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Cu-Pybox catalyzed synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines from 2-aminopyridines and propargyl alcohol derivatives

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ABSTRACT

A highly efficient cascade sequence for syntheses of 2,3-disubstituted imidazo[1,2-*a*]pyridines with exclusive regioselectivity in moderate to excellent yields has been developed. This cascade was initiated through propargylation of 2-aminopyridines at pyridine-nitrogen with propargyl alcohol derivatives using Cu(II)-Pybox as catalyst and followed by an intramolecular cyclization and isomerization. Besides 2-aminopyridine, less reactive 2-aminopyrimidine, 2-aminopyrazine and 3-aminopyridazine were also suitable in this cascade.

1. Introduction

Imidazo[1,2-*a*]pyridine is a well-known privileged structural motif present in various biologically active and pharmaceutically important compounds.[1] In particular, imidazo[1,2-*a*]pyridine moiety is also a core structure of several marketed drugs, including Zolpidem, Zolimidine, Olprinone, Alpidem, Necopidem and Saripidem (Fig. 1).

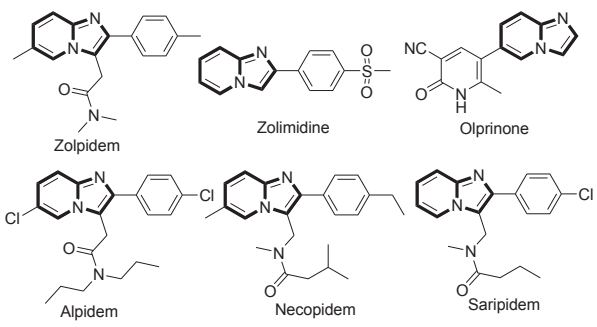

Fig. 1. Drugs containing an imidazo[1,2-*a*]pyridine moiety.

Because of the utilities of imidazo[1,2-*a*]pyridines, in the past decade tremendous efforts have been devoted to the investigation into the construction of imidazo[1,2-*a*]pyridines with different substitute patterns from either 2-aminopyridines or unfunctionalized pyridines.[2–4] These efforts have led to the discovery of various approaches toward privileged imidazo[1,2-*a*]pyridine structure. However, it is notable that a majority these methods require harsh reaction conditions, e.g., high temperature, and the use of polar solvents of high boiling point such as DMF and DMSO. Harsh conditions will limit the use of reaction components bearing sensitive functionalities, while the use of high boiling point solvents makes work-up a tedious job. Therefore, straightforward construction of the imidazo[1,2-*a*]pyridine moiety from easily available start materials under mild conditions is still highly desirable.

On the other hand, recently propargylic alcohols bearing a terminal acetylenic group and their derivatives are frequently used in propargylation with carbon-, nitrogen- or oxygen-based nucleophiles catalyzed by thiolate-bridged diruthenium complexes or complexes of copper salts and various bidentate or tridentate ligands.[5] When well-designed bis-nucleophiles were employed as reaction components, the propargylation at one nucleophilic site and following intramolecular cyclization between alkyne functionality and the other nucleophilic site rendered the preparation of various cyclic or bicyclic compounds in the presence of ruthenium-

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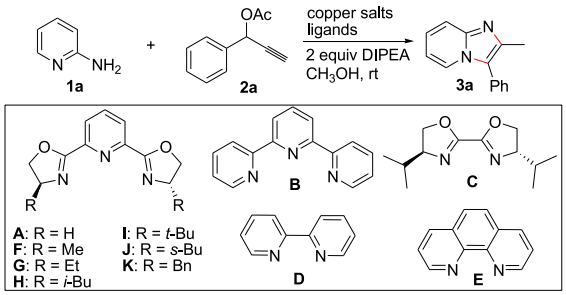
or copper-based catalysts.[6] Considering that 2-aminopyridine has two potential nucleophilic nitrogen atoms, the exo-cyclic amino nitrogen and the pyridine nitrogen, we surmised that the catalytic reaction between 2-aminopyridine and propargyl alcohol derivatives would lead to 2,3-disubstituted imidazo[1,2-*a*]pyridines in a cascade manner. 2-Aminopyridine is commercially available in both quantity and diversity, while propargyl alcohol bearing terminal acetylenic group can be prepared easily from ethynylmagnesium bromide and corresponding aldehyde. Furthermore, the catalytic reaction between propargyl alcohol derivatives bearing terminal acetylenic group and various nucleophiles usually takes place smoothly under relatively mild conditions.[5,6] Very recently, Jiang et al. disclosed a similar catalytic system, wherein the reactions were performed with catalytic amount of copper salt without any ligand. However, high temperature and high loading of copper salts were required to secure high yield. Furthermore, the regioselectivity in Jiang and co-workers' catalytic system was different to that of ours.[7] Therefore, successful implementation of our new strategy would lead to general and straightforward preparation of imidazo[1,2-*a*]pyridines under mild conditions.

2. Results and discussion

We commenced our investigation with the reaction between 2-aminopyridine (**1a**) and 1-phenylprop-2-yn-1-yl acetate (**2a**) promoted by a combination of CuI (5 mol %) and an achiral Pybox (**A**, 6 mol %) at 20 °C with methanol as the solvent and DIPEA as the base (Table 1, entry 1). Despite the fact that **1a** has two potential nucleophilic nitrogen atoms, to our delight the initial propargylation step occurred exclusively at pyridine nitrogen to afford 2-methyl-3-phenylimidazo[1,2-*a*]pyridine (**3a**) as the sole product in excellent yield after cyclization and isomerization.[8] Surprisingly, 2,2′:6′,2″-terpyridine (**B**), a type of tridentate N-donor ligands similar to Pybox was totally ineffective in this reaction (entry 2). As for bidentate N-donor ligands screened, ligand **C** derived from valinol and diethyl oxalate delivered the desired **3a** in a rather modest yield of 35% (entry 3), while combination of CuI with easily available bipyridine or 1,10-phenanthroline failed to promote this reaction (entries 4–5). Other Pybox ligands derived from chiral amino alcohols were also examined, and found to be inferior to ligand **A**, possibly due to the steric hindrance of substituents on oxazoline moiety (entries 6–11).

Next, various copper salts were examined. CuBr and CuCl worked well to afford **3a** in yields comparable to that of CuI (entries 12–13). $Cu(CH_3CN)_4PF_6$, $Cu(CH_3CN)_4BF_4$, and $Cu(CH_3CN)_4ClO_4$ were less efficient than simple copper(I) halogenides, as a dramatic drop of the yield was observed for reactions with this type of copper salts (entries 14–16 vs entries 1, 12–13). Replacement of copper(I) salts with copper(II) salts, led to an obvious increase in the yield, and copper(II) acetylacetonate proved to be the best, affording **3a** in highest yield of 94% (entries 17–18). Efforts to further improve the performance of this reaction by changing the base or the solvent were unsuccessful, as no better results were obtained (Table 2).

Table 1
Survey of copper salts and ligands for cyclization between **1a** and **2a**[a]



Entry	Ligand	Copper salts	Time (h)	Yield (%)[b]
1	**A**	CuI	6	84
2	**B**	CuI	18	—[c]
3	**C**	CuI	18	40
4	**D**	CuI	18	—[c]
5	**E**	CuI	18	—[c]
6	**F**	CuI	6	80
7	**G**	CuI	6	78
8	**H**	CuI	6	83
9	**I**	CuI	6	40
10	**J**	CuI	6	78
11	**K**	CuI	6	73
12	**A**	CuBr	6	78
13	**A**	CuCl	6	82
14	**A**	$Cu(CH_3CN)_4PF_6$	6	67
15	**A**	$Cu(CH_3CN)_4ClO_4$	6	41
16	**A**	$Cu(CH_3CN)_4BF_4$	6	63
17	**A**	$Cu(OTf)_2$	6	89
18	**A**	$Cu(acac)_2$	6	94

[a] General conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Copper salt (5 mol %), ligand (6 mol %), and DIPEA (2 equiv) in methanol (1.5 mL) at rt.
[b] Yield referred to isolated pure **3a**.
[c] No formation of **3a** was observed as shown by TLC. $Cu(acac)_2$: copper(II) acetylacetonate.

