# Copper-Promoted Annulation of Terminal Alkynes with 2-Aminopyridines to Assemble 2-Halogenated Imidazo[1,2-*a*]pyridines

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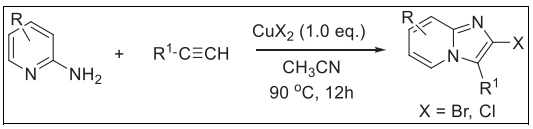


Copper-promoted annulation reactions of terminal alkynes with 2-aminopyridines have been developed for the synthesis of 2-halogenated imidazo[1,2-*a*]pyridines using copper halide as the halogen source. A variety of substrates survived under the reaction conditions and gave the desired products in good yields. This reaction features advantages such as easily available starting materials, broad substrate scope, and mild reaction conditions.

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## INTRODUCTION

In the past decades, imidazo[1,2-*a*]pyridines have exhibited significant biological activities [1–6] as well as broad application in material field [7–9], and much attention has been drawn to their syntheses [10,11]. Among these compounds, halogenated imidazo[1,2-*a*] pyridines are important synthetic target molecules and can be transformed into various functionalized imidazo[1,2-*a*]pyridines *via* Heck coupling [12,13], Sonogashira coupling [14,15], Suzuki coupling [16,17], Stille coupling [18,19], and so on.

The annulation reactions of haloalkynes [20], alkynoic acids [21], and terminal alkynes [22,23] with 2-aminopyridines are efficient synthetic strategies to 2-haloimidazo[1,2-*a*]pyridines. Compared with haloalkynes (Scheme 1a) and alkynoic acids (Scheme 1b), terminal alkynes are more attractive substrates because they are commercially available and do not need to be prepared before use. However, up to now, only the synthesis of 2-iodoimidazo[1,2-*a*]pyridines had been reported from terminal alkynes with molecule iodine as the halogen source (Scheme 1c and d). Hence, more general synthetic protocols to transform alkynes to 2-haloimidazo[1,2-*a*] pyridines are highly desired.

Recently, copper-catalyzed oxidative coupling of terminal alkynes with various nucleophilic reagents to form carbon–carbon bond or carbon–heteroatom bond has been developed rapidly for the preparation of organic molecules [24–31]. Encouraged by this, we reported herein a convenient synthesis of 2-bromo and 2-chloroimidazo[1,2-*a*]pyridines from terminal alkynes using copper halide as both catalyst and halogen source (Scheme 1e). In this reaction, haloalkynes were first generated *in situ via* oxidative coupling of terminal alkynes with copper halide and then reaction with 2-aminopyridines to form the target product 2-haloimidazo[1,2-*a*]pyridines.

## RESULT AND DISCUSSION

At the beginning of our work, we chose 2-aminopyridine **1a** and phenylacetylene **2a** as the model reactants to optimize the reaction conditions. Initially, we heated **1a** (1.5 mmol), **2a** (0.5 mmol), and $CuBr_2$ (0.5 mmol) in DCE at 90°C for 12 h, and we isolated product **3a** in 53% yield (Table 1, entry 1). Other solvents were then tried, and acetonitrile performed the best (Table 1, entries 2–5). With acetonitrile as solvent, we employed CuBr in place of $CuBr_2$ into this reaction but only detected little amount of **3a** (Table 1, entry 6). Adding 1.5 equiv of $CuBr_2$ also did not give better result (Table 1, entry 7). In addition, carrying out the reaction without $CuBr_2$ or under Ar atmosphere, no **3a** was formed (Table 1, entries 8–9). On the basis of this, we investigated the effect of different oxidants. The result showed that under 1 atm of $O_2$, **3a** was formed only in 65% yield (Table 1, entry 10). Other oxidants including TBHP, DTBP, or $K_2S_2O_8$ did not lead to **3a** in high yield as well

