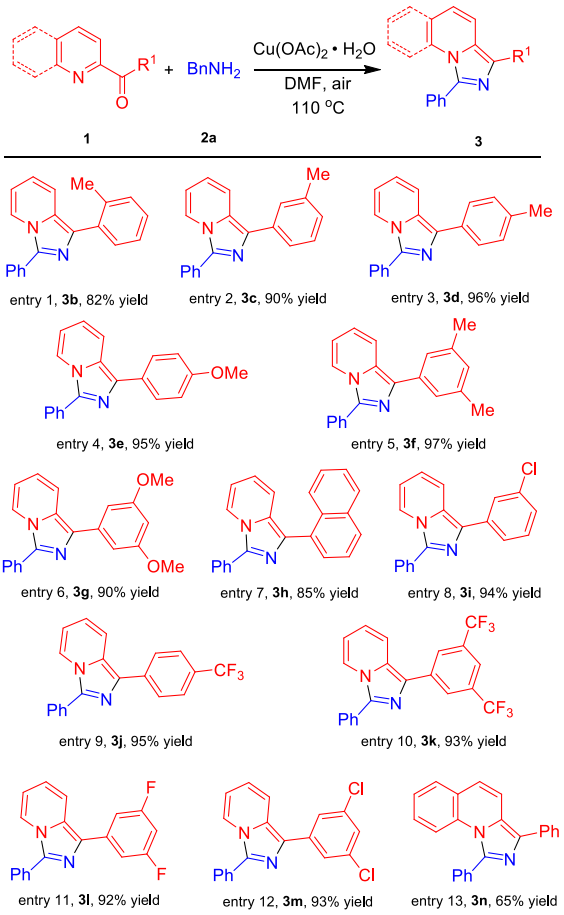
1a **2a** **3a**

Entry	Catalyst	Oxidant	Temp(°C)	Solvent	Yield(%)[b]
1	CuI	air	90	DMF	57
2	$Cu(OAc)_2 \cdot H_2O$	air	90	DMF	87
3	$Cu(OTf)_2$	air	90	DMF	72
4	$FeCl_3$	air	90	DMF	63
5	$Zn(OAc)_2$	air	90	DMF	0
6	-	air	90	DMF	0
7	$Cu(OAc)_2 \cdot H_2O$	TBHP	90	DMF	0
8	$Cu(OAc)_2 \cdot H_2O$	H_2O_2	90	DMF	40
9	$Cu(OAc)_2 \cdot H_2O$	PhOOH	90	DMF	0
10	$Cu(OAc)_2 \cdot H_2O$	air	90	CH_3CN	77
11	$Cu(OAc)_2 \cdot H_2O$	air	90	dioxane	43
12	$Cu(OAc)_2 \cdot H_2O$	air	78	EtOH	39
13	$Cu(OAc)_2 \cdot H_2O$	air	66	THF	12
14	$Cu(OAc)_2 \cdot H_2O$	air	40	CH_2Cl_2	0
15	$Cu(OAc)_2 \cdot H_2O$	air	70	DMF	41
16	$Cu(OAc)_2 \cdot H_2O$	air	110	DMF	93

[a] Reaction conditions: **1a** (1.0 equiv, 0.2 mmol), **2a** (3.0 equiv), catalyst (0.15 equiv), oxidant (1 atm for air, 2 equiv for peroxide) in solvent (1 mL), 8h. [b] Isolated yield.

With the optimized conditions in hand (Table 1, entry 16), we next investigated the substrate scope of pyridine ketone derivatives (Table 2). Common substituents including electron-donating and electron-withdrawing groups were all tolerated under the standard conditions, giving the corresponding products **3b**-**3m** in good to excellent yields. The electronic effects of R^1 group had little influence on the yield; however, the steric hindrance of R^1 group had an obvious effect on the yield. The *ortho*-substituted methyl group on R^1 decreased the yield to 82% (entry 1), while the *para*-substitution and *meta*-substitution had little effect on the yield (entries 2-12). In addition, when 2-benzoyl quinoline **1n** was employed as the substrate, the corresponding product **3n** could be obtained in 65% yield (entry 13).