Table 2
Screening of bases and solvents for cyclization between **1a** and **2a**[a]

Entry	Solvent	Base	Time (h)	Yield (%)[b]
1	MeOH	Et_3N	6	70
2	MeOH	DMAP	18	—[c]
3	MeOH	DBU	18	—[c]
4	MeOH	Cs_2CO_3	18	—[c]
5	EtOH	DIPEA	6	78
6	DCM	DIPEA	18	—[c]
7	THF	DIPEA	18	—[c]
8	Toluene	DIPEA	18	—[c]

[a] General conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $Cu(acac)_2$ (5 mol %), ligand **A** (6 mol %), and base (2 equiv) in methanol (1.5 mL) at rt.
[b] Yield referred to isolated pure **3a**.
[c] No formation of **3a** was observed as shown by TLC.

With optimized reaction condition in hand (Table 1, entry 18), we set out to explore the scope of the reaction concerning different substituents on the pyridine ring of **1**. As shown in Fig. 2, remarkable dependence of the reactivity of 2-aminopyridine on the electronic nature of the substituents on the pyridine ring was observed. 2-Aminopyridines with electron-donating groups, such as methyl or methoxy group performed very well to afford cyclized products in excellent yields (87–92%) in relatively shorter reaction time of 6 h (**3b**–**d**, **3f**). However, when aminopyridine substrates with electron-withdrawing groups, such as chloro, bromo and trifluoromethyl group, were employed, longer reaction time of 18 h was required to secure complete conversion of start material, with the yields ranged from 50% to 74% (**3g**–**j**, **3l**–**m**). Notably, 2-aminopyridines with substituents at C(3), C(4) or C(5), all participated well to afford the desired products, but derivatives with either electron-donating or electron-withdrawing substituents at C(6) did not afford the expected product even after longer reaction time (**3e**, **3k**). This is possibly due to the steric hindrance of substituent at C(6) preventing the approach of the nucleophilic site toward electrophilic site of allenylidene complexes in situ generated from propargyl alcohol derivatives.[5,6] Similar phenomena was also reported by other research groups for reactions between C(6)-substituted 2-aminopyridine with other coupling components.[3r,s]

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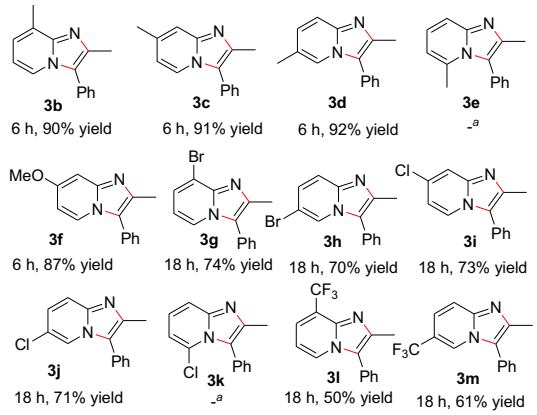
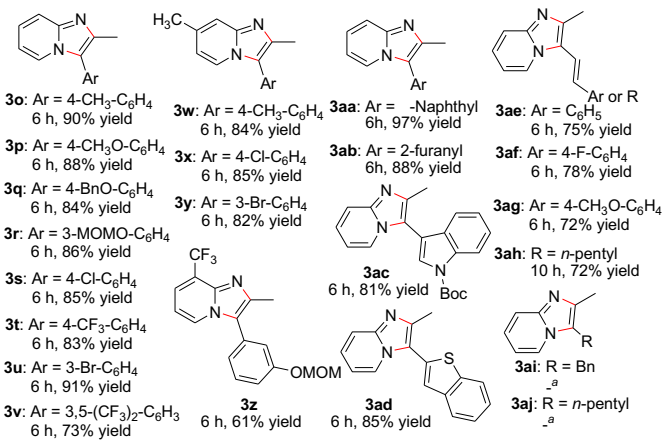


[a] No formation of desired product was observed

Fig. 2. Scope of the reaction regarding 2-aminopyridines.

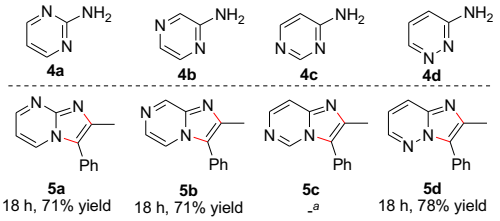
We next investigated the substrate scope of the reaction with regard to diversely substituted propargylic acetates (Fig. 3). To our pleasure, phenyl-substituted substrates with either electron-donating groups, such as methyl, methoxyl, benzyloxyl and methoxymethoxyl (MOMO) group, or electron-withdrawing groups, such as chloro, bromo, and trifluoromethyl group, on the benzene ring all performed well to deliver the cyclized products in good to excellent yields (**3o**–**z**). The reaction of **1a** with propargylic substrate bearing two trifluoromethyl groups on the benzene ring proceeded smoothly to afford **3v**, albeit in a lower yield of 73%. α-Naphthyl substituted propargylic substrate was also fit in the current system, and produced **3aa** in highest yield of 97%. Employment of heteroaryl substituted propargyl alcohol derivatives uneventfully led to bisheteroaryl compounds (**3ab**–**ad**) in excellent yields. Moreover, styryl or hept-1-enyl substituted propargylic components gave the corresponding products with good yields (**3ae**–**ah**). However, less reactive aliphatic substituted propargyl alcohol derivatives, such as 1-phenylbut-3-yn-2-yl acetate and hept-1-yn-3-yl acetate, did not afford the desired products (**3ai**–**aj**). Notably, imidazo[1,2-*a*]pyridine **3z** can be transformed into a key intermediate for preparation of liver X receptor agonist by removal of methoxymethyl group.[9]



[a] No formation of desired product was observed

Fig. 3. Scope of the reaction regarding propargyl alcohol derivatives.

The generality of the cascade was further shown by the preparation of related N-fused imidazoles other than imidazo[1,2-*a*]pyridines (Fig. 4). It is noteworthy that like imidazo[1,2-*a*]pyridine, other N-fused imidazoles and their derivatives are also therapeutically important,[10] yet their preparation was less investigated as compared with imidazo[1,2-*a*]pyridine. Thus, when reacting **2a** with **4a**, **4b**, or**4d** under above optimal conditions, the corresponding imidazo-fused heterocycles imidazo[1,2-*a*]pyrimidine (**5a**), imidazo[1,2-*a*]pyrazine (**5b**), and imidazo[1,2-*b*]pyridazine (**5d**) were obtained in good yields. On the other hand, when **4c** was employed as a reaction component there was no reaction even after longer reaction time. Considering that substrates **4a**–**d** are known to be less reactive as compared with 2-aminopyridine,[11] the generality of current method is remarkable, even though this method failed in the case of substrate **4c**.



[a] No formation of desired product was observed

Fig. 4. Further expansion of substrate scope.

The structure and regiochemistry of imidazo[1,2-*a*]pyridines **3** were determined by comparison of ^{1}H NMR spectrum of representative compounds **3a**, **3b**, **3o** and **3s** with that of known compounds, and further confirmed by single crystal analysis of **3i** (Fig. 5).[12] The structure of other cyclized products could be assigned by analogy.

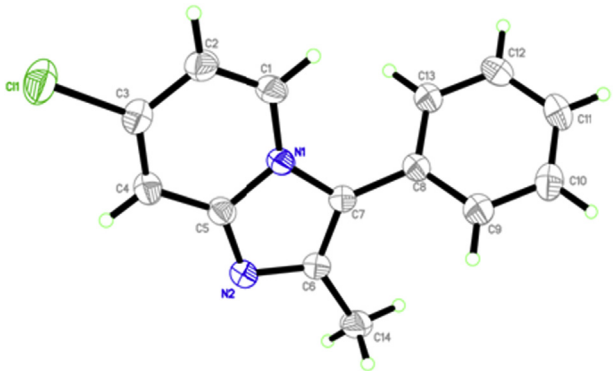


Fig. 5. Single crystal X-ray analysis of **3i**.

