JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

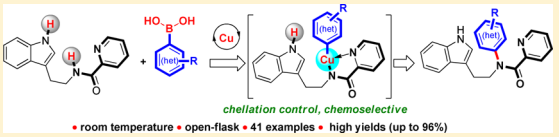
Copper Catalyzed C−N Cross-Coupling Reaction of Aryl Boronic Acids at Room Temperature through Chelation Assistance

Harekrishna Sahoo, Sayan Mukherjee, Gowri Sankar Grandhi, Jayaraman Selvakumar, and Mahiuddin Baidya*

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, Tamil Nadu, India

Supporting Information

ABSTRACT: A copper-catalyzed selective C−N cross-coupling has been developed based on chelation-assisted amidation of readily available aryl boronic acids at room-temperature under open-flask conditions. The reaction is scalable and tolerates a wide spectrum of functional groups delivering fully substituted unsymmetrical amides in high yields (up to 96%). The C−N cross coupling also established with aryl silanes, extending the palette of coupling partners of this strategy.



Fully substituted amides, particularly unsymmetrical systems possessing a (hetero)aryl substituent, represent a pivotal structural motif of many natural products and pharmaceuticals with diverse biological activities (Figure 1).[1] They also have

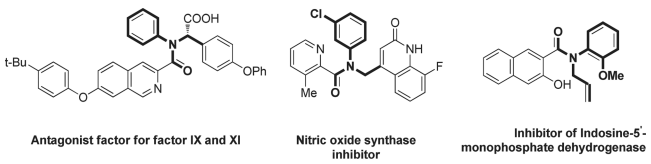


Figure 1. Selected examples of bioactive compounds having *N*-arylated amide linkage.

significant applications to functional materials and synthesis of different heterocyclic frameworks.[2] Consequently, the development of mild and efficient synthetic routes toward this scaffold is of utmost importance.

Traditionally, amides have been prepared by the reaction of amines with carboxylic acid derivatives,[3] aldehydes,[4] alcohols,[5] or hydration of nitriles,[6] and hydroamination of alkynes.[7] However, adaptation of these protocols for the synthesis of the aforementioned amides is usually plagued. The situation becomes adverse when multiple reaction sites are present. A straightforward route could be direct *N*-arylation of amides, and the Buchwald−Hartwig[8] and Chan−Lam[9] reactions are two related methods that are widely practiced for this purpose. While the pioneering works by Buchwald and Hartwig described a number of methods for the synthesis of amides and related compounds based on palladium-catalyzed amidation of aryl halides, requirements of precious palladium catalysts and phosphine ligands make this method expensive. On the other hand, copper-mediated oxidative amination of aryl boronic acids, the so-called Chan−Lam reaction, is cost-effective; however, when this protocol was employed for the amide derivatives, the *N*,*N*-disubstituted amide products were obtained in poor yields.[9b] Furthermore, various metal-catalyzed protocols, such as transamidation, alkylation of primary amides, and acylation of amines with ester, have also been established.[10] All these protocols are very general for the synthesis of secondary amides. However, they are not amenable to aryl substituted tertiary amides.[11]

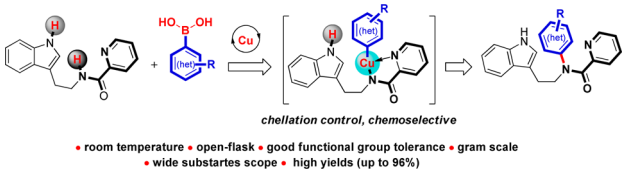
Recently, chelation-controlled transition-metal catalysis has emerged as a powerful tool for selective organic transformation and has been successfully implemented for the construction of various C−N bonds.[12−14] Furthermore, this strategy also provides a platform to execute previously unattainable reactions with more abundant and less expensive first-row transition metals.[13] We envisaged that incorporation of a chelating group in the form of an amide framework could promote the *N*-arylation with first-row transition metals and thus, fully substituted amides with unsymmetrical substitution patterns could be realized under mild conditions. However, a decisive choice of catalytic system is necessary to nullify the competing C−H bond functionalization pitfall of amides.[14] Toward this end, Nicholls's group reported an intriguing copper catalyzed amidation of aryl bromides using 8-amidoquinolines, albeit at elevated temperature.[15] Herein, we report an unprecedented copper-catalyzed picolinamide-assisted C−N cross-coupling with readily available boronic acids en route to unsymmetrical tertiary amides at room temperature under open-flask conditions (Scheme 1). In addition, we have also successfully demonstrated *N*-arylation with aryl silanes, extending the palette of coupling partners for this strategy.

We commenced our investigation by studying the reaction of picolinamide **1a** with phenylboronic acid **2a** (Scheme 2). After judicious evaluation of reaction parameters, we identified that a protocol based on $Cu(OAc)_2 \cdot H_2O$, DMAP, and KI[16] in 1,2-dimethoxy ethane (DME) at room temperature in the presence of air (open-flask) delivered **3aa** in 96% isolated yield (see SI for optimization details). The structure of **3aa** was

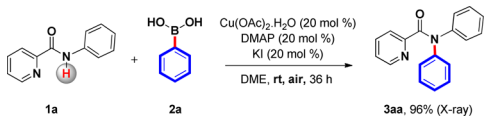
Received: January 2, 2017
Published: February 10, 2017

DOI: 10.1021/acs.joc.7b00002
J. Org. Chem. 2017, 82, 2764−2771

Scheme 1. Copper Catalyzed Chelation Assisted Selective C−N Bond Formation at Ambient Temperature Promoted by a Removable, Bidentate Auxiliary