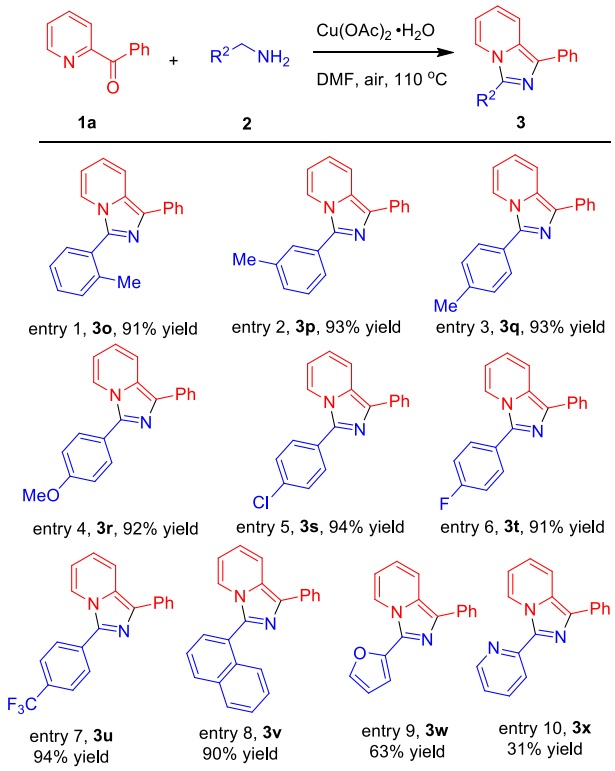
Table 2 The substrate scope of 2-benzoylpyridine derivatives [a]



[a] Reaction conditions: **1** (1.0 equiv, 0.2 mmol), **2a** (3.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (0.15 equiv) in solvent (1 mL), 8h. [b] Isolated yield.

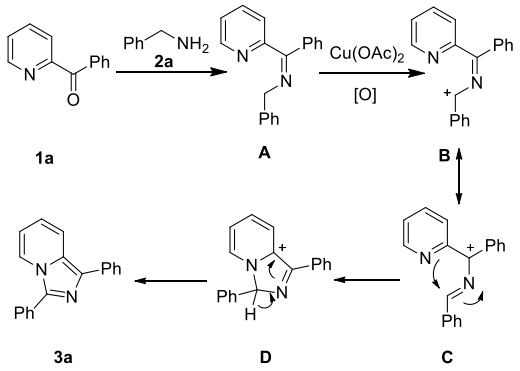
Subsequently, a series of benzylamine derivatives **2o**-**2w** were employed to react with 2-benzoylpyridine **1a** under the optimized conditions (Table 3). In general, a range of benzylamine derivatives with both electron-donating and electron-withdrawing groups worked well in this reaction, giving the corresponding products **3o**-**3u** in excellent yields (entries 1-7). The ring-fused benzylamine also gave the corresponding product **3v** in excellent yield (entry 8). Moreover, heterocyclic benzylamines could undergo the tandem reaction smoothly to give the corresponding product **3w** and **3x** in 63% and 31% yields respectively (entries 9 and 10). However, for other long chain aliphatic amines, no corresponding products were obtained.

Table 3 The substrate scope of benzylamine derivatives[a]



[a] Reaction conditions: **1a** (1.0 equiv, 0.2 mmol), **2** (3.0 equiv), $Cu(OAc)_2{\cdot}H_2O$ (0.15 equiv) in solvent (1 mL), 8h. [b] Isolated yield.