**Scheme 1.** Synthesis of 2-haloimidazo[1,2-*a*]pyridines.

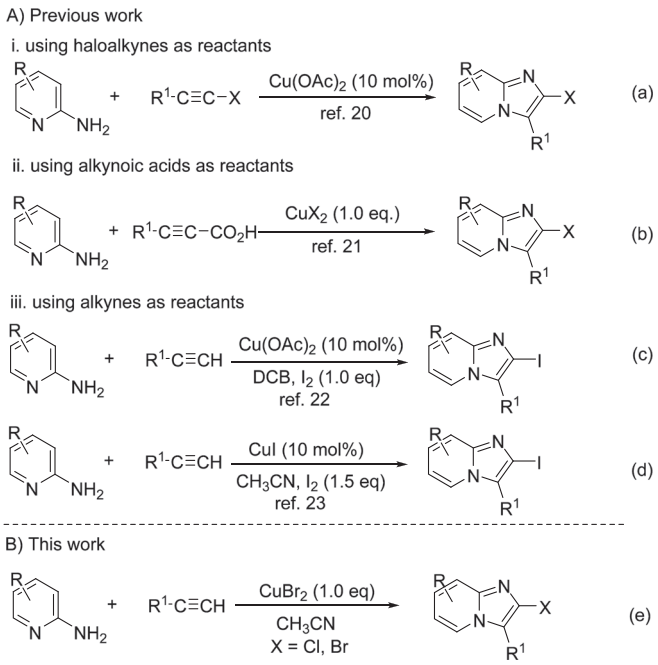
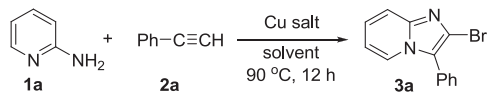



**Table 1**

Optimization of reaction conditions.[a]




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

| Entry | Solvent | Copper (equiv) | Oxidant (equiv) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | DCE | $CuBr_2$ (1) | Air | 53 |
| 2 | DMF | $CuBr_2$ (1) | Air | 48 |
| 3 | $C_6H_6$ | $CuBr_2$ (1) | Air | 62 |
| 4 | Dioxane | $CuBr_2$ (1) | Air | 51 |
| 5 | $CH_3CN$ | $CuBr_2$ (1) | Air | 78 |
| 6 | $CH_3CN$ | CuBr (1) | Air | Trace |
| 7 | $CH_3CN$ | $CuBr_2$ (1.5) | Air | 78 |
| 8 | $CH_3CN$ | None | Air | 0 |
| 9[c] | $CH_3CN$ | $CuBr_2$ (1) | None | 0 |
| 10 | $CH_3CN$ | $CuBr_2$ (1) | $O_2$ | 65 |
| 11 | $CH_3CN$ | $CuBr_2$ (1) | TBHP (2) | 62 |
| 12 | $CH_3CN$ | $CuBr_2$ (1) | DTBP (2) | 25 |
| 13 | $CH_3CN$ | $CuBr_2$ (1) | $K_2S_2O_8$ | Trace |
| 14[d] | $CH_3CN$ | Cu $(OTf)_2$ | Air | 72 |
| 15[d] | $CH_3CN$ | Cu $(OAc)_2$ | Air | 68 |
| 16[e] | $CH_3CN$ | $CuBr_2$ (1) | Air | 53 |
| 17[f] | $CH_3CN$ | $CuBr_2$ (1) | Air | 75 |

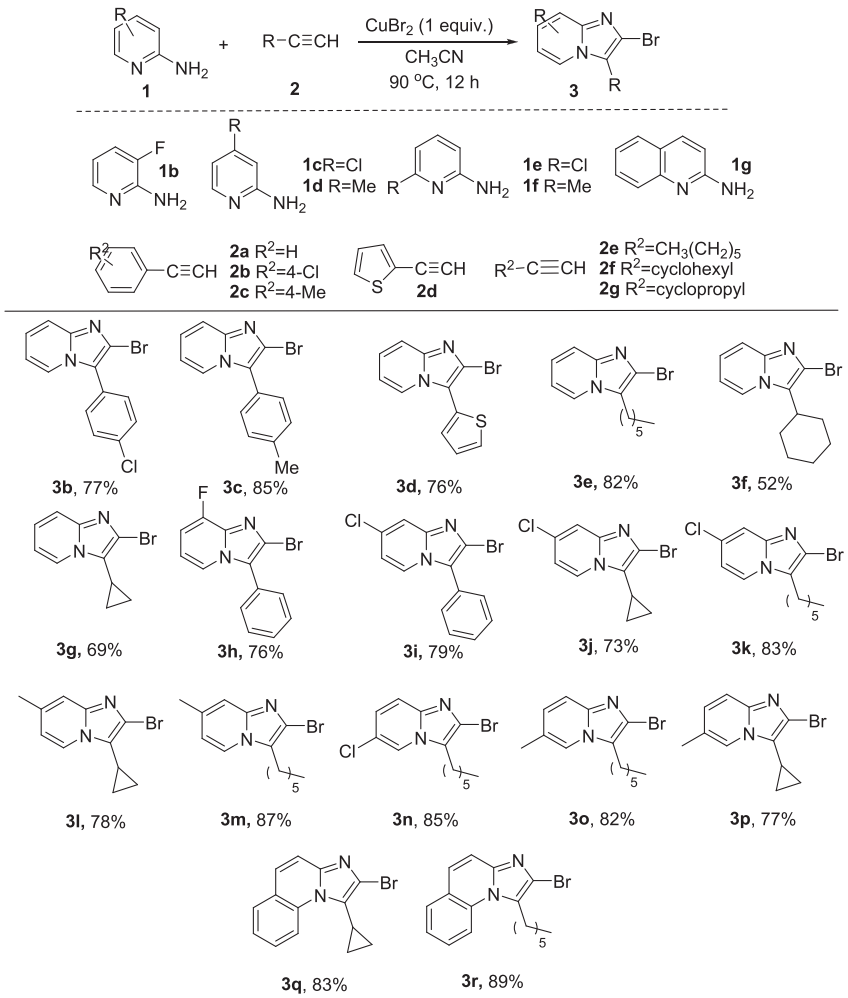
[a]Conditions: **1a** (1.5 mmol), **2a** (0.5 mmol), copper salt, oxidant, heating in solvent (5 mL) at 90°C for 12 h.
[b]Isolated yield.
[c]Under Ar.
[d]Adding 1 equiv of KBr.
[e]Heating at 70°C.
[f]Heating at 110°C.