Scheme 2. Copper-Catalyzed Chelation-Assisted Selective C−N Cross-Coupling



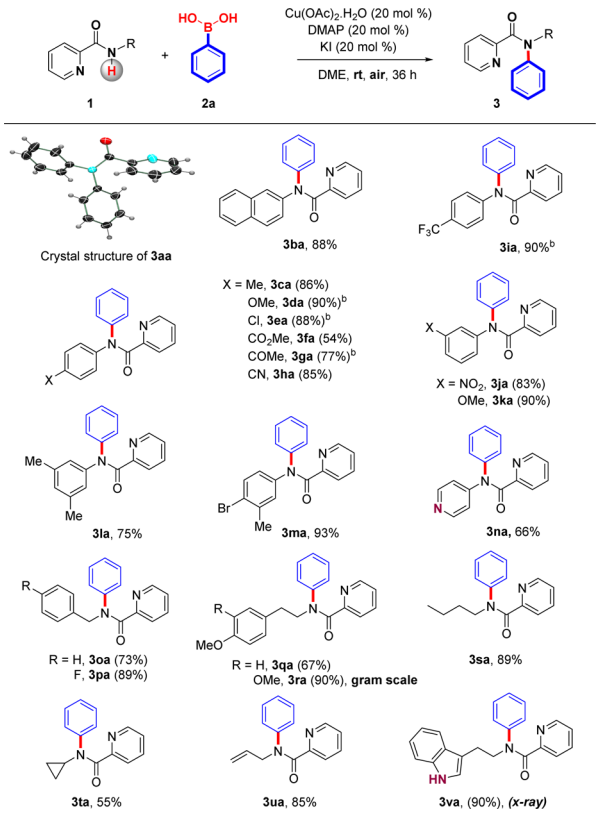
unambiguously established by X-ray analysis.[17] Interestingly, the *ortho* C−H arylation was not observed under these conditions. In general, the reaction is more fruitful in the presence of organic bases than inorganic bases. The catalytic system is also effective with silver oxidants; however, a higher temperature of 80 °C was necessary. The reaction completely shuts down in the absence of copper catalyst and is also not productive in the presence of $Co(OAc)_2{\cdot}4H_2O$, $Ni(OAc)_2{\cdot}4H_2O$, or $Fe(NO_3)_3{\cdot}9H_2O$ catalysts.

Prompted by these results, we sought to explore the chelation assisted C−N cross-coupling reaction for various substituted amides **1** (Table 1). The reaction is quite general, and the picolinamides having both electron-rich as well as electron-deficient groups furnished the *N*-arylated products **3ba**−**3ma** in good to excellent yield (54−93%). Various functional groups, such as methoxy (**3da**, **3ka**), chloro (**3ea**), ester (**3fa**), ketone (**3ga**), cyano (**3ha**), trifluoromethyl (**3ia**), and nitro (**3ja**) can be accommodated. Notably, nitrogen-containing heterocycles posed no problem, affording **3na** in 66% yield. The picolinamides having benzyl (**3oa**−**pa**) and tethered aliphatic amines (**3qa**−**ra**) also produced the corresponding products in very high yield. We were pleased to find that cyclopropyl (**3ta**) and allyl (**3ua**) residues were unaffected, demonstrating the mildness of the reaction conditions. Interestingly, the catalytic system boded well with the tryptamine derived picolinamide (**1v**). Although an unprotected nucleophilic nitrogen center is present at the indole moiety, C−N cross-coupling selectively took place at the amide-nitrogen, delivering **3va** in 90% yield. This result not only highlights the exquisite chemoselectivity of our protocol but also established the importance of chelation for this transformation.

Next, the adaptability of this copper catalysis was examined with a series of commercially available boronic acids **2b**−**j** (Table 2). As shown, the preparative scope was rather general regardless of whether electron-donating or electron-withdrawing groups were present or not, producing desired product in high yields (up to 91%). Remarkably, a variety of aryl halides (**3ea**, **4ad**−**ae**, **4ai**, **4ud**, and **4vd**), nitrile (**3ha** and **4vj**), aldehydes (**4ag** and **4aj**), and heterocycles (**4ak**, **4vd**−**vj**) are effective. Importantly, even a boronic acid containing free hydroxyl group could be employed as a coupling partner, giving **4ah** in 55% yield.

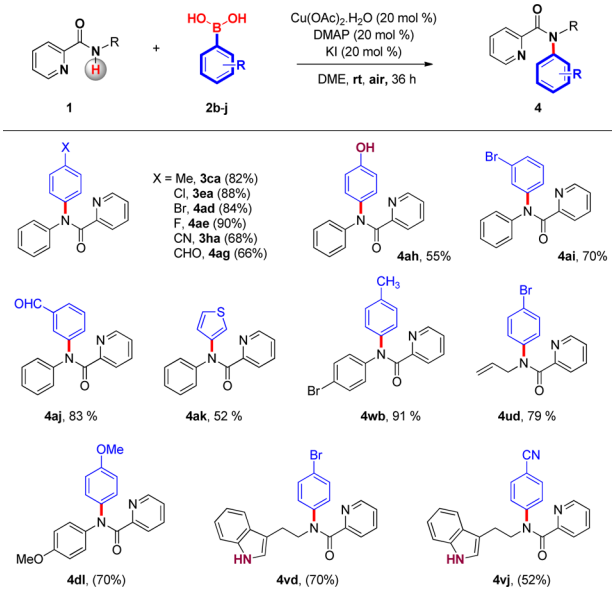
To extend the reaction scope further, we set out searching for other heterocycle-substituted amides and aryl coupling partners in a permutation way. Gratifyingly, we found that the reaction of amide **5a** derived from (2-aminophenyl)pyrazole (2-APP)[14f]

Table 1. Substrates Scope of Copper-Catalyzed Chelation-Assisted C−N Cross-Coupling Reaction[a]



[a]Conditions: **1** (0.2 mmol), **2a** (2.5 equiv), $Cu(OAc)_2{\cdot}H_2O$ (20 mol %), KI (20 mol%), DMAP (20 mol%), DME (1.5 mL), rt, air, and 36 h. Yields are isolated quantities. [b]Reaction time was 48 h.

Table 2. Scope of Aryl Boronic Acids for C−N Cross-Coupling Reaction[a]

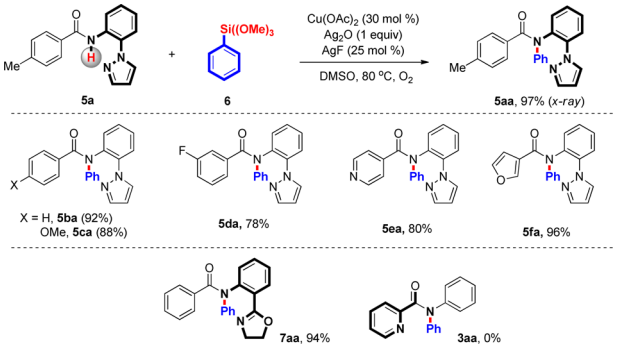


[a]Conditions: **1** (0.2 mmol), **2** (2.5 equiv), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), KI (20 mol%), DMAP (20 mol%), DME (1.5 mL), rt, air, and 36 h. Yields are isolated quantities. DMAP: 4-dimethylaminopyridine.

DOI: 10.1021/acs.joc.7b00002
J. Org. Chem. 2017, 82, 2764−2771

and aryl silane **6** was fruitful, and the tertiary amide **5aa** was obtained in 97% yield, albeit a modified reaction condition was necessary (Table 3, for details optimization, see SI, page S6).