A plausible mechanism for the cascade reaction is illustrated in Fig. 6. Propargylic substrate **2a** was activated by Cu-Pybox complex via the formation of allenylidene-copper intermediate (**I**).[5,6] Then, 2-aminopyridine **1a** coordinated with copper as depicted in **II**, followed by nucleophilic addition of the pyridine nitrogen atom of **1a** to γ-position of allenylidene moiety affording intermediate **III**. Protonation and subsequent intra-molecular cyclization in a 5-exo-dig manner via π-activation of the triple bond by copper led to the formation of V.[8] Finally, intermediate **V** could be preferably isomerized into the thermodynamic stable imidazo[1,2-*a*]pyridine **3a** in the presence of a base.

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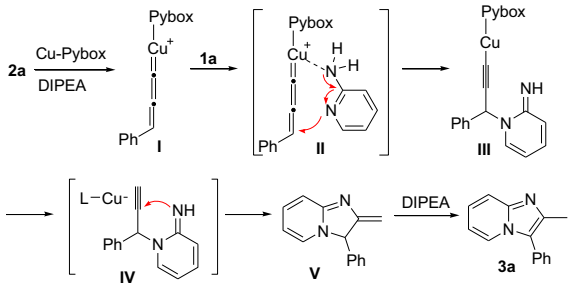
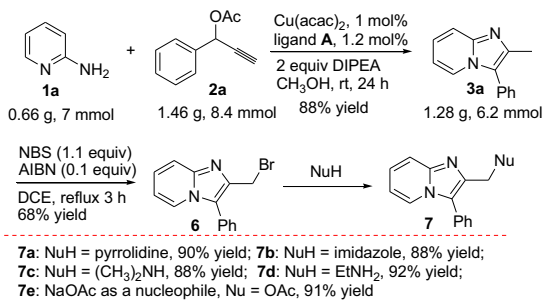


Fig. 6. The proposed mechanism.

In order to show the application potential of our method, we next carried out the reaction between **1a** and **2a** in relatively larger scale and further elaboration of cyclized product **3a** (Scheme 1). The reaction performed on gram scale between **1a** and **2a** led to cyclized product **3a** in 88% yield with as low as 1 mol % $Cu(acac)_2$ and 1.2 mol % ligand **A**. Bromination of the methyl group of **3a** in the presence of N-bromosuccinimide (NBS) and azobisisobutyronitrile (AIBN) with DCE as a solvent at reflux for 3 h afforded 6 (68% yield), which provided valuable opportunities for further elaboration. Thus, reaction between bromide **6** with various nitrogen- or oxygen-based nucleophiles proceeded smoothly to provide further functionalized imidazo[1,2-*a*]pyridines in excellent yields.



Scheme 1. Gram scale synthesis of **3a** and its further derivatization.

3. Conclusions

We have developed a cascade process between 2-aminopyridines and propargyl alcohol derivatives bearing terminal alkyne functionality in the presence of catalytic amount of copper salt and Pybox ligand under mild conditions, which provide access to various densely substituted imidazo[1,2-*a*]pyridines in moderate to excellent yields. The reaction proceeded through regioselective propargylation at pyridine nitrogen of 2-aminopyridine following an intramolecular cyclization catalyzed by copper-Pybox complex. The utility of this method was demonstrated by gram scale synthesis of **3a**, and further elaboration of **3a** by bromination and following coupling with various nucleophiles. Furthermore, this methodology was found to be also applicable to 2-aminopyrimidine, 2-aminopyrazine, and 2-aminopyridazine.

4. Experimental

4.1. General information

Thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) or iodine. Flash column chromatography was performed on silica gel H (10–40 μ). NMR spectra were recorded on Bruker AM500 (500 MHz). Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Optical rotations were taken on JASCO P1030. High-resolution mass spectra were recorded on Bruker ApeXIII 7.0 TESLA FTMS.

4.2. General procedure for preparation of propargylic acetates 2

Ethynylmagnesium bromide (0.5 M in THF, 50.0 mL, 25.0 mmol) was added dropwise to a solution of benzaldehyde (2.12 g, 20.0 mmol) in THF (20 mL) cooled to 0 °C. After addition was complete, the reaction mixture was warmed to ambient temperature and stirred for 2 h after completion of reaction. The reaction was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with diethyl ether (50 mL×3). The combined organic extracts were rinsed with brine (100 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel to afford the corresponding propargylic alcohol (2.0 g, 15.1 mmol) in 75% yield.

To a solution of propargylic alcohol (1.06 g, 8.0 mmol) in anhydrous DCM (20 mL), Et_3N (1.22 mL, 8.8 mmol) and DMAP (97 mg, 0.8 mmol) were added successively. The reaction mixture was cooled with an ice bath for 5 min. Then Ac_2O (0.8 mL, 8.4 mmol) was added dropwise. The reaction was gradually warmed to room temperature and stirred for 0.5 h at this temperature. After complete consumption of 1-phenylprop-2-yn-1-ol as followed by TLC, water (20 mL) was added to quench the reaction. The organic phase was isolated, and the aqueous phase was extracted with DCM (15 mL×2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford pure **2a** (1.50 g, 6.94 mmol) as a colorless oil in a yield of 87%.

*4.2.1. 1-Phenylprop-2-ynyl acetate (**2a**).*[13] Pale yellow oil, 1.50 g, 87% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52–7.54 (m, 2H), 7.36–7.41 (m, 3H), 6.45 (s, 1H), 2.65 (s, 1H), 2.11 (s, 3H).

*4.2.2. 1-p-Tolylprop-2-ynyl acetate (**2b**).*[13] Pale yellow oil, 1.30 g, 87% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.43 (m, 2H), 7.19–7.21 (m, 2H), 6.41–6.42 (m, 1H), 2.64 (s, 1H), 2.36 (s, 3H), 2.10 (s, 3H).

*4.2.3. 1-(4-Methoxyphenyl)prop-2-ynyl acetate (**2c**).*[13] Pale yellow oil, 1.35 g, 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46–7.47 (m, 2H), 6.89–6.91 (m, 2H), 6.40–6.41 (m, 1H), 3.80 (s, 3H), 2.66 (s, 1H), 2.08 (s, 3H).

*4.2.4. 1-(4-(Benzyloxy)phenyl)prop-2-yn-1-yl acetate (**2d**).* White solid, 1.97 g, yield 88%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.34 (m, 7H), 7.03–7.00 (m, 2H), 6.46 (d, J=2.2 Hz, 1H), 5.10 (s, 2H), 2.69 (d, J=2.2 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 159.4, 136.8, 129.4, 129.0, 128.7, 128.1, 127.5, 115.0, 80.5, 75.3, 70.1, 65.1, 21.1; HRMS (ESI) calcd for $(C_{18}H_{16}NaO_3)^+$ 303.0992, found 303.0999.

*4.2.5. 1-(3-(Methoxymethoxy)phenyl)prop-2-yn-1-yl acetate (**2e**).*[14] Brown oil, 2.0 g, 86% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, J=7.9 Hz, 1H), 7.21–7.20 (m, 1H), 7.17 (d, J=7.7 Hz, 1H), 7.06–7.04 (m, 1H), 6.41 (d, J=2.2 Hz, 1H), 5.18 (d, J=1.1 Hz, 2H), 3.48 (s, 3H), 2.66 (d, J=2.2 Hz, 1H), 2.11 (s, 3H).

*4.2.6. 1-(4-Chlorophenyl)prop-2-ynyl acetate (**2f**).*[13] Pale yellow oil, 1.38 g, 83% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46–7.47 (m, 2H), 7.34–7.36 (m, 2H), 6.41 (s, 1H), 2.67 (s, 1H), 2.10 (s, 3H).

*4.2.7. 1-(4-(Trifluoromethyl)phenyl)prop-2-ynyl acetate (**2g**).*[13] Pale yellow oil, 1.73 g, yield 89%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (s, 4H), 6.48 (s, 1H), 2.69 (s, 1H), 2.12 (s, 3H).