On the basis of the above results and previous reports, a possible mechanism is proposed and shown in Scheme 2. First, the condensation reaction between 2-benzoylpyridine **1a** and benzylamine **2a** generates intermediate **A**. Subsequently, an oxidative dehydrogenation in **A** gives intermediate **B**[9,10], which has a resonance structure of intermediate **C**. Then, the intramolecular amination in intermediate **C** leads to the formation of cyclised intermediate **D**[11], which can undergo sequential oxidative dehydrogenation and rearrangement to yield imidazo[1,5-a]pyridine **3a**.



Scheme 2. A tentative mechanism for the formation of **3a**.

In summary, we have developed an efficient oxidative amination of sp^3 C-H bonds under air. This tandem reaction is operationally simple, and a wide range of substituents are tolerated well to give 1,3-diarylated imidazo[1,5-a]pyridines in good to excellent yields. This protocol can serve as a new tool for the synthesis of 1,3-diarylated imidazo[1,5-a]pyridines.

Experimental Section

General methods. NMR spectra were recorded on 300MHz or 400 MHz NMR spectrometer with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts were reported in parts per million (ppm, δ scale) downfield from TMS at 0.00 ppm and referenced to the $CDCl_3$ at 7.26 ppm (for ^1H NMR) or 77.16 ppm (for ^{13}C NMR). HRMS was obtained by Electron Ionization (EI) or Electrospray Ionization (ESI, only for product **3x**) on a TOF mass analyzer. Melting points were determined on a melting point apparatus and are uncorrected. Pyridine ketones **1** were prepared by using the typical Grignard reactions according to the literatures.[12-16] The benzylamine derivatives were commercially available and were used without further purification. DMF was distilled over calcium hydride under reduced pressure.

General procedure for the preparation of pyridine ketones. A solution of the bromobenzene (10.0 mmol, 1.00 equiv) in 15 mL of dry THF was treated with magnesium (12 mmol, 1.2 equiv). After the formation of the Grignard reagent, the solution was added to a solution of the carbonitrile (8 mmol, 0.8 equiv) in THF (10 mL) at 0 ℃. After the reaction was completed, the reaction was quenched by addition of a solution of saturated NH_4Cl. The organic layer was separated and extracted twice with CH_2Cl_2. After evaporation, the organic layer was redissolved in Et_2O (30 mL) and 6 M HCl (6 mL) was added. After 30 min, the organic layer was separated, and the aqueous layer was basified with saturated $NaHCO_3$ and then extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography with petroleum ether and ethyl acetate (6:1) to afford **1a** as a white solid (79% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.70-8.67 (m, 1H), 8.10-8.06 (m, 1H), 7.89-7.86 (m, 1H), 7.47−7.38 (m, 3H), 7.29−7.23 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 155.2, 149.4, 137.9, 137.7, 137.5, 131.5, 131.4, 130.9, 126.7, 125.1, 124.2, 20.6.

Other pyridine ketones **1b**-**1w** were prepared with the similar procedures, and characterized by GC-MS.

General procedure for the synthesis of 1, 3-diarylated imidazo[1,5-a]pyridines (Tables 2 and 3). To a solution of phenyl-(pyridin-2-yl)-methanone **1a** (0.2 mmol) in distilled DMF (1.0 mL) was added $Cu(OAc)_2{\cdot}H_2O$ (0.03 mmol) and benzylamine **2a** (0.6 mmol) at room temperature. Then, the reaction mixture was stirred at 110˚C for 8 hours under air. After the reaction was completed, the resulting mixture was extracted with EtOAc (3×10 mL), dried with Na_2SO_4. Then the solvent was removed under reduced pressure and purified by silica gel column chromatography (Hex:EtOAc= 4:1-2:1) to afford the desired product as a yellow solid.