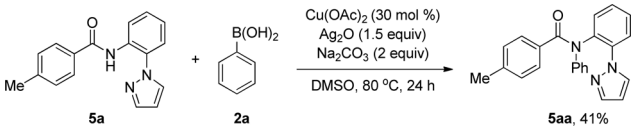
Table 3. Exploration of Chelation-Controlled C−N Cross-Coupling Reaction with Aryl Silane[a]



[a]Conditions: **5a** (0.2 mmol), **8** (3 equiv), $Cu(OAc)_2$ (30 mol%), Ag_2O (1 equiv), AgF (25 mol%), DMSO (1.5 mL), 80 °C, O_2, 24 h. Yields are isolated quantities.

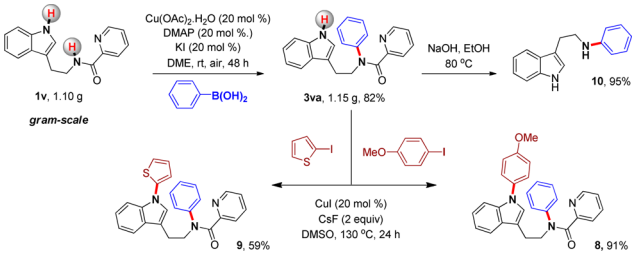
Other 2-APP-substituted amides have also efficiently participated in this reaction, delivering **5ba−fa** in excellent yields. Furthermore, this C−N cross-coupling reaction under the modified conditions was also effective with aminophenyloxazoline (**7aa**, 94% yield).[13b] However, the reactions of picolinamide substrates failed miserably with the recovery of respective starting materials. Furthermore, the amide **5a** also reacts with boronic acid **2a** and a moderate yield was obtained at elevated temperature (Scheme 3). Tentatively, the dissimilarity in ring-size of metal complexes is responsible for different trends in reactivity.

Scheme 3. Reaction of 5a with Phenyl Boronic Acid

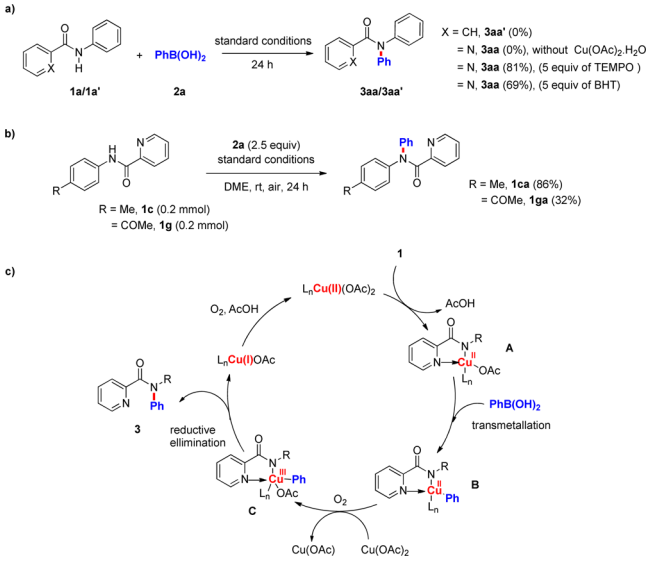


To highlight the synthetic utility of the present protocol, a gram-scale reaction with substrate **1v** was performed (Scheme 4) and the efficiency of the small-scale reaction was retained upon scale-up, delivering **3va** in 82% yield. The chemoselective installation of aryl functionality allowed us sequential *N*-arylation of the tryptamine moiety with ease and thus, tryptamine derivatives (**8**,**9**) with tunable substitutions patterns were synthesized in 91 and 59% yields with 4-iodoanisole and 2-iodothiophene, respectively, in the presence of catalytic copper iodide (Scheme 4). Furthermore, the picolinamide auxiliary can be easily cleaved under mild conditions to afford the free amine **10** in excellent yield.

Scheme 4. Gram-Scale Synthesis, Sequential *N*-Arylation, and Removal of the Auxiliary



Scheme 5. Control Experiments (a, b) and Plausible Reaction Mechanism (c)



for substrates **1a′** with the recovery of starting material, suggesting that the chelation with the picolinamide is crucial (Scheme 5a). Further, in the presence of radical scavengers such as TEMPO, and butylated hydroxytoluene (BHT), a significant amount of product **3aa** was isolated (Scheme 5a). These results refute the involvement of radical species in the reaction pathway. To investigate the electronic effects on the chelated complex, we have performed a parallel experiment with a 1:1 mixture of substrates **1c** and **1g** under standard condition (Scheme 5b). We have observed that the reaction of electron rich substrate **1c** proceeded much faster compared to that of electron poor substrate **1g**.

Although comprehensive mechanistic details must await further investigation, based on the preceding discussion and literature survey[18] a plausible reaction mechanism was depicted in Scheme 5c. After complexation of **1** with copper catalyst, Cu(II)cyclometalated species **A** is formed, which on transmetalation with $PhB(OH)_2$ produces the complex **B**. Next, disproportionation reaction or oxidation with air yields higher oxidation Cu(III) complex **C**,[18b−d] which undergoes smooth reductive elimination to deliver the product **3** with concurrent formation of low valent Cu(I) species. Finally, the low valent copper species converts to active catalyst Cu(II) with air as a terminal oxidant to continue the catalytic cycle.

In conclusion, we have developed a copper-catalyzed, practical C−N cross-coupling reaction based on chelation assisted amidation of readily available boronic acids. The protocol is operationally simple, chemoselective, scalable, and tolerates a wide range of functional groups, delivering fully substituted unsymmetrical amides in very high yields (up to 96%). The scope of the coupling protocol was further extended using 1-(2-aminophenyl)pyrazole and aminophenyloxazoline bidentate auxiliaries in combination with aryl silanes. Further

DOI: 10.1021/acs.joc.7b00002
J. Org. Chem. 2017, 82, 2764−2771

investigations on the reaction mechanism and application of this strategy in the synthesis of bioactive compounds are currently being pursued in our laboratory.