(Table 1, entries 11–13). Then we tried to use 1 equiv of KBr as the bromine source in combination with catalytic amount of Cu $(OTf)_2$ or Cu $(OAc)_2$ but found that the yield decreased slightly (entries 14–15). Finally, we changed the reaction temperature but did not get positive result (Table 1, entries 16–17). Hence, the optimal reaction conditions were heating 1.5 mmol of **1a**, 0.5 mmol of **2a**, and 1.0 equiv of $CuBr_2$ in acetonitrile at 90°C for 12 h.

On the basis of this, we then screened the scope of reactants (Table 2). Initially, we investigate the kind of terminal alkynes by employing 2-aminopyridine **1a** as the substrate. It was found that a variety of terminal alkynes **2** reacted with **1a** well, giving 2-bromoimidazo[1,2-*a*] pyridines **3** in good yields. For examples, alkynes **2b**–**2d** attached with phenyl and thienyl substituents formed products **3b**–**3d** in 76–85% yields, while alkynes **2e**–**2g** with aliphatic groups gave product **3e**–**3g** in 52–82% yields. Next, we examined the kind of substituted 2-aminopyridines by reacting them with aromatic or aliphatic alkynes. It showed that 2-aminopyridines **1b** and **1c** reacted with aromatic alkynes well under the optimal conditions, affording products **3h**–**3i** in high yields. Similarly, the reaction of 2-aminopyridines **1c**–**1f** with aliphatic alkynes proceeded smoothly and resulted in product **3j**–**3p** in 73–87% yields. For annulated 2-aminopyridine **1g**, products **3q** and **3r** were isolated in excellent yields as well. The structures of all products were confirmed by NMR and HRMS, and the spectra

**Table 2**

Synthesis of 2-bromoimidazo[1,2-*a*]pyridines.[a,b]




[a]Conditions: **1** (1.5 mmol), **2** (0.5 mmol), $CuBr_2$ (0.5 mmol), heating in $CH_3CN$ (5 mL) at 90°C for 12 h in a sealed tube.
[b]Isolated yield.

data of known products are in accordance with our previous report [13].

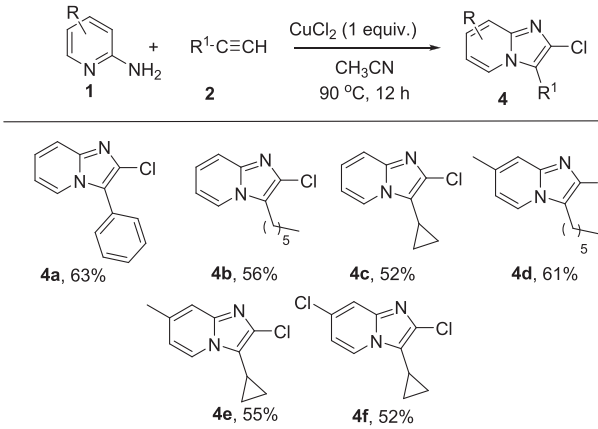
Subsequently, we tried to prepare chlorinated products by this protocol (Table 3). Pleasingly, by heating the mixture of 2-aminopyridine **1a**, aromatic or aliphatic alkynes **2,** and 1.0 equiv of $CuCl_2$ in acetonitrile at 90°C for 12 h, we obtained 2-chloroimidazo[1,2-*a*]pyridines **4a**–**4c** in good yields. Additionally, substituted 2-aminopyridines under the same conditions afforded products **4d**–**4f** in 52% to 61% yields.

