JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Copper-Mediated Aerobic Oxidative Synthesis of 3-Bromo-imidazo[1,2-*a*]pyridines with Pyridines and Enamides

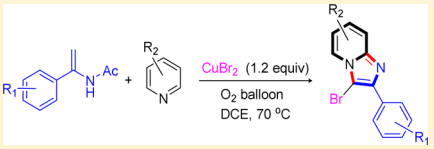
Xiaoqiang Zhou,[†] Hao Yan,[†,‡] Chaowei Ma,[†] Yongqin He,[†] Yamin Li,[†] Jinhui Cao,[†] Rulong Yan,*[,†] and Guosheng Huang*[,†]

[†]State Key Laboratory of Applied Organic Chemistry, Key Laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Department of Chemistry, Lanzhou University, Lanzhou, 730000, China

[‡]Shaanxi University of Chinese Medicine, Shiji Ave., Xi'an-Xianyang New Ecomic Zone, Shaanxi Province, Xianyang, 712046, China

Supporting Information

ABSTRACT: A conversion of pyridines and enamides for the synthesis of 3-bromo-imidazo[1,2-*a*]pyridines was developed by copper-mediated aerobic oxidative coupling in a one-pot manner. This procedure tolerates various functional groups and affords a series of 3-bromo-imidazo[1,2-*a*]pyridines under mild conditions.



INTRODUCTION

Intensive interest and research have been paid in the development of new and efficient strategies for the construction of an imidazo[1,2-*a*]pyridine core[1] due to its biological activities and medical applications.[2] In particular, different substituents at the C3-position of imidazo[1,2-*a*]pyridine can profoundly influence their bioactivities.[3] Additionally, this C3-alkylation imidazo[1,2-*a*]pyridine motif has been found in commercially available drugs such as zolpidem, saripidem, alpidem, and necopidem (Scheme 1). Halogenated imidazo-[1,2-*a*]pyridines as a class of important building blocks and versatile synthons could be further converted to more complex organic molecules through cross-coupling reactions. Despite that significant advances have been made recently for the construction of an imidazo[1,2-*a*]pyridine skeleton relying on 2-aminopyridine derivatives,[4] including our own contributions,[5−7] there are very few general methods that convert unfunctionalized pyridines in one step to halogenated imidazo-[1,2-*a*]pyridines. Thus, the development of efficient and general access to functionalized imidazo[1,2-*a*]pyridines is of great interest.

Direct transformation of simple pyridine gives a straightforward route to imidazo[1,2-*a*]pyridine[8] via intermolecular oxidative C−H/N−H cross-coupling reaction for its economic and practical feature. Transition-metal-catalyzed aerobic oxidative coupling reactions have emerged recently as a powerful strategy to form a C−N bond directly.[9] Noteworthily, the copper/oxygen catalytic system for oxidative functionalization of the C−H bond has attracted considerable attention for its efficient process, low cost, and sustainability.[10] Recently, copper(I)-catalyzed oxidative cyclization of pyridine with oxime esters,[11] *N*-(alkylidene)-4*H*-1,2,4-triazol-4-amines,[12] and vinyl azides[13] for imidazo[1,2-*a*]pyridines synthesis has been developed, respectively (Scheme 2, a−c). As an excellent oxidative coupling partner, enamides have been illuminated by copper-catalyzed oxidative coupling for the synthesis of nitrogen-containing heterocycles.[14−16] In connection with our interest in a copper/oxygen catalytic system to form *N*-heterocycles,[5,17] herein, we describe a copper-mediated aerobic oxidative coupling of pyridines with enamides for synthesis of 3-bromo-imidazo[1,2-*a*]pyridines in a one-pot manner (Scheme 2, d). In addition, these 3-bromo-substrates can be used as versatile synthetic blocks for further transformation.[18,19]

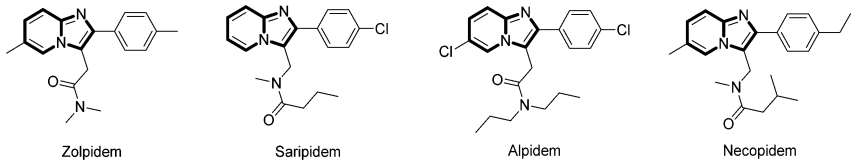
RESULTS AND DISCUSSION

To initiate our study, the reaction conditions were screened for the formation of 3-bromo-imidazo[1,2-*a*]pyridine with *N*-(1-phenylvinyl)acetamide (**1a**) and pyridine (**2a**) as model substrates (Table 1). Various solvents were first examined using $CuBr_2$ as a catalyst and halogen source. In a typical procedure, a mixture of **1a** (0.2 mmol, 1 equiv), **2a** (3 equiv), and $CuBr_2$ (1.2 equiv) in 2 mL of solvent was stirred under air at 70 °C. The desired product 3-bromo-2-phenylimidazo[1,2-*a*]pyridine (**3aa**) was detected when DCE, PhCl, CH_3CN, 1,4-dioxane, and toluene were used as the solvents, respectively. The results illustrated that DCE, PhCl, CH_3CN, and 1,4-dioxane were better solvents in this transformation, and the highest yield was given in DCE. **3aa** was obtained in 67% yield (Table 1, entries 1−9). To explore the catalyst and brominating agent, CuBr was tested, and the result showed that $CuBr_2$ displayed better ability than CuBr in this conversion clearly (Table 1, entries 10, 16). Subsequently, in the presence of nitrogen, no expected **3aa** was detected, which indicated that oxygen was essential to this reaction (Table 1, entry 11). Next, a range of oxidants such as TBHP, DTBP, $K_2S_2O_8$, and oxygen (balloon) were evaluated, and the oxygen exhibited an excellent ability (Table 1, entries 12−15). To reduce the dosage of copper salts, some Br donors such as LiBr, NaBr, KBr, NBS, and Br_2 were used with a catalytic amount of copper salts for this transformation, but the results were not pleasurable (Table 1, entries 17−24). It was worth mentioning that, when a

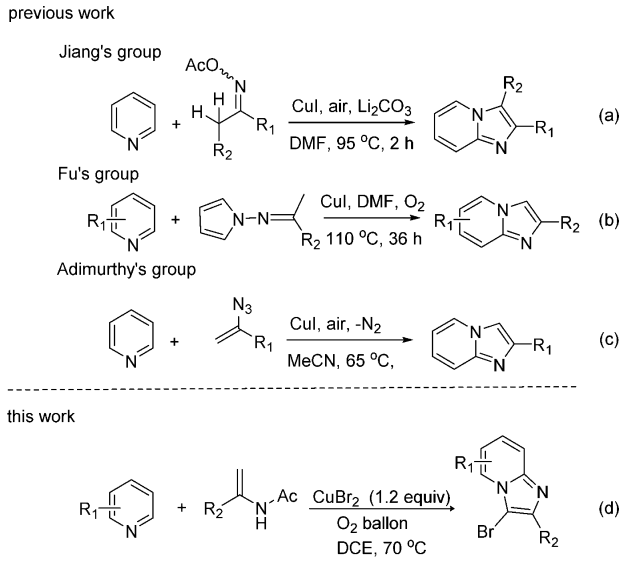
Received: March 31, 2015
Published: December 1, 2015

DOI: 10.1021/acs.joc.5b02384
J. Org. Chem. 2016, 81, 25−31

Scheme 1. Examples of Imidazo[1,2-*a*]pyridines with Biological Activities



Scheme 2. Direct Transformation of Pyridine to Imidazo[1,2-*a*]pyridines

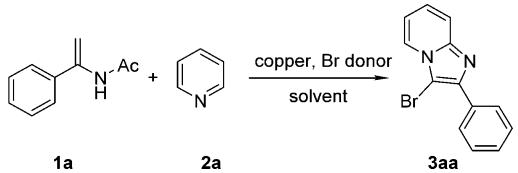


catalytic amount of CuI and an excess amount of LiBr were used in this conversion, the major 3-iodo-2-phenylimidazo[1,2-*a*]pyridine (**4aa**) was given in 14% yield (Table 1, entry 17). Finally, the optimized reaction conditions were obtained as follows: 1.2 equiv of $CuBr_2$ as a catalyst and brominating agent in DCE at 70 °C under an oxygen atmosphere (Table 1, entry 15).