1,3-diphenylimidazo[1,5-a]pyridine (3a)[17]. Isolated yield: 93% (50 mg), yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22-8.20 (d, *J* = 7.2 Hz, 1H), 7.95 (s, 1H), 7.93 (s, 1H), 7.83-7.81 (m, 3H), 7.54-7.41 (m, 5H), 7.31-7.27 (t, *J* = 7.2 Hz, 1H), 6.78-6.74 (m, 1H), 6.56-6.52 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 135.0, 132.0, 130.2, 129.0, 128.8, 128.7, 128.3, 127.7, 126.8, 126.5, 121.7, 119.7, 119.1, 113.2. MS (EI) *m/z* 270 (M^+); IR(KBr) 697, 841, 1518, 1598, 2921 cm^{-1}; mp110-111ºC.

3-phenyl-1-o-tolylimidazo[1,5-a]pyridine (3b). Isolated yield: 82% (47 mg), yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.3 Hz, 1H), 7.87–7.85 (m, 2H), 7.55–7.48 (m, 3H), 7.44-7.42 (m, 2H), 7.34-7.32 (m, 1H), 7.29–7.24 (m, 2H), 6.72-6.68 (m, 1H), 6.63–6.45 (m, 1H), 2.46 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 133.7, 132.9, 130.9, 130.5, 129.1, 128.7, 128.6, 128.2, 127.6, 125.7, 121.6, 119.3, 119.0, 113.3, 20.7. HRMS calc. $C_{20}H_{16}N_2$ (M^+): 284.1313, Found: 284.1315. IR(KBr) 694, 822, 1500, 1601, 2915cm^{-1}; mp 121-122ºC.

3-phenyl-1-m-tolylimidazo[1,5-a]pyridine (3c). Isolated yield: 90% (51 mg), greenyellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.2 Hz, 1H), 7.85-7.80 (m, 4H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 6.78 (dd, *J* = 9.0, 6.5 Hz, 1H), 6.56 (t, *J* = 6.7 Hz, 1H), 2.45 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 138.1, 134.9, 132.2, 130.2, 129.1, 128.9, 128.7, 128.4, 127.73, 127.70, 127.5, 123.9, 121.8, 119.7, 119.3, 113.3, 21.7. HRMS calc. $C_{20}H_{16}N_2$ (M^+): 284.1313, Found: 284.1318. IR(KBr) 698, 822, 1602, 2924cm^{-1}; mp111-112^{o}C.

3-phenyl-1-p-tolylimidazo[1,5-a]pyridine (3d)[17]. Isolated yield: 96% (55 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.3 Hz, 1H), 7.83-7.79 (m, 5H), 7.55-7.50 (m, 2H), 7.45-7.41 (m, 1H), 7.27 (d, *J* = 8 Hz, 2H), 6.73 (dd, *J* = 9.2, 6.3 Hz, 1H), 6.54-6.51 (m, 1H), 2.40 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 136.3, 132.23, 132.16, 130.3, 129.5, 129.1, 128.9, 128.4, 127.5, 126.8, 121.8, 119.5, 119.3, 113.3, 21.4. MS (EI) *m/z* 284 (M^+); IR(KBr) 696, 821, 1249, 1361, 1520, 1602, 2917cm^{-1}; mp 131-132^{o}C.

1-(4-methoxyphenyl)-3-phenylimidazo[1,5-a]pyridine (3e)[17]. Isolated yield: 95% (57 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.3 Hz, 1H), 7.87–7.82 (m, 4H), 7.78–7.76 (m, 1H), 7.55–7.51 (m, 2H), 7.44–7.42 (m, 1H), 7.04–7.00 (m, 2H), 6.73 (ddd, *J* = 9.2, 6.3, 0.8 Hz, 1H), 6.60–6.46 (m, 1H), 3.86 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 137.9, 132.1, 130.3, 129.1, 128.8, 128.4, 128.2, 127.8, 127.2, 121.7, 119.3, 114.3, 113.3, 55.5. MS (EI) *m/z* 300 (M^+); IR(KBr) 694, 841, 1246, 1502, 2924cm^{-1}; mp 112-113^{o}C.

