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Synthesis of 1,3-disubstituted imidazo[1,5-*a*]pyridines from amino acids via catalytic decarboxylative intramolecular cyclization

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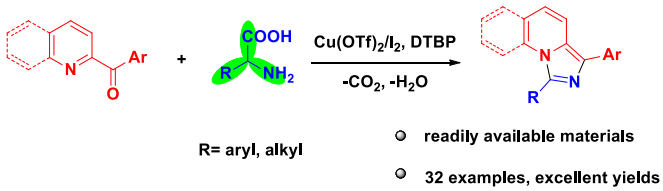
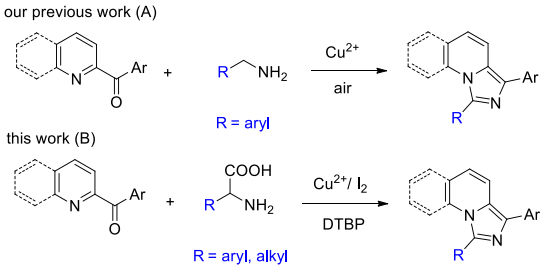


Abstract: A copper/iodine co-catalyzed decarboxylative cyclization of α-amino acids is described. Starting from the readily available amino acids and either 2-benzoylpyridines or 2-benzoylquinolines, 1,3-disubstituted imidazo[1,5-*a*]pyridines and 1,3-disubstituted imidazo[1,5-*a*]quinolines were prepared in excellent yields.

Introduction: Transition-metal catalyzed decarboxylation reactions have attracted much attention for their use in the site-specific introduction of functional groups.[1] Compared to other carboxylic acids, α-amino acids have the advantages of natural abundant, high stability and low cost, which make them extremely promising raw materials for chemical synthesis. Therefore, α-amino acids have been widely used to construct C-C,[2] C-N[3] and C-O[4] bonds via a decarboxylative coupling process. While various decarboxylation reaction of amino acids have been well-studied, new decarboxylative cyclization of α-amino acids for the synthesis of biologically important heterocycles, especially in a catalytic manner, is still highly desirable.

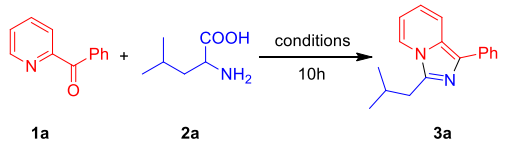
Imidazo[1,5-*a*]pyridine scaffolds are present in various drug-relevant molecules and biologically active agents.[5] Thus, method development for accessing this important structural motif is of high interest. Traditionally, imidazo[1,5-*a*]pyridines were prepared through Vilsmeier-type cyclizations or their variants.[6] Recent efforts on the oxidative cyclization reaction also provided a complementary way to access imidazo[1,5-*a*]pyridines.[7,8] However, most of these methods were ineffective for the construction of 1,3-disubstituted imidazo[1,5-*a*]pyridines.[9] To address this limition, our group recently developed an oxidative amination method to give 1,3-diarylimidazo[1,5-a]pyridine in excellent yields (Scheme 1A).[10] Unfortunately, the complementary 3-alkyl derivatives were not accessible via this oxidative amination process. In continuation of our recent work on decarboxylation reaction of amino acids,[4c] we report herein an efficient decarboxylative cyclization of amino acids for the synthesis of 3-alkyl-1-arylimidazo[1,5-*a*]pyridines (Scheme 1B). To the best of our knowledge, successful example on the synthesis of this type of scaffold is rather limited.[11]



Scheme 1. Our methods for the synthesis of 1,3-disubstituted imidazo[1,5-*a*]pyridines

Results and Discussion: Previous work reported by Li *et al.* has shown that the combination of copper salt with peroxide was effective for the decarboxylation of amino acids.[2a] To identify the best reaction conditions, the decarboxylative cyclization reaction between 2-benzoylpyridine **1a** and leucine **2a** was tested under different oxidative reaction conditions (Table 1). First, the efficiency of different copper salts was screened with molecular iodine as a cocatalyst. The results showed that $Cu(OTf)_2$ was the most efficient catalyst for this reaction (entry 1); while other copper catalysts resulted in a significant drop in yields (entries 2-5). In the absence of copper catalysts, the reaction gave the target product **3a** in 39% yield (entry 6), while only 20% yield of the desired product was obtained in the absence of molecular iodine (entry 7). Subsequently, *n*-Bu_4NI instead of molecular iodine as a catalyst was tested, however, the yield of product **3a** decreased to 51% (entry 8). Then, the influence of different peroxide on this decarboxylative cyclization reaction was investigated. The results revealed that DTBP (di-*t*-butyl peroxide) would be the best choice for this reaction (entries 1 *vs* 9-10). Further assessment of the reaction conditions indicated that toluene was the optimal solvent; while other commonly used solvents gave lower yields (entries 1 *vs* 11-14). By increasing or lowing the reaction temperature, no improvement in yield was observed (entries 15-16).