With the optimized reaction conditions in hand, the applicability to different enamides was investigated (Scheme 3). A variety of enamides transformed smoothly to 3-bromoimidazo[1,2-*a*]pyridines in this copper/oxygen catalytic system and displayed high functional group tolerance including methyl, methoxyl, phenyl, fluoro, chloro, and trifuoromethyl (**3aa**−**3ga**, **3ja**−**3na**). The yields remained relatively stable with the nature of the different groups in the aromatic ring of enamides, and regioselectivity favored the least sterically hindered position. Also 1- or 2-naphthalenylethanone enamides survived well, providing the desired **3ha** and **3ia** in good yields, respectively. Additionally, the heterocycle enamides derived from furan-2-yl and thiophen-2-yl ketones were tolerated in this transformation (**3oa**, **3pa**). Unfortunately, the employment of an aliphatic enamide such as methyl 2-acetamidoacrylate **1q** could not give the desired **3qa**.

This copper/oxygen catalytic system was further expanded to a range of substituted pyridines (Scheme 4). The results demonstrated that substituents at different positions of the pyridine ring (para, meta, and ortho positions) could affect the efficiency obviously. Either electron-withdrawing or electron-donating groups at the meta position of pyridine all can transform successfully (**3ad**−**3af′**). An interesting result was that the methyl at the C3-position gave the desired product with the C6-position in favor (**3ad**, **3ad′**), but at the para or

Table 1. Optimization of the Reaction Conditions[a]



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

entry	catalyst	Br donor	sovlent	oxidant	yield[b] (%)
1	$CuBr_2$	$CuBr_2$	DMF	air	nd[c]
2	$CuBr_2$	$CuBr_2$	CH_3NO_2	air	nd
3	$CuBr_2$	$CuBr_2$	DCE	air	67
4	$CuBr_2$	$CuBr_2$	PhCl	air	47
5	$CuBr_2$	$CuBr_2$	DMSO	air	nd
6	$CuBr_2$	$CuBr_2$	CH_3CN	air	64
7	$CuBr_2$	$CuBr_2$	1,4-dioxane	air	44
8	$CuBr_2$	$CuBr_2$	toluene	air	8
9	$CuBr_2$	$CuBr_2$	EtOH	air	nd
10	CuBr	CuBr	DCE	air	26
11[d]	$CuBr_2$	$CuBr_2$	DCE		nd
12	$CuBr_2$	$CuBr_2$	DCE	TBHP	nd
13	$CuBr_2$	$CuBr_2$	DCE	DTBP	nd
14	$CuBr_2$	$CuBr_2$	DCE	$K_2S_2O_8$	nd
15	**$CuBr_2$**	**$CuBr_2$**	**DCE**	**O_2**	**74**
16	CuBr	CuBr	DCE	O_2	23
17[e]	CuI	LiBr	DCE	O_2	trace[f]
18[e]	CuI	NaBr	DCE	O_2	32
19[e]	CuI	KBr	DCE	O_2	trace
20[e,g]	CuI	Br_2	DCE	O_2	17
21[e]	CuBr	NaBr	DCE	O_2	trace
22[e]	$CuBr_2$	NaBr	DCE	O_2	43
23[e]	$CuBr_2$	NBS	DCE	O_2	nd
24[e,g]	$CuBr_2$	Br_2	DCE	O_2	30

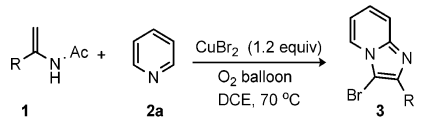
[a]Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (0.2 equiv), Br donor (1.0 equiv), solvent (2 mL), under 70 °C, oxidant (0.4 mmol), and monitored by TLC. DCE = 1,2-dichloroethane, PhCl = chlorobenzene, CH_3CN = acetonitrile, TBHP = *tert*-butyl hydroperoxide solution 5.5 M in decane, DTBP = di-*tert*-butyl peroxide. [b]Isolated yields. [c]nd = not detected. [d]Under nitrogen atmosphere. [e]Br donor (2.0 equiv). [f]3-Iodo-2-phenylimidazo[1,2-*a*]pyridine (**4aa**) was given in 14% yield. [g]After the mixture was kept stirring for 12 h and cooled to r.t., Br_2 was added and the mixture was stirred at r.t. for the desired time.

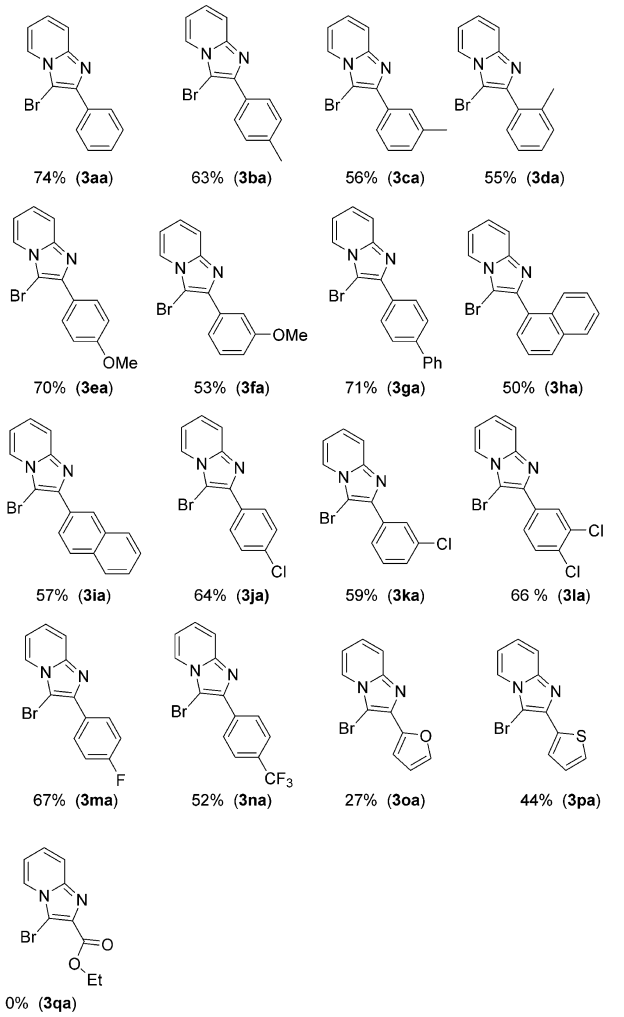
ortho position did not work under the standard conditions (**3ab**−**3ac**). Moreover, quinoline and isoquinoline were explored. To our disappointment, quinoline was not suited for this conversion, whereas isoquinoline was tolerated in this transformation as well to produce the corresponding 3-bromoimidazo[2,1-*a*]isoquinolines, respectively. Moderate yields can be given in some cases, but higher doses of $CuBr_2$ (1.5 equiv) were needed (**3ag**−**3mg**).