EXPERIMENTAL SECTION

General Information. All nonaqueous reactions were carried out under an atmosphere of nitrogen in flame-dried glassware and were stirred using a magnetic stir plate. All reactions were carried out using anhydrous solvent unless otherwise noted. DCE and PhCl were dried over calcium hydride. Dry toluene and DME were prepared by distilling over sodium ketyl. $Cu(OAc)_2 \cdot H_2O$, CuCl, $Cu(OAc)_2$, and $CuBr_2$ were purchased from Alfa Asear Company. All reactions were monitored by thin layer chromatography (TLC) on WhatmanPartisil K6F TLC plates (silica gel 60 Å, 0.25 mm thickness) and visualized using a UV lamp (366 or 254 nm) or by use of one of the following visualization reagents: PMA, 10 g phosphomolybdic acid/100 mL ethanol; $KMnO_4$, 0.75 g potassium permanganate, 5 g K_2CO_3/100 mL water. Products were isolated by column chromatography (Merck silica gel 100−200 μm). Yields refer to chromatographically and spectroscopically homogeneous materials unless noted otherwise. ^{13}C and ^1H NMR spectra were recorded on a Bruker 400 or Bruker 500 MHz spectrometers. Chemical shift values (δ) are reported in ppm and calibrated to the residual solvent peak $CDCl_3$ δ = 7.2600 ppm for ^1H, δ = 77.16 for ^{13}C and MeOH-d_4 δ = 3.3100 ppm for ^1H; δ = 49.15 for ^{13}C or calibrated to tetramethylsilane (δ = 0.00). All NMR spectra were recorded at ambient temperature (290 K) unless otherwise noted. ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constant, integration). The following abbreviations are used to indicate multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet, sext, sextet, sept, septet, m, multiplet; dd, doublet of doublet; dt, doublet of triplet; dq, doublet of quartet; td, triplet of doublet; tt, triplet of triplet; dq, doublet of quartet; br, broad; app, apparent. Mass spectra were recorded by electron spray ionization (ESI) method on a Q-TOF Micro with lock spray source. The crystal data were collected and integrated using a BrukerAxs kappa apex2 CCD diffractometer, with graphite monochromated Mo Kα radiation.

The picolinamides[19] **1** and (2-aminophenyl)pyrazole-based carboxamide derivatives[20] **5** were synthesized following previously published procedures. The aryl boronic acid derivatives **2** were purchased from Spectrochem Company.

General Procedure for the Copper Catalyzed C−N Cross-Coupling of Boronic Acids. The picolinamides **1** (0.20 mmol), aryl boronic acid derivatives **2** (0.50 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mol%), DMAP (20 mol%), and KI (20 mol%) were added to a dried Schlenk tube with a magnetic stir bar. Then DME (1.5 mL) was added with a syringe and the mixture was allowed to stir at room temperature for 36 h. After completion of the reaction (TLC monitored), it was transferred to a round-bottom flask after dilution with CH_2Cl_2 and extracted with saturated $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure and the resulting residue was purified by column chromatography on silica gel with a gradient eluent of hexane and ethyl acetate to give tertiary amides **3**/**4**.

*N,N-Diphenylpicolinamide (**3aa**).* White solid (53 mg, 96%), mp: (125−127 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.32 (dt, J^1 = 5.00 Hz, J^2 = 1.10 Hz, 1H), 7.67−7.62 (m, 2H), 7.27−7.14 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 154.5, 148.5, 143.4, 136.5, 129.1, 127.4, 126.5, 124.3, 124.2; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{18}H_{14}N_2OH$ 275.1184; Found 275.1201.

*N-(Naphthalen-2-yl)-N-phenylpicolinamide (**3ba**).* Pale brown solid (57 mg, 88%), mp (130−132 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.25−8.18 (m, 2H), 7.84−7.77 (m, 2H), 7.52−7.12 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9, 153.9, 148.0, 138.9, 135.8, 134.0, 130.0, 128.4, 127.9 (2 × C), 126.7, 125.9, 125.5, 125.0, 123.8, 122.9; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{22}H_{16}N_2OH$ 325.1341; Found 325.1358.

*N-Phenyl-N-(p-tolyl)picolinamide (**3ca**).* White solid (50 mg, 88%), mp (109−111 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.34 (d, J = 4.70 Hz, 1H), 7.66−7.60 (m, 2H), 7.25−7.07 (m, 10H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl3): δ = 168.8, 154.6, 148.5, 143.4, 140.7, 136.4, 129.7, 129.0, 127.2, 126.3, 124.2, 124.1, 21.0; ; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{19}H_{16}N_2ONa$ 311.1160; Found 311.1156.

*N-(4-Methoxyphenyl)-N-phenylpicolinamide (**3da**).* White solid (55 mg, 90%), mp (137−139 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, J = 4.76 Hz, 1H), 7.67−7.59 (m, 2H), 7.16−7.13 (m, 8H), 6.80 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 157.7, 154.3, 148.2, 143.2, 136.1, 135.8, 128.6, 128.4, 126.6, 125.9, 123.8, 123.7, 114.0, 55.1; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{19}H_{16}N_2O_2Na$ 327.1109; Found 327.1105.

*N-(4-Chlorophenyl)-N-phenylpicolinamide (**3ea**).* Pale yellow solid (54 mg, 88%), mp (118−120 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, J = 4.20 Hz, 1H), 7.69−7.66 (m, 2H), 7.25−7.13 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 153.8, 148.3, 142.8, 141.8, 136.4, 131.8, 129.0, 128.2, 127.2, 126.6, 124.3 124.1; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{18}H_{13}ClN_2ONa$ 331.0614; Found 331.0627.

*Methyl 4-(N-Phenylpicolinamido)benzoate (**3fa**).* White solid (36 mg, 52%), mp (107−109 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 4.30 Hz, 1H), 7.94 (d, J = 8.35 Hz, 2H), 7.69 (d, J = 4.05 Hz, 2H), 7.29 (t, J = 7.47 Hz, 2H), 7.22−7.15 (m, 6H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 164.2, 151.6, 146.2, 155.3, 140.5, 134.4, 128.2, 127.0, 125.4, 125.3, 124.7, 124.3, 122.4, 122.2, 50.0; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{20}H_{16}N_2O_3Na$ 355.1059;

*N-(4-Acetylphenyl)-N-phenylpicolinamide (**3ga**).* White solid (49 mg, 66%), mp (124−126 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 4.70 Hz, 1H), 7.87 (d, J = 8.55 Hz, 2H), 7.71−7.69 (m, 2H), 7.29 (t, J = 7.70 Hz, 2H), 7.26−7.21 (m, 4H), 7.15 (d, J = 7.55 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.1, 168.9, 154.0, 148.6, 147.8, 142.9, 136.7, 134.6, 129.4, 129.3, 127.9, 127.1, 126.7, 124.7, 124.5, 26.6; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{20}H_{16}N_2O_2Na$ 339.1059; Found 339.1089.