Table 1 Optimization of the reaction conditions[a]



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

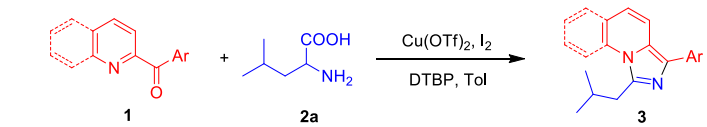
Entry	Cu^{n+}	Oxidant	Solvent	Yield(%)[b]
1	$Cu(OTf)_2$	DTBP	Tol	92
2	$Cu(OAc)_2$	DTBP	Tol	43
3	$CuBr_2$	DTBP	Tol	39
4	$CuCl_2$	DTBP	Tol	35
5	CuI	DTBP	Tol	29
6	-	DTBP	Tol	39
7[c]	$Cu(OTf)_2$	DTBP	Tol	20
8[d]	$Cu(OTf)_2$	DTBP	Tol	51
9	$Cu(OTf)_2$	TBHP	Tol	65
10	$Cu(OTf)_2$	BPO	Tol	56
11	$Cu(OTf)_2$	DTBP	DMF	53
12	$Cu(OTf)_2$	DTBP	Dioxane	88
13	$Cu(OTf)_2$	DTBP	DCE	68
14	$Cu(OTf)_2$	DTBP	CH_3CN	69
15[e]	$Cu(OTf)_2$	DTBP	Tol	87
16[f]	$Cu(OTf)_2$	DTBP	Tol	88

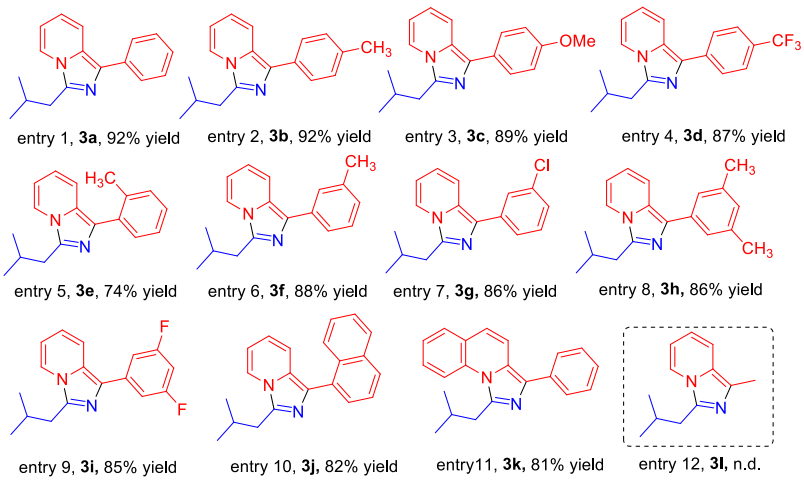
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), copper salt (0.045 mmol), I_2 (0.045 mmol), oxidant (0.75 mmol) in solvent (1 mL), 120 °C , 10h. DTBP= di-*tert*- butyl peroxide; TBHP= *tert*-butyl hydroperoxide; BPO= dibenzoyl peroxide. [b] Isolated yield. [c] no molecular iodine was used. [d] *n*-Bu_4NI was used instead of iodine. [e] the reaction temperature was 130 °C. [f] the reaction temperature was 100 °C.

Having identified the optimal reaction conditions, we next examined the substrate scope of this decarboxylative cyclization reaction by evaluating a variety of 2-benzoylpyridine derivatives **1**. As shown in Table 2, this cyclization reaction is relatively unaffected by the nature of the aryl group, with substrates bearing electron donating or withdrawing functionalities demonstrating excellent efficiency (entries 1-4). However, the *ortho*-substituted aryl group led to a decrease in the yield (entry 5), while *meta*-substituted aryl groups had little influence on the yield (entries 6-9). When aryl group was replaced to the bulky 1-naphthyl group, the decarboxylation reaction furnished the cyclized

product **3j** in 82% yield (entry 10). In addition, when 2-benzoyl quinoline was employed as the substrate, the corresponding product **3k** was obtained in 81% yield (entry 11). However, when 1-(pyridin-2-yl)ethanone was employed as the substrate, no corresponding product was detected (entry 12).

Table 2 The substrate scope of pyridine ketones[a]

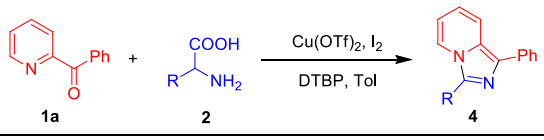


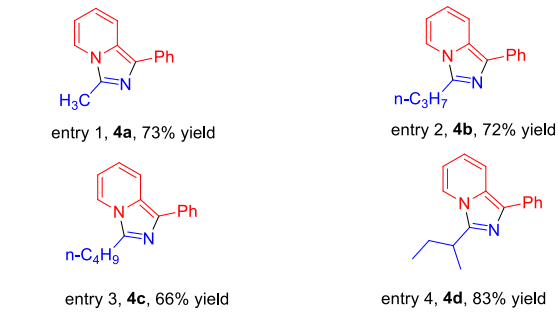


[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), $Cu(OTf)_2$ (0.045 mmol), I_2 (0.045 mmol), DTBP (0.75 mmol) in toluene (1 mL), 120 °C , 10h. [b] Isolated yield.

Under the optimal reaction conditions, we next sought to establish the scope of aliphatic amino acids in this decarboxylative cyclization reaction. As shown in Table 3, a range of linear and branched amino acids were successfully employed in this reaction to give the products **4a**-**4d** in moderate to good yields. For the linear amino acids, alanine and norvaline provided the desired products **4a**-**4b** with similar level of yields (entries 1-2), while the bulky norleucine led to a decrease of the yields (entry 3). For the branched amino acid, isoleucine was also tolerated well under the optimal reaction conditions to give product **4d** in 83% yield (entry 4).

