JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

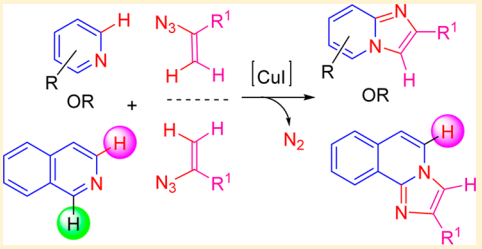
Copper-Catalyzed C−H Functionalization of Pyridines and Isoquinolines with Vinyl Azides: Synthesis of Imidazo Heterocycles

Ramachandra Reddy Donthiri,[†] Venkatanarayana Pappula,[†] N. Naresh Kumar Reddy,[†] Dipayan Bairagi,[‡] and Subbarayappa Adimurthy*[,†]

[†]Academy of Scientific & Innovative Research, CSIR-Central Salt & Marine Chemicals Research Institute, Gijubhai Badheka Marg, Bhavnagar-364 002, Gujarat, India

Supporting Information

ABSTRACT: Copper(I) iodide-catalyzed oxidative C(sp^2)−H functionalization of pyridines and isoquinolines for the synthesis of imidazo[1,2-*a*]pyridines and 2-phenylimidazo[2,1-*a*]isoquinolines with vinyl azides under mild aerobic conditions is reported. Good selectivity for 3-substituted pyridines and single isomer formation with isoquinolines were observed.

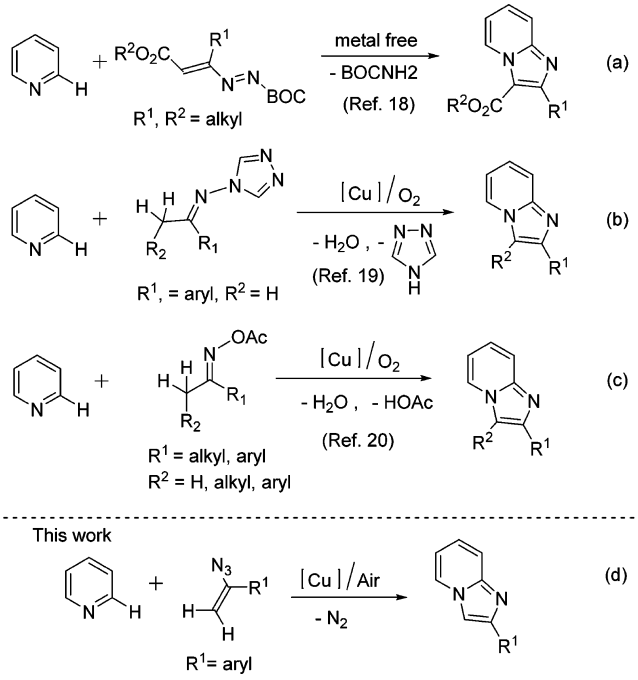


The development of an efficient strategy for the synthesis of azaheterocycles through direct functionalization of C−H bonds using transition-metal catalysts is of considerable interest. Direct C−N bond formation by the loss of H_2, N_2, or H_2O to build complex nitrogen heterocycles has enriched organic synthesis greatly. In particular, the synthesis of imidazo[1,2-*a*]pyridines (IPs) has received much attention because of their diverse and enhanced biological activities.[1−3] In this context, significant contributions have been made by various groups. Reported synthetic routes to IPs rely on 2-aminopyridine derivatives and various oxidative coupling partners.[4−15]

We also reported a facile method for the synthesis of IPs through a copper-catalyzed aerobic oxidative cyclization[16] and intramolecular hydroamination in aqueous media.[17] Although great advancements in constructing imidazo[1,2-*a*]pyridine core units have been made, the development of economical and environmentally benign systems is still appreciated. As 2-aminopyridines are derived from pyridine, the direct use of pyridines to construct desired IPs would be of significant advantage. However, few reports of the synthesis of IPs utilizing simple pyridine derivatives are available (Scheme 1a−c).[18−23] Toward the development of a more efficient and versatile method for the synthesis of functionalized imidazo[1,2-*a*]pyridines, we report an efficient synthesis of IPs utilizing simple starting substrates such as pyridine and vinyl azide derivatives (Scheme 1d).

Although vinyl azides have been utilized for the synthesis of various azaheterocycles,[24−26] to our knowledge no reports are available to date for the synthesis of IPs using vinyl azides. On the basis of our expertise in the synthesis of functionalized imidazo[1,2-*a*]pyridines,[16,17,27] we focused on utilizing *α*-aryl vinyl azides as the nitrogen source for the construction of imidazo[1,2-*a*]heterocyclic frameworks. Compared with previous works, the present protocol has significant merits such as

Scheme 1



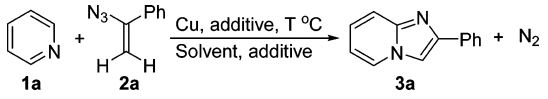
the liberation of only N_2 as a benign byproduct, the use of atmospheric air as an environmentally friendly oxidant, and mild reaction conditions.

On the basis of the above facts, we initiated our investigation with the reaction of pyridine (**1a**) and (1-azidovinyl)benzene (**2a**) using copper as a catalyst to obtain imidazo[1,2-*a*]pyridine

Received: September 20, 2014

   dx.doi.org/10.1021/jo5021618 | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	Cu source	additive	solvent	T (°C)	atm	yield (%)
1	CuI	Na_2CO_3	DMF	90	O_2	24
2	CuI	$NaHCO_3$	DMF	90	O_2	23
3	CuI	K_2CO_3	DMF	90	O_2	23
4	CuI	Li_2CO_3	DMF	90	O_2	38
5	CuI	Li_2CO_3	DMF	60	O_2	40
6	CuI	Li_2CO_3	DMSO	60	O_2	28
7	CuI	Li_2CO_3	toluene	60	O_2	20
8	CuI	Li_2CO_3	DCE	60	O_2	32
9	CuI	Li_2CO_3	cyclohexane	60	O_2	27
10	CuI	Li_2CO_3	chlorobenzene	60	O_2	25
11	CuI	Li_2CO_3	1,4-dioxane	60	O_2	34
12	CuI	Li_2CO_3	THF	60	O_2	–
13	CuI	Li_2CO_3	ethanol	60	O_2	–
14	CuI	Li_2CO_3	water	60	O_2	–
15	CuI	Li_2CO_3	acetonitrile	60	O_2	60
16	CuI	Li_2CO_3	acetonitrile	RT	O_2	28
17	CuI	Li_2CO_3	acetonitrile	50	O_2	43
18[b]	CuI	Li_2CO_3	acetonitrile	65	O_2	64
19[b]	CuI	Li_2CO_3	acetonitrile	70	O_2	50
20[b,c]	CuI	Li_2CO_3	acetonitrile	65	O_2	17
21[b,c]	CuI	Li_2CO_3	acetonitrile	65	O_2	42
22[b,c]	CuI	Li_2CO_3	acetonitrile	65	O_2	27
23[b]	CuBr	Li_2CO_3	acetonitrile	65	O_2	19
24[b]	CuCI	Li_2CO_3	acetonitrile	65	O_2	<1
25[b]	$Cu(OAc)_2$	Li_2CO_3	acetonitrile	65	O_2	–
26[b]	CuI	M.S.[e]	acetonitrile	65	O_2	68
27[b]	**CuI**	**M.S.**	**acetonitrile**	**65**	**air**	**71**
28[b,d]	CuI	M.S.	acetonitrile	65	Ar	47
29[b,d]	–	M.S.	acetonitrile	65	air	–