1-(3,5-dimethylphenyl)-3-phenylimidazo[1,5-a]pyridine (3f). Isolated yield: 97% (58 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.2 Hz, 1H), 7.84-7.81 (m, 3H), 7.55-7.50 (m, 4H), 7.43 (t, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 6.76 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.54 (t, *J* = 6.8 Hz, 1H), 2.39 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 138.0, 134.7, 132.3, 130.2, 129.1, 128.9, 128.5, 128.5, 127.7, 124.8, 121.8, 119.6, 119.4, 113.4, 21.6. HRMS calc. $C_{21}H_{18}N_2$ (M^+): 298.1470, Found: 298.1472. IR(KBr) 696, 824, 1602, 2929cm^{-1}; mp 123-124^{o}C.

1-(3,5-dimethoxyphenyl)-3-phenylimidazo[1,5-a]pyridine (3g). Isolated yield: 90% (59 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.24 (d, *J* = 7.2 Hz, 1H), 7.88-7.85 (m, 3H), 7.57-7.53(m, 2H), 7.49-7.45 (t, *J* = 14.8 Hz, 1H), 7.13-7.12 (d, *J* = 2.4 Hz, 2H), 6.84-6.80 (m, 1H), 6.63-6.60 (t, *J* = 13.2 Hz, 1H), 6.46-6.45 (t, *J* = 4 Hz, 1H), 3.89 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 137.9, 136.7, 131.7, 130.0, 129.1, 128.9, 128.4, 127.9, 121.8, 120.0, 119.2, 113.4, 104.9, 99.2, 55.5. HRMS calc. $C_{21}H_{18}N_2O_2$ (M^+): 330.1368, Found: 330.1371. IR(KBr) 698, 704, 829, 1156, 1204, 1601, 2933cm^{-1}; mp179-180^{o}C.

1-(naphthalen-1-yl)-3-phenylimidazo[1,5-a]pyridine (3h). Isolated yield: 85% (54 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41–8.36 (m, 1H), 8.34 (dt, *J* = 7.2, 1.0 Hz, 1H), 7.97–7.87 (m, 4H), 7.76 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.61–7.54 (m, 3H), 7.54–7.43 (m, 4H), 6.73 (ddd, *J* = 9.2, 6.3, 0.9 Hz, 1H), 6.66–6.54 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 134.3, 132.2, 131.9, 131.7, 130.4, 129.3 (d, *J* = 28.4 Hz), 128.9, 128.4, 128.0, 127.9, 126.6, 126.2, 125.9, 125.5, 121.7, 119.4, 113.5. HRMS calc. $C_{23}H_{16}N_2$ (M^+): 320.1313, Found: 320.1317. IR(KBr) 698, 769, 1506, 2926 cm^{-1}; mp119-121^{o}C.

1-(3-chlorophenyl)-3-phenylimidazo[1,5-a]pyridine (3i). Isolated yield: 94% (57 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27–8.18 (m, 1H), 7.97–7.91 (m, 1H), 7.86–7.77 (m, 4H), 7.58–7.50 (m, 2H), 7.49–7.42 (m, 1H), 7.39–7.33 (m, 1H), 7.27–7.21 (m, 1H), 6.82 (ddd, *J* = 9.3, 6.4, 0.9 Hz, 1H), 6.63–6.53 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 136.9, 134.8, 130.5, 130.03, 129.97, 129.2, 129.1, 128.4, 128.1, 126.7, 126.5, 124.7, 122.1, 120.6, 118.9, 113.5. HRMS calc. $C_{19}H_{13}ClN_2$ (M^+): 304.0767, Found: 304.0771. IR(KBr) 691, 792, 1316, 1590, 2921cm^{-1}; mp 136-137^{o}C.