Table 3 The substrate scope of aliphatic amino acids[a]

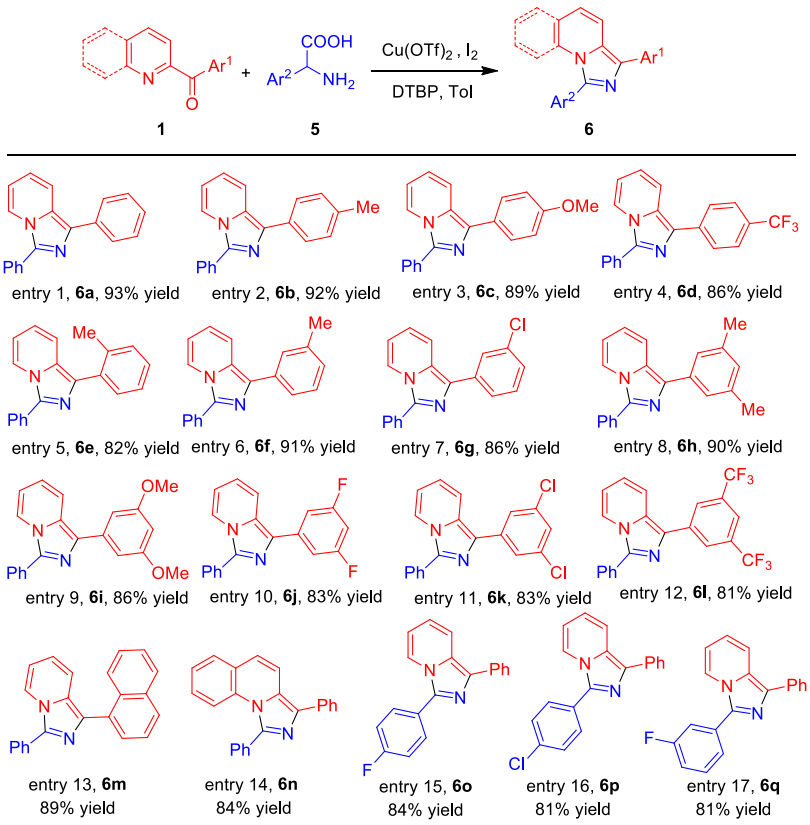




[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.9 mmol), $Cu(OTf)_2$ (0.045 mmol), I_2 (0.045 mmol), DTBP (0.75 mmol) in toluene (1 mL), 120 °C , 10h. [b] Isolated yield.

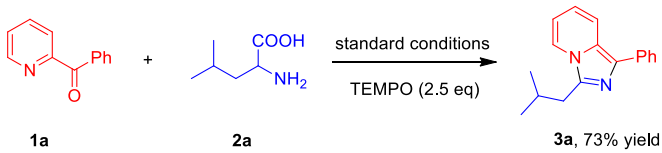
To further extend the utility of this decarboxylative cyclization reaction, we next turned our attention to the reaction of 2-benzoylpyridines with α-aryl-substituted amino acids (Table 4). First, various 2-benzoylpyridines were employed as substrates to react with phenylglycine under the optimal conditions. The results showed that 2-benzoylpyridines were excellent substrates regardless of the electronic nature of the aryl substituents, giving 1, 3-diarylimidazo[1,5-a]pyridines **6a-6m** in good to excellent yields (entries 1-13). Besides, 2-benzoylquinoline was also successfully employed as a substrate to give the corresponding product **6n** in 84% yield (entry 14). Finally, some other α-aryl-substituted amino acids were employed as substrates to react with 2-benzoylpyridine. The results showed that *para*-, and *meta*-halogenated phenylglycines were all compatible with the standard reaction conditions (entries 15-17).

Table 4 The substrate scope of the reaction between 2-benzoylpyridines and phenylglycine derivatives [a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), $Cu(OTf)_2$ (0.045 mmol), I_2 (0.045 mmol), DTBP (0.75 mmol) in toluene (1 mL), 120 °C , 10h. [b] Isolated yield.

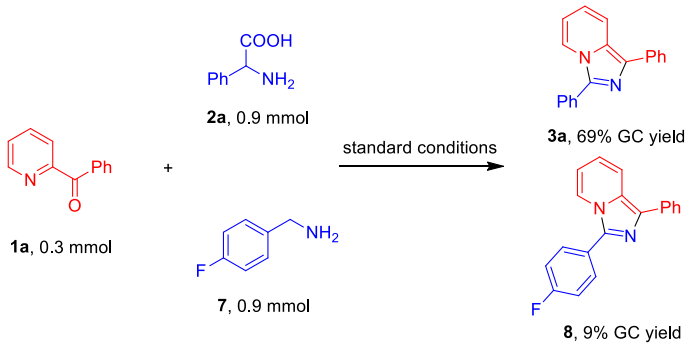
To probe the nature of this decarboxylative cyclization reaction, the radical-trapping reagent (TEMPO) was subjected into the reaction of **1a** with **2a** under the standard conditions (Scheme 2). The desired product **3a** was obtained in 73% yield, suggesting an ionic pathway was most probably involved in this decarboxylation reaction.