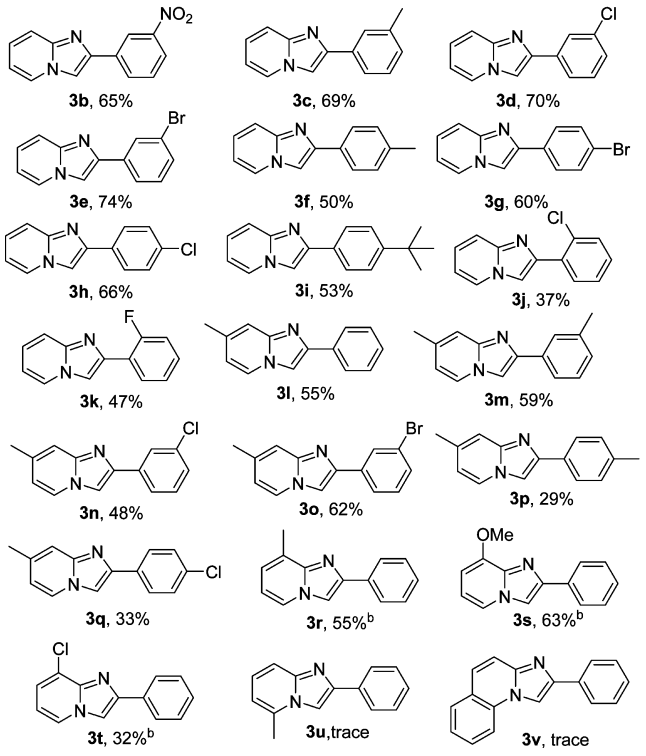
[a]Reaction conditions, unless otherwise stated: 0.9 mmol of **1a**, 0.3 mmol of **2a**, 0.03 mmol of the Cu source, 0.3 mmol of additive, and 1 mL of solvent were placed in a 10 mL screw-capped reaction tube, and O_2 was provided through a balloon with the help of a septum. [b]The solvent used was dried with CaH, distilled, and stored over molecular sieves. [c]For entries 20, 21, and 22, 0.06 mmol of the ligands 1,10-phenanthroline, 2,2′-bipyridyl, and tetramethylethylenediamine were used, respectively. [d]Air was considered as occupied air in the space of the reaction tube above the reaction mixture. [e]M.S. = molecular sieves (4 Å); 50 mg was used.

3a (Table 1). We found that **3a** can be obtained in 24% yield from **1a** (3.0 equiv) and **2a** (1.0 equiv) with CuI (10 mol %) in *N*,*N*-dimethylformamide (DMF) with Na_2CO_3 (1.0 equiv) as an additive at 90 °C under an O_2 atmosphere for 24 h (Table 1, entry 1). No improvement was observed upon screening of other additives such as $NaHCO_3$ (entry 2) and K_2CO_3 (entry 3). However, with Li_2CO_3 as an additive, a promising yield of **3a** (38%) was observed (entry 4). A similar yield was obtained by decreasing the reaction temperature to 60 °C (entry 5). Furthermore, no improvements were found using other solvents (entries 6−14). Notably, when the reaction was performed in acetonitrile at 60 °C, the desired product **3a** was obtained in 60% yield (entry 15). The yield decreased when the reaction was performed in acetonitrile either at room temperature or at 50 °C (entries 16 and 17). A marginal improvement (64% yield) was observed at 65 °C (entry 18). The yield dropped to 50% when the temperature was further increased (entry 19). The use of additional ligands did not improve the yield of **3a** (entries 20−22). Other copper catalysts such as CuBr, CuCl, and $Cu(OAc)_2$ were not effective (entries 23−25). To our delight, the use of molecular sieves (M.S.) as an additive increased the yield to 68% (entry 26). Furthermore, when the reaction was performed without an oxygen balloon, the maximum yield of **3a** (71%) was obtained (entry 27). The present transformation is also feasible under an argon (inert) atmosphere but gives a lower yield of 47% (entry 28), and formation of **3a** was not observed without a copper catalyst (entry 29). Therefore, the optimum conditions identified for the present protocol are as follows: 10 mol % CuI as the catalyst and 50 mg of molecular sieves (4 Å) as an additive in acetonitrile at 65 °C (Table 1, entry 27).

Under the optimized reaction conditions, the scope of the synthesis of substituted imidazo[1,2-*a*]pyridines was investigated (Table 2). The reaction was found to be very facile with both electron-withdrawing and electron-donating groups of (1-azidovinyl)benzenes and delivered the desired products in moderate to good yields (**3b**−**k**). It may be noted that halide (Cl, Br, or F)-substituted vinyl azides were also well-tolerated, affording good yields of the corresponding products, which could be further applied in traditional cross-coupling reactions. Electronic effects associated with electron-donating/withdrawing substituents at the *meta*/*para* position on the arene ring of the vinyl azide did not affect the efficiency of the process. Unfortunately, vinyl azides such as [(2-azidoallyl)oxy]benzene,

dx.doi.org/10.1021/jo5021618 | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Substrate Scope of Imidazo[1,2-*a*]pyridines[a]



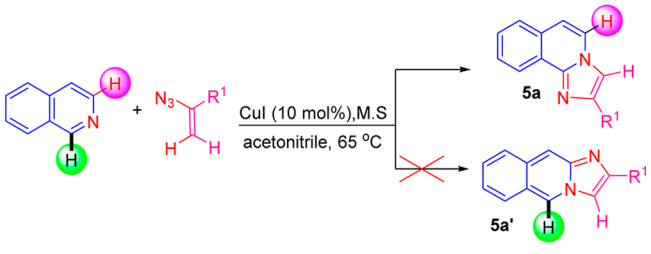
[a]Reaction conditions: 0.9 mmol of pyridine derivative, 0.3 mmol of vinyl azide derivative, 0.03 mmol of CuI, 50 mg molecular sieves (4 Å), and 1.0 mL of acetonitrile were placed in a screw-capped reaction tube, which was closed and then placed in a preheated oil bath at 65 °C for 24 h. [b]In addition to the desired product, the other isomer was obtained in 15%, 2%, and 3% yield for **3r**, **3s**, and **3t**, respectively.

