JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

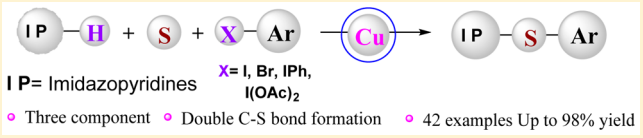
Copper-Catalyzed Three-Component System for Arylsulfenylation of Imidazopyridines with Elemental Sulfur

Chitrakar Ravi, N. Naresh Kumar Reddy, Venkatanarayana Pappula, Supravat Samanta, and Subbarayappa Adimurthy*

Academy of Scientific & Innovative Research, CSIR-Central Salt & Marine Chemicals Research Institute, G.B. Marg, Bhavnagar 364 002, Gujarat, India

Supporting Information

ABSTRACT: A one-pot three-component reaction for the regioselective synthesis of thioarylated imidazoheterocycles from aryl halides and elemental sulfur using copper(I) iodide as a catalyst has been developed. Reactions proceed with high efficiency and afford thioarylated imidazoheterocycles in good yields with broad functional group tolerance.

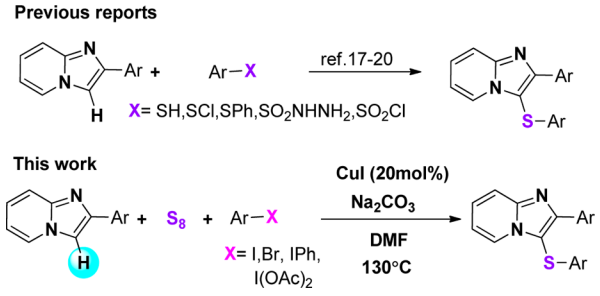


Among bioactive azaheterocycles, pyridine derivatives play a particularly significant role in medicinal chemistry.[1] Over the past decade, drastic developments in the synthesis of imidazopyridines have been achieved; special attention has been paid to imidazo[1,2-*a*]pyridines as these make up an important class of natural products[2] and have substantial applications in pharmaceutical and biological activities such as antiviral, cytotoxic, antibacterial, fungicidal, and anti-inflammatory activities,[3] including GABA inhibitors.[4] Imidazo[1,2-*a*]-pyridine derivatives represent a significant class of organic molecules with core entities in many commercially available drugs, including alpidem, zolpidem, olprinone, minodronic acid, zolimidine, necopidem, saripidem, and the optically active GSK812397 candidate (HIV infection).[5−7]

These heterocyclic moieties also have excited states with intramolecular proton transfer properties;[8] N-heterocyclic carbenes (NHC) in organometallic chemistry[9] have also received considerable attention as core ligands in the field of electronic devices (Figure S1).[10] Hence, numerous synthetic methods for accessing these molecules[11] have been developed with functionalization[12] and through multicomponent reactions.[13]

Copper-promoted Ullmann type condensations are fundamental reactions for the formation of carbon−heteroatom (C−N, C−O, etc.) and carbon−carbon (C−C) bonds in organic synthesis. These are the predominant building blocks for many privileged and biologically active structural moieties in organic synthesis and in biochemistry.[14] Synthesis of functionalized azaheterocycles is the common approach of biologically active N-heterocycles.[15] The C−S bond is one of the most abundant chemical bonds in many organic molecules and biomacromolecules.[16] Hence, a number of methods for accessing sulfenylated heterocycles mainly using disulfides, thiols, sulfenyl chlorides, or sulfonyl hydrazines have been developed.[17−19] Although many organic sulfenylating reagents are known, use of elemental sulfur as a source of C−S bond formation is of significant interest in organic synthesis.[20] Iodobenzene and elemental sulfur are not being reported for sulfenylation of heterocycles. However, haloarenes are known for arylations using transition metal catalysis.[21] As a continuation of our work on the synthesis and functionalization of azaheterocycles,[22] we report herein the selective sulfenylation of imidazo[1,2-*a*]pyridines through a one-pot three-component system using elemental sulfur and haloarenes as a thioarylation source with a copper catalyst (Scheme 1).

Scheme 1. Three-Component Sulfenylation



Aryl iodides and elemental sulfur with mild bases such as metal carbonates/acetates yield diaryl disulfides;[23a] however, strong bases such as metal hydroxides initially generate diaryl disulfides, which in the presence of copper generate diarylsulfane.[23a] To validate our present approach to sulfenylation of imidazo[1,2-*a*]pyridines via a three-component system, we initially performed a reaction of 2-phenylimidazo[1,2-*a*]-pyridine (0.25 mmol) **1a**, elemental sulfur (0.75 mmol) S_8, and 4-methyliodobenzene **3a** (0.75 mmol) in the presence of CuI (20 mol %) as a catalyst and Cs_2CO_3 as a base under an inert atmosphere (argon balloon) in toluene at 100 °C. Under these conditions, traces of the desired product were observed

Received: July 18, 2016
Published: September 23, 2016

DOI: 10.1021/acs.joc.6b01715
J. Org. Chem. 2016, 81, 9964−9972

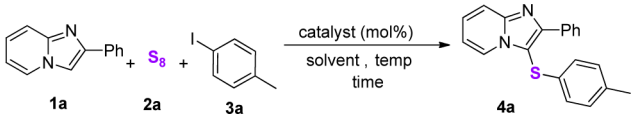
(Table 1, entry 1). The desired product was isolated in 23% yield when DMF used as a solvent instead of toluene (Table 1, entry 2). Surprisingly, the yield was increased to 57% when Na_2CO_3 was used as a base (Table 1, entry 3). Then, the reaction was performed using different catalysts like CuBr, CuCl, $Cu(OTf)_2$, Ag(OTf), $Zn(OTf)_2$, $Fe(OTf)_2$, $FeCl_2$, and $FeCl_3$, but the yield did not improve (Table 1, entries 4−11, respectively). When the reaction temperature was increased to 130 °C, gratifyingly, the yield was increased to 91% (Table 1, entry 12). With a decrease in catalyst loading (10 mol %) and reaction time (12 h), the yield was also decreased (Table 1, entries 13 and 14). No reaction was observed with toluene and NMP as solvents (Table 1, entries 15 and 16). The better reaction was observed only in DMF; it may be due to the coordination of DMF with an in situ-formed thiol derivative.[23a] A considerable yield was obtained in DMSO, however, inefficiently (Table 1, entry 17). When the reaction was conducted without sulfur, catalyst, or base or under an oxygen atmosphere (instead of argon) under these conditions, no reaction and low yields were observed (Table 1, entries 18−21). On the basis of the results obtained, the optimized conditions were set as 0.25 mmol of **1a**, 0.75 mmol of S_8, and 0.75 mmol of **3a**, in 2.0 mL, at 130 °C for 24 h for the transformation presented here.

With the optimized conditions in hand (Table 1, entry 12), we investigated the substrate scope of the three-component reaction system for the sulfenylation of imidazo[1,2-*a*]pyridines **1** with aryl iodides **3** and elemental sulfur (Scheme 2). Initially, the reaction of 2-phenylimidazo[1,2-*a*]pyridine and elemental sulfur (S_8) was examined with iodoarenes. The presence of electron rich and electron deficient groups at *p*- iodoarenes led to a smooth reaction under the optimized conditions and gave good to excellent yields (76−98%) of selective C-3 sulfenylated products **4a−e**. Unfortunately, no reaction was observed in the case of hydroxyl- and aldehyde-substituted iodoarenes **4f** and **4g**, and traces of the desired product were observed with 4-iodobenzamide **4h**. Also, *m*/*o*-iodoarenes reacted well and gave excellent yields of products **4i−k**. Similarly, different functional groups like electron-releasing and electron-withdrawing groups on the phenyl ring of imidazo[1,2-*a*]pyridines also reacted smoothly with iodoarenes and gave desired products **4l−q** in 57−87% yields, and one of the products, **4n**, was further confirmed by single-crystal X-ray diffraction (Figure 1).