For demonstrating the utility of these halogenated imidazo[1,2-*a*]pyridines, we attempted to synthesize 2-phenylimidazo[1,2-*a*]pyridine **5** from **3a** *via* Suzuki reaction (Scheme 2). As we expected, by heating **3a**, phenyl boronic acid (1.5 equiv) at 100°C under Ar atmosphere with 2 mol% of $PdCl_2(PPh_3)_2$ as catalyst and 2.0 equiv of $K_3PO_4$ as base, we obtained product **5** in 86% yield (Scheme 2).

To shed light on the mechanism, several control experiments were carried out. First, employing bromoalkyne **6** as substrate to react with **1a** under optimal conditions, we obtained **3a** in 66% yield (Scheme 3a). In addition, exposing **2a** with $CuBr_2$ in acetonitrile with base formed alkyne dimerization product **7** along with bromoalkyne **6** (Scheme 3b). These results illustrated that bromoalkyne **6** was the possible reaction intermediate. Second, no reaction occurred when exposing C2-unsubstituted imidazo[1,2-*a*]pyridine **8** with

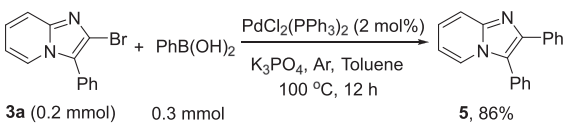
**Table 3**

Synthesis of 2-chloroimidazo[1,2-*a*]pyridines.[a,b]

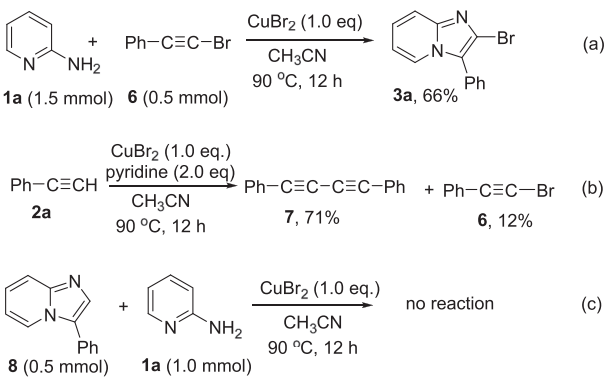



[a]Conditions: **1** (1.5 mmol), **2** (0.5 mmol), $CuCl_2$ (0.5 mmol), heating in $CH_3CN$ (5 mL) at 90°C for 12 h in a sealed tube.
[b]Isolated yield.

**Scheme 2.** Synthesis of compound **5**.



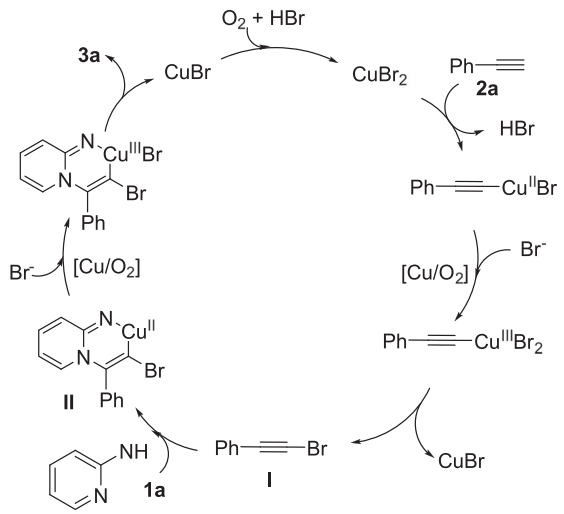

**Scheme 3.** Control experiments.




2-aminopyridine and $CuBr_2$ (Scheme 3c). This illustrated that the reaction should not proceed *via* bromination of intermediate **8**.

Based on our experimental results and previous literatures [22,23], a possible mechanism was suggested (Scheme 4). At first, oxidative coupling of alkyne **2a** with copper bromide led to bromoalkyne **I** *in situ*. Then, intermediate **I** underwent oxidative cyclization with 2-aminopyridine **1a**, forming Cu(II) intermediate **II**. Finally, intermediate **II** occurred tandem oxidation and reductive elimination, dispelling CuBr and giving the final product **3a**. In this reaction process, CuBr could be converted into $CuBr_2$ by the oxidation of molecular oxygen.