To further highlight the versatility of this strategy, other copper halides were tested (Scheme 5). A preliminary experiment showed that the addition of 2 equiv of CuI instead of $CuBr_2$ results in the expected iodinated product (**4aa**) in

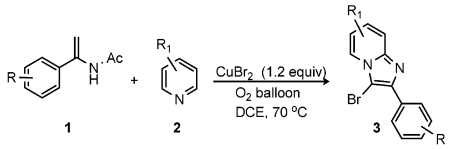
DOI: 10.1021/acs.joc.5b02384
J. Org. Chem. 2016, 81, 25−31

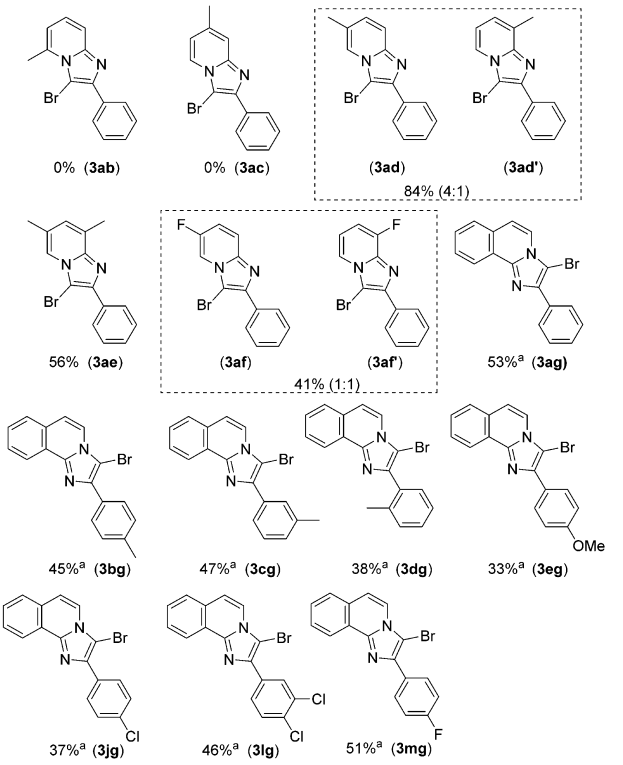
Scheme 3. Scope of Enamides





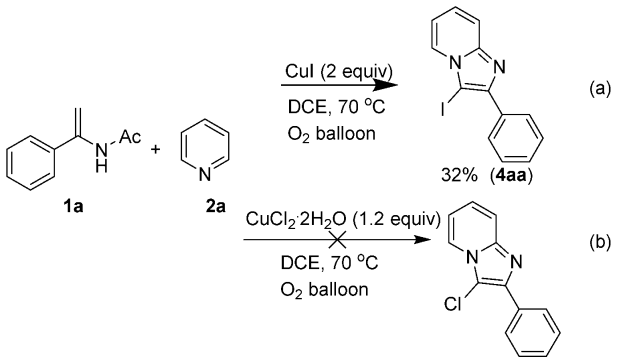
Scheme 4. Scope of Pyridines





[a]1.5 equiv of $CuBr_2$ was used.

Scheme 5. Substrate Scope for Copper Salts



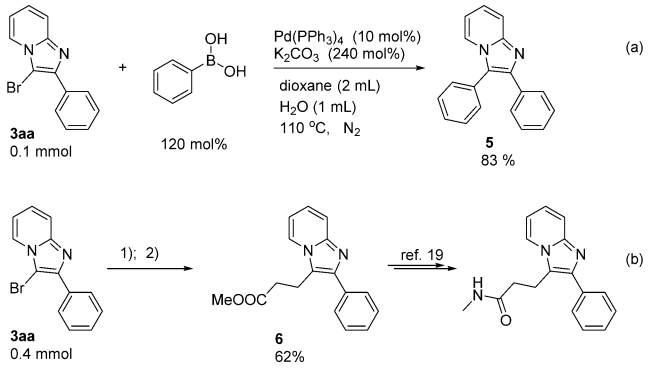
32% yield under similar conditions. However, the chlorinated product was not detected by the use of $CuCl_2 \cdot 2H_2O$ under analogous conditions. Moreover, the synthetic applications of 3-bromo-imidazo[1,2-*a*]pyridines are shown in Scheme 6, and C3-arylation and alkylation reactions can transform smoothly through a classical Pd-catalyzed cross-coupling strategy.

To gain mechanistic insight into this transformation, some control experiments were carried out. The reaction of **1a** (1.0 equiv), **2a** (3.0 equiv), and $CuBr_2$ (0.2 equiv) was investigated in DCE under an oxygen atmosphere and generated the intermediate 2-phenylimidazo[1,2-*a*]pyridine **7aa** in 57% yield; then **7aa** was subjected to the reaction with $CuBr_2$ (1.2 equiv) and pyridine (2.0 equiv) under an oxygen atmosphere. The desired product **3aa** was isolated in 95% yield (Scheme 7, a). Furthermore, the reaction of **1a** and **2a** in the addition of a free radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) generated TEMPO-trapped *N*-(1-phenylethylidene)acetamide **8a** in 38% yield under the standard conditions (Scheme 7, b). This result indicates the existence of the key intermediate radical ion **A** and its tautomer **B** (Scheme 8). Also, the intermolecular kinetic isotope effect (KIE) of the reaction was studied. The experiment shows that the C−H bond cleavage of pyridine was not the rate-determining step (KIE = 0.95) (Scheme 7, c).

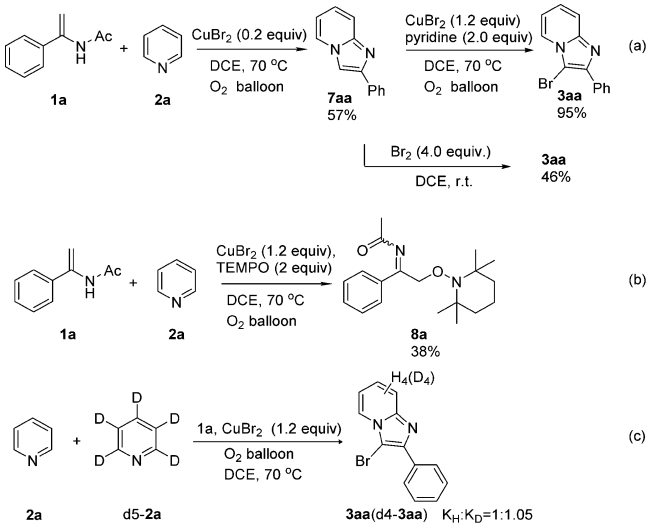
On the basis of the previous literature reports[11−13,17,20] and the above results, the possible mechanism for this transformation is proposed, as illustrated in Scheme 8. First, the copper/oxygen system converts enamide **1a** into carbocation **C** by a hydrogen atom abstraction and a two-step electron transfer process. Nucleophilic attack of **2a** on **C** gives intermediate **D**,

DOI: 10.1021/acs.joc.5b02384
J. Org. Chem. 2016, 81, 25−31

Scheme 6. Selected Transformations of Brominated Imidazo[1,2-*a*]pyridine



Scheme 7. Control Experiments



and the isomerization of **D** affords **E**. Then, coordination of the Cu(II) to **E** provides complex **F**. Subsequently, the intramolecular cycloaddition, hydrolysis, and oxidative aromatization lead to the block **7aa**. Finally, the bromination of **7aa** yields the target molecule **3aa** in the presence of $CuBr_2$ and molecular oxygen.