*N-(4-Cyanophenyl)-N-phenylpicolinamide (**3ha**).* Pale yellow solid (51 mg, 85%), mp (108−110 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, J = 4.45 Hz, 1H), 7.76−7.74 (m, 2H), 7.60 (d, J = 8.60 Hz, 2H), 7.34−7.23 (m, 6H), 7.15 (d, J = 4.50 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 153.4, 148.5, 147.5, 142.5, 136.8, 132.9, 129.5, 128.0, 127.4, 127.0, 124.9, 124.6, 118.5, 109.4; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{20}H_{16}N_2ONa$ 322.0956; Found 322.0960.

*N-Phenyl-N-(4-(trifluoromethyl)phenyl)picolinamide (**3ia**).* White solid (62 mg, 89%), mp (95−97 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (dt, J^1 = 4.92 Hz, J^2 = 1.20 Hz, 1H), 7.70−7.69 (m, 2H), 7.54 (d, J = 8.40 Hz, 2H), 7.31−7.26 (m, 4H), 7.22−7.13 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 153.8, 148.5, 146.6, 142.9, 136.7, 129.3, 128.1 (q, JC-F = 32.00 Hz), 127.8, 127.1, 127.0, 126.17 (q, J_{C-F} = 3.64 Hz), 124.7, 124.5, 123.9 (q, J_{C-F} = 270.28 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ − 62.41 (s, 3F); HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{19}H_{13}F_3N_2OH$ 343.1058; Found 343.1034.

*N-(3-Nitrophenyl)-N-phenylpicolinamide (**3ja**).* White solid (53 mg, 83%), mp (118−120 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (dt, J^1 = 4.68 Hz, J^2 = 1.32 Hz, 1H), 7.71−7.66 (m, 2H), 7.35−7.26 (m, 4H), 7.21−7.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 154.0, 148.5, 144.7, 142.9, 136.6, 130.2, 129.6, 129.3, 127.6, 126.9, 126.0, 124.6, 124.4, 122.4; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{18}H_{13}N_3O_3H$ 320.1035; Found 320.1042.

*N-(3-Methoxyphenyl)-N-phenylpicolinamide (**3ka**).* Yellow liquid (55 mg, 90%), mp (80−82 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1H), 7.67−7.63 (m, 2H), 7.27−7.17 (m, 7H), 6.74−6.72 (m, 3H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 160.1, 154.5, 144.4, 143.3, 136.5, 129.7, 129.1, 127.4, 126.6, 124.3, 124.2, 119.9, 113.3, 112.5, 55.4; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{19}H_{16}N_2O_2H$ 305.1290; Found 305.1288.

*N-(3,5-Dimethylphenyl)-N-phenylpicolinamide (**3la**).* White solid (45 mg, 75%), mp (127−129 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, J = 4.52 Hz, 1H), 7.66−7.60 (m, 2H), 7.26−7.13 (m, 6H), 6.82 (s, 3H), 2.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 154.7, 148.5, 143.5, 143.1, 138.8, 136.4, 129.0, 128.5, 127.3, 126.3,

DOI: 10.1021/acs.joc.7b00002
J. Org. Chem. 2017, 82, 2764−2771

124.2, 124.1, 21.2; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{20}H_{18}N_2ONa$ 325.1517; Found 325.1510.

*N-(4-Bromo-3-methylphenyl)-N-phenylpicolinamide (**3ma**).* White solid (68 mg, 91%), mp (96−98 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (dt, J^1 = 4.72 Hz, J^2 = 1.20 Hz, 1H), 7.70−7.64 (m, 2H), 7.42 (d, J = 6.88 Hz, 1H), 7.29−7.10 (m, 7H), 6.87 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 154.1, 148.6, 143.1, 142.5, 138.9, 136.7, 132.8, 129.4, 129.2, 127.4, 126.8, 126.2, 124.5, 124.3, 122.7, 23.0; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{19}H_{15}BrN_2OH$ 367.0446; Found 367.0427.

*N-Phenyl-N-(pyridin-4-yl)picolinamide (**3na**).* White solid (36 mg, 66%), mp (117−119 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.18 (s, 1H), 8.59−8.58 (m, 4H), 8.25 (d, J = 7.76 Hz, 1H), 8.04−8.03 (m, 1H), 7.89 (t, J = 7.52 Hz, 1H), 7.72 (s, 3H), 7.50−7.47 (m, 1H), 7.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 150.3, 148.7, 148.1, 144.8, 137.9, 133.6, 129.4, 127.5, 127.1, 122.7, 113.9; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{17}H_{13}N_3OH$ 276.1137; Found 276.1129.

*N-Phenyl-N-(pyridin-4-yl)picolinamide (**3oa**).* White solid (42 mg, 73%), mp (86−88 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1H), 7.56 (t, J = 7.12 Hz, 1H), 7.43−7.41 (m, 1H), 7.33−7.23 (m, 5H), 7.11−7.07 (m, 4H), 6.93−6.92 (m, 2H), 5.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 154.3, 148.6, 142.7, 137.1, 136.2, 134.3, 128.9, 128.5, 127.7, 127.5, 126.8, 123.9, 123.7, 53.6; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{19}H_{16}N_2OH$ 289.1341; Found 289.1349.

*N-(4-Fluorobenzyl)-N-phenylpicolinamide (**3pa**).* White solid (55 mg, 89%), mp (106−108 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1H), 7.56 (t, J = 7.08 Hz, 1H), 7.42−7.41 (m, 1H), 7.30−7.27 (m, 2H), 7.12−7.07 (m, 4H), 6.97−6.90 (m, 4H), 5.10 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 162.3 (d, J_{C-F} = 244.10 Hz), 154.2, 148.6, 142.6, 136.2, 132.9 (d, J_{C-F} = 3.33 Hz), 130.5 (d, J_{C-F} = 7.91 Hz), 129.0, 127.8, 126.9, 123.9 (d, J_{C-F} = 35.38 Hz), 115.4 (d, J_{C-F} = 21.2 Hz), 52.9; ^{19}F NMR (470 MHz, CDCl3): δ − 114.99 (s, 1F); HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{19}H_{15}FN_2OH$ 307.1247; Found 307.1245.

*N-(4-Methoxyphenethyl)-N-phenylpicolinamide (**3qa**).* White solid (45 mg, 67%), mp (109−111 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1H), 7.56−7.53 (m, 1H), 7.37−7.35 (m, 1H), 7.15−7.13 (m, 6H), 6.97 (s, 2H), 6.81 (d, J = 7.96 Hz, 2H), 4.12 (t, J = 6.76 Hz, 2H), 3.77 (s, 3H), 2.94 (t, J = 7.92 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 158.3, 154.6, 148.6, 143.1, 136.2, 130.9, 129.9, 129.1, 127.7, 126.7, 123.9, 123.7, 114.0, 55.3, 52.1, 33.0; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{21}H_{20}N_2O_2Na$ 355.1422; Found 355.1426.