1a **2a** **3a**, 73% yield

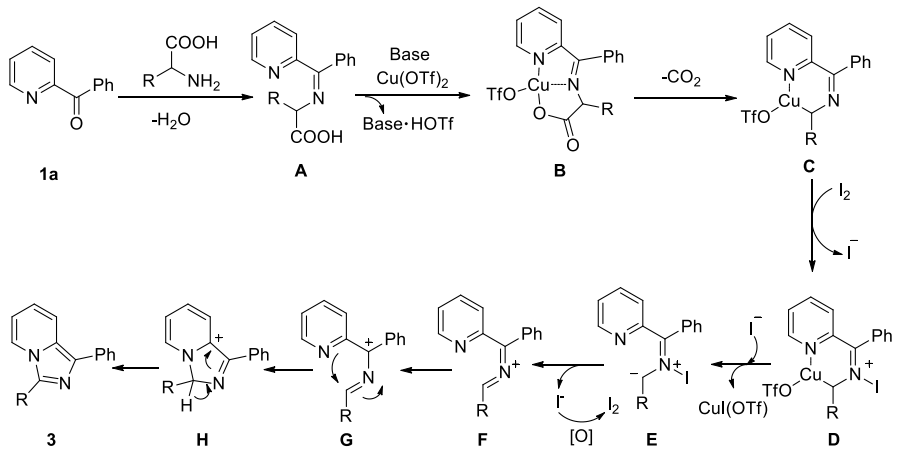
Scheme 2. Control experiment

In our previous work, benzylamine could react with 2-benzoylpyridine to afford imidazo[1,5-*a*]pyridine.[10] To determine whether amine was the intermediate of this reaction, the competitive experiment with phenylglycine and 4-fluorobenzylamine was carried out in the same reaction flask (Scheme 3). It was found that 4-fluorobenzylamine gave the corresponding product **8** in only 9% yield, which suggested that amine was not likely to be the intermediate of this decarboxylation reaction.



Scheme 3. Competitive reaction between phenylglycine and 4-fluorobenzylamine

On the basis of the control experiment and previous reports,[10-14] a plausible mechanism was proposed as shown in Scheme 4. First, the condensation reaction between 2-benzoylpyridine **1a** and amino acid generates imine **A**. The nitrogen source in the reaction mixture (could be any of the pyridine/amine/imine species) acts as a base to deprotonate imine **A** to generate an organic acid anion, which then reacts with copper salt to give copper carboxylate **B**.[12] In the structure of intermediate **B**, two five-membered chelates were formed upon metal binding. Subsequently, intermediate **B** undergoes a decarboxylation reaction to afford intermediate **C**, which then undergoes an oxidative iodination to give intermediate **D**. With the assistance of iodide anion, the copper-carbon bond in intermediate **D** could dissociate to generate azomethine ylide-type intermediate **E**[2a,13]. Then, the elimination of iodide anion furnishes intermediate **F**,[10-11] which could tautomerize to intermediate **G**. Intermediate **G** will not violate the geometric constrains imposed by the intermediate **F**. Finally, the intramolecular amination of intermediate **G** leads to the formation of cyclised intermediate **H**,[14] which then undergoes an oxidative dehydrogenation and rearrangement to yield product **3**.



Scheme 4. A plausible mechanism for the formation of product **3**.

Conclusion: In conclusion, we have developed an efficient copper/iodine cocatalytic system for the decarboxylative cyclization of α-amino acids with 2-benzoylpyridines. The present decarboxylative cyclization reaction not only provided an attractive alternative method for the synthesis of 1,3-diarylimidazo[1,5-*a*]pyridines, but also opened a new route to construct 3-alkyl-1-arylimidazo[1,5-*a*]pyridines, which are difficult to access by the existing methods.

Experimental Section

General methods. NMR spectra were recorded on 300 MHz or 400 MHz NMR spectrometer with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. HRMS was obtained by Electrospray Ionization (ESI) 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 same methods described in our previous report.[10] Amino acids were commercially available and were used without further purification.

General procedure for the synthesis of 1, 3-disubstituted imidazo[1,5-*a*]pyridines (Tables 2-4). To a sealed tube (10 mL) containing a solution of 2-benzoylpyridine **1a** (0.3 mmol) in Tol (1.0 mL) was added $Cu(OTf)_2$ (0.045 mmol), molecular iodine(0.045 mmol), DTBP (0.75 mmol) and amino acids (0.9 mmol) at room temperature. Then, the sealed tube was placed in an oil bath at room temperature. The oil bath was subsequently heated to 120 ˚C. The reaction mixture was stirred at 120 ˚C (oil bath temperature) for 10 hours. 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= 15:1-2:1) to afford the desired product as a yellow solid or pale green oil.

3-isobutyl-1-phenylimidazo[1,5-*a*]pyridine (3a)[11]. Isolated yield: 92% (69 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 2H), 7.78 – 7.76 (m, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.28 – 7.24 (m, 1H), 6.74 – 6.70 (m, 1H), 6.56 (t, *J* = 6.8 Hz, 1H), 2.94 (d, *J* = 7.2 Hz, 2H), 2.31 – 2.23 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 135.3, 130.1, 128.7, 126.7, 126.4, 126.2, 121.1, 119.1, 118.7, 112.5, 28.7, 20.7, 14.1. HRMS calc. $C_{17}H_{19}N_2$ ($M+H^+$): 251.1548, Found: 251.1551.

3-isobutyl-1-(*p*-tolyl)imidazo[1,5-*a*]pyridine (3b). Isolated yield: 92% (73 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 8.4 Hz, 4H), 7.26 (s, 1H), 7.24 (s, 1H), 6.66 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.51 (t, *J* = 6.7 Hz, 1H), 2.90 (d, *J* = 7.3 Hz, 2H), 2.38 (s, 3H), 2.30

– 2.21 (m,1H), 1.01 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 135.8, 132.5, 130.3, 129.4, 126.6, 126.1, 121.1, 119.1, 118.2, 112.3, 35.6, 27.9, 22.7, 21.3. HRMS calc. $C_{18}H_{21}N_2$ ($M+H^+$): 265.1705, Found: 265.1704.