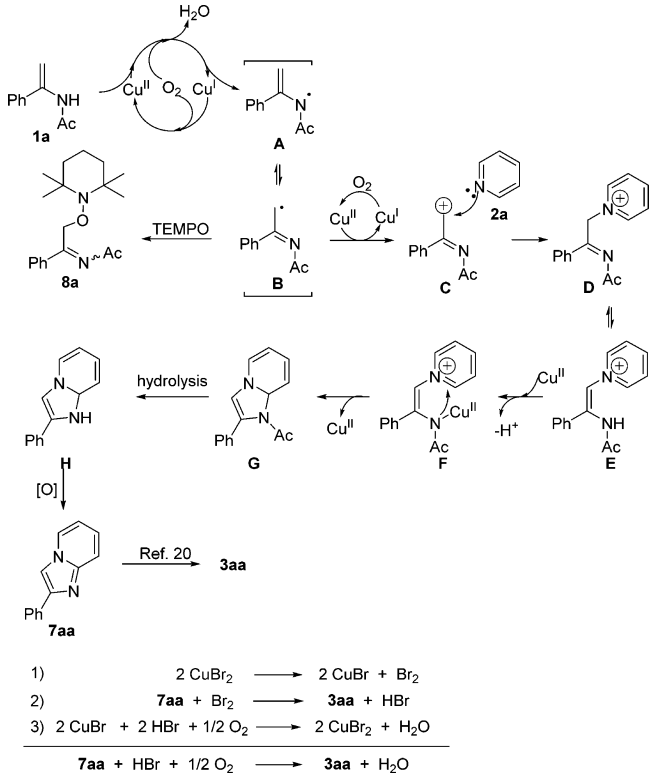
■ CONCLUSION

In conclusion, we have developed a one-pot copper-mediated aerobic oxidative coupling of enamides with pyridines to form 3-bromo-imidazo[1,2-*a*]pyridine derivatives, which are useful intermediates for the preparation of pharmaceutically and biologically active compounds as well as functional materials. This procedure employs oxygen as an oxidant, copper salt as a catalyst to activate the C−H/N−H bond, and a halogenating agent in the conversion. The avoidance of prefunctionalization of substrates and fewer synthetic steps make this protocol attractive.

■ EXPERIMENTAL SECTION

General Remarks. ^{1}H NMR spectra were recorded at 400 MHz. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0.00 ppm) in $CDCl_3$ as an internal standard. ^{13}C NMR spectra were obtained at 100 MHz and were calibrated with $CDCl_3$ (δ = 77.00 ppm). The high-resolution mass spectra (HRMS) were recorded on an FT-ICR mass spectrometer using electrospray ionization (ESI). Products were purified by flash chromatography on 200−300 mesh silica gels. All melting points were determined without correction. Unless otherwise noted, commercially available reagents and solvents were used without further purification. The enamides **1a**−**1p** were prepared from the corresponding ketoximes according to the reported literature,[15] and **1q** was prepared according to the reported literature.[21]

Scheme 8. Proposed Mechanism



General Experimental Procedure. A test tube equipped with a magnetic stir bar was charged with enamides **1** (0.2 mmol), pyridines **2** (0.6 mmol), $CuBr_2$ (53.5 mg, 0.24 mmol), and DCE (2 mL). The reaction tube was evacuated and backfilled with O_2 (3 times, balloon). Then, the reaction mixture was stirred at 70 °C (oil bath temperature) under an O_2 balloon. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate and quenched with $NH_3{\cdot}H_2O$; then the mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the residues were purified by column chromatography, eluting with petroleum ether/EtOAc to afford the disired 3-halo-imidazo[1,2-*a*]pyridines.

The intermolecular competition reaction was conducted using equal amounts of pyridine **1a** (0.3 mmol, 1.5 equiv) and D-labeled pyridine *d*5-**1a** (0.3 mmol, 1.5 equiv).

Experimental Procedure for 8a. A test tube equipped with a magnetic stir bar was charged with *N*-(1-phenylvinyl)acetamide **1a** (32.2 mg, 0.2 mmol), pyridine **2a** (47.4 mg, 0.6 mmol), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (62.4 mg, 0.4 mmol), $CuBr_2$ (53.5 mg, 0.24 mmol), and DCE (2 mL). The reaction tube was evacuated and backfilled with O_2 (3 times, balloon). Then, the reaction mixture was stirred at 70 °C (oil bath temperature) under an O_2 balloon for 5 h. The reaction mixture was filtered by 5 mm silica gels, washed with ethyl acetate. All the organic phase was concentrated in vacuo, and the residues were purified by column chromatography, eluting with petroleum ether/EtOAc to afford **8a**.

Analytical Data for Products. *3-Bromo-2-phenylimidazo[1,2-a]pyridine (**3aa**).* Yellow oil (74%, 40.3 mg). ^{1}H NMR (400 MHz,

DOI: 10.1021/acs.joc.5b02384
J. Org. Chem. 2016, 81, 25−31

$CDCl_3$) δ 8.15−8.12 (m, 3 H), 7.64−7.61 (d, *J* = 8.8 Hz, 1 H), 7.50−7.46 (m, 2 H), 7.40−7.36 (m, 1 H), 7.26−7.21 (t, *J* = 7.2 Hz, 1 H), 6.91−6.87 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 142.6, 132.8, 128.4, 128.2, 127.8, 125.0, 123.9, 117.6, 112.9, 91.6. ESI-HRMS: *m*/*z* Calcd for $C_{13}H_9BrN_2$ + H^+: 273.0022, found 273.0021.

3-Bromo-2-(p-tolyl)imidazo[1,2-a]pyridine (**3ba**). Yellow solid (63%, 36.0 mg), melting point: 104−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17−8.15 (d, *J* = 7.2 Hz, 1 H), 8.03−8.00 (m, 2 H), 7.66−7.64 (d, *J* = 9.2 Hz, 1 H), 7.30−7.23 (m, 3 H), 6.94−6.90 (t, *J* = 6.8 Hz, 1 H), 2.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 142.6, 138.2, 129.8, 129.2, 127.8, 125.1, 123.9, 117.4, 113.0, 91.4, 21.3. ESI-HRMS: *m*/*z* Calcd for $C_{14}H_{11}BrN_2$ + H^+: 287.0179, found 287.0183.

3-Bromo-2-(m-tolyl)imidazo[1,2-a]pyridine (**3ca**). Yellow oil (56%, 32.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.13 (d, *J* = 6.8 Hz, 1 H), 7.95−7.92 (m, 2 H), 7.64−7.61 (d, *J* = 9.2 Hz, 1 H), 7.38−7.34 (t, *J* = 7.6 Hz, 1 H), 7.26−7.19 (m, 2 H), 6.91−6.87 (t, *J* = 6.8 Hz, 1 H), 2.44 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 142.7, 138.1, 132.7, 129.0, 128.5, 128.2, 124.9, 124.9, 123.9, 117.5, 112.9, 91.6, 21.5. ESI-HRMS: *m*/*z* Calcd for $C_{14}H_{11}BrN_2$ + H^+: 287.0179, found 287.0181.

3-Bromo-2-(o-tolyl)imidazo[1,2-a]pyridine (**3da**). Yellow oil (55%, 31.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.16 (d, *J* = 6.8 Hz, 1 H), 7.64−7.62 (d, *J* = 9.2 Hz, 1 H), 7.46−7.44 (d, *J* = 7.6 Hz, 1 H), 7.33−7.24 (m, 4 H), 6.97−6.93 (t, *J* = 6.8 Hz, 1 H), 2.38 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 144.8, 137.5, 132.3, 130.6, 130.3, 128.6, 125.4, 124.7, 123.9, 117.7, 112.9, 93.6, 20.2. ESI-HRMS: *m*/*z* Calcd for $C_{14}H_{11}BrN_2$ + H^+: 287.0179, found 287.0183.