It was found that electronic effects were associated with electron-donating or -withdrawing substituents on the imidazo-[1,2-*a*]pyridines. Under the same conditions, the reaction of (*E*)-2-styrylimidazo[1,2-*a*]pyridine and 2-[4-(methylsulfonyl)-phenyl]imidazo[1,2-*a*]pyridine with 4-methyliodobenzene and elemental sulfur gave the corresponding C-3 sulfenylated products **4r** and **4s** in 18 and 56% yields, respectively.

However, only traces of product **4t** were observed with 2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine under these conditions. Then the strategy was extended to 2-phenylimidazo[2,1-*a*]isoquinoline derivatives. The electron-donating and -withdrawing

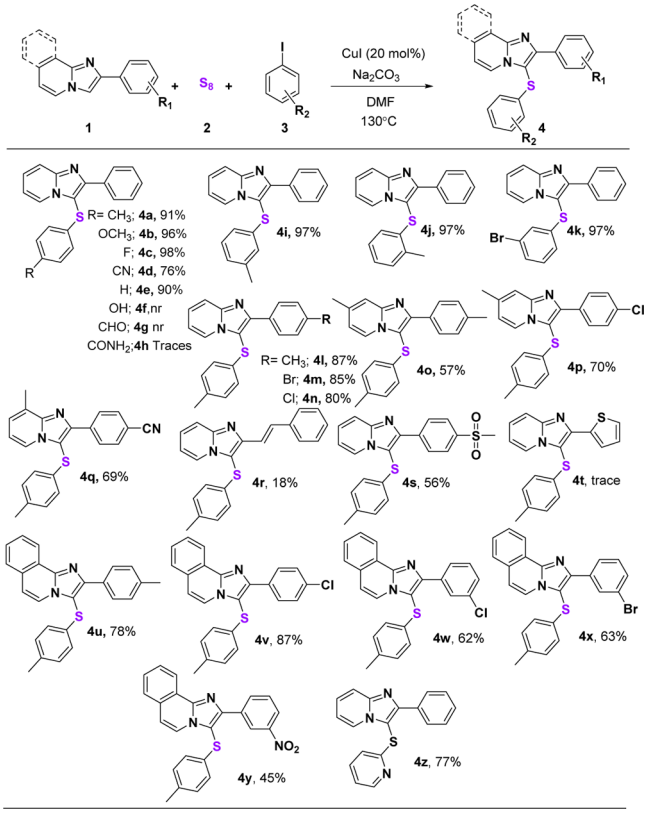
Table 1. Screening of Reaction Conditions[a]



entry	base (1 mmol)	catalyst (mol %)	solvent (mL)	temp (°C)	yield (%)
1	Cs_2CO_3	CuI (20)	toluene	100	trace
2	Cs_2CO_3	CuI (20)	DMF	100	23
3	Na_2CO_3	CuI (20)	DMF	100	57
4	Na_2CO_3	CuBr (20)	DMF	100	48
5	Na_2CO_3	CuCl (20)	DMF	100	41
6	Na_2CO_3	$Cu(OTf)_2$ (20)	DMF	100	49
7	Na_2CO_3	Ag(OTf) (20)	DMF	100	no reaction
8	Na_2CO_3	$Zn(OTf)_2$ (20)	DMF	100	no reaction
9	Na_2CO_3	$Fe(OTf)_2$ (20)	DMF	100	25
10	Na_2CO_3	$FeCl_2$ (20)	DMF	100	trace
11	Na_2CO_3	$FeCl_3$ (20)	DMF	100	7
12	**Na_2CO_3**	**CuI (20)**	**DMF**	**130**	**91**
13	Na_2CO_3	CuI (10)	DMF	130	75
14[b]	Na_2CO_3	CuI (20)	DMF	130	76
15	Na_2CO_3	CuI (20)	toulene	130	no reaction
16	Na_2CO_3	CuI (20)	NMP	130	trace
17	Na_2CO_3	CuI (20)	DMSO	130	82
18[c]	Na_2CO_3	CuI (20)	DMF	130	no reaction
19	Na_2CO_3	–	DMF	130	21
20	–	CuI (20)	DMF	130	32
21[d]	Na_2CO_3	CuI (20)	DMF	130	71

[a]Reaction conditions: 0.25 mmol of **1a**, 0.75 mmol of **2a**, 0.75 mmol of **3a**, CuI (20 mol %), DMF (1 mL), 24 h, 130 °C, argon balloon, isolated yields. [b]In 12 h. [c]Without sulfur. [d]O_2 balloon.

Scheme 2. Scope for Three-Component Coupling Reactions[a]



[a]Reaction conditions: 0.25 mmol of **1**, 0.75 mmol of S_8, 0.75 mmol of **3**, DMF (2 mL), Na_2CO_3 (1.0 mmol), 24 h, isolated yields.

DOI: 10.1021/acs.joc.6b01715
J. Org. Chem. 2016, 81, 9964−9972

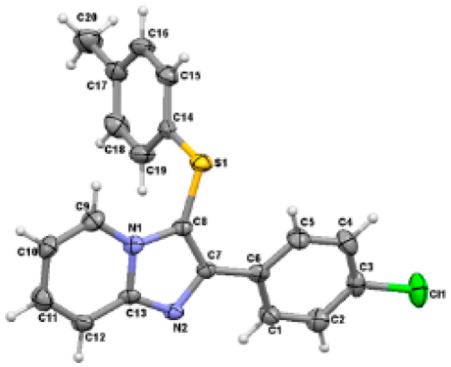
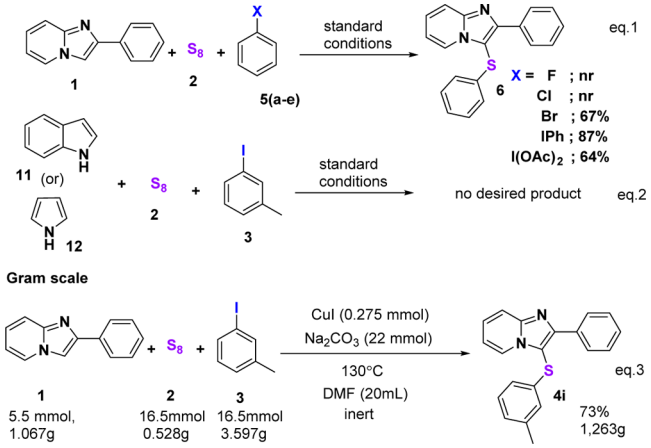


Figure 1. Crystal structure of **4n**.

substituents (methyl, chloro, bromo, and nitro) on the 2-phenylimidazo[2,1-*a*]isoquinoline unit reacted smoothly and gave desired products **4u**−**w** in 45−87% yields. The strategy was extended to iodoheteroarenes like 2-iodopyridine; in this case, desired product **4z** was isolated in 77% yield.

In addition, we verified the reactivity of other haloarenes such as fluorobenzene **5a**, chlorobenzene **5b**, bromobenzene **5c**, diphenyliodonium chloride **5d**, and (diacetoxyiodo)benzene **5e** under the reaction conditions described here (Scheme 3, eq 1).