3-phenyl-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine (3j)[3c]. Isolated yield: 95% (64 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.2 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 2H), 7.84 (dd, *J* = 8.1, 6.7 Hz, 3H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.56 (t, *J* = 7.4 Hz,

2H), 7.48 (ddd, *J* = 7.4, 3.8, 1.2 Hz, 1H), 6.88 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.63 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.6, 129.3, 128.5, 128.1 (d, *J* = 32.4 Hz), 126.6, 125.8 (q, *J* = 3.7 Hz), 124.6 (d, *J* = 270 Hz), 122.1, 120.9, 118.9, 113.6. MS (EI) *m/z* 338 (M^+); IR(KBr) 697, 853, 1020, 1516, 2927cm^{-1}; mp 184-185°C.

1-(3,5-bis(trifluoromethyl)phenyl)-3-phenylimidazo[1,5-a]pyridine (3k). Isolated yield: 93% (75 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 2H), 8.29 (d, *J* = 7.2 Hz, 1H), 7.94–7.80 (m, 3H), 7.76 (s, 1H), 7.57 (t, *J* = 7.4 Hz, 2H), 7.54–7.44 (m, 1H), 6.97 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.68 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 137.3, 132.1 (q, *J* = 33.0 Hz), 129.6, 129.5, 129.4, 128.8, 128.6, 126.1, 123.7 (d, *J* = 270 Hz), 122.5, 121.9, 119.6 (q, *J* = 4.0 Hz), 118.3, 113.8. HRMS calc. $C_{21}H_{12}F_6N_2$ (M^+): 406.0905, Found: 406.0907. IR(KBr) 698, 859, 1517, 2929cm^{-1}; mp 133-134°C.

1-(3,5-difluorophenyl)-3-phenylimidazo[1,5-a]pyridine (3l). Isolated yield: 92% (56 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.3 Hz, 1H), 7.91–7.74 (m, 3H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.52–7.43 (m, 3H), 6.89 (dd, *J* = 9.0, 6.5 Hz, 1H), 6.71 (tt, *J* = 9.0, 2.3 Hz, 1H), 6.63 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (101 MHz, CDCl3) δ 163.6 (d, *J* = 245 Hz), 163.5 (d, *J* = 245 Hz), 138.6, 138.3 (t, *J* = 10.4 Hz), 129.8, 129.6, 129.3, 129.2, 128.5, 128.4, 122.3, 121.2, 118.6, 113.6, 109.2, 109.1, 109.0, 108.9, 101.6 (t, *J* = 25.6 Hz). HRMS calc. $C_{19}H_{12}F_2N_2$ (M^+): 306.0969, Found: 306.0975. IR(KBr) 698, 1067, 1127, 2927cm^{-1}; mp160-161°C.

1-(3,5-dichlorophenyl)-3-phenylimidazo[1,5-a]pyridine (3m). Isolated yield: 93% (63 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.3 Hz, 1H), 7.84–7.79 (m, 5H), 7.56-7.49 (m, 2H), 7.48-7.45 (m, 1H), 7.24 (t, *J* = 1.9 Hz, 1H), 6.89 (dd, *J* = 9.3, 6.4 Hz, 1H), 6.68–6.58 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.1, 135.3, 129.8, 129.3, 129.2, 129.0, 128.5, 126.1, 124.7, 122.3, 121.2, 118.6, 113.6. HRMS calc. $C_{19}H_{12}Cl_2N_2$ (M^+): 338.0378, Found: 338.0384. IR(KBr) 696, 1091, 1519, 2926cm^{-1}; mp185-186°C.

1,3-diphenylimidazo[1,5-a]quinoline (3n). Isolated yield: 65% (42 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 2H), 7.74–7.65 (m, 3H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.59–7.53 (m, 3H), 7.49 (t, *J* = 7.9 Hz, 3H), 7.33 (dt, *J* = 10.2, 7.5 Hz, 2H), 7.17 (dd, *J* = 11.6, 4.2 Hz, 1H), 7.09 (d, *J* = 9.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 134.2, 133.6, 133.3, 132.5, 129.9, 129.7, 129.1, 128.8, 128.6, 127.7, 127.6, 127.2, 126.5, 125.8, 125.4, 122.4, 117.6, 117.5. HRMS calc. $C_{23}H_{16}N_2$ (M^+): 320.1313, Found: 320.1315. IR(KBr) 696, 843, 1519, 2923 cm^{-1}; mp134-135°C.