*N-(3,4-Dimethoxyphenethyl)-N-phenylpicolinamide (**3ra**).* White solid (65 mg, 90%), mp (108−110 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1H), 7.52 (s, 1H), 7.34 (s, 1H), 7.13−7.09 (m, 4H), 6.92 (s, 2H), 6.75 (s, 3H), 4.14−4.11 (m, 2H), 3.82−3.81 (m, 6H), 2.96−2.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 154.5, 148.9, 148.5, 147.6, 143.1, 136.1, 131.4, 129.0, 127.7, 126.7, 123.8, 123.6, 120.9, 112.2, 111.3, 56.0, 55.9, 52.0, 33.4; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{22}H_{22}N_2O_3H$ 363.1709; Found 363.1696.

*N-Butyl-N-phenylpicolinamide (**3sa**).* Yellow liquid (45 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1H), 7.50 (s, 1H), 7.32 (s, 1H), 7.15−7.02 (m, 6H), 3.93−3.90 (m, 2H), 1.59 (quint, J = 7.50 Hz, 2H), 1.37−1.32 (m, 2H), 0.87 (t, J = 6.40 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 154.7, 148.5, 142.8, 136.1, 128.9, 127.7, 126.6, 123.7, 123.5, 49.8, 29.7, 20.1, 13.8; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{16}H_{18}N_2ONa$ 277.1317; Found 277.1307.

*N-Cyclopropyl-N-phenylpicolinamide (**3ta**).* Yellow solid (26 mg, 55%), mp (53−55 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 3.88 Hz, 1H), 7.63 (td, J^1 = 7.72 Hz, J^2 = 1.32 Hz, 1H), 7.44 (d, J = 7.72 Hz, 1H), 7.27−7.23 (m, 2H), 7.19−7.12 (m, 4H), 3.37 (sept, J = 3.71 Hz, 1H), 0.80−0.78 (m, 2H), 0.57−0.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 155.3, 148.5, 141.9, 136.4, 128.8, 127.8, 126.7, 123.9, 123.2, 32.4, 8.5; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{15}H_{14}N_2ONa$ 261.1004; Found 261.1012.

*N-Allyl-N-phenylpicolinamide (**3ua**).* White liquid (41 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 7.17−7.04 (m, 6H), 6.03−5.94 (m, 1H), 5.23−5.15 (m, 2H), 4.54 (d, J = 5.84 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 154.4, 148.6, 143.0, 136.2, 132.9, 128.9, 127.5, 126.7, 124.0, 123.7, 118.3, 53.0; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{15}H_{14}N_2OH$ 239.1184; Found 239.1171.

*N-(2-(1H-Indol-3-yl)ethyl)-N-phenylpicolinamide (**3va**).* Pale yellow solid (61 mg, 90%), mp (130−132 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1H), 8.22 (s, 1H), 7.58−7.52 (m, 2H), 7.37 (d, J = 7.80 Hz, 1H), 7.33 (d, J = 8.05 Hz, 1H), 7.17−7.02 (m, 9H), 4.27−4.25 (m, 2H), 3.17−3.15 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7, 154.6, 148.6, 143.0, 136.3, 136.2, 129.1, 127.8, 127.5, 126.8, 123.9, 123.6, 122.2, 122.0, 119.4, 118.9, 112.8, 111.2, 50.9, 23.5; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{22}H_{19}N_3OH$ 342.1606; Found 342.1593.

*N-(4-Bromophenyl)-N-phenylpicolinamide (**4ad**).* White solid (59 mg, 84%), mp (127−129 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, J = 4.50 Hz, 1H), 7.70−7.66 (m, 2H), 7.40 (d, J = 4.90 Hz, 2H), 7.27−7.04 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7, 154.0, 148.5, 143.0, 142.5, 136.6, 132.2, 129.2, 128.8, 127.5, 126.8, 124.5, 124.3, 120.0; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{18}H_{13}BrN_2ONa$ 375.0109; Found 375.0101.

*N-(4-Fluorophenyl)-N-phenylpicolinamide (**4ae**).* White solid (56 mg, 90%), mp (110−112 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33−8.32 (m, 1H), 7.68−7.64 (m, 2H), 7.26−7.15 (m, 8H), 6.97 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8, 160.9 (d, JC-F = 245.27 Hz), 154.2, 148.5, 143.3, 139.4, 136.6, 129.1 (2 × C), 127.3, 126.6, 124.3 (d, JC-F = 16.78 Hz), 115.9 (d, JC-F = 22.65 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ − 115.15 (s, 1F); HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{18}H_{13}FN_2ONa$ 315.0910; Found 315.0934.

*N-(4-Formylphenyl)-N-phenylpicolinamide (**4ag**).* Pale yellow solid (40 mg, 66%), mp (107−109 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.94 (s, 1H), 8.30 (dt, J^1= 4.68 Hz, J^2= 1.28 Hz, 1H), 7.81−7.78 (m, 2H), 7.74−7.68 (m, 2H), 7.33−7.27 (m 4H), 7.24−7.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.1, 168.8, 153.6, 148.9, 148.5, 142.7, 136.7, 133.7, 130.4, 129.4, 127.9, 127.2, 126.9, 124.8, 124.5; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{19}H_{14}N_2O_2H$ 303.1134; Found 303.1127.

*N-(4-Hydroxyphenyl)-N-phenylpicolinamide (**4ah**).* White solid (32 mg, 55%), mp (203−205 °C). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.38−8.37 (m, 1H), 7.75 (td, J^1= 7.76 Hz, J^2= 1.64 Hz, 1H), 7.54 (d, J = 7.76 Hz, 1H), 7.32−7.05 (m, 8H), 6.68 (s, 2H); ^{13}C NMR (125 MHz, MeOH-d_4): δ = 170.7, 158.0, 155.9, 149.7, 144.5, 138.5, 135.7, 130.2, 128.0, 125.8, 125.1, 116.8; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{18}H_{14}N_2O_2H$ 291.1134; Found 291.1118.

*N-(3-Bromophenyl)-N-phenylpicolinamide (**4ai**).* White solid (50 mg, 70%), mp (115−117 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (dt, J^1= 4.80 Hz, J^2= 1.32 Hz, 1H), 7.71−7.66 (m, 2H), 7.34−7.26 (m, 4H), 7.20−7.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 153.9, 148.6, 144.6, 142.9, 136.7, 133.9, 130.2, 129.6, 129.3, 127.6, 126.9, 126.0, 124.6, 124.4, 122.5; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{18}H_{13}N_2OBrH$ 353.0290; Found 353.0305.