(*E*)-(1-azidoprop-1-en-1-yl)benzene, and 4-azido-1,2-dihydronaphthalene were not amenable to this procedure.

The substrate scope of substituted pyridines was also evaluated. Methyl-substituted pyridines such as 4-picoline and 3-picoline reacted with various vinyl azide derivatives and afforded the desired products **3l**–**r** in moderate to good yields. Strongly electron-donating 3-methoxypyridine gave the desired product **3s** in 63% yield. Moderately electron-withdrawing 3-chloropyridine also gave a moderate yield of the corresponding product **3t**. The reactions of **2a** with 2-picoline and isoquinoline gave traces of products **3u** and **3v**, respectively.

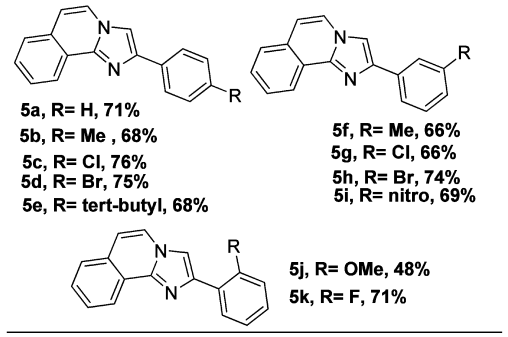
Interestingly, under these optimized conditions the reaction of isoquinoline (**4a**) with **2a** gave the regioselective 2-phenylimidazo[2,1-*a*]isoquinoline (2-phenyl-IIQ) product **5a** over the other isomer **5a′** (Scheme 2). The same regioselectivity

Scheme 2. Regioselectivity of the Reaction of Isoquinoline with Vinyl Azides



was also observed by the Jiang group for such products.[20] In view of the importance of these functionalized IIQs in medicinal chemistry,[28,29] we extended the generality of the copper-catalyzed aerobic oxidative regioselective synthesis of phenylimidazo[2,1-*a*]isoquinolines **5** (Table 3). Similar to **1a**, the reaction of **4a** with

Table 3. Substrate Scope of Imidazo[2,1-*a*]isoquinolines[a]

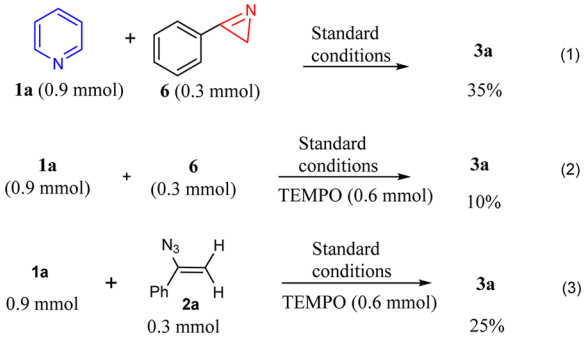


[a]Reaction conditions: 0.9 mmol of isoquinoline, 0.3 mmol of vinyl azide derivative, 0.03 mmol of CuI, 50 mg of molecular sieves (4 Å) and 1.0 mL of acetonitrile were taken in a sealed tube, placed in a preheated oil bath at 65 °C for 24 h.

compounds **2** bearing various phenyl substituents gave the corresponding products **5a**–**k** in good yields. Irrespective of the substituent (alkyl or halogen) and position (*ortho*, *meta*, or *para*) on the arene ring of the vinyl azide, the desired products were obtained in good yields (48–76%), including 2-methoxy derivative **5j** and 2-fluoro derivative **5k**.

To gain insight into the reaction mechanism, we performed some additional reactions as shown in Scheme 3. Initially,

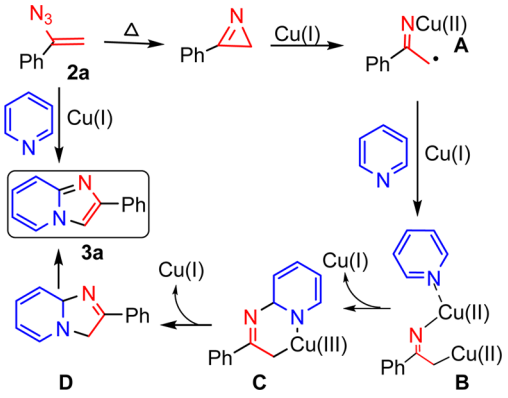
Scheme 3. Mechanistic Investigation



the reaction of **1a** was performed with freshly prepared 3-phenyl-2*H*-azirine (**6**) instead of **2a** (assuming that the reaction may proceed via **6** as an intermediate) under the standard conditions of Table 2, and **3a** was obtained in 35% yield (Scheme 3, eq 1). When the same reaction was conducted in the presence of 2 equiv of TEMPO (w.r.t. **6**), only a 10% yield of **3a** was observed (Scheme 3, eq 2). Furthermore, when the reaction of **1a** and **2a** was performed with the addition of 2 equiv of TEMPO (w.r.t. **2a**) under the standard reaction conditions, the desired product **3a** was obtained in 25% yield (Scheme 3, eq 3). These results reveal that the reaction not only proceeds via a radical pathway but may also proceed through ionic path. The ionic path could be similar to that described by Fu and co-workers,[19] in which 4*H*-1,2,4-triazole acts as a leaving group, although in the present transformation the leaving

dx.doi.org/10.1021/jo5021618 | J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 4. Plausible Mechanism



group would be N_2. On the basis of these results and literature reports, a radical mechanism is proposed (Scheme 4).[20,25] Initially **2a** undergoes thermal decomposition to form the 2*H*-azirine, which in the presence of Cu(I) generates iminylcopper(II) radical intermediate **A** with homolytic cleavage of the C−N bond. Intermediate **A** in the presence of pyridine and Cu(I) generates another intermediate, **B**. Oxidative cyclization of **B** provides Cu(III) complex **C**, and reductive elimination followed by oxidation gives the desired product **3a**.

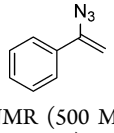
In conclusion, we have developed a copper-catalyzed oxidative synthesis of IPs and IIQs through C−H functionalization of pyridines and isoquinolines, respectively, with vinyl azides. The use of atmospheric air as an oxidant, simple starting substrates including the catalyst, and the mild reaction temperature (65 °C) are the added advantages of the present protocol. Mechanistic studies revealed that the reaction may proceed by both radical and ionic pathways.

EXPERIMENTAL SECTION

General Methods. All commercially available chemicals and reagents were used without any further purification, unless otherwise indicated. Acetonitrile was dried with CaH, distilled, and stored with molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. The spectra were recorded in $CDCl_3$ as the solvent. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), etc. Coupling constants (J) are given in hertz. Chemical shifts (δ) are reported in parts per million relative to TMS as an internal standard. The peaks around δ 7.26 (^{1}H NMR) and 77.0 (^{13}C NMR) correspond to $CDCl_3$. Progress of the reactions was monitored by thin-layer chromatography (TLC). Silica gel (100−200 mesh size) was used for column chromatography.