**Scheme 4.** Possible mechanism for the formation of **3a**.




## CONCLUSION

In conclusion, we have developed a copper bromide-promoted annulation reaction of 2-aminopyridines with terminal alkynes to assemble 2-halogenated imidazo[1,2-*a*]pyridines. By this protocol, 2-brominated or 2-

chlorinated products were generated in good yields. The reaction features advantages such as easily available starting materials, broad substrate scope, and mild reaction conditions.

## EXPERIMENTAL

**General.** $^1$H NMR spectra were measured on 400 MHz. $^{13}$C NMR spectra were measured on 100 MHz. HRMS (ESI) data were obtained in the electron impact (EI) mode.

**General preparation procedure of 3.** 2-Aminopyridine **1a** (1.5 mmol, 3 equiv), terminal alkynes **2** (0.5 mmol, 1 equiv), $CuBr_2$ (0.5 mmol, 1 equiv), and $CH_3CN$ (5 mL) were mixed into a sealed tube and heated at 90°C for 12 h. Then the reaction mixture was separated by flash column chromatography on silica gel to give product **3**.

***2-Bromo-3-phenylimidazo[1,2-a]pyridine (3a).*** White solid, mp 150–151°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.78–6.81 (m, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.45–7.49 (m, 1H), 7.53–7.60 (m, 5H), 8.11 (d, *J* = 6.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.6, 129.6, 129.2, 129.0, 127.6, 125.1, 123.2, 122.2, 117.3, 113.0. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{10}BrN_2$ $[M + H]^+$ 273.0027, found 273.0022.

***2-Bromo-3-(4-chlorophenyl)imidazo[1,2-a]pyridine (3b).*** White solid, mp 178–180°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.81–6.83 (m, 1H), 7.48–7.51 (m, 1H), 7.54–7.60 (m, 5H), 8.07 (d, *J* = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.9, 134.6, 131.8, 129.6, 129.4, 129.3, 129.2, 126.7, 123.6, 120.1, 116.2, 114.7. HRMS (ESI) *m*/*z* calcd for $C_{13}H_9BrClN_2$ $[M + H]^+$ 306.9638, found 306.9646.

***2-Bromo-3-p-tolylimidazo[1,2-a]pyridine (3c).*** Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 6.77–7.80 (m, 1H), 7.19–7.23 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 9.2 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.5, 139.1, 129.9, 129.5, 125.0, 124.5, 123.2, 122.3, 122.1, 117.2, 112.9, 21.5. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{12}BrN_2$ $[M + H]^+$ 287.0184, found 287.0193.

***2-Bromo-3-(thiophen-2-yl)imidazo[1,2-a]pyridine (3d).*** Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.86 (td, *J* = 6.8, 1.2 Hz, 1H), 723–7.25 (m, 2H), 7.35 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.55–7.60 (m, 2H), 8.23 (d, *J* = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 145.0, 129.2, 127.9, 127.8, 127.6, 125.6, 124.1, 123.7, 117.2, 113.3. HRMS (ESI) *m*/*z* calcd for $C_{11}H_8BrN_2S$ $[M + H]^+$ 278.9592, found 278.9583.

***2-Bromo-3-hexylimidazo[1,2-a]pyridine (3e).*** White solid, mp 115–116°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.26–1.39 (m, 6H), 1.59–1.67 (m, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 6.84 (td, *J* = 6.8, 0.8 Hz, 1H), 7.16 (td, *J* = 8.0, 0.8 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 6.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.1, 123.8, 122.8,. 121.9, 117.2, 112.6, 31.5, 28.9, 27.1, 22.6, 14.1. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{18}BrN_2$ $[M + H]^+$ 281.0653, found 281.0642.

***2-Bromo-3-cyclohexylimidazo[1,2-a]pyridine (3f).*** White solid, mp 93–95°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.39–1.46 (m, 3H), 1.81–2.02 (m, 7H), 3.00–3.06 (m, 1H), 6.81 (td, *J* = 6.8, 0.8 Hz, 1H), 7.14 (td, *J* = 6.8, 0.8 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 8.06 (d, *J* = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.1, 124.9, 123.7, 123.2, 120.1, 117.4, 112.3, 35.1, 29.6, 26.8, 25.9. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{16}BrN_2$ $[M + H]^+$ 279.0497, found 279.0488.