3-Bromo-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine (**3ea**). Yellow solid (70%, 42.3 mg), melting point: 92−94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.12 (d, *J* = 6.8 Hz, 1 H), 8.09−8.06 (m, 2 H), 7.62−7.60 (d, *J* = 6.8 Hz, 1 H), 7.24−7.20 (m, 1 H), 7.02−7.00 (m, 2 H), 6.91−6.87 (m, 1 H), 3.85 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 145.3, 142.4, 129.1, 125.3, 124.9, 123.8, 117.3, 113.8, 112.8, 90.8, 55.2. ESI-HRMS: *m*/*z* Calcd for $C_{14}H_{11}BrN_2O$ + H^+: 303.0128, found 303.0125.

3-Bromo-2-(3-methoxyphenyl)imidazo[1,2-a]pyridine (**3fa**). Yellow oil (53%, 32.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17−8.15 (d, *J* = 6.8 Hz, 1 H), 7.74−7.69 (m, 2 H), 7.64−7.62 (d, *J* = 7.2 Hz, 1 H), 7.41−7.37 (t, *J* = 8.0 Hz, 1 H), 7.26−7.22 (m, 1 H), 6.96−6.89 (m, 2 H), 3.89 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 145.3, 142.4, 134.1, 129.4, 125.1, 123.9, 120.3, 117.6, 114.5, 113.0, 112.8, 91.8, 55.3. ESI-HRMS: *m*/*z* Calcd for $C_{14}H_{11}BrN_2O$ + H^+: 303.0128, found 303.0129.

2-([1,1′-Biphenyl]-4-yl)-3-bromoimidazo[1,2-a]pyridine (**3ga**). White solid (71%, 49.4 mg), melting point: 112−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.21 (m, 2 H), 8.15−8.13 (d, *J* = 7.2 Hz,1 H), 7.72−7.70 (m, 2 H), 7.66−7.62 (m, 3 H), 7.46−7.42 (m, 2 H), 7.36−7.32 (t, *J* = 7.2 Hz, 1 H), 7.24−7.20(m, 1 H), 6.90−6.86 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 142.3, 140.9, 140.6, 131.8, 128.7, 128.2, 127.4, 127.1, 127.0, 125.0, 123.9, 117.6, 113.0, 91.7. ESI-HRMS: *m*/*z* Calcd for $C_{19}H_{13}BrN_2$ + H^+: 349.0335, found 349.0337.

3-Bromo-2-(naphthalen-1-yl)imidazo[1,2-a]pyridine (**3ha**). Yellow solid (50%, 32.2 mg), melting point: 154−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.21 (dd, J_1 = 6.8 Hz, J_2 = 2.8 Hz, 1 H), 8.15−8.13 (dd, J_1 = 6.8 Hz, J_2 = 2.8 Hz, 1 H), 7.94−7.90 (m, 2 H), 7.72−7.69 (m, 2 H), 7.58−7.55 (m, 1 H), 7.51−7.46 (m, 2 H), 7.32−7.25(m, 1 H), 6.99−6.96 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 143.7, 133.8, 131.8, 130.2, 129.1, 128.7, 128.2, 126.4, 126.3, 125.9, 125.0, 124.9, 124.1, 117.8, 113.1, 94.5. ESI-HRMS: *m*/*z* Calcd for $C_{17}H_{11}BrN_2$ + H^+: 323.0179, found 323.0176.

3-Bromo-2-(naphthalen-2-yl)imidazo[1,2-a]pyridine (**3ia**). Yellow solid (57%, 36.7 mg), melting point: 84−86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1 H), 8.29−8.26 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz,1 H), 8.17−8.15 (d, *J* = 7.2 Hz,1 H), 7.96−7.92 (m, 2 H), 7.86−7.84 (m, 1 H), 7.68−7.66 (d, *J* = 8.8 Hz, 1 H), 7.51−7.47 (m, 2 H), 7.27−7.23(m, 1 H), 6.93−6.89 (td, J_1 = 6.8 Hz, J_2 = 0.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 142.5, 133.3, 133.1, 130.2, 128.5, 128.0, 127.6, 127.1, 126.3, 126.2, 125.5, 125.2, 123.9, 117.6, 113.1, 92.0. ESI-HRMS: *m*/*z* Calcd for $C_{17}H_{11}BrN_2$ + H^+: 323.0179, found 323.0177.

3-Bromo-2-(4-chlorophenyl)imidazo[1,2-a]pyridine (**3ja**). Yellow solid (64%, 39.2 mg), melting point: 136−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.14 (m, 1 H), 8.09−8.07 (m, 2 H), 7.63−7.61 (m, 1 H), 7.45−7.43 (m, 2 H), 7.28−7.24 (m, 1 H), 6.94−6.91 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 141.5, 134.2, 131.4, 129.0, 128.6, 125.3, 123.9, 117.6, 113.2, 91.7. ESI-HRMS: *m*/*z* Calcd for $C_{13}H_8BrClN_2$ + H^+: 306.9632, found 306.9630.

3-Bromo-2-(3-chlorophenyl)imidazo[1,2-a]pyridine (**3ka**). Yellow solid (59%, 36.1 mg), melting point: 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17−8.15 (m, 2 H), 8.04−8.02 (m, 1 H), 7.64−7.61 (d, *J* = 9.2 Hz, 1 H), 7.42−7.33 (m, 2 H), 7.29−7.24 (m, 1 H), 6.96−6.92 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 141.2, 134.7, 134.5, 129.7, 128.3, 127.8, 125.8, 125.4, 124.0, 117.7, 113.3, 92.0. ESI-HRMS: *m*/*z* Calcd for $C_{13}H_8BrClN_2$ + H^+: 306.9632, found 306.9631.

3-Bromo-2-(3,4-dichlorophenyl)imidazo[1,2-a]pyridine (**3la**). White solid (66%, 44.9 mg), melting point: 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.26 (d, *J* = 2 Hz, 1 H), 8.16−8.14 (m, 1 H), 8.01−7.98 (dd, J_1 = 2 Hz, J_2 = 4.4 Hz, 1 H), 7.63−7.60 (m, 1 H), 7.53−7.51 (t, *J* = 4.4 Hz, 1 H), 7.30−7.26 (m, 1 H), 6.97−6.93 (m,1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 140.2, 132.9, 132.7, 132.2, 130.4, 129.4, 126.7, 125.6, 124.0, 117.7, 113.4, 92.1. ESI-HRMS: *m*/*z* Calcd for $C_{13}H_7BrCl_2N_2$ + H^+: 340.9243, found 340.9244.

3-Bromo-2-(4-fluorophenyl)imidazo[1,2-a]pyridine (**3ma**). White solid (67%, 38.9 mg), melting point: 96−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.09 (m, 3 H), 7.63−7.60 (d, *J* = 9.2 Hz, 1 H), 7.27−7.23 (d, *J* = 7.2 Hz, 1 H), 7.18−7.14 (m, 2 H), 6.93−6.90 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, *J* = 246 Hz), 145.4, 141.8, 129.6 (d, *J* = 8 Hz), 129.0 (d, *J* = 3 Hz), 125.1, 123.9, 117.5, 115.4 (d, *J* = 21 Hz), 113.1, 91.4. ESI-HRMS: *m*/*z* Calcd for $C_{13}H_8BrFN_2$ + H^+: 290.9928, found 290.9929.