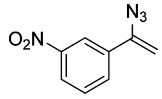
General Procedure for the Preparation of Starting Vinyl Azides 2a−l.[30] To a solution of styrene dibromide (6.5 mmol) in dry DMF (25 mL) was added NaN_3 (19.5 mmol). After the reaction mixture was stirred for 24 h at room temperature and then diluted with water, the product was extracted with diethyl ether. The combined organic layers were washed with water (3 × 10 mL) and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude residue was purified by column chromatography using silica gel with hexane as the eluent to get the pure product.

Characterization Data for Vinyl Azides. *(1-Azidovinyl)benzene (**2a**).*[31]



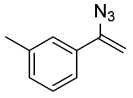
Yield: 80% (754 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (d, J = 2.5 Hz, 1H), 5.41 (d, J = 2.5 Hz, 1H), 7.33−7.36 (m, 3H), 7.53−7.55 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 97.9, 125.5, 128.4, 129.1, 134.2, 145.0.

*1-(1-Azidovinyl)-3-nitrobenzene (**2b**).*[30]



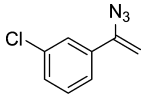
Yield: 27% (333 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.11 (d, J = 3.0 Hz, 1H), 5.61 (d, J = 3.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.88−7.90 (m, 1H), 8.17−8.19 (m, 1H), 8.41 (t, J = 2.0 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 99.7, 120.5, 123.6, 129.4, 131.1, 139.9, 143.0, 148.3.

*1-(1-Azidovinyl)-3-methylbenzene (**2c**).*



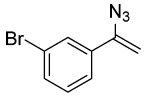
Yellow liquid. Yield: 90% (930 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.3 (s, 3H), 4.91 (d, J = 2.5 Hz, 1H), 5.38 (d, J = 2.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H) 7.22 (t, J = 7.5 Hz, 1H), 7.33 (d, J = 9 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 21.4, 97.8, 122.7, 126.2, 128.3, 129.9, 134.2, 138.1, 145.2. HRMS: calcd for $C_9H_{10}N_3$ 160.0875, found 160.0854.

*1-(1-Azidovinyl)-3-chlorobenzene (**2d**).*



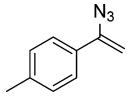
Yellow liquid. Yield: 47% (547 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 (d, J = 3.0 Hz, 1H), 5.44 (d, J = 2.5 Hz, 1H), 7.24−7.31 (m, 2H), 7.42−7.43 (m, 1H), 7.54 (t, J = 1.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 98.7, 125.7, 129.0, 129.6, 134.5, 136.0, 143.8. HRMS: calcd for $C_8H_7ClN_3$ 180.0328, found 180.0334.

*1-(1-Azidovinyl)-3-bromobenzene (**2e**).*[25]



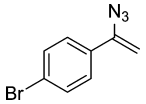
Yield: 75% (1.0 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.97 (d, J = 3.0 Hz, 1H), 5.44 (d, J = 2.5 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.44−7.48 (m, 2H), 7.70 (t, J = 2.0 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 98.8, 122.6, 124.0, 128.6, 129.9, 132.0, 136.2, 143.7.

*1-(1-Azidovinyl)-4-methylbenzene (**2f**).*[31]



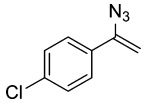
Yield: 89% (920 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H), 4.88 (d, J = 2.0 Hz, 1H), 5.36 (d, J = 2.5 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 21.2, 97.1, 125.5, 129.1, 131.5, 139.1, 145.0.

*1-(1-Azidovinyl)-4-bromobenzene (**2g**).*[31]



Yield: 75% (1.0 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.92 (d, J = 2.5 Hz, 1H), 5.40 (d, J = 2.5 Hz, 1H), 7.37−7.39 (m, 2H), 7.42−7.45 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 98.1, 123.2, 127.0, 131.5, 133.1, 144.1.

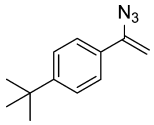
*1-(1-Azidovinyl)-4-chlorobenzene (**2h**).*[31]



Yield: 65% (750 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (d, J = 3.0 Hz, 1H), 5.41 (d, J = 3.0 Hz, 1H), 7.29−7.32 (m, 2H), 7.46−7.48 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 98.1, 126.8, 128.6, 132.7, 135.0, 144.0.

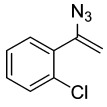
dx.doi.org/10.1021/jo5021618 | J. Org. Chem. XXXX, XXX, XXX−XXX

*1-(1-Azidovinyl)-4-(tert-butyl)benzene (**2i**).*[32]



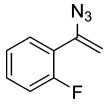
Yield: 60% (784 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (s, 9H), 4.89 (d, J = 2.0 Hz, 1H), 5.37 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 30.2, 33.6, 96.2, 124.31, 124.38, 130.49, 143.9, 151.3.

*1-(1-Azidovinyl)-2-chlorobenzene (**2j**).*



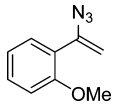
Yellow liquid. Yield: 29% (337 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (d, J = 1.0 Hz, 1H), 5.41 (d, J = 1.0 Hz, 1H), 7.07−7.16 (m, 2H), 7.29−7.33 (m, 1H), 7.47 (t, J = 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 102.5, 115.0, 121.3, 123.1, 128.2, 129.5, 138.6, 157.9, 159.9. HRMS: calcd for $C_8H_7ClN_3$ 180.0328, found 180.0305.

*1-(1-Azidovinyl)-2-fluorobenzene (**2k**).*



Yellow liquid. Yield: 40% (424 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (d, J = 1.0 Hz, 1H), 5.41 (d, J = 1.0 Hz, 1H), 7.07−7.16 (m, 2H), 7.29−7.33 (m, 1H), 7.47 (t, J = 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 102.5, 115.0, 121.3, 123.1, 128.2, 129.5, 138.6, 157.9, 159.9. HRMS: calcd for $C_8H_7FN_3$ 164.0624, found 164.0600.

*1-(1-Azidovinyl)-2-methoxybenzene (**2l**).*[30]

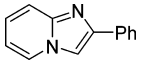


Yield: 87% (989 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (s, 3H), 4.92 (s, 1H), 5.02 (s, 1H), 6.92−6.97 (m, 2H), 7.30−7.36 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 54.6, 102.0, 109.9, 119.7, 122.5, 129.3, 129.6, 142.0, 155.7.