1-phenyl-3-o-tolylimidazo[1,5-a]pyridine (3o). Isolated yield: 91% (52 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 2H), 7.87 (d, *J* = 9.3 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.53–7.44 (m, 3H), 7.44-7.37 (m, 2H), 7.36–7.26 (m, 2H), 6.80 (dd, *J* = 9.0, 6.1 Hz, 1H), 6.54 (t, *J* = 6.7 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 137.9, 135.2, 131.2, 130.9, 130.7, 129.7, 129.3, 128.8, 126.7, 126.4, 126.2, 122.0, 119.7, 119.1, 112.9, 19.9. HRMS calc. $C_{20}H_{16}N_2$ (M^+): 284.1313, Found: 284.1317. IR(KBr) 696, 822, 1249, 1360, 1521, 1603, 2918cm^{-1}; mp119-120°C.

1-phenyl-3-m-tolylimidazo[1,5-a]pyridine (3p). Isolated yield: 93% (53 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.55 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.1 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.61 (dd, *J* = 9.0, 6.5 Hz, 1H), 6.40 (t, *J* = 6.8 Hz, 1H), 2.32 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 138.3, 135.1, 131.9, 130.1, 129.7, 129.3, 128.8, 128.8, 127.6, 126.8, 126.5, 125.1, 121.9, 119.7, 119.1, 113.2, 21.5. HRMS calc. $C_{20}H_{16}N_2$ (M^+): 284.1313, Found: 284.1315. IR(KBr) 696, 821, 1250, 1363, 1520, 2916cm^{-1}; mp107-109°C.

1-phenyl-3-p-tolylimidazo[1,5-a]pyridine (3q)[3c]. Isolated yield: 93% (53 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.3 Hz, 1H), 7.97–7.89 (m, 2H), 7.84 (d, *J* = 9.3 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.78 (dd, *J* = 9.2, 6.3 Hz, 1H), 6.57 (t, *J* = 6.8 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 138.3,

135.1, 131.8, 129.7, 128.7, 128.3, 127.6, 127.3, 126.8, 126.5, 121.9, 119.6, 119.1, 113.1, 21.5. MS (EI) *m/z* 284 (M^+); IR(KBr) 696, 1518, 1601, 2915cm^{-1}; mp137-138°C.

3-(4-methoxyphenyl)-1-phenylimidazo[1,5-a]pyridine (3r)[3c]. Isolated yield: 92% (55 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.0 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.82 (d, *J* = 9.3 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.86–6.70 (m, 1H), 6.55 (t, *J* = 6.5 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 138.0, 134.8, 131.5, 130.0, 128.8, 127.4, 127.0, 126.6, 122.4, 121.9, 119.7, 119.3, 114.6, 113.3, 55.5. MS (EI) *m/z* 300 (M^+); IR(KBr) 699, 835, 1169, 1511, 2927cm^{-1}; mp161-162°C.

3-(4-chlorophenyl)-1-phenylimidazo[1,5-a]pyridine (3s)[18]. Isolated yield: 94% (57 mg), yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21-8.18 (d, *J* = 6.6 Hz, 1H), 7.94-7.79 (m, 5H), 7.53-7.45 (m, 4H), 7.33-7.26 (m, 1H), 6.85-6.79 (m, 1H), 6.64-6.60 (t, *J* = 13.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 134.74, 134.65, 132.3, 129.5, 129.3, 128.8, 128.6, 127.9, 126.8, 126.7, 121.5, 119.9, 119.3, 113.6. MS (EI) *m/z* 304 (M^+); IR(KBr) 694, 1089, 1518, 1315, 1598, 2921cm^{-1}; mp169-170°C.