*4.2.8. 1-(3-Bromophenyl)prop-2-yn-1-yl acetate (**2h**).*[15] Pale yellow oil, 1.69 g, 84% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.49

(dd, *J*=7.9, 1.2 Hz, 1H), 7.44 (d, *J*=7.9 Hz, 1H), 7.25 (td, *J*=7.9, 1.2 Hz, 1H), 6.40 (d, *J*=2.2 Hz, 1H), 2.68 (d, *J*=2.2 Hz, 1H), 2.12 (s, 3H).

*4.2.9. 1-(3,5-bis(Trifluoromethyl)phenyl)prop-2-ynyl acetate (**2i**).*[16] Pale yellow oil, 2.13 g, 86% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 2H), 7.89 (s, 1H), 6.52 (s, 1H), 2.74 (s, 1H), 2.15 (s, 3H).

*4.2.10. 1-(Naphthalen-1-yl)prop-2-ynyl acetate (**2j**).*[13] White solid, 85% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J*=8.6 Hz, 1H), 7.93–7.89 (m, 3H), 7.63–7.60 (m, 1H), 7.57–7.50 (m, 2H), 7.16 (t, *J*=2.3 Hz, 1H), 2.78 (d, *J*=2.3 Hz, 1H), 2.15 (s, 3H).

*4.2.11. 1-(Furan-2-yl)prop-2-yn-1-yl acetate (**2k**).*[6d] Pale yellow oil, 1.14 g, yield 87% of **2k**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J*=1.8, 0.9 Hz, 1H), 6.50–6.49 (m, 1H), 6.44 (d, *J*=2.3 Hz, 1H), 6.33 (dd, *J*=3.3, 1.8, Hz, 1H), 2.61 (d, *J*=2.3 Hz, 1H), 2.02 (s, 3H).

*4.2.12. tert-Butyl 3-(1-acetoxyprop-2-yn-1-yl)-1H-indole-1-carboxylate (**2l**).*[17] White solid, 2.05 g, 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J*=7.8 Hz, 1H), 7.81 (s, 1H), 7.74–7.72 (m, 1H), 7.38–7.35 (m, 1H), 7.30–7.27 (m, 1H), 6.74 (dd, *J*=2.3, 0.7 Hz, 1H), 2.67 (d, *J*=2.3 Hz, 1H), 2.12 (s, 3H), 1.68 (s, 9H).

*4.2.13. 1-(Benzo[b]thiophen-2-yl)prop-2-yn-1-yl acetate (**2m**).* White solid, 1.53 g, 83% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.76 (m, 2H), 7.51 (s, 1H), 7.39–7.34 (m, 2H), 6.78 (dd, *J*=2.3, 0.8 Hz, 1H), 2.77 (d, *J*=2.3 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 145.1, 142.5, 135.5, 129.3, 126.0, 125.0, 124.0, 123.1, 120.2, 116.9, 115.7, 113.7, 111.7, 109.2, 84.4, 28.2, 14.1; HRMS (ESI) calcd for $(C_{13}H_{10}NaO_2S)^+$ 253.0294, found 253.0303.

*4.2.14. (E)-1-Phenylpent-1-en-4-yn-3-yl acetate (**2n**).*[13] Pale yellow oil, 1.36 g, 85% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.27 (m, 5H), 6.91 (d, *J*=15.8 Hz, 1H), 6.27 (dd, *J*=15.8, 6.5 Hz, 1H), 6.08–6.06 (m, 1H), 2.67 (d, *J*=2.2 Hz, 1H), 2.13 (s, 3H).

*4.2.15. (E)-1-(4-Fluorophenyl)pent-1-en-4-yn-3-yl acetate (**2o**).* Pale yellow oil, 1.46 g, 85% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.35 (m, 2H), 7.03 (t, *J*=8.7 Hz, 2H), 6.85 (d, *J*=15.7 Hz, 1H), 6.14 (dd, *J*=15.7, 6.5 Hz, 1H), 6.03 (d, *J*=6.5 Hz, 1H), 2.66 (d, *J*=2.2 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 163.8, 161.9, 133.7, 131.7, 131.7, 128.63, 128.56, 123.1, 115.7, 115.6, 79.3, 75.5, 63.9, 21.0; HRMS (ESI) calcd for $(C_{13}H_{11}FNaO_2)^+$ 241.0635, found 241.0643.

*4.2.16. (E)-1-(4-Methoxyphenyl)pent-1-en-4-yn-3-yl acetate (**2p**).* Pale yellow oil, 1.46 g, 85% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dt, *J*=8.6, 2.2 Hz, 2H), 6.86–6.81 (m, 3H), 6.10 (dd, *J*=15.6, 6.7 Hz, 1H), 6.03 (ddd, *J*=6.7, 2.2, 1.0 Hz, 1H), 3.78 (s, 3H), 2.66 (d, *J*=2.2 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 159.9, 134.5, 128.3, 128.2, 121.0, 114.1, 79.6, 75.3, 64.2, 55.3, 21.1; HRMS (ESI) calcd for $(C_{14}H_{14}NaO_3)^+$ 253.0835, found 253.0846.

*4.2.17. (E)-Dec-4-en-1-yn-3-yl acetate (**2q**).* Pale yellow oil, 1.24 g, 80% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00–5.94 (m, 1H), 5.78–5.77 (m, 1H), 5.49 (ddt, *J*=15.3, 6.5, 1.3 Hz, 1H), 2.53 (d, *J*=2.2 Hz, 1H), 2.05–2.00 (m, 5H), 1.39–1.33 (m, 2H), 1.28–1.22 (m, 4H), 0.85 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 137.0, 124.3, 79.8, 74.7, 64.0, 31.9, 31.3, 28.3, 22.4, 21.0, 14.0; HRMS (ESI) calcd for $(C_{12}H_{18}NaO_2)^+$ 217.1199, found 217.1207.

4.3. General procedure for Cu-Pybox catalyzed synthesis of 2,3-disbustituted imidazo[1,2-*a*]pyridines (3) and related N-fused imidazoles (5)

Under an atmosphere of nitrogen, a 25 mL dry Schlenk flask was placed with $Cu(acac)_2$ (1.6 mg, 0.01 mmol) and ligand **A** (2.6 mg, 0.012 mmol). Anhydrous MeOH (1.0 mL) was added, and the mixture was magnetically stirred at 20 °C for 15 min. Then a solution of 1-phenylprop-2-yn-1-yl acetate **2a** (0.24 mmol), 2-aminopyridine **1a** (0.2 mmol) and diisopropylethylamine (0.07 mL, 0.4 mmol) in MeOH (0.5 mL) were added dropwise. The reaction flask was kept at room temperature for 6 h. After **1a** was completely consumed as monitored by TLC, H_2O (10 mL) was added to quench the reaction. The resulting mixture was then extracted three times with diethyl ether (10 mL×3). The combined organic layer was dried over Na_2SO_4. After evaporation of the volatile solvent under reduced pressure, the residue was purified by flash chromatography on silica gel to afford pure **3a** (39 mg, 0.19 mmol) as a brown oil in a yield of 94%.

*4.3.1. 2-Methyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyridine (**3a**).*[18] Brown oil, 39 mg, 94% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J*=6.8 Hz, 1H), 7.56–7.50 (m, 3H), 7.45–7.39 (m, 3H), 7.15 (t, *J*=6.8, Hz, 1H), 6.70 (t, *J*=6.8, Hz, 1H), 2.47 (s, 3H).

*4.3.2. 2,8-Dimethyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyridine (**3b**).*[19] White solid, 40 mg, 90% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J*=6.9 Hz, 1H), 7.48–7.45 (m, 2H), 7.40–7.33 (m, 3H), 6.88 (d, *J*=6.9 Hz, 1H), 6.55 (t, *J*=6.9 Hz, 1H), 2.59 (s, 3H), 2.47 (s, 3H).