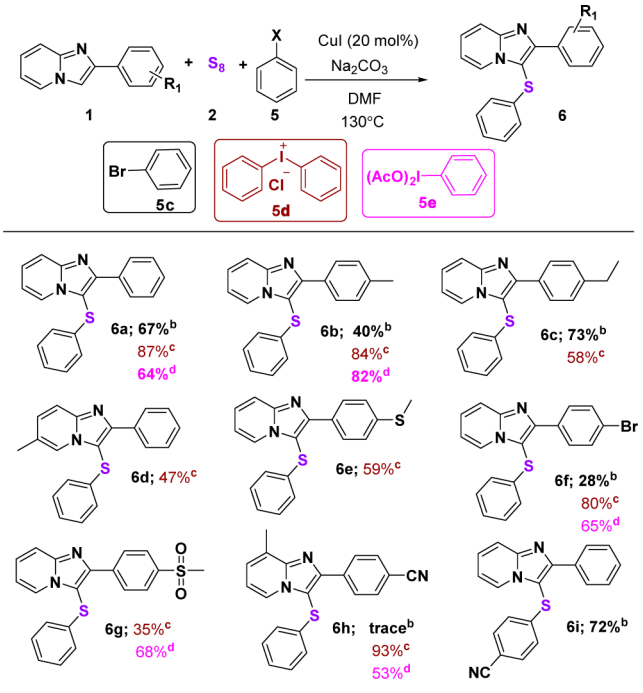
Scheme 3. Various Halogens, Heterocyclic Sources, and Gram Scale Synthesis



Under the optimized conditions, no reaction of **1a** was observed with **5a** or **5b**. The reaction of **1a** with **5c**, **5d**, and **5e** gave desired sulfenylated product **6a** in 67, 87, and 64% yields, respectively. Compared to **5c** and **5d**, **5a** and **5b** are less reactive toward diphenyl disulfide intermediate formation via the oxidative addition with metal. Also, these reaction conditions were extended to various heterocycles like indole and imidazole; unfortunately, no desired product was observed (Scheme 3, eq 2). To confirm the feasibility of the process for scale-up studies, we synthesized one of the molecules at a gram scale under the same optimized conditions. The reaction of **1** (1.067 g, 5.5 mmol), S_8 (0.528 g, 16.5 mmol), and **3** (3.597 g, 16.5 mmol) was conducted, and desired product **4i** was obtained in 73% yield [1.263 g (Scheme 3, eq 3)].

Then with these haloarenes (Scheme 3), three-component coupling reactions were extended to different imidazoheterocycles to ascertain the scope of our methodology (Scheme 4). The reaction of 2-(*p*-tolyl)imidazo[1,2-*a*]pyridine and 2-(4-ethylphenyl)imidazo[1,2-*a*]pyridine with haloarenes **5c**−**e** gave

Scheme 4. Reactivity of Haloarenes[a]

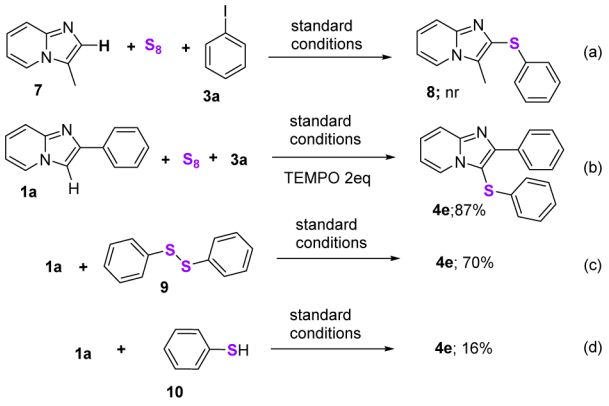


[a]Reaction conditions: 0.25 mmol of **1**, 0.75 mmol of S_8, 0.75 mmol of **5**, DMF (2 mL), Na_2CO_3 (1.0 mmol) 24 h, isolated yields. [b]Yield with **5c**. [c]Yield with **5d**. [d]Yield with **5e**.

the corresponding sulfenylated products **6b** and **6c** with yields ranging from 40 to 84%. Further, the representative imidazopyridines with different substituent groups (CH_3, SCH_3, SO_2CH_3, Br, and CN) on the phenyl ring were subjected to these conditions with haloarenes **5c**−**e**, and the corresponding sulfenylated products **6d**−**h** were obtained in moderate to good yields. Under these optimized conditions, the reaction of **1a** with 4-bromobenzonitrile gave desired sulfenylated product **6i** in 72% yield.

To understand the reaction mechanism, some selective and control experiments were performed (Scheme 5). Principally,

Scheme 5. Control Experiments



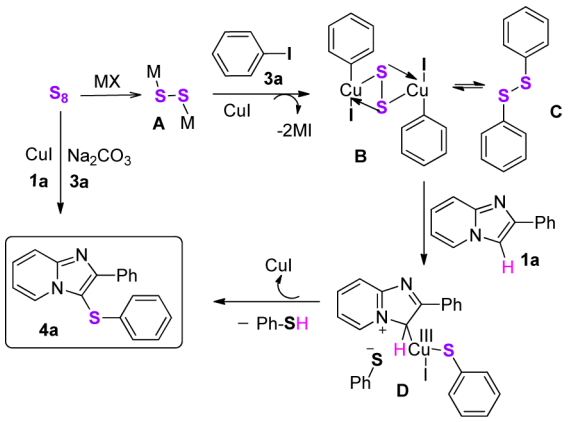
the reaction of 3-methylimidazo[1,2-*a*]pyridine **7** containing a methyl group at the C-3 position and vacant at the C-2 position was conducted with iodobenzene **3a** and elemental sulfur (S_8), but the reaction does not yield the desired product, 3-methyl-2-(phenylthio)imidazo[1,2-*a*]pyridine **8** (Scheme 5, eq a).

DOI: 10.1021/acs.joc.6b01715
J. Org. Chem. 2016, 81, 9964−9972

This reaction indicates that the regioselective sulfenylation takes place only at the C-3 position of the imidazopyridine unit. Further study of the reaction was conducted by the addition of radical scavenger TEMPO under optimized conditions to determine whether the reaction proceeds via a radical pathway or an ionic path; under these conditions, desired sulfenylated product **4e** was isolated in 87% yield, and that indicates the reaction is not going through the radical pathway (Scheme 5, eq b). When the reaction of **1a** was conducted with only diphenyl disulfide **9**, under the optimized conditions, 70% of desired product **4e** was obtained (Scheme 5, eq c). This indicates **9** may be generated in situ under these conditions, which triggers the reaction. In addition, the same reaction was performed with thiophenol **10**, instead of **9**, but only 16% of the desired product was isolated; this finding supports the idea that **B** and **C** are the intermediates in the particular reaction mechanism (Scheme 5, eq d).

On the basis of the literature reports[23] and our observations described above (Scheme 5), a plausible reaction mechanism has been proposed (Scheme 6). Initially, sulfur powder reacts

Scheme 6. Plausible Reaction Mechanism



with the base (Na_2CO_3) and generates metal sulfide **A**, and its reaction with haloarenes in the presence of copper by oxidative addition generates another intermediate, **B**. Intermediates **B** and **C** may exist in equilibrium with each other. Intermediate **B** reacts with **1a** and generates imidazolium intermediate **D**.[23b−e] Finally, reductive elimination gives desired sulfenylated product **4a** through the elimination of thiophenol, and it will be further converted into dimethyl sulphide (di-*m*-tolylsulfane **13**) after reaction with iodobenzene.[23f]

CONCLUSION

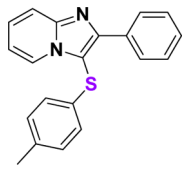
We have revealed a copper-catalyzed, expeditious one-pot three-component procedure for the synthesis of sulfenylated imidazo[1,2-*a*]pyridine and phenylimidazo[2,1-*a*]isoquinoline using commercially available starting substrates. The method has a broad substrate scope, with a variety of substituent groups on haloarenes as well as an imidazopyridine moiety, and produced good to excellent yields of sulfenylated products.[24]

EXPERIMENTAL SECTION

General. All commercially available chemicals and reagents were used without any further purification unless otherwise indicated. ^{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. Multiplicity was 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 are reported in parts per million relative to TMS as an internal standard. The peaks around δ values of ^{1}H NMR (7.2) and ^{13}C NMR (77.0) correspond to deuterated solvent chloroform. Mass spectra were recorded using the electron impact (EI) HRMS (ESI-TOF) ionization method. Progress of the reactions was monitored by thin layer chromatography (TLC). All products were purified via column chromatography using silica gel 100−200 mesh size using a hexane/ethyl acetate eluent unless otherwise indicated.