3-Bromo-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridine (**3na**). White solid (52%, 35.4 mg), melting point: 120−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.26 (m, 2 H), 8.18−8.16 (d, *J* = 6.8 Hz, 1 H), 7.73−7.71 (m, 2 H), 7.65−7.63 (d, *J* = 9.2 Hz, 1 H), 7.30−7.26 (m, 1 H), 6.97−6.93 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 141.0, 136.4, 129.9 (q, *J* = 32 Hz), 127.9, 125.5, 125.33 (q, *J* = 4 Hz), 124.2 (q, *J* = 270 Hz), 124.0, 117.8, 113.4, 92.5. ESI-HRMS: *m*/*z* Calcd for $C_{14}H_8BrF_3N_2$ + H^+: 340.9896, found 340.9893.

3-Bromo-2-(furan-2-yl)imidazo[1,2-a]pyridine (**3oa**). Yellow oil (27%, 14.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.13 (d, *J* = 6.8 Hz, 1 H), 7.64−7.59 (m, 2 H), 7.28−7.24 (m, 1 H), 7.09−7.08 (d, *J* = 3.6 Hz, 1 H), 6.95−6.92 (m, 1 H), 6.56−6.55 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 145.5, 142.8, 135.6, 125.4, 123.8, 117.6, 113.3, 111.4, 108.9, 90.7. ESI-HRMS: *m*/*z* Calcd for $C_{11}H_7BrN_2O$ + H^+: 262.9815, found 262.9813.

3-Bromo-2-(thiophen-2-yl)imidazo[1,2-a]pyridine (**3pa**). Yellow solid (44%, 24.5 mg), melting point: 104−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.10 (d, *J* = 6.8 Hz, 1 H), 7.87−7.86 (d, *J* = 3.2 Hz, 1 H), 7.62−7.60 (d, *J* = 8.8 Hz, 1 H), 7.40−7.39 (d, *J* = 5.2 Hz, 1 H), 7.26−7.22 (m, 1 H), 7.16−7.14(m, 1 H), 6.93−6.90 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 138.5, 135.9, 127.7, 126.1, 125.5, 125.3, 123.7, 117.4, 113.1, 90.7. ESI-HRMS: *m*/*z* Calcd for $C_{11}H_7BrN_2S$ + H^+: 278.9586, found 278.9589.

3-Bromo-6-methyl-2-phenylimidazo[1,2-a]pyridine (**3ad**).[7] Yellow solid (67%, 38.3 mg), melting point: 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.11 (m, 2 H), 7.93 (s, 1 H), 7.53−7.45 (m, 3 H), 7.39−7.35 (t, *J* = 7.2 Hz, 1 H), 7.09−7.07 (m, 1 H), 2.37 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 142.4, 133.0, 128.4, 128.2, 128.1, 127.7, 122.8, 121.6, 116.9, 91.2, 18.3. ESI-HRMS: *m*/*z* Calcd for $C_{14}H_{11}BrN_2$ + H^+: 287.0179, found 287.0181.

3-Bromo-8-methyl-2-phenylimidazo[1,2-a]pyridine (**3ad′**).[7] Yellow oil (17%, 9.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.11 (m, 2 H), 8.05−8.03 (d, *J* = 6.8 Hz, 1 H), 7.50−7.46 (m, 2 H), 7.40−7.36 (t, *J* = 7.2 Hz, 1 H), 7.05−7.03 (d, *J* = 7.2 Hz, 1 H), 6.85−6.81 (t, *J* = 6.8 Hz, 1 H), 2.67 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 142.2, 133.2, 128.4, 128.1, 128.0, 127.7, 123.7, 121.8, 113.0, 92.0, 16.5. ESI-HRMS: *m*/*z* Calcd for $C_{14}H_{11}BrN_2$ + H^+: 287.0179, found 287.0182.

DOI: 10.1021/acs.joc.5b02384
J. Org. Chem. 2016, 81, 25−31

*3-Bromo-6,8-dimethyl-2-phenylimidazo[1,2-a]pyridine (**3ae**).* Red solid (56%, 33.6 mg), melting point: 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.10 (m, 2 H), 7.80 (s, 1 H), 7.48−7.44 (m, 2 H), 7.38−7.34 (t, J = 7.2 Hz, 1 H), 6.89 (s, 1 H), 2.62 (s, 3 H), 2.33 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 141.9, 133.3, 128.4, 127.9, 127.1, 126.8, 122.7, 119.5, 91.5, 18.3, 16.4. ESI-HRMS: m/z Calcd for $C_{15}H_{13}BrN_2$ + H^+: 301.0335, found 301.0337.

*3-Bromo-6-fluoro-2-phenylimidazo[1,2-a]pyridine (**3af**).*[7] Yellow solid (21%, 12.2 mg), melting point: 98−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.08 (m, 3 H), 7.63−7.59 (m, 1 H), 7.50−7.46 (m, 2 H), 7.41−7.37 (m, 1 H), 7.20−7.14 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8 (d, J = 237 Hz), 144.1, 143.1, 132.6, 128.5, 128.4, 127.7, 118.2(d, J = 9 Hz), 117.1 (d, J = 26 Hz), 110.9 (d, J = 43 Hz), 92.9. ESI-HRMS: m/z Calcd for $C_{13}H_8BrFN_2$ + H^+: 290.9928, found 290.9926.

*3-Bromo-8-fluoro-2-phenylimidazo[1,2-a]pyridine (**3af′**).* Yellow solid (20%, 11.6 mg), melting point: 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.22 (m, 2 H), 8.08−8.06 (d, J = 6.8 Hz, 1 H), 7.50−7.46 (m, 2 H), 7.42−7.38 (t, J = 7.2 Hz, 1 H), 7.00−6.96 (m, 1 H), 6.88−6.83 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2 (d, J = 253 Hz), 143.2, 138.0 (d, J = 29 Hz), 132.3, 128.5, 128.4, 128.0, 120. Three (d, J = 5 Hz), 112.0 (d, J = 6 Hz), 107.7 (d, J = 15 Hz), 93.3. ESI-HRMS: m/z Calcd for $C_{13}H_8BrFN_2$ + H^+: 290.9928, found 290.9927.

*3-Bromo-2-phenylimidazo[2,1-a]isoquinoline (**3ag**).* White solid (53%, 34.1 mg), melting point: 156−158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73−8.71 (d, J = 8.0 Hz, 1 H), 8.19−8.17 (m, 2 H), 7.97−7.95 (d, J = 7.2 Hz, 1 H), 7.72−7.48 (m, 5 H), 7.41−7.36 (m,1 H), 7.15−7.13 (d, J = 7.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 140.8, 133.0, 129.4, 128.6, 128.5, 128.4, 127.9, 127.7, 127.0, 123.4, 123.0, 120.9, 113.7, 93.6. ESI-HRMS: m/z Calcd for $C_{17}H_{11}BrN_2$ + H^+: 323.0179, found 323.0176.

*3-Bromo-2-(p-tolyl)imidazo[2,1-a]isoquinoline (**3bg**).* White solid (45%, 30.3 mg), melting point: 112−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72−8.69 (m, 1 H), 8.07−8.05 (m, 2 H), 7.94−7.92 (d, J = 7.2 Hz, 1 H), 7.70−7.54 (m, 3 H), 7.31−7.28 (m, 2 H), 7.11−7.09 (d, J = 7.2 Hz, 1 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 140.9, 137.8, 130.1, 129.4, 129.2, 128.5, 128.3, 127.6, 127.0, 123.4, 123.1, 120.9, 113.5, 93.3, 21.3. ESI-HRMS: m/z Calcd for $C_{18}H_{13}BrN_2$ + H^+: 337.0335, found 337.0337.