*4.3.3. 2,7-Dimethyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyridine (**3c**).* Brown solid, 40.5 mg, 91% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J*=7.0 Hz, 1H), 7.50 (t, *J*=7.0 Hz, 2H), 7.42–7.35 (m, 3H), 7.28 (s, 1H), 6.51 (d, *J*=7.0 Hz, 1H), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 140.6, 135.0, 129.7, 129.3, 129.1, 127.8, 122.3, 120.8, 115.4, 114.4, 21.2, 13.9; HRMS (ESI) calcd for $(C_{15}H_{15}N_2)^+$ 223.1230, found 223.1237.

*4.3.4. 2,6-Dimethyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyridine (**3d**).* Brown solid, 41 mg, 92% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.56–7.51 (m, 3H), 7.48–7.42 (m, 3H), 7.02 (dd, *J*=9.1, 1.6 Hz, 1H), 2.47 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 140.4, 129.6, 129.5, 129.1, 128.0, 127.4, 121.6, 121.2, 120.7, 116.2, 18.3, 13.7; HRMS (ESI) calcd for $(C_{15}H_{15}N_2)^+$ 223.1230, found 223.1234.

*4.3.5. 6-Methoxy-2-methyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyridine (**3f**).* Brown solid, 42 mg, 87% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J*=2.3 Hz, 1H), 7.54–7.51 (m, 2H), 7.46–7.39 (m, 4H), 6.94 (dd, *J*=9.7, 2.3 Hz, 1H), 3.70 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 141.6, 141.0, 129.8, 129.3, 129.2, 128.1, 122.3, 118.9, 117.1, 105.3, 56.2, 14.0; HRMS (ESI) calcd for $(C_{15}H_{15}N_2O)^+$ 239.1179, found 239.1183.

*4.3.6. 8-Bromo-2-methyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyridine (**3g**).* Brown solid, 43 mg, 74% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, *J*=6.8, 1.0 Hz, 1H), 7.54–7.51 (m, 2H), 7.45–7.40 (m, 4H), 6.60 (t, *J*=6.8 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 141.8, 129.6, 129.3, 129.1, 128.5, 126.5, 123.3, 122.5, 111.9, 111.0, 14.1; HRMS (ESI) calcd for $(C_{14}H_{12}BrN_2)^+$ 287.0178, found 287.0186.

*4.3.7. 6-Bromo-2-methyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyridine (**3h**).* Brown solid, 40 mg, 70% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J*=1.8, 0.8 Hz, 1H), 7.56–7.53 (m, 2H), 7.46–7.43 (m, 4H), 7.20 (dd, *J*=9.5, 1.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 142.0, 129.4, 129.3, 128.8, 128.5, 127.3, 123.1, 122.0, 117.6, 106.7, 14.0; HRMS (ESI) calcd for $(C_{14}H_{12}BrN_2)^+$ 287.0178, found 287.0186.

*4.3.8. 7-Chloro-2-methyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyridine (**3i**).* White solid, 36 mg, 73% yield; a crystalline sample suitable for X-ray diffraction analysis was developed from a solvent mixture of ethyl acetate and petroleum ether. Mp 114–116 °C; ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J*=7.3, 0.7 Hz, 1H), 7.52–7.49 (m, 3H), 7.42–7.39 (m, 3H), 6.67 (dd, *J*=7.3, 2.1 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 141.9, 130.37, 129.4, 129.3, 128.9, 128.4, 123.3, 121.7, 115.8, 113.4, 14.0; HRMS (ESI) calcd for $(C_{14}H_{12}ClN_2)^+$ 243.0684, found 243.0690.

*4.3.9. 6-Chloro-2-methyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyridine (**3j**).* White solid, 35 mg, 71% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, *J*=2.0, 0.8 Hz, 1H), 7.54–7.51 (m, 2H), 7.49 (dd, *J*=9.5, 0.8 Hz, 1H), 7.44–7.42 (m, 3H), 7.09 (dd, *J*=9.5, 2.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 142.1, 129.4, 129.3, 128.8, 128.5, 125.2, 122.1, 120.9, 120.2, 117.3, 14.0; HRMS (ESI) calcd for $(C_{14}H_{12}ClN_2)^+$ 243.0684, found 243.0690.

*4.3.10. 2-Methyl-3-phenyl-8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridine (**3l**).* Brown solid, 28 mg, 50% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J*=6.7 Hz, 1H), 7.57–7.54 (m, 2H), 7.51–7.46 (m, 2H), 7.46–7.43 (m, 3H), 6.80 (t, *J*=6.7 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 139.8, 129.7, 129.4, 128.74, 128.68, 127.4, 126.3, 123.0 (q, *J*=270.6 Hz), 122.6, 122.5 (q, *J*=5.4 Hz), 121.9, 118.5 (q, *J*=33.1 Hz), 110.2, 14.1; HRMS (ESI) calcd for $(C_{15}H_{12}F_3N_2)^+$ 277.0947, found 277.0955.

*4.3.11. 2-Methyl-3-phenyl-6-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridine (**3m**).* Brown solid, 34 mg, 61% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.66 (d, *J*=9.4 Hz, 1H), 7.58–7.55 (m, 2H), 7.49–7.44 (m, 3H), 7.30 (dd, *J*=9.4, 1.7 Hz 1H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 143.1, 129.52, 129.49, 128.8, 128.4, 123.7 (q, *J*=268.8 Hz), 122.8, 122.0 (q, *J*=5.5 Hz), 119.8 (q, *J*=2.7 Hz), 117.6, 116.3 (q, *J*=33.7 Hz), 14.0; HRMS (ESI) calcd for $(C_{15}H_{12}F_3N_2)^+$ 277.0947, found 277.0955.

*4.3.12. 2-Methyl-3-(p-tolyl)-2,3-dihydroimidazo[1,2-a]pyridine (**3o**).*[18] Brown solid, 40 mg, 90% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J*=6.8 Hz, 1H), 7.66 (d, *J*=9.0 Hz, 1H), 7.32 (s, 4H), 7.17 (ddd, *J*=9.0, 6.8, 1.1 Hz, 1H), 6.73 (td, *J*=6.8, 1.1 Hz, 1H), 2.45 (s, 3H), 2.43 (s, 3H).

*4.3.13. 3-(4-Methoxyphenyl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3p**).* Brown solid, 42 mg, 88% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (dt, *J*=6.8, 1.2 Hz, 1H), 7.54 (dt, *J*=9.0, 1.2 Hz, 1H), 7.37–7.34 (m, 2H), 7.13 (ddd, *J*=9.0, 6.8, 1.2 Hz, 1H), 7.06–7.03 (m, 2H), 6.70 (td, *J*=6.8, 1.2 Hz, 1H), 3.87 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 144.3, 140.6, 130.9, 123.8, 123.0, 121.6, 121.2, 116.9, 114.6, 111.7, 55.4, 13.9; HRMS (ESI) calcd for $(C_{15}H_{15}N_2O)^+$ 239.1179, found 239.1175.

*4.3.14. 3-(4-(Benzyloxy)phenyl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3q**).* Brown solid, 53 mg, 84% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J*=6.8 Hz, 1H), 7.53 (d, *J*=9.0 Hz, 1H), 7.46 (d, *J*=7.3 Hz, 2H), 7.40 (t, *J*=7.3 Hz, 2H), 7.34–7.31 (m, 3H), 7.12–7.06 (m, 3H), 6.66 (t, *J*=6.8, Hz, 1H), 5.10 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 144.3, 140.6, 136.7, 130.9, 128.7, 128.1, 127.5, 123.8, 123.0, 121.8, 121.2, 116.8, 115.5, 111.8, 70.1, 13.9. HRMS (ESI) calcd for $(C_{21}H_{19}N_2O)^+$ 315.1492, found 315.1501.

*4.3.15. 3-(3-(Methoxymethoxy)phenyl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3r**).* Brown solid, 46 mg, 86% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J*=6.8 Hz, 1H), 7.55 (d, *J*=9.0 Hz, 1H), 7.44 (t, *J*=7.9 Hz, 1H), 7.14–7.08 (m, 4H), 6.71 (td, *J*=6.8, 1.1 Hz, 1H), 5.21 (s, 2H), 3.50 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 144.5, 141.1, 130.8, 130.2, 124.1, 123.1, 122.8, 121.1, 117.3, 117.0, 115.8, 111.9, 94.5, 56.1, 14.0; HRMS (ESI) calcd for $(C_{16}H_{17}N_2O_2)^+$ 269.1285, found 269.1292.