Typical Procedure for the Synthesis of IPs: Synthesis of 2-Phenylimidazo[1,2-*a*]pyridine (3a). Pyridine (**1a**) (71 mg, 0.9 mmol), (1-azidovinyl)benzene (**2a**) (43.5 mg, 0.3 mmol), copper iodide (5.7 mg, 0.03 mmol), and 4 Å molecular sieves (50 mg) were placed in a 10 mL screw-capped tube. Dry acetonitrile (1 mL) was added to the reaction mixture, and the reaction vessel was closed with the cap. After the reaction tube was placed in a preheated oil bath at 65 °C for 24 h, the reaction mixture was allowed to attain room temperature and was transferred to a 50 mL round-bottom flask with the help of 10−15 mL of ethyl acetate or DCM. After removal of volatiles, the crude mixture was subjected to column chromatography with 200 mesh silica gel and 30% ethyl acetate in hexane as the eluent to isolate the desired product **3a** in 71% yield (41.32 mg). The same procedure was followed for the synthesis of the remaining products **3b−v**. The eluent used for **3t** was 10% ethyl acetate in hexane.

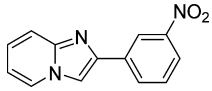
Typical Procedure for the Synthesis of IIQs: Synthesis of 2-Phenylimidazo[2,1-*a*]isoquinoline (5a). The same procedure as mentioned above for **3a−v** was followed for the synthesis of **5a** by using isoquinoline (116 mg, 0.9 mmol) instead of pyridine and 10% ethyl acetate in hexane as the eluent. The desired product **5a** was obtained in 71% yield (52 mg). The same procedure was followed to obtain the remaining products **5b−k**.

Characterization Data for All of the Products. *2-Phenylimidazo[1,2-a]pyridine (**3a**).*[19]



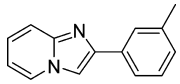
Yield: 71% (41.32 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75 (t, J = 6.5 Hz, 1H), 7.153 (t, J = 8 Hz, 1H), 7.328 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.62 (d, J = 9 Hz, 1H), 7.83 (s, 1H), 7.94 (d, J = 8 Hz, 2H), 8.08 (d, J = 6 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 107.1, 111.4, 116.5, 123.6, 124.5, 125.0, 126.9, 127.7, 132.7, 144.6, 144.7. Mass $[M + H]^+$ = 195.03.

*2-(3-Nitrophenyl)imidazo[1,2-a]pyridine (**3b**).*[13]



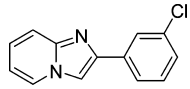
Yield: 65% (46.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (t, J = 6.5 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz, 1H), 7.64 (d, J = 9 Hz, 1H), 7.98 (s, 1H), 8.14 (d, J = 7.5 Hz, 2H), 8.32 (d, J = 7.5 Hz, 1H), 8.75 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 108.0, 112.0, 116.7, 119.7, 121.4, 124.4, 124.7, 128.6, 130.7, 134.6, 142.4, 144.8, 147.7. Mass $[M + H]^+$ = 240.02.

*2-(m-Tolyl)imidazo[1,2-a]pyridine (**3c**).*[19]



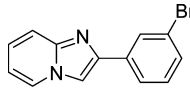
Yield: 69% (43.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 6.64 (t, J = 6.5 Hz, 1H), 7.03−7.06 (m, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.54 (d, J = 9 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.72 (d, J = 10 Hz, 2H), 7.97 (d, J = 7 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 20.4, 107.1, 111.3, 116.4, 122.1, 123.5, 124.5, 125.7, 127.5, 127.7, 132.5, 137.3, 144.6, 144.8. Mass $[M + H]^+$ = 209.11.

*2-(3-Chlorophenyl)imidazo[1,2-a]pyridine (**3d**).*[19]



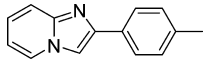
Yield: 70% (47.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 (t, J = 7 Hz, 1H), 7.17−7.20 (m, 1H), 7.27 (d, J = 8 Hz, 1H), 7.34 (t, J = 8 Hz, 1H), 7.63 (d, J = 9.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.84 (s, 1H), 7.95 (s, 1H), 8.10 (d, J = 7.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 107.5, 111.6, 116.5, 123.0, 124.0, 124.6, 125.0, 126.8, 128.8, 133.6, 134.5, 143.2, 144.6. Mass $[M + H]^+$ = 229.00.

*2-(3-Bromophenyl)imidazo[1,2-a]pyridine (**3e**).*[20]



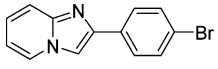
Yield: 74% (60.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.71 (t, J = 7 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 7.19 (t, J = 8 Hz, 1H), 7.34 (d, J = 8 Hz, 1H), 7.57 (d, J = 9 Hz, 1H), 7.76 (t, J = 7 Hz, 2H), 8.02 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 107.5, 111.7, 116.6, 121.8, 123.5, 124.0, 124.6, 127.9, 129.1, 129.7, 134.8, 143.2, 144.7. Mass $[M + H]^+$ = 273.11.

*2-(p-Tolyl)imidazo[1,2-a]pyridine (**3f**).*[19]



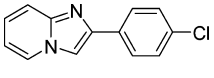
Yield: 50% (31.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 6.75 (t, J = 6.5 Hz, 1H), 7.14−7.17 (m, 1H), 7.26 (s, 2H), 7.62 (d, J = 9 Hz, 1H), 7.83 (s, 1H), 7.84 (d, J = 8 Hz, 1H), 8.10 (d, J = 7 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 21.2, 107.8, 112.3, 117.3, 124.5, 125.5, 125.9, 129.4, 130.8, 137.7, 142.6, 145.8. Mass $[M + H]^+$ = 209.26.

*2-(4-Bromophenyl)imidazo[1,2-a]pyridine (**3g**).*[19]



Yield: 60% (49.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75 (t, J = 6.5 Hz, 1H), 7.15−7.84 (m, 1H), 7.53 (d, J = 7 Hz, 2H), 7.59 (d, J = 9 Hz, 1H), 7.80 (d, J = 8.5 Hz, 3H), 8.08 (d, J = 6.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 107.2, 111.6, 116.5, 120.8, 123.9, 124,5, 126.5, 130.8, 131.7, 143.6, 144.7. Mass $[M + H]^+$ = 273.26.

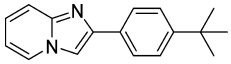
*2-(4-Chlorophenyl)imidazo[1,2-a]pyridine (**3h**).*[19]



dx.doi.org/10.1021/jo5021618 | J. Org. Chem. XXXX, XXX, XXX−XXX

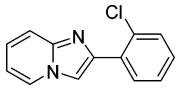
Yield: 66% (45.1 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (t, J = 7 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 9 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 8.01 (d, J = 7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 107.1, 111.5, 116.5, 123.8, 124.5, 126.2, 127.8, 131.2, 132.6, 143.6, 144.7. Mass $[M + H]^+$ = 229.21.

*2-(4-(tert-Butyl)phenyl)imidazo[1,2-a]pyridine (**3i**).*



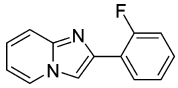
Light-yellow solid, observed melting point 105.6 °C. Yield: 53% (39.7 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 9H), 6.75 (t, J = 7 Hz, 1H), 7.14 (t, J = 7 Hz, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 9 Hz, 1H), 7.80 (s, 1H), 7.86 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 31.0, 34.3, 107.5, 112.0, 117.1, 124.2, 125.2, 125.3, 125.5, 130.4, 145.3, 145.4, 150.7. HRMS: calcd for $C_{17}H_{19}N_2$ 251.1548, found 251.1542.