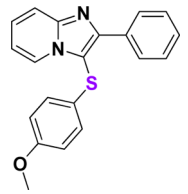
General Procedure for 4a. A clean washed boiling tube equipped with a magnetic stir bar was charged with imidazo[1,2-*a*]pyridine **1a** (0.0485 g, 0.25 mmol), elemental sulfur (S_8) (0.024 g, 0.75 mmol), iodobenzene **3a** (0.165 g, 0.75 mmol), copper(I) iodide (0.0095 g, 0.050 mmol), sodium carbonate (0.106 g, 1 mmol), and DMF (2 mL), and this mixture was stirred for 24 h at 130 °C in an argon balloon atmosphere. After completion of the reaction, the mixture was poured into 10 mL of a sodium bicarbonate solution. The product was extracted with ethyl acetate (3 × 10 mL) and dried with anhydrous Na_2SO_4. Via removal of the solvent under reduced pressure, the omitted residue was purified via column chromatography using silica gel (20% EtOAc/hexane) to produce **4a** in 91% yield (0.0721 g).

Characterization Data. *2-Phenyl-3-(p-tolylthio)imidazo[1,2-a]-pyridine (**4a**).*[2]



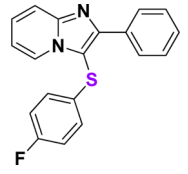
Eluent, 20% EtOAc/hexane; white solid; 91% yield (72.1 mg); R_f = 0.31 (8:2 *n*-hexane/ethyl acetate); mp 98−100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 7.0 Hz, 1H), 8.14 (d, J = 7.5 Hz, 2H), 7.63 (d, J = 9.5 Hz, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.74 (t, J = 7.0 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 146.9, 135.9, 133.3, 131.4, 130.1, 128.4, 128.3, 126.4, 125.7, 124.4, 117.5, 112.9, 106.7, 20.8.

*3-[(4-Methoxyphenyl)thio]-2-phenylimidazo[1,2-a]pyridine (**4b**).*[5]



Eluent, 20% EtOAc/hexane; white solid; 97% yield (80.7 mg); R_f = 0.20 (8:2 *n*-hexane/ethyl acetate); mp 115−118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (q, J = 6.5 Hz, 3H), 7.70 (d, J = 9.0 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 9.0 Hz, 2H), 6.81 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 9.0 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 150.6, 146.7, 133.3, 128.4, 128.2, 127.8, 126.3, 125.3, 124.3, 117.4, 115.0, 112.8, 107.6, 55.1.

*3-[(4-Fluorophenyl)thio]-2-phenylimidazo[1,2-a]pyridine (**4c**).*

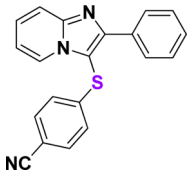


Eluent, 20% EtOAc/hexane; white solid; 98% yield (78.0 mg); R_f = 0.28 (8:2 *n*-hexane/ethyl acetate); mp 130−132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (q, J = 6.4 Hz, 3H), 7.71 (d, J = 9.0 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.0 Hz, 1H), 7.29 (t, J = 7.0 Hz, 1H), 6.98−6.95 (m, 2H), 6.88 (t, J = 8.5 Hz, 2H), 6.83 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3 (d, J_{C-F} = 244.6 Hz), 151.2, 146.9, 133.1, 129.9, 128.5, 128.3, 128.2, 127.5

DOI: 10.1021/acs.joc.6b01715
J. Org. Chem. 2016, 81, 9964−9972

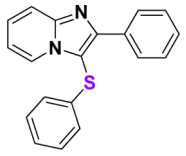
(d, J_{C-F} = 7.6 Hz), 126.6, 124.1, 117.6, 116.5 (d, J_{C-F} = 22.1 Hz), 113.0, 106.4; HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{14}N_2FS$ 321.0862, found 321.0851.

*4-[(2-Phenylimidazo[1,2-a]pyridin-3-yl)thio]benzonitrile (**4d**).*



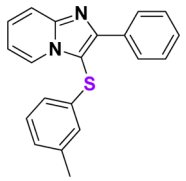
Eluent, 20% EtOAc/hexane; white solid; 76% yield (61.5 mg); R_f = 0.14 (8:2 *n*-hexane/ethyl acetate); mp 192−195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.0 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.46−7.40 (m, 4H), 7.36 (t, *J* = 7.0 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.90 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 147.4, 142.4, 132.8, 128.8, 128.4, 128.1, 127.1, 125.3, 124.0, 118.3, 117.8, 113.4, 109.3,103.5; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{14}N_3S$ 328.0908, found 328.0921.

*2-Phenyl-3-(phenylthio)imidazo[1,2-a]pyridine (**4e**).*[1]



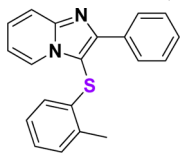
Eluent, 20% EtOAc/hexane; white solid; 90% yield (68.0 mg); R_f = 0.31 (8:2 *n*-hexane/ethyl acetate); mp 95−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.0 Hz, 1H), 8.21 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 9 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.31 (t, *J* = 7.0 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 7.0 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.84 (t, *J* = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 147.0, 135.1, 133.2, 129.3, 128.5, 128.35, 128.30 126.5, 125.9, 125.4, 124.4, 117.6, 113.0, 106.2.

*2-Phenyl-3-(m-tolylthio)imidazo[1,2-a]pyridine (**4i**).*



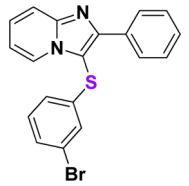
Eluent, 20% EtOAc/hexane; white solid; 97% yield (77.0 mg); R_f = 0.31 (8:2 *n*-hexane/ethyl acetate); mp 83−85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.5 Hz, 3H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.0 Hz, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.73 (s, 1H), 6.68 (t, *J* = 7.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 146.9, 139.2, 134.7, 133.2, 129.1, 128.4, 128.26, 128.21, 126.8, 126.4, 125.8, 124.3, 117.4, 112.8, 106.2, 21.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{17}N_2S$ 317.1112, found 317.1115.

*2-Phenyl-3-(o-tolylthio)imidazo[1,2-a]pyridine (**4j**).*



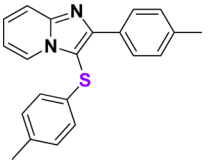
Eluent, 20% EtOAc/hexane; white solid; 97% yield (77.7 mg); R_f = 0.28 (8:2 *n*-hexane/ethyl acetate); mp 130−132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (q, *J* = 8.0 Hz, 3H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.40 (t, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.80 (q, *J* = 7.0 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 147.1, 134.7, 133.9, 133.2, 130.5, 128.4, 128.26, 128.23, 126.8, 126.4, 125.5, 124.3, 123.9, 117.5, 112.9, 105.4, 19.6; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{17}N_2S$ 317.1112, found 317.1098.

*3-[(3-Bromophenyl)thio]-2-phenylimidazo[1,2-a]pyridine (**4k**).*



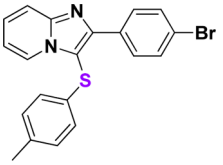
Eluent, 20% EtOAc/hexane; white solid; 95% yield (90.2 mg); R_f = 0.25 (8:2 *n*-hexane/ethyl acetate); mp 128−132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 6.5 Hz, 1H), 8.17 (d, *J* = 9.0 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.39−7.32 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.18 (s, 1H), 6.88−6.83 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 147.2, 137.6, 133.0, 130.6, 129.1, 128.7, 128.4, 128.2, 127.9, 126.8, 124.2, 123.7, 123.3, 117.6, 113.2, 104.9; HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{14}N_2SBr$ 381.0061, found 381.0061.

*2-(p-Tolyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (**4l**).*[4]



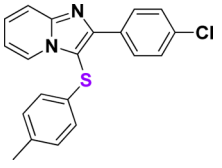
Eluent, 20% EtOAc/hexane; white solid; 87% yield (71.6 mg); R_f = 0.31 (8:2 *n*-hexane/ethyl acetate); mp 138−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 6.5 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.23 (d, *J* = 7.0 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.79 (t, *J* = 6.5 Hz, 1H), 2.36 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 146.8, 138.3, 135.8, 131.5, 130.4, 130.0, 129.0, 128.1, 126,3, 125.6, 124.3, 117.3, 112.7, 106.3, 21.2, 20.7.