*N-(3-Formylphenyl)-N-phenylpicolinamide (**4aj**).* Pale yellow solid (50 mg, 83%), mp (114−116 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (s, 1H), 8.31−8.29 (m, 1H), 7.72−7.67 (m, 4H), 7.51−7.45 (m, 2H), 7.30−7.26 (m, 2H), 7.21−7.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.4, 168.8, 153.7, 148.4, 144.3, 142.8, 137.2, 136.7, 132.9, 129.7, 129.3, 127.8, 127.6, 127.4, 127.0, 124.6, 124.4; HRMS (ESI/TOF-Q) m/z: [M+Na]+ Calcd for $C_{19}H_{14}N_2O_2Na$ 325.0953; Found 325.0940.

*N-Phenyl-N-(thiophen-3-yl)picolinamide (**4ak**).* Pale yellow solid (29 mg, 52%), mp (99−101 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, J = 4.32 Hz, 1H), 7.64 (td, J^1 = 7.72 Hz, J^2 = 1.60 Hz, 1H), 7.58−7.56 (m, 1H), 7.27−7.14 (m, 7H), 6.98 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 154.5, 148.6, 142.8, 141.5, 136.5, 129.1 (2 × C), 127.6, 127.0, 125.2, 124.7, 124.2, 123.8; HRMS (ESI/TOF-Q) m/z: [M+H]+ Calcd for $C_{16}H_{12}N_2OSH$ 281.0749; Found 281.0767.

*N-(4-Bromophenyl)-N-(p-tolyl)picolinamide (**4wb**).* White solid (67 mg, 91%), mp (127−129 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (dt, J^1 = 4.75 Hz, J^2 = 1.25 Hz, 1H), 7.68−7.62 (m, 2H), 7.38 (s, 2H), 7.19−7.06 (m, 7H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):

DOI: 10.1021/acs.joc.7b00002
J. Org. Chem. 2017, 82, 2764−2771

δ = 168.7, 154.2, 148.6, 142.6, 140.4, 136.7, 136.6, 132.1, 129.9, 128.6, 127.3, 124.4, 124.2, 119.8, 21.1; HRMS (ESI/TOF-Q) *m/z*: [M+Na]+ Calcd for $C_{19}H_{15}N_2OBrNa$ 389.0265; Found 389.0244.

*N-Allyl-N-(4-bromophenyl)picolinamide (**4ud**).* White liquid (50 mg, 79%) ^{1}H NMR (400 MHz, CDCl3): δ = 8.32 (s, 1H), 7.62 (t, *J* = 6.80 Hz, 1H), 7.50−7.49 (m, 1H), 7.29−7.26 (m 2H), 7.15 (s, 1H), 6.91 (s, 2H), 5.99−5.89 (m, 1H), 5.20−5.14 (m, 2H), 4.49 (d, *J* = 5.92 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 153.8, 148.5, 142.1, 136.5, 132.6, 132.0, 129.0, 124.3, 123.9, 120.3, 118.4, 53.0; HRMS (ESI/TOF-Q) *m/z*: [M+H]+ Calcd for $C_{15}H_{13}N_2OBrH$ 317.0290; Found 317.0278.

*N,N-Bis(4-methoxyphenyl)picolinamide (**4dl**).* Pale brown solid (47 mg, 70%), mp (107−109 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37−8.35 (m, 1H), 7.63 (td, J^1 = 7.66, Hz, J^2 = 1.72 Hz, 1H), 7.57−7.55 (m, 1H), 7.25−6.80 (m, 9H), 3.75 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9, 157.9, 154.8, 148.6, 136.4, 129.0, 127.7, 124.0 (2 × C), 114.3, 55.5; HRMS (ESI/TOF-Q) *m/z*: [M+H]+ Calcd for $C_{20}H_{18}N_2O_3H$ 335.1396; Found 335.1378.

*N-(2-(1H-Indol-3-yl)ethyl)-N-(4-bromophenyl)picolinamide (**4vd**).* Yellow solid (59 mg, 70%), mp (134−136 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40−8.34 (m, 2H), 7.56 (t, *J* = 7.20 Hz, 2H), 7.14−6.82 (m, 10H), 4.21−4.18 (m, 2H), 3.13−3.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 154.0, 148.5, 136.5, 136.3, 132.1, 129.2, 127.4, 124.2, 123.7, 122.3, 122.0, 120.3, 119.3, 118.7, 112.4, 111.3, 51.0, 23.5; HRMS (ESI/TOF-Q) *m/z*: [M+H]+ Calcd for $C_{22}H_{18}N_3OBrH$ 420.0711; Found 420.0721.

*N-(2-(1H-Indol-3-yl)ethyl)-N-(4-cyanophenyl)picolinamide (**4vj**).* Pale yellow solid (38 mg, 52%), mp (162−164 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30−8.25 (m, 2H), 7.65 (td, J^1 = 7.68 Hz, J^2 = 1.40 Hz, 1H), 7.58−7.50 (m, 2H), 7.42 (d, *J* = 8.24 Hz, 2H), 7.31 (d, *J* = 8.08 Hz, 1H), 7.21−7.14 (m, 2H), 7.09−7.00 (m, 4H), 4.26 (t, *J* = 7.66 Hz, 2H), 3.15 (t, *J* = 7.64 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3): δ = 168.4, 153.3, 148.3, 147.5, 136.8, 136.3, 132.8, 127.7, 127.3, 124.8, 124.3, 122.3, 122.2, 119.5, 118.7, 118.4, 112.3, 111.3, 109.8, 51.4, 23.9; HRMS (ESI/TOF-Q) *m/z*: [M+H]+ Calcd for $C_{23}H_{18}N_4OH$ 367.1559; Found 367.1550.

General Procedure for the Copper Catalyzed C−N Cross-Coupling of Aryl Silanes. In a dried Schlenk tube, the AgF (25 mol %) was taken inside the glovebox, the carboxamides 5 (0.20 mmol), aryl silane derivative 6 (0.60 mmol), $Cu(OAc)_2$ (30 mol%), Ag_2O (1 equiv), were added under nitrogen atmosphere. Then DMSO (1.5 mL) was added with a syringe, subsequently purged the oxygen and allowed to stir at 80 °C for 24 h. After completion of the reaction (TLC monitored), it was extracted with saturated $NaHCO_3$ solution and EtOAc. The organic layer was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel with a gradient eluent of hexane and ethyl acetate to give pure products.