*4.3.16. 3-(4-Chlorophenyl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3s**).*[18] Brown solid, 41 mg, 85% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (dt, *J*=6.8, 1.1 Hz 1H), 7.55 (dt, *J*=9.0, 1.1 Hz, 1H), 7.50–7.47 (m, 2H), 7.39–7.37 (m, 2H), 7.16 (ddd, *J*=9.0, 6.8, 1.1 Hz 1H), 6.73 (td, *J*=6.8, 1.1 Hz, 1H), 2.44 (s, 3H).

*4.3.17. 2-Methyl-3-(4-(trifluoromethyl)phenyl)-2,3-dihydroimidazo[1,2-a]pyridine (**3t**).* Brown solid, 46 mg, 83% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J*=6.8 Hz, 1H), 7.78 (d, *J*=8.0 Hz, 2H), 7.61–7.57 (m, 3H), 7.20 (ddd, *J*=9.0, 6.8, 1.2 Hz, 1H), 6.77 (td, *J*=6.8, 1.2 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 141.8, 133.3, 129.9 (q, *J*=32.8 Hz), 129.8, 129.54, 129.47, 126.2 (q, *J*=3.6 Hz), 124.8, 124.0 (q, *J*=270.5 Hz), 122.8, 120.1, 117.2, 112.4, 13.9; HRMS (ESI) calcd for $(C_{15}H_{12}F_3N_2)^+$ 277.0947, found 277.0960.

*4.3.18. 3-(3-Bromophenyl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3u**).* Brown solid, 52 mg, 91% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J*=6.8 Hz, 1H), 7.55–7.47 (m, 3H), 7.35–7.33 (m, 2H), 7.12 (ddd, *J*=9.0, 6.8, 1.2 Hz, 1H), 6.69 (td, *J*=6.8, 1.2 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 141.6, 132.1, 131.6, 131.0, 130.7, 128.0, 124.4, 123.1, 122.8, 119.9, 117.1, 112.2, 14.0; HRMS (ESI) calcd for $(C_{14}H_{12}BrN_2)^+$ 287.0178, found 287.0183.

*4.3.19. 3-(3,5-bis(Trifluoromethyl)phenyl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3v**).* Brown solid, 50 mg, 73% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J*=6.8 Hz, 1H), 7.91 (s, 3H), 7.60 (d, *J*=9.0 Hz, 1H), 7.25 (ddd, *J*=9.0, 6.8, 1.2 Hz, 1H), 6.84 (td, *J*=6.8, 1.2 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 142.7, 132.8 (q, *J*=33.6 Hz), 132.0, 129.1 (q, *J*=3.7 Hz), 125.2, 123.1 (q, *J*=271.4 Hz), 122.3, 121.7–121,5 (m), 118.6, 117.5, 112.9, 13.9; HRMS (ESI) calcd for $(C_{16}H_{11}F_6N_2)^+$ 345.0821, found 345.0823.

*4.3.20. 2,7-Dimethyl-3-(p-tolyl)-2,3-dihydroimidazo[1,2-a]pyridine (**3w**).* Brown solid, 40 mg, 84% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J*=7.0 Hz, 1H), 7.26–7.25 (m, 5H), 6.46 (d, *J*=7.0, 1H), 2.40 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 140.3, 137.7, 134.7, 129.8, 129.2, 126.7, 122.3, 120.8, 115.3, 114.2, 21.3, 21.2, 13.9; HRMS (ESI) calcd for $(C_{16}H_{17}N_2)^+$ 237.1386, found 237.1393.

*4.3.21. 3-(4-Chlorophenyl)-2,7-dimethyl-2,3-dihydroimidazo[1,2-a]pyridine (**3x**).* Brown solid, 44 mg, 85% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J*=7.0 Hz, 1H), 7.42–7.40 (m, 2H), 7.30–7.24 (m, 3H), 6.48 (dd, *J*=7.0 Hz, 1H), 2.37 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 140.8, 135.3, 133.7, 130.5, 129.4, 129.3, 129.1, 128.1, 122.1, 119.6, 115.5, 114.6, 21.2, 13.9; HRMS (ESI) calcd for $(C_{15}H_{14}ClN_2)^+$ 257.0840, found 257.0848.

*4.3.22. 3-(3-Bromophenyl)-2,7-dimethyl-2,3-dihydroimidazo[1,2-a]pyridine (**3y**).* Brown solid, 50 mg, 82% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J*=7.0 Hz, 1H), 7.53–7.45 (m, 2H), 7.33–7.29 (m, 2H), 7.25 (s, 1H), 6.52 (dd, *J*=7.0, 1.6 Hz, 1H), 2.39 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 141.2, 135.4, 131.9, 131.8, 130.8, 130.6, 127.8, 123.1, 122.1, 119.3, 115.5, 114.7, 21.2, 13.9; HRMS (ESI) calcd for $(C_{15}H_{14}BrN_2)^+$ 301.0335, found 301.0341.

*4.3.23. 3-(3-(Methoxymethoxy)phenyl)-2-methyl-8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridine (**3z**).* Brown solid, 41 mg, 61% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J*=6.9 Hz, 1H), 7.51–7.45 (m, 2H), 7.16–7.07 (m, 3H), 6.80 (t, *J*=6.9 Hz, 1H), 5.23 (s, 2H), 3.51 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 142.5, 139.9, 130.5, 130.0, 126.4, 124.1, 123.0, 123.0 (q, *J*=270.6 Hz), 122.5 (q, *J*=5.5 Hz), 122.3, 118.5 (q, *J*=32.8 Hz), 117.6, 116.4, 110.2, 94.6, 56.2, 14.2; HRMS (ESI) calcd for $(C_{17}H_{16}F_3N_2O_2)^+$ 337.1158, found 337.1166.

*4.3.24. 2-Methyl-3-(naphthalen-1-yl)-2,3-dihydroimidazo[1,2-a]pyridine (**3aa**).*[18] Brown solid, 50 mg, 97% yield; ^1H NMR (500 MHz,

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$CDCl_3$) δ 7.95 (d, *J*=8.5 Hz, 1H), 7.93 (d, *J*=6.8 Hz, 1H), 7.61 (d, *J*=9.0 Hz, 1H), 7.57 (d, *J*=7.5 Hz, 1H), 7.51–7.46 (m, 3H), 7.38–7.31 (m, 2H), 7.12 (ddd, *J*=9.0, 6.8, 1.1 Hz, 1H), 6.57 (td, *J*=6.8, 1.1 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 142.2, 134.0, 132.3, 129.7, 129.6, 128.8, 126.9, 126.6, 126.4, 125.7, 125.2, 124.0, 123.8, 119.7, 116.8, 111.7, 13.9.

*4.3.25. 3-(Furan-2-yl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3ab**).* Brown solid, 35 mg, 88% of yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dt, *J*=6.8, 1.2 Hz, 1H), 7.53 (dd, *J*=1.9, 0.5 Hz, 1H), 7.51 (d, *J*=9.0 Hz, 1H), 7.13 (ddd, *J*=9.0, 6.8, 1.2 Hz, 1H), 6.75 (td, *J*=6.8, 1.2 Hz, 1H), 6.53 (dd, *J*=3.3, 1.9 Hz, 1H), 6.48 (dd, *J*=3.3, 0.5 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 144.7, 142.5, 141.8, 124.7, 124.5, 116.8, 113.5, 112.3, 111.3, 108.1, 14.7; HRMS (ESI) calcd for $(C_{12}H_{11}N_2O)^+$ 199.0866, found 199.0869.