*2-(4-Bromophenyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (**4m**).*[2]



Eluent, 20% EtOAc/hexane; white solid; 85% yield (83.4 mg); R_f = 0.33 (8:2 *n*-hexane/ethyl acetate); mp 148−150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.0 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.81 (t, *J* = 6.5 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 146.8, 136.0, 132.2, 131.4, 130.9, 130.1, 129.6, 126.6, 125.7, 124.3, 122.7, 117.4, 113.0, 106.9, 20.7.

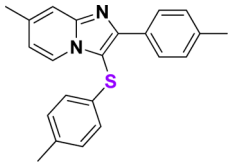
*2-(4-Chlorophenyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (**4n**).*[2]



Eluent, 20% EtOAc/hexane; white solid; 80% yield (69.9 mg); R_f = 0.36 (8:2 *n*-hexane/ethyl acetate); mp 135−138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.0 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.28 (t, *J* = 7.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.82 (t, *J* = 7.0 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 146.8, 136.0, 134.3, 131.8, 131.0, 130.1, 129.4, 128.4, 126.6, 125.7, 124.3, 117.4, 113.0, 106.9, 20.7.

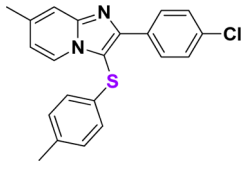
DOI: 10.1021/acs.joc.6b01715
J. Org. Chem. 2016, 81, 9964−9972

*7-Methyl-2-(p-tolyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (**4o**).*



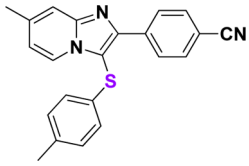
Eluent, 20% EtOAc/hexane; white solid; 57% yield (48.9 mg); R_f = 0.30 (8:2 *n*-hexane/ethyl acetate); mp 132−135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.0 Hz, 2H), 8.06 (s, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 10.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 2.37 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 145.9, 138.2, 135.7, 131.9, 130.6, 130.0, 129.5, 129.0, 128.0, 125.5, 122.6, 122.1, 116.7, 105.7, 21.2, 20.8, 18.3; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{21}N_2S$ 345.1425, found 345.1421.

*2-(4-Chlorophenyl)-7-methyl-3-(p-tolylthio)imidazo[1,2-a]-pyridine (**4p**).*[4]



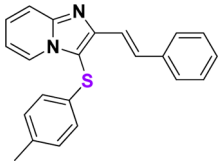
Eluent, 20% EtOAc/hexane; white solid; 70% yield (63.8 mg); R_f = 0.40 (8:2 *n*-hexane/ethyl acetate); mp 135−138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 7.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.47 (s, 1H), 7.23 (t, J = 8.0 Hz, 2H), 7.19 (t, J = 7.5 Hz, 2H), 7.11 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 7.0 Hz, 1H), 2.42 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 147.4, 138.3, 137.7, 135.5, 130.5, 129.3, 129.0, 128.1, 125.8, 125.4, 123.5, 116.0, 115.5, 105.0, 21.36, 21.31.

*4-[7-Methyl-3-(p-tolylthio)imidazo[1,2-a]pyridin-2-yl]benzonitrile (**4q**).*[2]



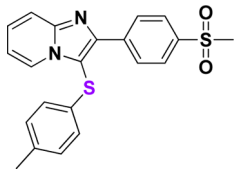
Eluent, 20% EtOAc/hexane; white solid; 69% yield (59.2 mg); R_f = 0.43 (8:2 *n*-hexane/ethyl acetate); mp 168−170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 6.5 Hz, 2H), 8.15 (d, J = 6.5 Hz, 1H), 7.68 (d, J = 6.5 Hz, 2H), 7.13 (d, J = 7.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 6.79 (t, J = 7.0 Hz, 1H), 2.68 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 147.3, 138.1, 136.2, 132.0, 130.8, 130.2, 128.6, 127.9, 125.7, 122.2, 119.0, 113.4, 111.3, 108.4, 20.7, 16.6.

*(E)-2-Styryl-3-(p-tolylthio)imidazo[1,2-a]pyridine (**4r**).*[2]



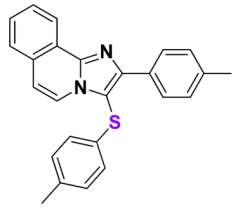
Eluent, 20% EtOAc/hexane; white solid; 18% yield (13.3 mg); R_f = 0.20 (8:2 *n*-hexane/ethyl acetate); mp 114−116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 7.0 Hz, 1H), 7.81 (d, J = 16.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 2H), 7.49 (d, J = 16.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.32−7.27 (m, 2H), 7.02 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 6.82 (t, J = 7.0 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 147.4, 137.0, 136.3, 132.6, 131.3, 130.1, 128.6, 128.0, 126.9, 126.5, 124.3, 118.2, 117.2, 112.6, 109.6, 20.8.

*2-[4-(Methylsulfonyl)phenyl]-3-(p-tolylthio)imidazo[1,2-a]-pyridine (**4s**).*



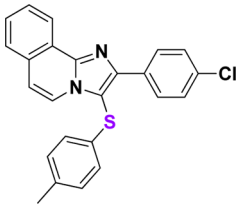
Eluent, 20% EtOAc/hexane; white solid; 56% yield (54.7 mg); R_f = 0.26 (5:5 *n*-hexane/ethyl acetate); mp 174−176 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, J = 8.5 Hz, 2H), 8.32 (d, J = 7.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 9.0 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.92 (q, J = 6.5 Hz, 3H), 3.07 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 147.0, 139.7, 138.8, 136.4, 130.5, 130.2, 128.8, 127.3, 127.1, 125.8, 124.5, 117.8, 113.5, 108.5, 44.4, 20.7; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{19}N_2O_2S_2$ 395.0888, found 395.0877.

*2-(p-Tolyl)-3-(p-tolylthio)imidazo[2,1-a]isoquinoline (**4u**).*



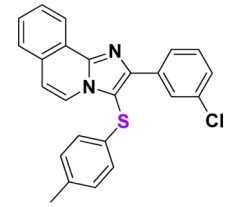
Eluent, 10% EtOAc/hexane; white solid; 78% yield (73.9 mg); R_f = 0.53 (9:1 *n*-hexane/ethyl acetate); mp 205−208 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 8.0 Hz, 2H), 8.10 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 144.8, 138.0, 135.8, 132.1, 130.7, 130.2, 130.1, 129.1, 128.8, 128.1, 128.0, 126.9, 125.7, 123.6, 121.2, 113.3, 108.4, 29.6, 21.3; HRMS (ESI-TOF) m/z calcd for $C_{25}H_{21}N_2S$ 381.1425, found 381.1423.

*2-(4-Chlorophenyl)-3-(p-tolylthio)imidazo[2,1-a]isoquinoline (**4v**).*



Eluent, 10% EtOAc/hexane; white solid; 87% yield (86.6 mg); R_f = 0.60 (9:1 *n*-hexane/ethyl acetate); mp 209−212 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 8.0 Hz, 2H), 8.11 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.69 (t, J = 7.0 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 7.5 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 144.9, 136.1, 134.1, 132.1, 131.6, 130.2, 129.3, 129.0, 128.5, 128.2, 126.9, 125.8, 123.5, 123.4, 121.1, 113.6, 109.1, 20.8; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{18}N_2SCl$ 401.0879, found 401.0868.