***2-Bromo-3-cyclopropylimidazo[1,2-a]pyridine (3g).*** White solid, mp 69–71°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 0.77–0.80 (m, 2H), 1.04–1.08 (m, 2H), 1.67–1.71 (m, 1H), 6.81 (t, *J* = 6.8 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 9.2 Hz, 1H), 8.14 (d, *J* = 6.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.8, 124.4, 123.2, 122.4, 121.3, 116.8, 112.4, 5.57, 3.3. HRMS (ESI) *m*/*z* calcd for $C_{10}H_{10}BrN_2$ $[M + H]^+$ 237.0027, found 237.0038.

***2-Bromo-8-fluoro-3-phenylimidazo[1,2-a]pyridine (3h).*** White solid, mp 143–145°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.72–6.77 (m, 1H), 6.92–6.97 (m, 1H), 7.49–7.58 (m, 5H), 7.94 (d, *J* = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.8 (d, *J* = 253 Hz), 137.2 (d, *J* = 28 Hz), 129.7, 129.4, 129.3, 127.2, 124.0, 122.3, 119.6 (d, *J* = 5 Hz), 112.1 (d, *J* = 7 Hz), 107.9, 107.7. HRMS (ESI) *m*/*z* calcd for $C_{13}H_9BrFN_2$ $[M + H]^+$ 290.9933, found 290.9928.

***2-Bromo-7-chloro-3-phenylimidazo[1,2-a]pyridine (3i).*** White solid, mp 127–129°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.48–7.60 (m, 6H), 8.03 (d, *J* = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.2, 131.7, 129.6, 129.3, 129.2, 127.0, 123.5, 122.9, 122.6, 116.1, 114.6. HRMS (ESI) *m*/*z* calcd for $C_{13}H_9BrClN_2$ $[M + H]^+$ 306.9638, found 306.9647.

***2-Bromo-7-chloro-3-cyclopropylimidazo[1,2-a]pyridine (3j).*** White solid, mp 166–167°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 0.83–0.87 (m, 2H), 1.13–1.17 (m, 2H), 1.72–1.76 (m, 1H), 6.87 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.51 (d, *J* = 1.2 Hz, 1H), 8.14 (d, *J* = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.4, 131.3, 123.5, 123.2, 121.8, 115.8, 114.2, 5.7, 3.2. HRMS (ESI) *m*/*z* calcd for $C_{10}H_9BrClN_2$ $[M + H]^+$ 270.9638, found 270.9647.

***2-Bromo-7-chloro-3-hexylimidazo[1,2-a]pyridine (3k).*** White solid, mp 78–79°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 0.87–0.90 (m, 3H), 1.29–1.38 (m, 6H), 1.60–1.66 (m, 2H), 2.87–2.91 (m, 2H), 6.87 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.58 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.5, 131.1, 123.2, 122.5, 121.8, 115.8, 114.5, 31.5, 28.8, 27.0, 23.2, 22.5, 14.0. HRMS

(ESI) *m/z* calcd for $C_{13}H_{17}BrClN_2$ $[M + H]^+$ 315.0264, found 315.0251.

***2-Bromo-3-cyclopropyl-7-methylimidazo[1,2-a]pyridine (3l).*** White solid, mp 160–161°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.82–0.84 (m, 2H), 1.10–1.12 (m, 2H), 1.70–1.75 (m, 1H), 2.40 (s, 3H), 6.70 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.27 (s, 1H), 8.08 (d, *J* = 7.2 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 144.2, 135.6, 122.5, 121.9, 120.7, 115.3, 115.1, 21.3, 5.6, 3.3. HRMS (ESI) *m/z* calcd for $C_{11}H_{12}BrN_2$ $[M + H]^+$ 251.0184, found 251.0171.

***2-Bromo-3-hexyl-7-methylimidazo[1,2-a]pyridine (3m).*** White solid, mp 57–59°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.29–1.36 (m, 6H), 1.59–1.63 (m, 2H), 2.39 (s, 3H), 2.87 (t, *J* = 7.6 Hz, 2H), 6.67 (d, *J* = 7.2 Hz, 1H), 7.28 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 144.5, 134.8, 122.0, 121.3, 121.1, 115.6, 115.1, 31.5, 28.8, 27.2, 23.3, 22.6, 21.2, 14.0. HRMS (ESI) *m/z* calcd for $C_{14}H_{20}BrN_2$ $[M + H]^+$ 295.0810, found 295.0816.

***2-Bromo-6-chloro-3-hexylimidazo[1,2-a]pyridine (3n).*** White solid, mp 55–56°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.88–0.91 (m, 3H), 1.31–1.40 (m, 6H), 1.61–1.65 (m, 2H), 2.87–2.91 (m, 2H), 7.15 (dd, *J* = 9.2 Hz, 1H), 7.50 (d, *J* = 9.6 Hz, 1H), 7.93 (s, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 142.4, 125.4, 122.7, 122.5, 121.3, 120.7, 117.5, 31.5, 28.8, 26.9, 23.3, 22.6, 14.0. HRMS (ESI) *m/z* calcd for $C_{13}H_{17}BrClN_2$ $[M + H]^+$ 315.0264, found 315.0276.