3-isobutyl-1-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine (3c). Isolated yield: 89% (75 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.71 (dd, *J* = 12.6, 8.3 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.72 – 6.62 (m, 1H), 6.53 (t, *J* = 6.7 Hz, 1H), 3.85 (s, 3H), 2.93 (d, *J* = 7.3 Hz, 2H), 2.33 – 2.20 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 138.2, 130.2, 128.2, 127.9, 125.8, 121.0, 119.1, 118.0, 114.3, 112.3, 55.4, 35.6, 28.0, 22.7. HRMS calc. $C_{18}H_{21}N_2O$ ($M+H^+$): 281.1654, Found: 281.1653.

3-isobutyl-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]pyridine (3d). Isolated yield: 87% (83 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.78 (t, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 6.80 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.61 (t, *J* = 6.7 Hz, 1H), 2.93 (d, *J* = 7.3 Hz, 2H), 2.33 – 2.26 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.9, 128.5, 127.6 (d, $^2J_{CF}$ = 31 Hz), 127.3, 126.3, 125.7 (q, $^3J_{CF}$ = 4 Hz), 124.6 (d, $^1J_{CF}$ = 270 Hz), 121.5, 119.9, 118.7, 112.7, 35.6, 27.9, 22.7. HRMS calc. $C_{18}H_{17}F_3N_2$ ($M+H^+$): 319.1422, Found: 319.1424.

3-isobutyl-1-(*o*-tolyl)imidazo[1,5-*a*]pyridine (3e). Isolated yield: 74% (59 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 1H), 7.45 – 7.43 (m, 1H), 7.36 (d, *J* = 9.1 Hz, 1H), 7.30 (d, *J* = 4.2 Hz, 1H), 7.25 – 7.23 (m, 2H), 6.63 (t, *J* = 6.6 Hz, 1H), 6.54 (t, *J* = 6.6 Hz, 1H), 2.92 (d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.32 – 2.24 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 137.4, 134.0, 130.8, 130.4, 127.3, 127.1, 125.6, 120.8, 119.0, 117.7, 112.3, 35.6, 27.7, 22.7, 20.6. HRMS calc. $C_{18}H_{21}N_2$ ($M+H^+$): 265.1705, Found: 265.1706.

3-isobutyl-1-(*m*-tolyl)imidazo[1,5-*a*]pyridine (3f). Isolated yield: 88% (70 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, *J* = 7.3 Hz, 2H), 7.70 (s, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.68 (dd, *J* = 9.1, 6.5 Hz, 1H), 6.53 (t, *J* = 6.8 Hz, 1H), 2.91 (d, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 2.25 – 2.22 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 135.2, 130.4, 128.6, 127.5, 127.1, 126.4, 123.7, 121.2, 119.2, 118.5, 112.4, 35.6, 28.0, 22.7, 21.7. HRMS calc. $C_{18}H_{21}N_2$ ($M+H^+$): 265.1705, Found: 265.1704.

1-(3-chlorophenyl)-3-isobutylimidazo[1,5-*a*]pyridine (3g). Isolated yield: 86% (73 mg), pale green foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 1H), 7.75 (dd, *J* = 11.2, 7.2 Hz, 3H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 6.76 (dd, *J* = 9.2, 6.3 Hz, 1H), 6.58 (t, *J* = 6.8 Hz, 1H), 2.91 (d, *J* = 7.3 Hz, 2H), 2.27 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.2, 134.7, 129.9, 128.7, 126.9, 126.4, 126.1, 124.5, 121.4, 119.4, 118.8, 112.6, 35.6, 27.9, 22.8. HRMS calc. $C_{17}H_{18}N_2Cl$ ($M+H^+$): 285.1159, Found: 285.1158.

1-(3,5-dimethylphenyl)-3-isobutylimidazo[1,5-*a*]pyridine (3h). Isolated yield: 86% (72 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, *J* = 9.4 Hz, 2H), 7.47 (s, 2H), 6.91 (s, 1H), 6.72 – 6.63 (m, 1H), 6.52 (t, *J* = 6.7 Hz, 1H), 2.91 (d, *J* = 7.3 Hz, 2H), 2.38 (s, 6H), 2.30 – 2.21 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.2, 135.2, 130.5, 128.1, 126.4, 124.5, 121.1, 119.3, 118.3, 112.4, 35.6, 28.0, 22.7, 21.5. HRMS calc. $C_{19}H_{23}N_2$ ($M+H^+$): 279.1861, Found: 279.1860.

1-(3,5-difluorophenyl)-3-isobutylimidazo[1,5-*a*]pyridine (3i). Isolated yield: 85% (73 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 4 Hz, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.41 – 7.38 (m, 2H), 6.83 – 6.79 (m, 1H), 6.70-6.64 (m, 1H), 6.61 (t, *J* = 4 Hz, 1H), 2.90

(d, *J* = 7.3 Hz, 2H), 2.33 – 2.20 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, *J* = 244 Hz), 163.5 (d, *J* = 244 Hz), 139.04, 138.7 (t, *J* = 10.4 Hz), 127.9 (t, *J* = 3.2 Hz), 127.2, 121.6, 120.0, 118.6, 112.7, 108.8 (d, *J* = 25 Hz), 108.8 (d, *J* = 11 Hz), 101.1 (t, *J* = 26 Hz), 35.6, 27.9, 22.8. HRMS calc. $C_{17}H_{17}F_2N_2$ ($M+H^+$): 287.1360, Found: 287.1359.