*2-(3-Chlorophenyl)-3-(p-tolylthio)imidazo[2,1-a]isoquinoline (**4w**).*

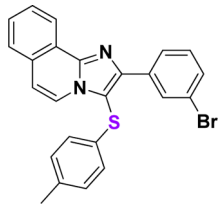


Eluent, 10% EtOAc/hexane; white solid; 62% yield (62.3 mg); R_f = 0.56 (9:1 *n*-hexane/ethyl acetate); mp 180−183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, J = 8.0 Hz, 1H), 8.33 (s, 1H), 8.19 (d, J = 8.0 Hz,

DOI: 10.1021/acs.joc.6b01715
J. Org. Chem. 2016, 81, 9964−9972

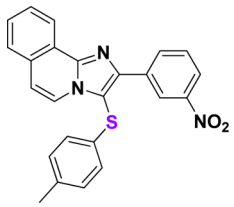
1H), 8.12 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 7.0 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.0 Hz, 1H), 7.38−7.32 (m, 2H), 7.13 (d, J = 7.5 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 136.2, 135.4, 134.3, 131.5, 130.3, 130.2, 129.6, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.1, 127.0, 126.1, 126.0, 123.6, 123.5, 121.1, 113.7, 109.6, 20.8; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{18}N_2SCl$ 401.0879, found 401.0868.

*2-(3-Bromophenyl)-3-(p-tolylthio)imidazo[2,1-a]isoquinoline (**4x**).*



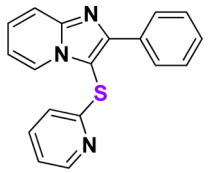
Eluent, 10% EtOAc/hexane; white solid; 63% yield (69.9 mg); R_f = 0.56 (9:1 n-hexane/ethyl acetate); mp 172−175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 8.0 Hz, 1H), 8.48 (s, 1H), 8.23 (d, J = 7.5 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.75−7.68 (m, 2H), 7.65 (t, J = 7.0 Hz, 1H), 7.49 (d, J = 7.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 7.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 7.5 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 144.9, 136.2, 135.6, 131.5, 131.0, 130.9, 130.3, 130.2, 129.8, 129.0, 128.8, 128.3, 127.0, 126.5, 126.0, 123.6, 122.6, 121.1, 113.7, 109.7, 20.8; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{18}N_2SBr$ 445.0374, found 445.0394.

*2-(3-Nitrophenyl)-3-(p-tolylthio)imidazo[2,1-a]isoquinoline (**4y**).*



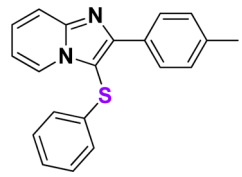
Eluent, 10% EtOAc/hexane; yellow solid; 45% yield (46.1 mg); R_f = 0.40 (9:1 n-hexane/ethyl acetate); mp 215−220 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.73 (d, J = 8.0 Hz, 1H), 8.59 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 7.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.0 Hz, 1H), 7.58 (t, J = 7.0 Hz, 1H), 7.52 (t, J = 7.0 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 7.0 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 146.4, 145.0, 136.5, 135.4, 133.7, 131.1, 130.3, 129.2, 128.5, 127.0, 126.1, 123.6, 123.5, 123.0, 122.6, 121.0, 114.1, 110.5, 20.8; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{18}N_3O_2S$ 412.1120, found 412.1125.

*2-Phenyl-3-(pyridin-2-ylthio)imidazo[1,2-a]pyridine (**4z**).*



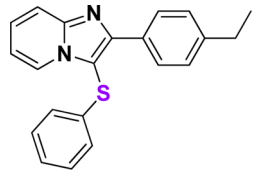
Eluent, 50% EtOAc/hexane; white solid; 77% yield (56.5 mg); R_f = 0.36 (6:4 n-hexane/ethyl acetate); mp 120−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 4.0 Hz, 1H), 8.31 (d, J = 7.0 Hz, 1H), 8.19 (d, J = 7.5 Hz, 2H), 7.75 (d, J = 9.0 Hz, 1H), 7.43−7.39 (m, 3H), 7.36−7.27 (m, 2H), 7.03 (q, J = 5.0 Hz, 1H), 6.88 (t, J = 7.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 151.3, 150.1, 147.2, 137.2, 136.9, 133.1, 128.5, 128.3, 126.7, 125.8, 124.4, 120.5, 119.3, 117.6, 113.0, 105.2; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{14}N_3S$ 304.0908, found 304.0907.

*3-(Phenylthio)-2-(p-tolyl)imidazo[1,2-a]pyridine (**6b**).*[1]



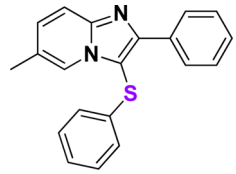
Eluent, 20% EtOAc/hexane; white solid; 84% yield (66.2 mg); R_f = 0.20 (8:2 n-hexane/ethyl acetate); mp 118−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 7.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 6.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.19 (t, J = 7.5 Hz, 2H), 7.13 (t, J = 7.0 Hz, 1H), 7.10 (d, J = 7.5 Hz, 2H), 6.83 (t, J = 7.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 147.0, 138.4, 135.2, 130.4, 129.3, 129.0, 128.1, 126.4, 125.9, 125.4, 124.3, 117.4, 112.8, 105.8, 21.2.

*2-(4-Ethylphenyl)-3-(phenylthio)imidazo[1,2-a]pyridine (**6c**).*[1]



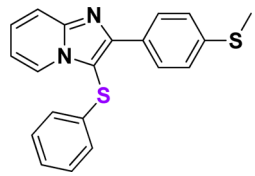
Eluent, 20% EtOAc/hexane; white solid; 58% yield (47.4 mg); R_f = 0.26 (8:2 n-hexane/ethyl acetate); mp 98−100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 6.0 Hz, 1H), 8.14 (d, J = 7.5 Hz, 2H), 7.72 (d, J = 9.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.19 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 2H), 6.84 (t, J = 7.0 Hz, 1H), 2.70 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 147.0, 144.7, 135.2, 130.6, 129.3, 128.2, 127.9, 126.5, 125.9, 125.4, 124.4, 117.5, 112.9, 105.8, 28.6, 15.3.

*6-Methyl-2-phenyl-3-(phenylthio)imidazo[1,2-a]pyridine (**6d**).*[1]



Eluent, 20% EtOAc/hexane; yellow solid; 47% yield (37.2 mg); R_f = 0.23 (8:2 n-hexane/ethyl acetate); mp 116−118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 7.5 Hz, 2H), 8.06 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.23−7.17 (m, 3H), 7.13 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 7.0 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 146.1, 135.5, 133.4, 129.7, 129.4, 128.4, 128.3, 128.2, 125.8, 125.3, 122.9, 122.1, 116.9, 18.3.

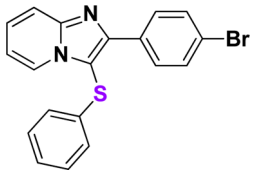
*2-[4-(Methylthio)phenyl]-3-(phenylthio)imidazo[1,2-a]pyridine (**6e**).*[1]



Eluent, 20% EtOAc/hexane; yellow solid; 59% yield (51.4 mg); R_f = 0.13 (8:2 n-hexane/ethyl acetate); mp 106−108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 7.0 Hz, 1H), 8.17 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 9.0 Hz, 1H), 7.34 (q, J = 7.0 Hz, 3H), 7.21 (t, J = 7.5 Hz, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 8.0 Hz, 2H), 6.86 (t, J = 6.5 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 147.0, 139.2, 135.0, 129.9, 129.4, 128.5, 127.6, 126.6, 126.0, 125.5, 124.4, 117.5, 113.0, 105.9, 15.4.