*2-(2-Chlorophenyl)imidazo[1,2-a]pyridine(**3j**).*[15]



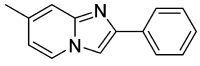
Yield: 37% (25.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 (t, J = 6.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.24–7.27 (m, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.63 (d, J = 9 Hz, 1H), 8.13 (d, J = 7 Hz, 1H), 8.27 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 111.9, 112.0, 117.0, 124.5, 125.3, 126.5, 128.1, 129.8, 130.4, 131.2, 131.7, 141.2, 143.9. Mass $[M + H]^+$ = 229.05.

*2-(2-Fluorophenyl)imidazo[1,2-a]pyridine(**3k**).*[19]



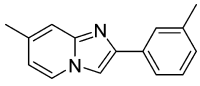
Yield: 47% (29.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 (t, J = 6.5 Hz, 1H), 7.12–7.18 (m, 2H), 7.26–7.31 (m, 2H), 7.62 (d, J = 9.5 Hz, 1H), 8.03 (d, J = 9 Hz, 1H), 8.09 (d, J = 7 Hz, 1H), 8.33–8.37 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 112.1 (J = 14.75 Hz), 112.5, 115.6 (J = 21.8 Hz), 117.4, 121.5 (J = 12 Hz), 124.6, 125.0, 125.8, 128.8, 129.0 (J = 8.25 Hz), 139.2, 144.9, 159.4 (J = 247.5 Hz). Mass $[M + H]^+$ = 213.18.

*7-Methyl-2-phenylimidazo[1,2-a]pyridine (**3l**).*[20]



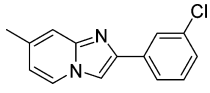
Yield: 55% (34.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 6.59 (d, J = 7 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.38 (s, 1H), 7.42 (t, J = 8 Hz, 2H), 7.77 (s, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.98 (d, J = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 22.8, 108.9, 116.5, 117.3, 126.2, 127.4, 129.2, 130.1, 135.3, 137.0, 146.9, 147.5. Mass $[M + H]^+$ = 209.19.

*7-Methyl-2-(m-tolyl)imidazo[1,2-a]pyridine (**3m**).*[15]



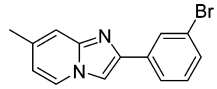
Yield: 59% (39.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.40 (s, 3H), 6.55 (d, J = 6 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.36 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.72 (s, 1H), 7.79 (s, 1H), 7.92 (d, J = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 22.8, 22.9, 108.9, 116.4, 117.2, 124.4, 126.1, 128.1, 129.9, 130.0, 135.1, 137.0, 139.7, 146.9, 147.5. Mass $[M + H]^+$ = 223.26.

*2-(3-Chlorophenyl)-7-methylimidazo[1,2-a]pyridine (**3n**).*[15]



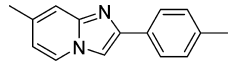
Yield: 48% (34.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H), 6.58 (d, J = 7 Hz, 1H), 7.25 (t, J = 8 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.37 (s, 1H), 7.70 (s, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.90 (s, 1H), 7.93 (d, J = 7 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 20.3, 106.9, 114.3, 114.8, 122.9, 123.8, 124.9, 126.6, 128.8, 133.6, 134.7, 135.0, 142.9, 145.1. Mass $[M + H]^+$ = 243.09.

*2-(3-Bromophenyl)-7-methylimidazo[1,2-a]pyridine (**3o**).*



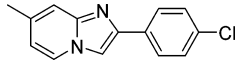
Light-yellow crystalline solid, observed melting point 160.7 °C. Yield: 62% (53.1 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 6.60 (d, J = 7 Hz, 1H), 7.26 (t, J = 8 Hz, 1H), 7.38 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.73 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.95 (d, J = 7 Hz, 1H), 8.07 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 20.4, 106.9, 114.3, 114.9, 121.8, 123.4, 123.8, 127.8, 129.1, 129.5, 135.0, 135.05, 142.9, 145.1. HRMS: calcd for $C_{14}H_{12}BrN_2$ 287.0184, found 287.0169.

*7-Methyl-2-(p-tolyl)imidazo[1,2-a]pyridine (**3p**).*[13]



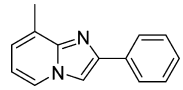
Yield: 29% (19.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.39 (s, 3H), 6.59 (d, J = 7 Hz, 1H), 7.22 (d, J = 8 Hz, 2H), 7.38 (s, 1H), 7.73 (s, 1H), 7.81 (d, J = 8 Hz, 2H), 7.97 (d, J = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 20.80, 20.87, 106.6, 114.4, 115.2, 124.2, 125.2, 128.8, 130.4, 135.0, 137.1, 144.9, 145.5. Mass $[M + H]^+$ = 223.23.

*2-(4-Chlorophenyl)-7-methylimidazo[1,2-a]pyridine (**3q**).*[13]



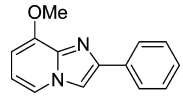
Yield: 33% (24 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H), 6.55 (d, J = 6.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 3H), 7.69 (s, 1H), 7.79 (d, J = 7.5 Hz, 2H), 7.91 (d, J = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 21.1, 107.3, 115.0, 115.6, 124.5, 126.9, 128.5, 132.1, 133.2, 135.7, 144.0, 145.9. Mass $[M + H]^+$ = 243.04.

*8-Methyl-2-phenylimidazo[1,2-a]pyridine (**3r**).*[19]



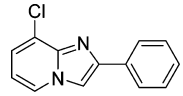
Yield: 55% (34.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.66 (s, 3H), 6.67 (t, J = 7 Hz, 1H), 6.93 (d, J = 6.5 Hz, 1H), 7.31 (t, J = 7 Hz, 1H), 7.43 (t, J = 8 Hz, 2H), 7.83 (s, 1H), 7.96–7.98 (m, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 17.1, 108.6, 112.3, 123.3, 123.4, 126.1, 127.5, 127.7, 128.6, 134.0, 145.2, 146.2. Mass $[M + H]^+$ = 209.19.

*8-Methoxy-2-phenylimidazo[1,2-a]pyridine (**3s**).*



Yellow viscous liquid. Yield: 63% (42.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.01 (s, 3H), 6.41 (d, J = 7.5 Hz, 1H), 6.64 (t, J = 7 Hz, 1H), 7.30 (t, J = 7 Hz, 1H), 7.40 (t, J = 8 Hz, 2H), 7.71 (d, J = 6.5 Hz, 1H), 7.80 (s, 1H), 8.00 (d, J = 7.5 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 54.7, 99.6, 108.1, 111.2, 117.4, 125.1, 126.7, 127.5, 132.5, 139.0, 143.8, 147.9. HRMS: calcd for $C_{14}H_{13}N_2O$ 225.1028, found 225.1011.