3-(4-fluorophenyl)-1-phenylimidazo[1,5-a]pyridine (3t)[17]. Isolated yield: 91% (52 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.88–7.73 (m, 3H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.25-7.20 (m, 2H), 6.78 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.57 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0 (d, *J* = 249.2 Hz), 137.2, 134.9, 132.1, 130.4 (d, *J* = 8.3 Hz), 128.9, 127.7, 126.9, 126.7, 126.5 (d, *J* = 2 Hz), 121.6, 119.8, 119.3, 116.3 (d, *J* = 21.8 Hz), 113.5. MS (EI) *m/z* 288 (M^+); IR(KBr) 698, 1065, 1126, 2925cm^{-1}; mp167-168°C.

1-phenyl-3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine (3u)[3c]. Isolated yield: 94% (63 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.2 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 2H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 9.3 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.63 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 134.7, 133.8, 132.9, 130.5 (q, *J* = 33 Hz), 128.9, 128.42, 128.36, 127.0, 126.1 (q, *J* = 3.7 Hz), 124.1 (d, *J* = 272.1 Hz), 121.7, 120.4, 119.5, 114.1. MS (EI) *m/z* 338 (M^+); IR(KBr) 697, 1067, 1124, 1167, 1321, 2926cm^{-1}; mp138-139°C.

3-(naphthalen-1-yl)-1-phenylimidazo[1,5-a]pyridine (3v). Isolated yield: 90% (58 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–7.99 (m, 3H), 7.94 (dd, *J* = 12.3, 8.7 Hz, 2H), 7.80 (d, *J* = 7.0 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.68–7.58 (m, 2H), 7.57–7.43 (m, 4H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 9.3, 6.3 Hz, 1H), 6.49 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 135.2, 134.1, 132.0, 131.7, 130.1, 128.9, 128.8, 128.7, 127.3, 127.2, 126.8, 126.5, 126.4, 125.7, 125.5, 122.3, 120.0, 119.0, 112.9. HRMS calc. $C_{23}H_{16}N_2$ (M^+): 320.1313, Found: 320.1319. IR(KBr) 669, 840, 1351, 2921cm^{-1}; mp123-124°C.

3-(furan-2-yl)-1-phenylimidazo[1,5-a]pyridine (3w)[18]. Isolated yield: 63% (33 mg), yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 9.3Hz, 1H), 7.60 (s, 1H), 7.49-7.44 (m, 2H), 7.33-7.31 (m, 1H), 7.08 (s, 1H), 6.85-6.80 (t, *J* = 15.6 Hz, 1H), 6.71-6.66 (t, *J* = 13.2 Hz, 1H), 6.61 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 142.1, 134.7, 132.4, 130.2, 128.7, 127.4, 127.0, 126.7, 123.2, 119.9, 118.9, 113.8, 111.7, 108.7. MS (EI) *m/z* 260 (M^+); IR(KBr) 921, 1520, 1600, 2921cm^{-1}; mp123-124°C.

1-phenyl-3-(pyridin-2-yl)imidazo[1,5-a]pyridine (3x) Isolated yield: 31% (17 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (d, *J* = 7.3 Hz, 1H), 8.69–8.62 (m, 1H), 8.50 (d, *J* = 8.1 Hz, 1H), 8.02–7.94 (m, 2H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.80 (td, *J* = 7.6, 1.5 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.25–7.17 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 148.2, 136.6, 135.1, 135.0,

132.4, 129.3, 128.9, 127.1, 126.9, 126.5, 122.4, 121.8, 121.2, 118.5, 113.9. HRMS calc. $C_{18}H_{14}N_3$ $(M+H)^+$: 272.1188, Found: 272.1192. IR(KBr) 921, 1520, 1600, 2921cm^{-1}; mp100-101°C.

Associated content

The ^1H and ^{13}CNMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

Note: The authors declare no competing financial interest.

Acknowledgments

We are grateful to the Natural Science Foundation of China (21302105) and the financial support from Nanyang Normal University (ZX2015009, ZX2015010).

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