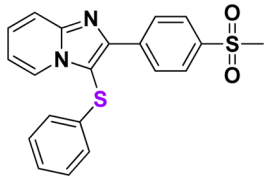
DOI: 10.1021/acs.joc.6b01715
J. Org. Chem. 2016, 81, 9964−9972

*2-(4-Bromophenyl)-3-(phenylthio)imidazo[1,2-a]pyridine (**6f**).*[1]



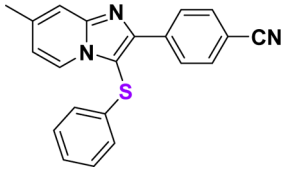
Eluent, 20% EtOAc/hexane; white solid; 80% yield (75.8 mg); R_f = 0.33 (8:2 *n*-hexane/ethyl acetate); mp 148−150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 6.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 7.0 Hz, 1H), 7.20 (t, J = 7.5 Hz, 2H), 7.13 (t, J = 7.0 Hz, 1H), 6.98 (d, J = 7.5 Hz, 2H), 6.86 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 147.0, 134.7, 132.2, 131.5, 129.7, 129.4, 126.8, 126.1, 125.5, 124.4, 122.8, 117.6, 113.1, 106.4.

*2-[4-(Methylsulfonyl)phenyl]-3-(phenylthio)imidazo[1,2-a]-pyridine (**6g**).*[1]



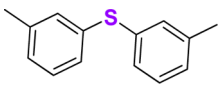
Eluent, 40% EtOAc/hexane; white solid; 35% yield (33.6 mg); R_f = 0.26 (5:5 *n*-hexane/ethyl acetate); mp 188−190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, J = 6.5 Hz, 2H), 8.32 (d, J = 7.0 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 9.0 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 7.0 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 7.5 Hz, 2H), 6.93 (t, J = 6.5 Hz, 1H), 3.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 147.2, 139.8, 138.7, 134.3, 129.5, 128.9, 127.4, 127.3, 126.4, 125.6, 124.5, 117.9, 113.6, 107.9, 44.5.

*4-[8-Methyl-3-(phenylthio)imidazo[1,2-a]pyridin-2-yl)benzo-nitrile (**6h**).*



Eluent, 30% EtOAc/hexane; white solid; 93% yield (79.6 mg); R_f = 0.23 (8:2 *n*-hexane/ethyl acetate); mp 168−171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.48 (d, J = 7.5 Hz, 1H), 8.16 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 2H), 7.17 (q, J = 5.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.84 (t, J = 7.0 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 147.5, 135.0, 134.6, 132.4, 131.9, 131.6, 129.5, 129.3, 129.1, 128.0, 126.3, 125.9, 125.6, 122.3, 118.9, 113.5, 112.6, 107.5, 16.6; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{16}N_3S$ 342.1065, found 342.1057.

*Di-m-tolylsulfane (**13**).*



Eluent, hexane; liquid; R_f = 0.43 (*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 7.5 Hz, 4H), 7.17 (t, J = 7.5 Hz, 2H), 7.02 (d, J = 7.5 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 136.8, 128.8, 127.9, 124.5, 21.3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01715.

Crystallographic data for compound **4n** (CCDC 1484511) (CIF)

Copies of NMR spectra for all compounds and HRMS spectra for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: adimurthy@csmcri.org.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

CSIR-CSMCRI Communication 093/2016. C.R., N.N.K.R., V.P., and S.S. are thankful to AcSIR for Ph.D. enrollment and the "Analytical Discipline and Centralized Instrumental Facilities" for providing instrumentation facilities, and special thanks to Dr. E. Suresh for providing the crystal data. V.P. and S.S. are also thankful to UGC and CSIR, New Delhi, for their fellowships. We thank DST, Government of India (EMR/2016/000010), and CSIR-CSMCRI (OLP-087) for financial support.

■ REFERENCES

(1) (a) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*, 4th ed.; Blackwell: Oxford, U.K., 2000. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627.

(2) (a) Couty, F.; Evano, G. In *Comprehensive Heterocyclic Chemistry III*; Elsevier: Oxford, U.K., 2008; Vol. *11*, p 409. (b) Liu, J.; Chen, Q. *Huaxue Jinzhan* **2010**, *22*, 631. (c) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888. (d) DiMauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2007**, *72*, 1013.

(3) (a) Kaminski, J. J.; Doweyko, A. M. *J. Med. Chem.* **1997**, *40*, 427. (b) 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. (c) Kotovskaya, S. K.; Baskakova, Z. M.; Charushin, V. N.; Chupakhin, O. N.; Belanov, E. F.; Bormotov, N. I.; Balakhnin, S. M.; Serova, O. A. *Pharm. Chem. J.* **2005**, *39*, 574.

(4) (a) Byth, K. F.; Culshaw, J. D.; Green, S.; Oakes, S. E.; Thomas, A. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2245. (b) Hamdouchi, C.; Zhong, B.; Mendoza, J.; Collins, E.; Jaramillo, C.; De Diego, J. E.; Robertson, D.; Spencer, C. D.; Anderson, B. D.; Watkins, S. A.; Zhang, F.; Brooks, H. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1943.

(5) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. *Adv. Biochem. Psychopharmacol.* **1990**, *46*, 61.

(6) (a) Okubo, T.; Yoshikawa, R.; Chaki, S.; Okuyama, S.; Nakazato, A. *Bioorg. Med. Chem.* **2004**, *12*, 423. (b) Mizushige, K.; Ueda, T.; Yukiiri, K.; Suzuki, H. *Cardiovasc. Drug Rev.* **2002**, *20*, 163. (c) Mori, H.; Tanaka, M.; Kayasuga, R.; Masuda, T.; Ochi, Y.; Yamada, H.; Kishikawa, K.; Ito, M.; Nakamura, T. *Bone.* **2008**, *43*, 840.

(7) (a) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. *J. Med. Chem.* **1965**, *8*, 305. (b) Boerner, R. J.; Möller, H. J. *Psychopharmakotherapy* **1997**, *4*, 145. (c) Gudmundsson, K.; Boggs, S. D. PCT Int. Appl. WO 2006026703, 2006.

(8) Stasyuk, A. J.; Banasiewicz, M.; Cyrański, M. K.; Gryko, D. T. *J. Org. Chem.* **2012**, *77*, 5552.

(9) John, A.; Shaikh, M. M.; Ghosh, P. *Dalton Trans.* **2009**, 10581.

(10) Douhal, A.; Amat-Guerri, F.; Acuña, A. U. *J. Phys. Chem.* **1995**, *99*, 76.

(11) (a) Rasheed, Sk.; Rao, D. N.; Das, P. *J. Org. Chem.* **2015**, *80*, 9321. (b) Wang, C.; Lei, S.; Cao, H.; Qiu, S.; Liu, J.; Deng, H.; Yan, C. *J. Org. Chem.* **2015**, *80*, 12725. (c) Adiyala, P. R.; Mani, G. S.; Nanubolu, J. B.; Shekar, K. C.; Maurya, R. A. *Org. Lett.* **2015**, *17*, 4308. (d) Nguyen, T. B.; Corbin, M.; Retailleau, P.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2015**, *17*, 4956. (e) McDonald, I. M.; Peese, K. M. *Org. Lett.* **2015**, *17*, 6002. (f) Donohoe, T. J.; Kabeshov, M. A.; Rathi, A. H.; Smith, I. E. D. *Org. Biomol. Chem.* **2012**, *10*, 1093. (g) He, Y.; Huang, J.; Liang, D.; Liu, L.; Zhu, Q. *Chem. Commun.* **2013**, *49*,