3-isobutyl-1-(naphthalen-1-yl)imidazo[1,5-*a*]pyridine (3j). Isolated yield: 82% (74 mg), pale green foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.1 Hz, 1H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.39 (d, *J* = 9.2 Hz, 1H), 6.67 – 6.58 (m, 1H), 6.54 (t, *J* = 6.7 Hz, 1H), 2.97 (d, *J* = 7.3 Hz, 2H), 2.32 (td, *J* = 13.7, 6.9 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 134.3, 132.2, 132.1, 129.7, 128.2, 127.9, 127.7, 127.6, 126.6, 126.0, 125.7, 125.4, 120.9, 119.0, 118.1, 112.5, 35.7, 27.8, 22.8. HRMS calc. $C_{21}H_{21}N_2$ ($M+H^+$): 301.1705, Found: 301.1707.

1-isobutyl-3-phenylimidazo[1,5-*a*]quinoline (3k). Isolated yield: 81% (72 mg), pale green foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 2H), 7.61 (dd, *J* = 13.0, 8.6 Hz, 2H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 9.5 Hz, 1H), 3.32 (d, *J* = 7.0 Hz, 2H), 2.45 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.11 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 135.0, 133.2, 132.3, 128.7, 128.5, 127.8, 127.4, 126.7, 126.3, 126.0, 124.8, 121.1, 117.6, 116.6, 41.1, 26.6, 22.7. HRMS calc. $C_{21}H_{21}N_2$ ($M+H^+$): 301.1705, Found: 301.1704.

3-methyl-1-phenylimidazo[1,5-*a*]pyridine (4a)[11]. Isolated yield: 73% (45 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.74 (dd, *J* = 9.1, 6.5 Hz, 1H), 6.59 (t, *J* = 6.7 Hz, 1H), 2.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 135.0, 130.0, 128.8, 126.6, 126.5, 126.3, 121.1, 119.1, 118.7, 112.6, 12.6. HRMS calc. $C_{14}H_{13}N_2$ ($M+H^+$): 209.1079, Found: 209.1081.

1-phenyl-3-propylimidazo[1,5-*a*]pyridine (4b). Isolated yield: 72% (51 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.78 – 7.71 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.27-7.23 (m, 1H), 6.72 – 6.68 (m, 1H), 6.54 (t, *J* = 6.6 Hz, 1H), 2.99 (t, *J* = 7.6 Hz, 2H), 1.94 – 1.82 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 135.3, 130.1, 128.7, 126.7, 126.5, 126.2, 121.1, 119.1, 118.7, 112.5, 28.7, 20.7, 14.1. HRMS calc. $C_{16}H_{17}N_2$ ($M+H^+$): 237.1392, Found: 237.1394.

3-butyl-1-phenylimidazo[1,5-*a*]pyridine (4c). Isolated yield: 66% (50 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.75 (dd, *J* = 13.1, 8.2 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.20 (m, 1H), 6.71 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.55 (t, *J* = 6.7 Hz, 1H), 3.06 – 3.01 (m, 2H), 1.88 – 1.80 (m, 2H), 1.53 – 1.44 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.4, 130.1, 128.8, 126.7, 126.5, 126.2, 121.1, 119.1, 118.7, 112.5, 29.4, 26.6, 22.8, 14.0. HRMS calc. $C_{17}H_{19}N_2$ ($M+H^+$): 251.1548, Found: 251.1550.

3-(sec-butyl)-1-phenylimidazo[1,5-*a*]pyridine (4d). Isolated yield: 83% (62 mg), pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.8 Hz, 2H), 7.74 (t, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.22 (m, 1H), 6.76 – 6.59 (m, 1H), 6.51 (t, *J* = 6.7 Hz, 1H), 3.11 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.02 (dt, *J* = 14.3, 7.2 Hz, 1H), 1.79 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.45 (d, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 135.5, 130.1, 128.7, 126.8, 126.4, 126.1, 121.0, 119.1, 118.6, 112.3, 33.1, 28.3, 18.3, 12.2. HRMS calc. $C_{17}H_{19}N_2$ ($M+H^+$): 251.1548, Found: 251.1550.

1,3-diphenylimidazo[1,5-*a*]pyridine (6a)[10,11,15]. Isolated yield: 93% (75 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.15 (m, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.82 (dd, *J* = 9.1, 2.0 Hz, 3H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.49 – 7.40 (m, 3H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.83 –

6.71 (m, 1H), 6.60 – 6.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 135.0, 132.0, 130.2, 129.1, 128.9, 128.8, 128.4, 127.8, 126.9, 126.6, 121.8, 119.8, 119.2, 113.3. MS (EI) *m/z* 270 (M^+); mp 111-112°C.

3-phenyl-1-(*p*-tolyl)imidazo[1,5-*a*]pyridine (6b)[10,11]. Isolated yield: 92% (78 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.2Hz, 1H), 7.84 – 7.80 (m, 5H), 7.54 – 7.50 (m, 2H), 7.46 – 7.42 (m, 1H), 7.28 – 7.25 (m, 2H), 6.77 – 6.73 (m, 1H), 6.56 – 6.52 (m, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 136.2, 132.1, 132.0, 130.2, 129.4, 129.0, 128.8, 128.4, 127.4, 126.7, 121.7, 119.4, 119.3, 113.2, 21.3. MS (EI) *m/z* 284 (M^+); mp 133-134°C.