*4.3.26. tert-Butyl 3-(2-methyl-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)-3a,7a-dihydro-1H-indole-1-carboxylate (**3ac**).* Brown solid, 56 mg, 81% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J*=7.9 Hz, 1H), 7.86 (d, *J*=6.8 Hz, 1H), 7.75 (s, 1H), 7.58 (d, *J*=9.0 Hz, 1H), 7.40–7.36 (m, 1H), 7.23–7.19 (m, 2H), 7.15 (ddd, *J*=9.0, 6.8, 1.1 Hz, 1H), 6.68 (td, *J*=6.8, 1.1 Hz, 1H), 2.46 (s, 3H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 145.1, 142.5, 135.5, 129.3, 126.0, 125.0, 124.0, 123.1, 120.2, 116.9, 115.7, 113.7, 111.7, 109.2, 84.4, 28.2, 14.1; HRMS (ESI) calcd for $(C_{21}H_{22}N_3O_2)^+$ 348.1707, found 348.1713.

*4.3.27. 3-(Benzo[b]thiophen-2-yl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3ad**).* Brown solid, 45 mg, 85% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J*=6.8 Hz, 1H), 7.84–1.79 (m, 2H), 7.56 (d, *J*=8.9 Hz, 1H), 7.39–7.32 (m, 3H), 7.16 (ddd, *J*=8.9, 6.8, 1.1 Hz, 1H), 6.74 (td, *J*=6.8, 1.1 Hz, 1H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 143.6, 140.0, 139.8, 130.5, 124.78, 124.75, 124.72, 124.2, 123.7, 122.2, 117.0, 115.1, 112.4, 14.5. HRMS (ESI) calcd for $(C_{16}H_{13}N_2S)^+$ 265.0794, found 265.0803.

*4.3.28. (E)-2-Methyl-3-styryl-2,3-dihydroimidazo[1,2-a]pyridine (**3ae**).*[20] Brown oil, 35 mg, 75% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J*=7.0 Hz, 1H), 7.56 (d, *J*=7.0 Hz, 1H), 7.53 (d, *J*=7.5 Hz, 2H), 7.38 (t, *J*=7.5 Hz, 2H), 7.28 (d, *J*=7.5 Hz, 1H), 7.18 (d, *J*=16.4 Hz, 1H), 7.16 (td, *J*=7.0, 1.2 Hz, 1H), 6.93 (d, *J*=16.4 Hz, 1H), 6.85 (td, *J*=7.0, 1.2 Hz, 1H) 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 143.1, 137.5, 128.8, 128.3, 127.6, 126.1, 124.1, 123.4, 119.4, 117.1, 114.4, 112.5, 15.4; HRMS (ESI) calcd for $(C_{16}H_{15}N_2)^+$ 235.1230, found 235.1232.

*4.3.29. (E)-3-(4-Fluorostyryl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3af**).* Brown solid, 39 mg, 78% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J*=6.8 Hz, 1H), 7.56 (d, *J*=9.0 Hz, 1H), 7.49–7.46 (m, 2H), 7.18 (ddd, *J*=9.0, 6.8, 1.1 Hz, 1H), 7.10–7.04 (m, 3H), 6.89 (d, *J*=16.4 Hz, 1H), 6.85 (td, *J*=6.8, 1.1 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3 (d, *J*=246 Hz), 144.7, 143.1, 133.7, 127.6 (d, *J*=8.3 Hz), 127.2, 124.2, 123.3, 117.2, 115.8 (d, *J*=21.0 Hz), 115.7, 114.2 (d, *J*=2.8 Hz), 112.5, 15.4; HRMS (ESI) calcd for $(C_{16}H_{14}FN_2)^+$ 253.1136, found 253.1139.

*4.3.30. (E)-3-(4-Methoxystyryl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3ag**).* Brown solid, 38 mg, 72% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J*=6.8 Hz, 1H), 7.50 (d, *J*=8.7 Hz, 1H), 7.41 (d, *J*=8.7 Hz, 2H), 7.09 (ddd, *J*=8.7, 6.8, 1.1 Hz, 1H), 6.97 (d, *J*=16.4 Hz, 1H), 6.88 (d, *J*=8.7 Hz, 2H), 6.83 (d, *J*=16.4 Hz, 1H), 6.76 (dt, *J*=6.8, 1.1 Hz, 1H), 3.79 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 144.4, 142.4, 130.2, 128.3, 127.3, 123.8, 123.2, 119.6, 117.0, 114.2, 112.3, 112.2, 55.3, 15.3; HRMS (ESI) calcd for $(C_{17}H_{17}N_2O)^+$ 265.1335, found 265.1338.

*4.3.31. (E)-3-(Hept-1-en-1-yl)-2-methyl-2,3-dihydroimidazo[1,2-a]pyridine (**3ah**).* Brown oil, 34 mg, 72% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J*=6.8 Hz, 1H), 7.47 (d, *J*=9.0 Hz, 1H), 7.08 (ddd, *J*=9.0, 6.8, 1.2 Hz, 1H), 6.74 (td, *J*=6.8, 1.1 Hz, 1H), 6.41 (d, *J*=16.4 Hz, 1H), 6.05 (dt, *J*=16.4, 6.8 Hz, 1H), 2.48 (s, 3H), 2.33–2.18 (m, 2H), 1.57–1.41 (m, 2H), 1.38–1.22 (m, 4H), 0.93–0.82 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 141.2, 133.1, 123.3, 123.1, 119.2, 116.8, 115.8, 111.8, 33.9, 31.4, 29.2, 22.5, 14.8, 14.0; HRMS (ESI) calcd for $(C_{15}H_{21}N_2)^+$ 229.1699, found 229.1693.

*4.3.32. 2-Methyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyrimidine (**5a**).* Brown oil, 30 mg, 71% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (dd, *J*=4.1, 2.0 Hz, 1H), 8.39 (dd, *J*=6.8, 2.0 Hz, 1H), 7.54–7.51 (m, 2H), 7.45–7.42 (m, 3H), 6.80 (dd, *J*=6.8, 4.1 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 147.6, 143.0, 130.4, 129.4, 129.3, 128.6, 128.2, 112.0, 108.4, 14.1; HRMS (ESI) calcd for $(C_{13}H_{12}N_3)^+$ 210.1026, found 210.1035.

*4.3.33. 2-Methyl-3-phenyl-2,3-dihydroimidazo[1,2-a]pyrazine (**5b**).* Brown solid, 29 mg, 70% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.01 (dd, *J*=4.6, 1.2 Hz, 1H), 7.80 (d, *J*=4.6 Hz, 1H), 7.56 (t, *J*=7.5 Hz, 2H), 7.50–7.40 (m, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 143.0, 139.7, 129.6, 129.4, 129.2, 128.9, 128.0, 123.0, 115.9, 14.1; HRMS (ESI) calcd for $(C_{13}H_{12}N_3)^+$ 210.1026, found 210.1033.

*4.3.34. 2-Methyl-3-phenyl-2,3-dihydroimidazo[1,2-b]pyridazine (**5d**).* Brown solid, 33 mg, 78% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J*=4.4 Hz, 1H), 7.91 (d, *J*=9.0 Hz, 1H), 7.71 (d, *J*=7.4 Hz, 2H), 7.54 (t, *J*=7.4 Hz, 2H), 7.43 (t, *J*=7.4 Hz, 1H), 7.01 (dd, *J*=9.0, 4.4 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 141.1, 138.2, 129.3, 128.7, 128.6, 128.1, 125.2, 124.6, 116.2, 15.0; HRMS (ESI) calcd for $(C_{13}H_{12}N_3)^+$ 210.1026, found 210.1038.

4.4. Gram scale synthesis of 3a and procedures for its further elaboration

*4.4.1. Gram scale synthesis of **3a**.* Under an atmosphere of nitrogen, a 50 mL dry round-bottom flask was placed with $Cu(acac)_2$ (11.4 mg, 0.07 mmol) and ligand **A** (18.2 mg, 0.084 mmol). Anhydrous MeOH (15.0 mL) was added, and the mixture was magnetically stirred at 20 °C for 15 min. Then a solution of 1-phenylprop-2-yn-1-yl acetate **2a** (1.46 g, 8.4 mmol), 2-aminopyridine **1a** (0.66 g, 7.0 mmol) and diisopropylethylamine (2.45 mL, 14 mmol) in MeOH (5.0 mL) were added dropwise. The reaction flask was kept at room temperature for 8 h. After **1a** was completely consumed as monitored by TLC, H_2O (30 mL) was added to quench the reaction. The resulted mixture was then extracted three times with diethyl ether (50 mL×3). The combined organic layer was dried over Na_2SO_4. After evaporation of the volatile solvent under reduced pressure, the residue was purified by flash chromatography on silica gel to afford pure **3a** (1.28 g, 6.2 mmol) as a brown oil in a yield of 88%.