DOI: 10.1021/acs.joc.6b01715
J. Org. Chem. 2016, 81, 9964−9972

7352. (h) Dixon, L. I.; Carroll, M. A.; Gregson, T. J.; Ellames, G. J.; Harrington, R. W.; Clegg, W. *Org. Biomol. Chem.* **2013**, *11*, 5877.
(12) (a) Yang, D.; Yan, K.; Wei, W.; Li, G.; Lu, S.; Zhao, C.; Tian, L.; Wang, H. *J. Org. Chem.* **2015**, *80*, 11073. (b) Liu, P.; Gao, Y.; Gu, W.; Shen, Z.; Sun, P. *J. Org. Chem.* **2015**, *80*, 11559. (c) Wang, C.; Lei, S.; Cao, H.; Qiu, S.; Liu, J.; Deng, H.; Yan, C. *J. Org. Chem.* **2015**, *80*, 12725. (d) Wang, Y.; Frett, B.; McConnell, N.; Li, H.-y. *Org. Biomol. Chem.* **2015**, *13*, 2958.
(13) (a) Ramesha, A. B.; Raghavendra, G. M.; Nandeesh, K. N.; Rangappa, K. S.; Mantelingu, K. *Tetrahedron Lett.* **2013**, *54*, 95. (b) Rassokhina, I. V.; Shirinian, V. Z.; Zavarzin, I. V.; Gevorgyan, V.; Volkova, Y. A. *J. Org. Chem.* **2015**, *80*, 11212. (c) Wen, Q.; Lu, P.; Wang, Y. *Chem. Commun.* **2015**, *51*, 15378.
(14) (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (c) Ouyang, K.; Hao, W.; Zhang, W.-X.; Xi, Z. *Chem. Rev.* **2015**, *115*, 12045.
(15) (a) Wu, W.; Su, W. *J. Am. Chem. Soc.* **2011**, *133*, 11924. (b) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522. (c) Chandra Mohan, D.; Ravi, C.; Pappula, V.; Adimurthy, S. *J. Org. Chem.* **2015**, *80*, 6846.
(16) (a) Frasto da Silva, J. R.; Williams, R. J. P. *The Biological Chemistry of the Elements*; Oxford University Press: New York, 2001. (b) Nudelman, A. *The Chemistry of Optically Active Sulfur Compounds*; Gordon Breach: New York, 1984. (c) Damani, L. A. *Sulphur-Containing Drugs and Related Organic Compounds*; Wiley: New York, 1989. (d) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem.* **2011**, *7*, 582. (e) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev.* **2015**, *44*, 291.
(17) (a) Fukuzawa, S.; Shimizu, E.; Atsuumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374. (b) Ranjit, S.; Lee, R.; Heryadi, D.; Shen, C.; Wu, J.; Zhang, P.; Huang, K.; Liu, X. *J. Org. Chem.* **2011**, *76*, 8999. (c) Dai, C.; Xu, Z.; Huang, F.; Yu, Z.; Gao, Y. *J. Org. Chem.* **2012**, *77*, 4414. (d) Ge, W.; Wei, Y. *Green Chem.* **2012**, *14*, 2066. (e) Alves, D.; Lara, R. G.; Contreira, M. E.; Radatz, C. S.; Duarte, L. F. B.; Perin, G. *Tetrahedron Lett.* **2012**, *53*, 3364. (f) Klečka, M.; Pohl, R.; Čejka, J.; Hocek, M. *Org. Biomol. Chem.* **2013**, *11*, 5189. (g) Oliveira, D.; Alves, D.; Jacob, R.; Xavier, M. *Curr. Org. Synth.* **2015**, *12*, 822. (h) Fukuzawa, S.-i.; Shimizu, E.; Atsuumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374.
(18) (a) Ge, W.; Zhu, X.; Wei, Y. *Eur. J. Org. Chem.* **2013**, *2013*, 6015. (b) Bagdi, A. K.; Mitra, S.; Ghosh, M.; Hajra, A. *Org. Biomol. Chem.* **2015**, *13*, 3314. (c) Hiebel, M.; Berteina-Raboin, S. *Green Chem.* **2015**, *17*, 937. (d) Gao, Z.; Zhu, X.; Zhang, R. *RSC Adv.* **2014**, *4*, 19891. (e) Cao, H.; Chen, L.; Liu, J.; Cai, H.; Deng, H.; Chen, G.; Yan, C.; Chen, Y. *RSC Adv.* **2015**, *5*, 22356. (f) Huang, X.; Wang, S.; Li, B.; Wang, X.; Ge, Z.; Li, R. *RSC Adv.* **2015**, *5*, 22654. (g) Zheng, Z.; Qi, D.; Shi, L. *Catal. Commun.* **2015**, *66*, 83. (h) Rafique, J.; Saba, S.; Rosário, A. R.; Braga, A. L. *Chem. - Eur. J.* **2016**, *22*, 11854.
(19) (a) Ravi, C.; Chandra Mohan, D.; Adimurthy, S. *Org. Lett.* **2014**, *16*, 2978. (b) Mohan, D. C.; Rao, S. N.; Ravi, C.; Adimurthy, S. *Asian J. Org. Chem.* **2014**, *3*, 609.
(20) (a) Shen, C.; Spannenberg, A.; Wu, Xi. Fe. *Angew. Chem., Int. Ed.* **2016**, *55*, 5067. (b) Chen, J.; Li, G.; Xie, Y.; Liao, Y.; Xiao, F.; Deng, G. *Org. Lett.* **2015**, *17*, 5870. (c) Xu, J.; Zhang, L.; Li, X.; Gao, Y.; Tang, G.; Zhao, Y. *Org. Lett.* **2016**, *18*, 1266. (d) Nguyen, T. B.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2014**, *16*, 310. (e) Xu, J.; Zhang, L.; Li, X.; Gao, Y.; Tang, G.; Zhao, Y. *Org. Lett.* **2016**, *18*, 1266. (f) Chen, C.; Chu, L.; Qing, F. L. *J. Am. Chem. Soc.* **2012**, *134*, 12454. (g) Li, J.; Li, C.; Yang, S.; An, Y.; Wu, W.; Jiang, H. *J. Org. Chem.* **2016**, *81*, 2875−2887. (h) Yu, J.-T.; Guo, H.; Yi, Y.; Fei, H.; Jiang, Y. *Adv. Synth. Catal.* **2014**, *356*, 749−752.
(21) (a) Cao, H.; Zhan, H.; Lin, Y.; Lin, X.; Du, Z.; Jiang, H. *Org. Lett.* **2012**, *14*, 1688. (b) Bagdi, A. K.; Rahman, M.; Santra, S.; Majee, A.; Hajra, A. *Adv. Synth. Catal.* **2013**, *355*, 1741. (c) Fu, H. Y.; Chen, L.; Doucet, H. *J. Org. Chem.* **2012**, *77*, 4473. (d) Huang, G.; Sun, H.; Qiu, X.; Jin, C.; Lin, C.; Shen, Y.; Jiang, J.; Wang, L. *Org. Lett.* **2011**, *13*, 5224.
(22) (a) Chandra Mohan, D.; Nageswara Rao, S.; Adimurthy, S. *J. Org. Chem.* **2013**, *78*, 1266. (b) Chandra Mohan, D.; Sarang, N. B.; Adimurthy, S. *Tetrahedron Lett.* **2013**, *54*, 6077. (c) Donthiri, R. R.; Pappula, V.; Reddy, N. N. K.; Bairagi, D.; Adimurthy, S. *J. Org. Chem.* **2014**, *79*, 11277. (d) Chandra Mohan, D.; Reddy Donthiri, R.; Nageswara Rao, S.; Adimurthy, S. *Adv. Synth. Catal.* **2013**, *355*, 2217.
(23) (a) Chen, H. Y.; Peng, W. T.; Lee, Y. H.; Chang, Y. L.; Chen, Y. J.; Lai, Y. C.; Jheng, N. Y.; Chen, H. Y. *Organometallics* **2013**, *32*, 5514. (b) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (c) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (d) Mishra, S.; Mondal, P.; Ghosh, M.; Mondal, S.; Hajra, A. *Org. Biomol. Chem.* **2016**, *14*, 1432. (e) Ravi, C.; Chandra Mohan, D.; Adimurthy, S. *Org. Biomol. Chem.* **2016**, *14*, 2282. (f) Sperotto, E.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *J. Org. Chem.* **2008**, *73*, 5625.
(24) While the manuscript was being revised, a related work has been published: Li, J.; Li, C.; Yang, S.; An, Y.; Wu, W.; Jiang, H. *J. Org. Chem.* **2016**, *81*, 7771.

DOI: 10.1021/acs.joc.6b01715
J. Org. Chem. 2016, 81, 9964−9972