1-(4-methoxyphenyl)-3-phenylimidazo[1,5-*a*]pyridine (6c)[10,11]. Isolated yield: 89% (80 mg), yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 8.20 (d, *J* = 7.2 Hz, 1H), 7.87 – 7.76 (m, 5H), 7.55 – 7.41 (m, 3H), 7.03 – 7.00 (d, *J* = 8.4Hz, 2H), 6.76 – 6.71 (m, 1H), 6.56 – 6.52 (m, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 137.8, 132.0, 130.2, 129.0, 128.7, 128.3, 128.1, 127.7, 127.1, 121.6, 119.2, 119.2, 114.2, 113.2, 55.4. MS (EI) *m/z* 300 (M^+); mp 115-116°C.

3-phenyl-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]pyridine (6d)[9a,10,11]. Isolated yield: 86% (87 mg), yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.5 Hz, 1H), 8.05 (d, *J* = 8.1Hz, 2H), 7.86 – 7.81 (m, 3H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.44 (m, 3H), 6.89 – 6.84 (m, 1H), 6.60 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.7, 131.4, 130.3, 130.0, 129.2, 128.5, 128.4, 128.2 (d, *J* = 40 Hz), 126.6, 125.7 (q, *J* = 4 Hz), 124. 6 (d, *J* = 270 Hz), 122.2, 121.0, 118.8, 113.6. MS (EI) *m/z* 338 (M^+); mp 184-185°C.

3-phenyl-1-(*o*-tolyl)imidazo[1,5-*a*]pyridine (6e)[10,11]. Isolated yield: 82% (70 mg), greenyellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.25 (m, 1H), 7.87 – 7.84 (m, 2H), 7.53 – 7.49 (m, 3H), 7.44 – 7.39 (m, 2H), 7.33 – 7.31 (m, 1H), 7.27 – 7.25 (m, 2H), 6.71 – 6.67 (m, 3H), 6.57-6.53 (m, 3H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.40, 137.39, 133.6, 132.8, 130.8, 130.4, 129.9, 128.6, 128.5, 128.1, 127.4, 125.6, 121.4, 119.1, 118.8, 113.2, 20.6. MS (EI) *m/z* 284 (M^+); mp 118-119°C.

3-phenyl-1-(*m*-tolyl)imidazo[1,5-*a*]pyridine (6f)[10,11]. Isolated yield: 91% (77 mg), greenyellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.21 (d, *J* = 7.2 Hz, 1H), 7.85 – 7.80 (m, 4H), 7.72 – 7.70 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.47 – 7.44 (m, 1H), 7.38 – 7.33 (t, *J* = 15.3 Hz,1H), 7.13 – 7.10 (d, *J* = 7.5 Hz, 1H), 6.80 – 6.74 (m, 1H), 6.60 – 6.63 (m, 1H), 2.44 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.1, 134.8, 132.2, 130.2, 129.0, 128.8, 128.6, 128.4, 127.6, 127.4, 123.8, 121.7, 119.6, 119.3, 113.2, 21.6. MS (EI) *m/z* 284 (M^+); mp 111-112°C.

1-(3-chlorophenyl)-3-phenylimidazo[1,5-*a*]pyridine (6g)[10,11]. Isolated yield: 86% (78 mg), greenyellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 – 8.24 (d, *J* = 7.2 Hz, 1H), 7.96 (s, 1H), 7.85 – 7.82 (m, 4H), 7.57 – 7.36 (m, 4H), 7.26 (s, 1H), 6.88 – 6.83 (m, 1H), 6.64 – 6.59 (t, *J* = 13.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.9, 134.7, 130.4, 129.9, 129.9, 129.1, 129.0, 128.4, 128.0, 126.6, 126.4, 124.6, 121.9, 120.4, 118.8, 113.4. HRMS calc. $C_{19}H_{14}ClN_2$ ($M+H^+$): 305.0846, Found: 305.0848; mp 131-132°C.

1-(3,5-dimethylphenyl)-3-phenylimidazo[1,5-*a*]pyridine (6h)[10]. Isolated yield: 90% (80 mg), greenyellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.21 (d, *J* = 7.2 Hz, 1H), 7.86 – 7.83 (m, 3H), 7.56 – 7.44 (m, 5H), 6.95 (s, 1H), 6.80 – 6.75 (m, 1H), 6.59 – 6.54 (m, 1H), 2.40 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 138.0, 134.8, 132.3, 130.2, 129.0, 128.8, 128.4, 127.6, 124.7, 121.7, 119.4, 119.4, 113.2, 21.5. MS (EI) *m/z* 298 (M^+); mp 125-126°C.

1-(3,5-dimethoxyphenyl)-3-phenylimidazo[1,5-*a*]pyridine (6i)[10]. Isolated yield: 86% (85 mg), greenyellow 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. MS (EI) *m/z* 330 (M^+); mp 178-179°C.

1-(3,5-difluorophenyl)-3-phenylimidazo[1,5-*a*]pyridine (6j)[10]. Isolated yield: 83% (76 mg), greenyellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.25 (d, *J* = 7.2 Hz, 1H), 7.84 – 7.82 (m, 3H), 7.58 – 7.50 (m, 5H), 6.93 – 6.88 (m, 1H), 6.75 – 6.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (d, *J* = 245 Hz), 163.5 (d, *J* = 245 Hz), 138.5, 138.3, 129.8, 129.6, 129.2, 129.1, 128.4, 128.3, 122.2, 121.0, 118.6, 113.5, 109.1, 109.0, 108.9, 108.8, 101.4 (t, *J* = 25.5 Hz). MS (EI) *m/z* 306 (M^+); mp 164-165°C.