*3-Bromo-2-(m-tolyl)imidazo[2,1-a]isoquinoline (**3cg**).* Yellow solid (47%, 31.5 mg), melting point: 128−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72−8.70 (d, J = 8.4 Hz, 1 H), 8.00−7.92 (m, 3 H), 7.70−7.68 (d, J = 8.0 Hz, 1 H), 7.66−7.62 (m, 1 H), 7.59−7.55 (m, 1 H), 7.40−7.36 (t, J = 7.6 Hz, 1 H), 7.21−7.19 (d, J = 7.2 Hz, 1 H), 7.11−7.09 (d, J = 7.2 Hz, 1 H), 2.46 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 140.9, 138.1, 132.9, 129.4, 128.7, 128.5, 128.4, 128.3, 127.0, 124.7, 123.4, 123.0, 120.9, 113.6, 93.6, 21.6. ESI-HRMS: m/z Calcd for $C_{18}H_{13}BrN_2$ + H^+: 337.0335, found 337.0337.

*3-Bromo-2-(o-tolyl)imidazo[2,1-a]isoquinoline (**3dg**).* Yellow solid (38%, 25.3 mg), melting point: 132−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70−8.68 (d, J = 7.6 Hz, 1 H), 7.99−7.97 (d, J = 7.2, 1 H), 7.7.76−7.74 (m, 1 H), 7.67−7.58 (m, 2 H), 7.51−7.49 (d, J = 7.2 Hz, 1 H), 7.34−7.26 (m, 3 H), 7.19−7.17 (d, J = 7.2 Hz, 1 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 142.6, 137.7, 132.4, 130.7, 130.4, 129.3, 128.5, 128.5, 128.4, 127.0, 125.5, 123.5, 122.9, 121.1, 113.6, 95.5, 20.3. ESI-HRMS: m/z Calcd for $C_{18}H_{13}BrN_2$ + H^+: 337.0335, found 337.0336.

*3-Bromo-2-(4-methoxyphenyl)imidazo[2,1-a]isoquinoline (**3eg**).* White solid (33%, 23.2 mg), melting point: 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71−8.69 (d, J = 8.0 Hz, 1 H), 8.13−8.11 (m, 2 H), 7.97−7.95 (d, J = 7.6 Hz, 1 H), 7.73−7.71 (d, J = 8.0 Hz, 1 H), 7.67−7.63 (m,1 H), 7.60−7.56 (m, 1 H), 7.14−7.12 (d, J = 7.6 Hz,1 H), 7.04−7.02 (m, 2 H), 3.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 143.2, 140.7, 129.4, 129.0, 128.4, 128.3, 127.0, 125.7, 123.4, 123.0, 121.0, 113.9, 113.4, 92.7, 55.3. ESI-HRMS: m/z Calcd for $C_{18}H_{13}BrN_2O$ + H^+: 353.0284, found 353.0286.

*3-Bromo-2-(4-chlorophenyl)imidazo[2,1-a]isoquinoline (**3jg**).* Yellow solid (37%, 26.4 mg), melting point: 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70−8.68 (d, J = 8.0 Hz, 1 H), 8.15−8.13 (m, 2 H), 7.98−7.96 (d, J = 7.2 Hz, 1 H), 7.75−7.73 (d, J = 7.6 Hz, 1 H), 7.69−7.65 (m,1 H), 7.63−7.59 (m, 1 H), 7.47−7.45 (m, 2 H), 7.18−7.16 (d, J = 7.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 139.7, 133.8, 131.6, 129.5, 128.9, 128.7, 128.6, 128.5, 127.1, 123.4, 123.0, 120.9, 113.9, 93.7. ESI-HRMS: m/z Calcd for $C_{17}H_{10}BrClN_2$ + H^+: 356.9789, found 356.9791.

*3-Bromo-2-(3,4-dichlorophenyl)imidazo[2,1-a]isoquinoline (**3lg**).* White solid (46%, 36.0 mg), melting point: 166−168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69−8.67 (d, J = 7.6 Hz, 1 H), 8.33−8.32 (d, J = 2.0 Hz, 1 H), 8.07−8.04 (m, 1 H), 7.96−7.94 (d, J = 7.2 Hz, 1 H), 7.75−7.72(d, J = 8.0 Hz, 1 H), 7.69−7.59 (m, 2 H), 7.54−7.52 (d, J = 8.4 Hz, 1 H), 7.18−7.16 (d, J = 7.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.3, 133.2, 132.6, 131.7, 130.4, 129.5, 129.2, 128.9, 128.6, 127.1, 126.5, 123.3, 123.1, 120.8, 114.1, 94.1. ESI-HRMS: m/z Calcd for $C_{17}H_9BrCl_2N_2$ $[M + H]^+$: 390.9399, found 390.9401.

*3-Bromo-2-(4-fluorophenyl)imidazo[2,1-a]isoquinoline (**3mg**).* White solid (51%, 34.8 mg), melting point: 144−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69−8.67 (d, J = 8.0 Hz, 1 H), 8.17−8.13 (m, 2 H), 7.95−7.93 (d, J = 7.2 Hz, 1 H), 7.72−7.70 (d, J = 8.0 Hz, 1 H), 7.67−7.63 (m, 1 H), 7.61−7.57 (m, 1 H), 7.20−7.12 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J = 246 Hz), 143.3, 139.9, 129.4 (d, J = 9 Hz), 129.4, 129.2 (d, J = 3 Hz), 128.6, 128.4, 127.0, 123.3, 123.0, 120.9, 115.4 (d, J = 22 Hz), 113.7, 93.3. ESI-HRMS: m/z Calcd for $C_{17}H_{10}BrFN_2$ + H^+: 341.0084, found 341.0087.

*3-Iodo-2-phenylimidazo[1,2-a]pyridine (**4aa**).* Yellow solid (32%, 20.5 mg), melting point: 148−150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.22 (d, J = 6.8 Hz, 1 H), 8.08−8.06 (m, 2 H), 7.63−7.61 (d, J = 8.8 Hz, 1 H), 7.50−7.47 (m, 2 H), 7.42−7.38 (m, 1 H), 7.28−7.24 (m, 1 H), 6.94−9.91 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 148.1, 133.6, 128.5, 128.3, 126.5, 125.5, 117.6, 113.1, 59.4. ESI-HRMS: m/z Calcd for $C_{13}H_9IN_2$ + H^+: 320.9883, found 320.9887.

*2,3-Diphenylimidazo[1,2-a]pyridine (**5**).*[22] Yellow solid (83%, 22.3 mg). melting point: 146−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.94 (m, 1 H), 7.70−7.65 (m, 3 H), 7.55−7.43 (m, 5 H), 7.30−7.23 (m, 3 H), 7.22−7.17 (m, 1 H), 6.75−6.71 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 142.3, 134.0, 130.7, 129.8, 129.5, 128.9, 128.2, 128.1, 127.5, 124.7, 123.3, 121.1, 117.5, 112.3. EI-MS m/z: 270.

*Methyl 3-(2-Phenylimidazo[1,2-a]pyridin-3-yl)propanoate (**6**).*[19] White solid (62%, 69.3 mg). melting point: 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−8.00 (m, 1 H), 7.78−7.76 (m, 2 H), 7.64−7.62 (m, 1 H), 7.48−7.44 (m, 2 H), 7.37−7.33 (m, 1 H), 7.18−7.14 (m, 1 H), 6.84−6.80 (m, 1 H), 3.65−3.64 (d, J = 3.2 Hz, 3 H), 3.46−3.42 (td, J_1 = 8.0 Hz, J_2 = 2.8 Hz, 2 H), 2.70−2.65 (td, J_1 = 8.0 Hz, J_2 = 2.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 144.5, 142.7, 134.5, 128.5, 128.0, 127.5, 123.8, 122.8, 118.3, 117.6, 112.1, 51.8, 32.0, 19.1. EI-MS m/z: 280.