***2-Bromo-3-hexyl-6-methylimidazo[1,2-a]pyridine (3o).*** White solid, mp 77–78°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.87–0.91 (m, 3H), 1.30–1.40 (m, 6H), 1.61–1.64 (m, 2H), 2.35 (s, 3H), 2.85–2.89 (m, 2H), 7.01 (dd, *J* = 9.2 Hz, 1H), 7.43 (d, *J* = 9.2 Hz, 1H), 7.65 (s, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 143.1, 127.0, 122.3, 121.5, 121.2, 120.5, 116.4, 31.5, 28.8, 27.0, 23.3, 22.6, 18.4, 14.1. HRMS (ESI) *m/z* calcd for $C_{14}H_{20}BrN_2$ $[M + H]^+$ 295.0810, found 295.0803.

***2-Bromo-3-cyclopropyl-6-methylimidazo[1,2-a]pyridine (3p).*** White solid, mp 147–148°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.84–0.85 (m, 2H), 1.12–1.14 (m, 2H), 1.69–1.76 (m, 1H), 2.37 (s, 3H), 7.05 (d, *J* = 9.2 Hz, 1H), 7.42 (d, *J* = 9.2 Hz, 1H), 7.98 (s, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 142.9, 127.6, 122.2, 121.9, 121.0, 116.2, 18.4, 5.6, 3.4. HRMS (ESI) *m/z* calcd for $C_{11}H_{12}BrN_2$ $[M + H]^+$ 251.0184, found 251.0177.

***2-Bromo-1-cyclopropylimidazo[1,2-a]quinoline (3q).*** White solid, mp 142–143°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.02–1.05 (m, 2H), 1.29–1.32 (m, 2H), 2.13–2.27 (m, 1H), 7.38–7.47 (m, 3H), 7.56–7.59 (m, 1H), 7.75 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.94 (d, *J* = 8.4 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 143.1, 134.2, 129.0, 128.0, 126.7, 125.8, 124.7, 124.4, 122.9, 117.4, 116.6, 10.3, 8.3. HRMS (ESI) *m/z* calcd for $C_{14}H_{12}BrN_2$ $[M + H]^+$ 287.0184, found 287.0172.

***2-Bromo-1-hexylimidazo[1,2-a]quinoline (3r).*** White solid, mp 57–58°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.88–0.92 (t, *J* = 7.2 Hz, 3H), 1.32–1.36 (m, 4H), 1.47–1.49 (m, 2H), 1.71–1.78 (m, 2H), 3.26 (t, *J* = 7.6 Hz, 2H), 7.42–7.47 (m, 3H), 7.58–7.63 (m, 1H), 7.76 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 143.5, 133.8, 129.4, 128.5, 126.3, 126.0, 124.8, 124.4, 122.5, 116.9, 115.7, 31.5, 28.8, 28.2, 27.0, 22.6, 14.1. HRMS (ESI) *m/z* calcd for $C_{17}H_{20}BrN_2$ $[M + H]^+$ 331.0810, found 331.0802.

**General preparation procedure of 4.** 2-Aminopyridine **1a** (1.5 mmol, 3 equiv), terminal alkynes **2** (0.5 mmol, 1 equiv), $CuCl_2$ (0.5 mmol, 1 equiv), and $CH_3CN$ (5 mL) were mixed into a sealed tube and heated at 90°C for 12 h. Then the reaction mixture was separated by flash column chromatography on silica gel to give product **4**.

***2-Chloro-3-phenylimidazo[1,2-a]pyridine (4a).*** Colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 6.83 (t, *J* = 6.8 Hz, 1H), 7.23–7.27 (m, 1H), 7.47–7.49 (m, 1H), 7.54–7.61 (m, 5H), 8.16 (d, *J* = 7,2 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 143.2, 129.3, 129.2, 128.9, 128.8, 127.2, 125.2, 123.2, 117.3, 113.0. HRMS (ESI) *m/z* calcd for $C_{13}H_{10}ClN_2$ $[M + H]^+$ 229.0533, found 229.0530.