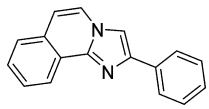
*8-Chloro-2-phenylimidazo[1,2-a]pyridine (**3t**).*[19]



Yield: 32% (21.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.71 (t, J = 7 Hz, 1H), 7.24 (t, J = 7 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.90 (s, 1H), 7.98 (d, J = 7.5 Hz, 2H), 8.05 (d, J = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 109.6, 111.9, 123.2, 123.5, 124.2, 126.3, 128.2, 128.6, 133.1, 143.0, 146.3. Mass $[M + H]^+$ = 229.20.

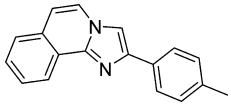
dx.doi.org/10.1021/jo5021618 | J. Org. Chem. XXXX, XXX, XXX–XXX

*2-Phenylimidazo[2,1-a]isoquinoline (**5a**).*[20]



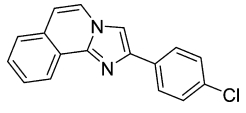
Yield: 71% (52.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, J = 7 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.52−7.55 (m, 1H), 7.60−7.66 (m, 2H), 7.76 (s, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 7 Hz, 2H), 8.71 (d, J = 8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 109.8, 113.0, 122.8, 123.4, 123.7, 125.8, 127.5, 128.0, 128.6, 129.4, 133.9, 143.2, 143.9. Mass $[M + H]^+$ = 245.16.

*2-(p-Tolyl)imidazo[2,1-a]isoquinoline (**5b**).*



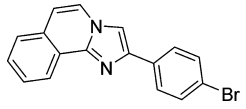
White solid, observed melting point 149.8 °C. Yield: 68% (52.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 7.02 (d, J = 7.5 Hz, 1H), 7.25 (m, 2H), 7.54−7.57 (m, 1H), 7.61−7.65 (m, 1H), 7.68 (d, J = 8 Hz, 1H), 7.79 (s, 1H), 7.89−7.91 (m, 3H), 8.72 (d, J = 8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 109.4, 112.8, 122.8, 123.4, 123.7, 125.6, 126.8, 127.9, 129.3, 131.1, 137.2, 143.1, 144.0. HRMS: calcd for $C_{18}H_{15}N_2$ 259.1235, found 259.1231.

*2-(4-Chlorophenyl)imidazo[2,1-a]isoquinoline (**5c**).*



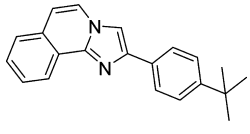
White crystalline solid, observed melting point 189.1 °C. Yield: 76% (63.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00 (d, J = 7 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.54−7.57 (m, 1H), 7.63 (t, J = 7 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.75 (s, 1H), 7.83 (d, J = 7 Hz, 1H), 7.91 (d, J = 8 Hz, 2H), 8.68 (d, J = 8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 109.8, 113.2, 122.8, 123.4, 123.6, 126.9, 127.0, 128.1, 128.2, 128.8, 129.4, 132.4, 133.1, 142.8, 143.3. HRMS: calcd for $C_{17}H_{12}ClN_2$ 279.0689, found 279.0685.

*2-(4-Bromophenyl)imidazo[2,1-a]isoquinoline (**5d**).*[19]



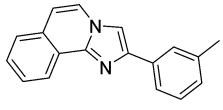
Yield: 75% (72.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (d, J = 7 Hz, 1H), 7.54−7.58 (m, 3H), 7.63 (t, J = 7.5 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.78 (s, 1H), 7.85−7.87 (m, 3H), 8.68 (d, J = 8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 109.9, 113.3, 121.3, 122.8, 123.4, 123.7, 126.9, 127.3, 128.1, 128.2, 129.4, 131.7, 132.9, 142.8, 143.3. Mass $[M + H]^+$ = 323.26.

*2-(4-(tert-Butyl)phenyl)imidazo[2,1-a]isoquinoline (**5e**).*



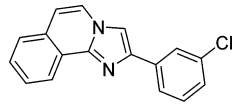
White solid, observed melting point 149.2 °C. Yield: 68% (61.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (s, 9H), 6.95 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.59−7.65 (m, 2H), 7.73 (s, 1H), 7.80 (d, J = 7 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 8.71 (d, J = 8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 31.3, 34.5, 109.4, 112.8, 122.8, 123.4, 123.7, 125.5, 126.8, 127.9, 129.3, 131.1, 143.1, 144.0, 150.5. HRMS: calcd for $C_{21}H_{21}N_2$ 301.1705, found 301.1725.

*2-(m-Tolyl)imidazo[2,1-a]isoquinoline (**5f**).*[20]



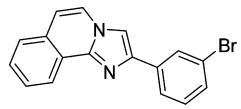
Yield: 66% (51.1 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H), 6.96 (d, J = 7 Hz, 1H), 7.12 (d, J = 7 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.60−7.66 (m, 2H), 7.75 (s, 2H), 7.81 (d, J = 7 Hz, 1H), 7.86 (s, 1H), 8.71 (d, J = 8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 21.4, 109.8, 112.9, 122.8, 123.4, 123.7, 126.4, 126.8, 128.0, 128.3, 128.5, 129.4, 133.7, 138.2, 143.1, 144.0. Mass $[M + H]^+$ = 259.23.

*2-(3-Chlorophenyl)imidazo[2,1-a]isoquinoline (**5g**).*



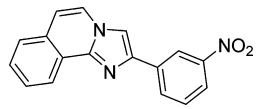
Light-brown crystalline solid, observed melting point 150.7 °C. Yield: 66% (55.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (d, J = 7 Hz, 1H), 7.26 (d, J = 8 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.64 (t, J = 7 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.78 (s, 1H), 7.84 (d, J = 7 Hz, 2H), 8.00 (s, 1H), 8.69 (d, J = 8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 110.2, 113.3, 122.8, 123.4, 123.7, 123.8, 125.8, 126.9, 127.4, 128.2, 128.3, 129.4, 129.9, 134.6, 135.8, 142.5, 143.3. HRMS: calcd for $C_{17}H_{12}ClN_2$ 279.0689, found 279.0681.

*2-(3-Bromophenyl)imidazo[2,1-a]isoquinoline (**5h**).*



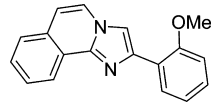
Light-brown crystalline solid, observed melting point 164.3 °C. Yield: 74% (71.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (d, J = 7 Hz, 1H), 7.29 (d, J = 8 Hz, 1H), 7.42 (d, J = 8 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 7.67 (d, J = 8 Hz, 1H), 7.77 (s, 1H), 7.84 (d, J = 7 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 8.16 (s, 1H), 8.69 (d, J = 8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 110.2, 113.3, 122.8, 122.9, 123.4, 123.7, 124.2, 126.9, 128.2, 128.3, 128.7, 129.4, 130.1, 130.3, 136.0, 142.4, 143.3. HRMS: calcd for $C_{17}H_{12}N_2Br$ 323.0184, found 323.0189.