*4.4.2. Bromination of **3a**.* A mixture of 2-methyl-3-phenylimidazo[1,2-*a*]pyridine **3a** (1.0 g, 4.8 mmol), N-bromosuccinimide (0.95 g, 5.2 mmol) and azodiisobutyronitrile (0.078 g, 0.480 mmol) in DCE (20 mL) was refluxed for 3 h. The solvent was removed and the resulting material was partitioned between dichloromethane and water. The layers were separated and the aqueous layer was further extracted with dichloromethane. The combined dichloromethane layer was dried over Na_2SO_4. After evaporation of the volatile solvent under reduced pressure, the residue was purified by flash chromatography on silica gel to afford compound **6** (0.93 g, 3.24 mmol) as a white solid in a yield of 68%.

*4.4.3. 2-(Bromomethyl)-3-phenylimidazo[1,2-a]pyridine (**6**).* White solid, 0.93 g, 68% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J*=6.8 Hz, 1H), 7.63 (d, *J*=9.0 Hz, 1H), 7.58–7.43 (m, 5H), 7.23 (ddd,

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J=9.0, 6.8, 1.1 Hz, 1H), 6.77 (t, *J*=6.8 Hz, 1H), 4.75 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 139.8, 129.5, 129.5, 129.0, 128.0, 125.3, 123.7, 123.4, 118.1, 112.8, 39.4; HRMS (ESI) calcd for $(C_{14}H_{12}BrN_2)^+$ 287.0178, found 287.0187.

4.4.4. Addition of nucleophiles to bromide ***6****.* To a solution of **6** (57.4 mg, 0.2 mmol) in DMSO (2 mL) was added pyrrolidine (71 mg, 1 mmol). The mixture was stirred for 30 h at room temperature. After **6** was completely consumed as monitored by TLC, K_2CO_3 (5 mL, 0.5 N) was added to basify the reaction. Then 10 mL EA was added, the resulted mixture was washed three times with H_2O (10 mL×3). The combined organic layer was dried over Na_2SO_4. After evaporation of the volatile solvent under reduced pressure, the residue was purified by flash chromatography on silica gel to afford pure **7a** (50 mg, 0.180 mmol) as white solid in a yield of 90%.

*4.4.5. 3-Phenyl-2-(pyrrolidin-1-ylmethyl)imidazo[1,2-a]pyridine (****7a****).* White solid, 50 mg, 90% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J*=6.8 Hz, 1H), 7.60 (d, *J*=9.0 Hz, 1H), 7.52–7.48 (m, 4H), 7.43–7.40 (m, 1H), 7.15 (ddd, *J*=9.0, 6.8, 1.1 Hz, 1H), 6.71 (td, *J*=6.8, 1.1 Hz, 1H), 3.82 (s, 2H), 2.65 (s, 4H), 1.75–1.74 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 141.0, 130.0, 129.2, 128.9, 128.5, 124.4, 123.4, 123.2, 117.7, 112.2, 53.9, 51.6, 23.5; HRMS (ESI) calcd for $(C_{18}H_{20}N_3)^+$ 278.1652, found 278.1659.

*4.4.6. 2-((1H-Imidazol-1-yl)methyl)-3-phenylimidazo[1,2-a]pyridine (****7b****).*[21] Compound **7b** was prepared in the same manner as example **7a** but using imidazole in place of pyrrolidine; white solid, 48 mg, 88% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J*=6.8 Hz, 1H), 7.61 (d, *J*=9.1 Hz, 1H), 7.56–7.48 (m, 4H), 7.34 (d, *J*=7.0 Hz, 2H), 7.22 (t, *J*=6.8 Hz, 1H), 6.97 (s, 2H), 6.78 (t, *J*=6.8 Hz, 1H), 5.20 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 138.9, 137.4, 130.3, 130.1, 129.8, 129.6, 128.2, 125.8, 124.1, 123.8, 119.7, 118.3, 113.3, 44.6; HRMS (ESI) calcd for $(C_{17}H_{15}N_4)^+$ 275.1291, found 275.1299.

*4.4.7. N,N-Dimethyl-1-(3-phenylimidazo[1,2-a]pyridin-2-yl)methanamine (****7c****).* Compound **7c** was prepared in the same manner as example **7a** but using dimethylamine in place of pyrrolidine; white solid, 46 mg, 91% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J*=6.8 Hz, 1H), 7.69–7.34 (m, 6H), 7.24–7.08 (m, 1H), 6.73 (t, *J*=6.8 Hz, 1H), 3.74 (s, 2H), 2.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 139.2, 129.9, 129.3, 128.8, 128.5, 124.8, 124.2, 123.5, 117.7, 112.4, 54.9, 44.6; HRMS (ESI) calcd for $(C_{16}H_{18}N_3)^+$ 252.1495, found 252.1503.

*4.4.8. N-((3-Phenylimidazo[1,2-a]pyridin-2-yl)methyl)ethanamine (****7d****).* To a solution of **6** (57.4 mg, 0.2 mmol) in EtOH (2 mL) was added ethanamine (70% in H_2O) (64 mg, 1 mmol). The mixture was stirred for 24 h at room temperature. After **6** was completely consumed as monitored by TLC, K_2CO_3 (5 mL, 0.5 N) was added to basify the reaction mixture. Then 10 mL H_2O was added, the resulting mixture was then extracted with diethyl ether (10 mL×3). The combined organic layer was dried over Na_2SO_4. After evaporation of the volatile solvent under reduced pressure, the residue was purified by flash chromatography on silica gel to afford pure **7d** (46 mg, 0.183 mmol) as a white solid in 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J*=6.8 Hz, 1H), 7.62–7.42 (m, 6H), 7.20–7.17 (m, 1H), 6.76 (t, *J*=6.8 Hz, 1H), 6.08 (s, 1H), 4.10 (s, 2H), 2.96–2.91 (m, 2H), 1.23 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 138.4, 129.9, 129.4, 128.9, 127.9, 125.2, 123.6, 123.4, 117.6, 112.6, 44.3, 44.0, 13.2; HRMS (ESI) calcd for $(C_{16}H_{18}N_3)^+$ 252.1495, found 252.1499.

*4.4.9. (3-Phenylimidazo[1,2-a]pyridin-2-yl)methyl acetate (****7e****).* To a solution of **6** (57.4 mg, 0.2 mmol) in DMF (2 mL) was added NaOAc (82 mg, 1 mmol). The mixture was stirred for 24 h at room temperature. After **6** was completely consumed as monitored by TLC. Then 15 mL EA was added, the resulted mixture was washed with H_2O (10 mL×3). The organic layer was dried over Na_2SO_4. After evaporation of the volatile solvent under reduced pressure, the residue was purified by flash chromatography on silica gel to afford pure **7e** (48 mg, 0.182 mmol) as a white solid in 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J*=6.8 Hz, 1H), 7.65 (d, *J*=9.0 Hz, 1H), 7.55–7.52 (m, 2H), 7.49–7.44 (m, 3H), 7.22 (ddd, *J*=9.0, 6.8, 1.1 Hz, 1H), 6.76 (t, *J*=6.8 Hz, 1H), 5.22 (s, 2H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 145.0, 138.2, 129.8, 129.3, 128.9, 128.1, 125.1, 124.2, 123.6, 118.0, 112.7, 60.1, 21.0; HRMS (ESI) calcd for $(C_{16}H_{15}N_2O_2)^+$ 267.1128, found 267.1136.

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Supplementary data

Supplementary data (The original spectra of ^{1}H NMR and ^{13}C NMR of all products are supplied.) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.09.013.

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