*2-Phenylimidazo[1,2-a]pyridine (**7aa**).*[7] White solid (57%, 22.1 mg), melting point: 107−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 1 H), 7.96−7.94 (m, 2 H), 7.82 (s, 1 H), 7.63−7.60 (d, J = 9.2 Hz, 1 H), 7.45−7.41 (m, 2 H), 7.34−7.30 (t, J = 7.6 Hz, 1 H), 7.16−7.11 (m, 1 H), 6.75−9.71 (t, J = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 145.6, 133.7, 128.6, 127.9, 126.0, 125.5, 124.5, 117.4, 112.3, 108.0. EI-MS m/z: 194.

*N-(1-Phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethylidene)acetamide (**8a**).* Yellow oil (38%, 24.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.50 (m, 2 H), 7.50−7.39 (m, 3 H), 5.05 (s, 2 H), 2.35 (s, 3 H), 1.60−1.32 (m, 6 H), 1.20 (s, 6 H), 1.14 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 158.8, 135.0, 131.5, 128.5, 127.3, 75.9, 60.3, 39.8, 32.6, 25.8, 20.5, 16.9. ESI-MS m/z ($M + H^+$): 317.

3aa:d_4-**3aa** = 1:1.05. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.12 (m, 5.11 H), 7.64−7.62 (d, J = 9.2 Hz, 1 H), 7.50−7.46 (m, 4.27 H), 7.40−7.37 (m, 2 H), 7.26−7.22 (m, 1 H), 6.93−6.89 (m, 1 H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02384.

NMR spectra of all compounds (PDF)

DOI: 10.1021/acs.joc.5b02384
J. Org. Chem. 2016, 81, 25−31

AUTHOR INFORMATION

Corresponding Authors

*Fax: +86 931 8912596. Tel: +86 931 8912586. E-mail: yanrl@lzu.edu.cn (R.Y.).

*E-mail: hgs@lzu.edu.cn (G.H.).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for the reviewers' useful suggestions on this manuscript.

REFERENCES

(1) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun.* **2015**, *51*, 1555 and the references cited therein.

(2) (a) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 347. (b) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170. (c) Katsura, Y.; Nishino, S.; Inoue, Y.; Tomoi, M.; Takasugi, H. *Chem. Pharm. Bull.* **1992**, *40*, 371. (d) Hanson, S. M.; Morlock, E. V.; Satyshur, K. A.; Czajkowski, C. *J. Med. Chem.* **2008**, *51*, 7243. (e) Wiegand, M. H. *Drugs* **2008**, *68*, 2411.

(3) Kim, O.; Jeong, Y.; Lee, H.; Hong, S.-S.; Hong, S. *J. Med. Chem.* **2011**, *54*, 2455−2466.

(4) For some recent examples of imidazo[1,2-*a*]pyridine synthesis from 2-aminopyridine, see: (a) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2743. (b) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333. (c) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2012**, *14*, 4580. (d) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 11073. (e) Mohan, D. C.; Donthiri, R. R.; Rao, S. N.; Adimurthy, S. *Adv. Synth. Catal.* **2013**, *355*, 2217. (f) Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. *Adv. Synth. Catal.* **2013**, *355*, 2686. (g) Cao, H.; Liu, X.; Zhao, L.; Cen, J.; Lin, J.; Zhu, Q.; Fu, M. *Org. Lett.* **2014**, *16*, 146. (h) Monir, K.; Bagdi, A. K.; Ghosh, M.; Hajra, A. *Org. Lett.* **2014**, *16*, 4630.

(5) (a) Yan, R.; Yan, H.; Ma, C.; Ren, Z.; Gao, X.; Huang, G.; Liang, Y. *J. Org. Chem.* **2012**, *77*, 2024. (b) Yan, H.; Yan, R.; Yang, S.; Gao, X.; Wang, Y.; Huang, G.; Liang, Y. *Chem. - Asian J.* **2012**, *7*, 2028.

(6) Yan, H.; Yang, Y.; Gao, X.; Zhou, K.; Ma, C.; Yan, R.; Huang, G. *Synlett* **2012**, *23*, 2961.

(7) Yan, H.; Wang, Y.; Pan, C.; Zhang, H.; Yang, S.; Ren, X.; Li, J.; Huang, G. *Eur. J. Org. Chem.* **2014**, *2014*, 2754.

(8) Attanasi, O. A.; Bianchi, L.; Campisi, L. A.; Crescentini, L. D.; Favi, G.; Mantellini, F. *Org. Lett.* **2013**, *15*, 3646.

(9) For some reviews, see: (a) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (b) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (d) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.

(10) For some reviews, see: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (b) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (c) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234. (d) Guo, X.; Gu, D.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622.

(11) Huang, H.; Ji, X.; Tang, X.; Zhang, M.; Li, X.; Jiang, H. *Org. Lett.* **2013**, *15*, 6254.

(12) Yu, J.; Jin, Y.; Zhang, H.; Yang, X.; Fu, H. *Chem. - Eur. J.* **2013**, *19*, 16804.

(13) Donthiri, R. R.; Pappula, V.; Reddy, N. N. K.; Bairagi, D.; Adimurthy, S. *J. Org. Chem.* **2014**, *79*, 11277.

(14) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599.

(15) Guan, Z.; Zhang, Z.; Ren, Z.; Wang, Y.; Zhang, X. *J. Org. Chem.* **2011**, *76*, 339.

(16) For some examples, see: (a) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (b) Stuart, D.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (c) Zhao, M.; Ren, Z.; Wang, Y.; Guan, Z. *Chem. Commun.* **2012**, *48*, 8105. (d) Chen, M.; Ren, Z.; Wang, Y.; Guan, Z. *Angew. Chem.* **2013**, *125*, 14446; *Angew. Chem., Int. Ed.* **2013**, *52*, 14196. (e) Zhao, M.; Ren, Z.; Wang, Y.; Guan, Z. *Chem. - Eur. J.* **2014**, *20*, 1839. (f) Zhao, M.; Ren, Z.; Wang, Y.; Guan, Z. *Org. Lett.* **2014**, *16*, 608.

(17) (a) Yan, R.; Liu, X.; Pan, C.; Zhou, X.; Li, X.; Kang, X.; Huang, G. *Org. Lett.* **2013**, *15*, 4876. (b) Yan, R.; Luo, J.; Wang, C.; Ma, C.; Huang, G.; Liang, Y. *J. Org. Chem.* **2010**, *75*, 5395.

(18) Koubachi, J.; El Kazzouli, S.; Bousmina, M.; Guillaumet, G. *Eur. J. Org. Chem.* **2014**, *2014*, 5119 and the references cited therein.

(19) El Kazzouli, S.; du Bellay, A. G.; Berteina-Raboin, S.; Delagrange, P.; Caignard, D. H.; Guillaumet, G. *Eur. J. Med. Chem.* **2011**, *46*, 4252.

(20) (a) Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.* **2009**, 6460. (b) Raja, R.; Ratnasamy, P. *J. Catal.* **1997**, *170*, 244.

(21) Li, B.; Wang, N.; Liang, Y.; Xu, S.; Wang, B. *Org. Lett.* **2013**, *15*, 136.

(22) Xiao, X.; Xie, Y.; Bai, S.; Deng, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2015**, *17*, 3998.

DOI: 10.1021/acs.joc.5b02384
J. Org. Chem. 2016, 81, 25−31