1-(3,5-dichlorophenyl)-3-phenylimidazo[1,5-*a*]pyridine (6k)[10]. Isolated yield: 83% (84 mg), greenyellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.25 (d, *J* = 7.2 Hz, 1H), 7.85 – 7.81 (m, 4H), 7.58 – 7.48 (m, 4H), 6.93 – 6.88 (m, 1H), 6.67 – 6.62 (t, *J* = 13.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.0, 135.3, 129.8, 129.2, 129.1, 129.0, 128.4, 126.0, 124.6, 122.2, 121.1, 118.6, 113.5. MS (EI) *m/z* 339 (M^+); mp 188-189°C.

1-(3,5-bis(trifluoromethyl)phenyl)-3-phenylimidazo[1,5-*a*]pyridine (6l)[10]. Isolated yield: 81% (98 mg), greenyellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 2H), 8.31 – 8.28 (d, *J* = 6.9 Hz, 1H), 7.85 – 7.83 (m, 3H), 7.75 (s, 1H), 7.60 – 7.48 (m, 3H), 7.00 – 6.94 (m, 1H), 6.71 – 6.66 (t, *J* = 13.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 137.3, 132.0 (q, *J* = 33 Hz), 129.6, 129.4, 129.2, 128.7, 128.5, 126.1, 123.6 (d, *J* = 277 Hz), 122.4, 121.8, 119.4 (q, *J* = 3.8 Hz), 118.2, 113.7. MS (EI) *m/z* 406 (M^+); mp 134-135°C.

1-(naphthalen-1-yl)-3-phenylimidazo[1,5-*a*]pyridine (6m)[10]. Isolated yield: 89% (85 mg), greenyellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 – 8.36 (m, 1H), 8.31 – 8.29 (d, *J* = 7.2 Hz, 1H), 7.92 – 7.85 (m, 4H), 7.75 – 7.73 (m, 1H), 7.58 – 7.41 (m, 7H), 6.71 – 6.66 (m, 1H), 6.59 – 6.54 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 134.2, 132.1, 131.8, 131.7, 130.3, 129.3, 129.0, 128.7, 128.2, 127.7, 128.6, 126.1, 125.8, 125.4, 121.6, 119.2, 119.2, 113.4. MS (EI) *m/z* 320 (M^+); mp 118-119°C.

1,3-diphenylimidazo[1,5-*a*]quinoline (6n)[10]. Isolated yield: 84% (81 mg), greenyellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.4 Hz, 2H), 7.72 – 7.64 (m, 3H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.51 (m, 3H), 7.47 (t, *J* = 7.9 Hz, 3H), 7.36 – 7.28 (m, 2H), 7.16 (dd, *J* = 11.6, 4.2 Hz, 1H), 7.07 (d, *J* = 9.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 134.2, 133.7, 133.4, 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, 117.8, 117.5. MS (EI) *m/z* 320 (M^+); mp 136-137°C.

3-(4-fluorophenyl)-1-phenylimidazo[1,5-*a*]pyridine (6o)[10,11]. Isolated yield: 84% (73 mg), greenyellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.87 – 7.74 (m, 3H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.26 – 7.20 (m, 2H), 6.78 (dd, *J* = 9.0, 6.5 Hz, 1H), 6.57 (t, *J* = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, *J* = 250 Hz), 137.3, 135.0, 132.1, 130.4 (d, *J* = 8.3 Hz), 128.9, 127.8, 126.9, 126.7, 126.50 (d, *J* = 3.2 Hz), 121.6, 119.8, 119.3, 116.2 (d, *J* = 22 Hz), 113.5. HRMS calc. $C_{19}H_{14}FN_2$ (M^+): 289.1141, Found: 289.1139; mp 168-169 °C.

3-(4-chlorophenyl)-1-phenylimidazo[1,5-*a*]pyridine (6p)[10,11,16]. Isolated yield: 81% (74 mg), greenyellow 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, 134.7, 134.7, 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^+); mp 172-173°C.

3-(3-fluorophenyl)-1-phenylimidazo[1,5-*a*]pyridine (6q). Isolated yield: 81% (70 mg), greenyellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.1 Hz, 1H), 7.92 (d, *J* = 7.4 Hz, 2H), 7.85 (d, *J* = 9.2 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 9.5 Hz, 1H), 7.48 (dt, *J* = 13.5, 7.9 Hz, 3H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.20 – 7.08 (m, 1H), 6.87 – 6.73 (m, 1H), 6.61 (t, *J* = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, *J* = 250 Hz), 136.8 (d, *J* = 3 Hz), 134.9, 132.5, 132.4 (d, *J* = 8 Hz), 130.8 (d, *J* = 8 Hz), 128.9, 128.1, 126.9, 126.8, 123.8 (d, *J* = 3 Hz), 121.7, 120.1, 119.4, 115.8 (d, *J* = 21 Hz), 115.4 (d, *J* = 23 Hz), 113.8. HRMS calc. $C_{19}H_{14}FN_2$ ($M+H^+$): 289.1141, Found: 289.1140; mp 150-151°C.

Associated content

The ^{1}H 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.

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