*2-(3-Nitrophenyl)imidazo[2,1-a]isoquinoline (**5i**).*



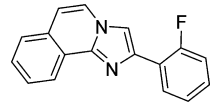
Yellow solid, observed melting point 188.9 °C. Yield: 69% (59.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (d, J = 7 Hz, 1H), 7.57−7.61 (m, 2H), 7.66 (t, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.89 (d, J = 8 Hz, 2H), 8.12 (d, J = 7.5 Hz, 1H), 8.33 (d, J = 7.5 Hz, 1H), 8.69 (d, J = 8 Hz, 1H), 8.79 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 110.7, 113.7, 120.4, 122.0, 122.8, 123.4, 123.6, 127.0, 128.4, 128.5, 129.5, 131.5, 135.8, 141.5, 143.6, 148.6. HRMS: calcd for $C_{17}H_{12}N_3O_2$ 290.0930, found 290.0926.

*2-(2-Methoxyphenyl)imidazo[2,1-a]isoquinoline (**5j**).*



White crystalline solid, observed melting point 150.9 °C. Yield: 48% (39.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.96 (s, 3H), 6.92 (d, J = 6.5 Hz, 1H), 6.96 (d, J = 8 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.26−7.30 (m, 1H), 7.51 (t, J = 8 Hz, 1H), 7.58−7.64 (m, 2H), 7.82 (d, J = 7 Hz, 1H), 8.11 (s, 1H), 8.54 (dd, J_1 = 9 Hz, J_2 = 1.5 Hz, 1H), 8.72 (d, J = 8 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 55.2, 110.6, 112.5, 114.1, 120.9, 122.5, 122.9, 123.4, 123.6, 126.7, 127.8, 128.1, 128.5, 129.4, 139.2, 141.9, 156.4. HRMS: calcd for $C_{18}H_{15}N_2O$ 275.1184, found 275.1180.

*2-(2-Fluorophenyl)imidazo[2,1-a]isoquinoline (**5k**).*



White crystalline solid, observed melting point 126.9 °C. Yield: 71% (55.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (d, J = 7 Hz, 1H), 7.12−7.16 (m, 1H), 7.26−7.29 (m, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 7 Hz, 1H),

dx.doi.org/10.1021/jo5021618 | J. Org. Chem. XXXX, XXX, XXX−XXX

7.97 (d, J = 4 Hz, 1H), 8.45−8.49 (m, 1H), 8.70 (d, J = 8 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 113.1, 113.7 (J = 14.7 Hz), 115.4 (J = 21.7 Hz), 121.6 (J = 12.3 Hz), 122.9, 123.4, 123.6, 124.4, 126.9, 128.0, 128.2, 128.3 (J = 8.1 Hz), 128.6, 129.5, 137.2, 142.5, 159.1 (J = 247 Hz). HRMS: calcd for $C_{17}H_{12}FN_2$ 263.0985, found 263.0980.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for all compounds and HRMS spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: adimurthy@csmcri.org.

Notes

‡Dissertation student at CSIR-CSMCRI.

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

CSIR-CSMCRI Communication no. 160/2014. R.R.D. and V.P. are thankful to AcSIR for Ph.D. enrollment and Analytical Discipline and Centralized Instrumental Facilities for providing instrumentation facilities. R.R.D. and V.P. are also thankful to UGC (New Delhi, India) for their fellowships. We thank Professor B. C. Ranu for his helpful discussions. We thank DST, Government of India (SR/S1/OC-13/2011) for financial support and CSIR-CSMCRI (OLP-0076) for partial assistance.

■ REFERENCES

(1) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888.

(2) Lhassani, M.; Chavignon, O.; Chezal, J.-M.; Teulade, J.-C.; Chapat, J.-P.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271.

(3) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 347.

(4) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2743.

(5) Wang, H. G.; Wang, Y.; Peng, C. L.; Zhang, J. C.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217.

(6) Wang, H. G.; Wang, Y.; Liang, D. D.; Liu, L. Y.; Zhang, J. C.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678.

(7) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333.

(8) Chunavala, K. C.; Joshi, G.; Suresh, E.; Adimurthy, S. *Synthesis* **2011**, 635.

(9) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2012**, *14*, 4580.

(10) Yan, R.-L.; Yan, H.; Ma, C.; Ren, Z.-Y.; Gao, X.-A.; Huang, G.-S.; Liang, Y.-M. *J. Org. Chem.* **2012**, *77*, 2024.

(11) Zeng, J.; Tan, Y. J.; Leow, M. L.; Liu, X.-W. *Org. Lett.* **2012**, *14*, 4386.

(12) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 11073.

(13) Bagdi, A. K.; Rahman, M.; Santra, S.; Majee, A.; Hajra, A. *Adv. Synth. Catal.* **2013**, *355*, 1741.

(14) Gulevich, A. V.; Helan, V.; Wink, D. J.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 956.

(15) Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. *Adv. Synth. Catal.* **2013**, *355*, 2686.

(16) Mohan, D. C.; Donthiri, R. R.; Rao, S. N.; Adimurthy, S. *Adv. Synth. Catal.* **2013**, *355*, 2217.

(17) Mohan, D. C.; Rao, S. N.; Adimurthy, S. *J. Org. Chem.* **2013**, *78*, 1266.

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

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

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

(21) Adib, M.; Ali, M.; Sheikhi, E.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2010**, 1606.

(22) Motevalli, K.; Yaghoubi, Z.; Mirzazadeh, R. *E-J. Chem.* **2012**, *9*, 1047.

(23) Prasanna, P.; Vivek, K. S.; Gunasekaran, P.; Perumal, S. *Tetrahedron Lett.* **2013**, *54*, 3740.

(24) Farney, E. P.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 793.

(25) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y; Chiba, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5927.

(26) Wang, Y.-F.; Lonca, G. H.; Runigo, M. L.; Chiba, S. *Org. Lett.* **2014**, *16*, 4272 and references therein.

(27) Ravi, C.; Mohan, D. C.; Adimurthy, S. *Org. Lett.* **2014**, *16*, 2978.

(28) Deady, L. W.; Rodemann, T.; Finlay, G. J.; Baguley, B.; Denny, W. A. C. *Anti-Cancer Drug Des.* **2001**, *15*, 339.

(29) Rhee, H.-K.; Lim, S. Y.; Jung, M.-J.; Kwon, Y.; Kim, M.-H.; Choo, H.-Y. P. *Bioorg. Med. Chem.* **2009**, *17*, 7537.

(30) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019.

(31) Liu, Z.; Liao, P.; Bi, X. *Org. Lett.* **2014**, *16*, 3668.

(32) Stephan, C.-B.; Kupracz, L.; Kirschning, A. *Beilstein J. Org. Chem.* **2013**, *9*, 1745.