***2-Chloro-3-hexylimidazo[1,2-a]pyridine (4b).*** Colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.30–1.37 (m, 6H), 1.60–1.68 (m, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 6.86 (td, *J* = 6.8, 0.8 Hz, 1H), 7.18 (td, *J* = 6.8, 0.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 6.8 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 142.8, 133.4, 123.9, 122.8, 119.2, 117.2, 112.6, 31.5, 28.9, 27.0, 22.7, 22.6, 14.1. HRMS (ESI) *m/z* calcd for $C_{13}H_{18}ClN_2$ $[M + H]^+$ 237.1159, found 237.1159.

***2-Chloro-3-cyclopropylimidazo[1,2-a]pyridine (4c).*** White solid, mp 65–67°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.76–0.80 (m, 2H), 1.03–1.07 (m, 2H), 1.68–1.71 (m, 1H), 6.83 (t, *J* = 7.2 Hz, 1H), 7.15 (td, *J* = 7.2, 0.8 Hz, 1H), 7.44 (d, *J* = 9.2 Hz, 1H), 8.12 (d, *J* = 6.8 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 142.3, 134.0, 124.5, 123.3, 119.0, 116.8, 112.5, 5.3, 2.8. HRMS (ESI) *m/z* calcd for $C_{10}H_{10}ClN_2$ $[M + H]^+$ 193.0533, found 193.0542.

***2-Chloro-3-hexyl-7-methylimidazo[1,2-a]pyridine (4d).*** Colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.26–1.37 (m, 6H), 1.60–1.64 (m, 2H), 2.40 (s, 3H), 2.87 (t, *J* = 7.6 Hz, 2H), 6.68 (d, *J* = 6.8 Hz, 1H), 7.27 (s, 1H), 7.75 (d, *J* = 6.8 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 143.1, 135.0, 132.7, 122.1, 118.5, 115.6, 115.2, 31.5, 28.8, 27.1, 22.6, 22.5, 21.3, 14.0. HRMS (ESI) *m/z* calcd for $C_{14}H_{20}ClN_2$ $[M + H]^+$ 251.1315, found 251.1326.

***2-Chloro-3-cyclopropyl-7-methylimidazo[1,2-a]pyridine (4e).*** White solid, mp 140–142°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.82–0.83 (m, 2H), 1.09–1.11 (m, 2H), 1.73–1.76 (m, 1H), 2.41 (s, 3H), 6.72 (d, *J* = 6.8 Hz, 1H), 7.28 (s, 1H), 8.06 (d, *J* = 7.2 Hz, 1H). $^{13}C$ NMR (100 MHz,

$CDCl_3$) δ 142.7, 135.8, 133.6, 118.4, 115.3, 115.2, 21.3, 5.3, 2.8. HRMS (ESI) *m/z* calcd for $C_{11}H_{12}ClN_2$ $[M + H]^+$ 207.0689, found 207.0695.

***2,7-Dichloro-3-cyclopropylimidazo[1,2-a]pyridine (4f).*** White solid, mp 147–148°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.83–0.85 (m, 2H), 1.12–1.14 (m, 2H), 1.73–1.77 (m, 1H), 6.88 (d, $J$ = 7.2 Hz, 1H), 7.50 (s, 1H), 8.11 (d, $J$ = 7.2 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 142.0, 134.8, 131.4, 123.6, 119.5, 115.7, 114.3, 5.4, 2.7. HRMS (ESI) *m/z* calcd for $C_{10}H_9Cl_2N_2$ $[M + H]^+$ 227.0143, found 227.0155.

**Procedure for the preparation of 5.** Imidazo[1,2-*a*] pyridine **3a** (0.2 mmol), phenyl boronic acid (0.3 mmol), $PdCl_2(PPh_3)_2$ (0.004 mmol), and $K_3PO_4$ (0.4 mmol) were mixed in 2.0 mL of toluene and heated at 100°C under Ar atmosphere for 12 h. After completion of the reaction, the mixture was cooled and separated by flash column chromatography on silica gel to afford product **5**.

***2,3-Diphenylimidazo[1,2-a]pyridine (5).*** White solid, mp 151–152°C. $^1H$ NMR (400 MHz, $CDCl_3$) δ 6.68–6.72 (m, 1H), 7.15–7.29 (m, 4H), 7.43–7.52 (m, 5H), 7.66–7.69 (m, 3H), 7.93 (dd, $J$ = 7.2, 1.2 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 144.7, 142.3, 134.1, 130.6, 129.7, 129.4, 128.8, 128.2, 128.0, 127.4, 124.6, 123.2, 121.0, 117.4, 112.2. HRMS (ESI) *m/z* calcd for $C_{19}H_{15}N_2$ $[M + H]^+$ 271.1235, found 271.1247.

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