*N-(2-(1H-Pyrazol-1-yl)phenyl)-4-methyl-N-phenylbenzamide (**5aa**).* White solid (65 mg, 96%), mp (147−149 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 1.6 Hz, 2H), 7.49−7.47 (m, 1H), 7.39−7.36 (m, 2H), 7.28−7.23 (m, 3H), 7.16−7.12 (m, 2H), 7.08−7.02 (m, 3H), 6.94 (d, *J* = 7.92, 2H), 6.29 (t, *J* = 2.1, 1H), 2.25 (s, 3H) ; ^{13}C NMR(100 MHz, $CDCl_3$): δ = 170.6, 143.7, 140.9, 140.7, 138.7, 137.9, 132.3, 130.7, 130.2, 129.3, 128.9, 128.4, 128.2, 127.1, 127.0, 126.1, 106.8, 21.5; HRMS (ESI/TOF-Q) *m/z*: [M+Na]+Calcd for $C_{23}H_{19}N_3ONa$ 376.1426; Found 376.1409.

*N-(2-(1H-Pyrazol-1-yl)phenyl)-N-phenylbenzamide (**5ba**).* White solid (65 mg, 96%), mp (174−176 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 1.36 Hz, 2H), 7.50 (d, *J* = 4.64 Hz, 1H), 7.42−7.36 (m, 4H), 7.31−7.25 (m, 2H), 7.19−7.15 (m, 4H), 7.11−7.07 (m, 3H), 6.33 (t, *J* = 2.02 Hz, 1H) ; ^{13}C NMR(100 MHz, $CDCl_3$): δ = 170.6, 143.5, 141.0, 138.5, 137.9, 135.3, 130.7, 130.3, 129.3, 129.2, 128.9, 128.3, 127.8, 127.1, 126.2, 106.9; HRMS (ESI/TOF-Q) *m/z*: [M+Na]+Calcd for $C_{22}H_{17}N_3ONa$ 362.1269; Found 362.1253.

*N-(2-(1H-Pyrazol-1-yl)phenyl)-4-methoxy-N-phenylbenzamide (**5ca**).* White solid (65 mg, 96%), mp (128−130 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 1.56 Hz, 2H), 7.49−7.47 (m, 1H), 7.39−7.37 (m, 2H), 7.32 (d, *J* = 8.76 Hz, 2H), 7.27−7.24 (m, 1H), 7.17−7.13 (m, 2H), 7.08−7.01 (m, 3H), 6.67−6.63 (m, 2H), 6.28 (t, *J* = 2.08 Hz, 1H), 3.73 (s, 3H) ; ^{13}C NMR(100 MHz, $CDCl_3$): δ = 170.3, 161.2, 143.9, 140.9, 138.9, 137.9, 131.4, 130.7, 130.2, 129.3, 128.9, 128.1, 127.3, 127.2, 126.9, 126.0, 113.1, 106.9, 55.3; HRMS (ESI/TOF-Q) *m/z*: [M+H]+Calcd for $C_{23}H_{19}N_3O_2H$ 370.1556; Found 370.1573.

*N-(2-(1H-Pyrazol-1-yl)phenyl)-3-fluoro-N-phenylbenzamide (**5da**).* White solid (56 mg, 78%), mp (155−157 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68−7.60 (m, 2H), 7.45−7.38 (m, 3H), 7.26−7.24 (m, 1H), 7.19−7.08 (m, 8H), 6.96−6.91 (m, 1H), 6.32 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0, 162.0 (d, J_{C-F} = 245.4 Hz), 143.1, 141.1, 138.2, 137.7, 137.5 (d, J_{C-F} = 7.12 Hz), 130.5, 130.1, 129.4 (2 × C), 129.3, 129.0, 128.4, 127.0, 126.6, 124.8, 117.3 (d, J_{C-F} = 21.12 Hz), 116.2 (d, J_{C-F} = 22.98 Hz), 107.0; ^{19}F NMR (470 MHz, CDCl3): δ − 112.64 (s, 1F); HRMS (ESI/TOF-Q) *m/z*: [M+Na]+Calcd for $C_{22}H_{16}FN_3ONa$ 380.1175; Found 380.1174.

*N-(2-(1H-Pyrazol-1-yl)phenyl)-N-phenylisonicotinamide (**5ea**).* White solid (54 mg, 80%), mp (157−159 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (s, 2H), 7.73−7.69 (m, 2H), 7.46−7.11 (m, 11H), 6.33 (s, 1H), ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 149.7, 143.1, 141.2, 137.6, 130.7, 129.2, 128.7, 127.8, 127.1, 126.9, 122.8, 107.1; HRMS (ESI/TOF-Q) *m/z*: [M+H]+Calcd for $C_{21}H_{16}N_4OH$ 341.1402; Found 341.1420.

*N-(2-(1H-Pyrazol-1-yl)phenyl)-N-phenylfuran-3-carboxamide (**5fa**).* Pale yellow solid (63 mg, 96%), mp (122−124 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64−7.63 (m, 2H), 7.54−7.51 (m, 1H), 7.45−7.36 (m, 3H), 7.25−7.14 (m, 5H), 7.07−7.05 (m, 2H), 6.33 (t, *J* = 2.00 Hz, 1H), 6.14 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 146.7, 142.4, 142.2, 141.0, 138.2, 137.5, 130.5, 130.4, 129.2, 128.8, 127.2, 121.8, 110.8, 107.1; HRMS (ESI/TOF-Q) *m/z*: [M+Na]+ Calcd for $C_{20}H_{15}N_3O_2Na$ 352.1062; Found 352.1078.

*N-(2-(1H-Pyrazol-1-yl)phenyl)-N-phenylfuran-3-carboxamide (**7aa**).* Pale brown solid (64 mg, 91%), mp (182−184 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 1H), 7.50 (d, *J* = 7.28 Hz, 2H), 7.39−7.10 (m, 11H), 4.26 (t, *J* = 8.76 Hz, 2H), 3.91 (t, *J* = 8.40 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 163.2, 144.2, 142.6, 136.1, 131.8, 130.9, 130.1, 129.2, 128.8, 127.8, 127.0, 126.4, 126.0, 67.5, 54.9; HRMS (ESI/TOF-Q) *m/z*: [M+H]+Calcd for $C_{22}H_{18}N_2O_2H$ 343.1447; Found 343.1430.

Gram-Scale Synthesis of Compound 3va. The picolinamide (**1v**) (4.1 mmol, 1.10 g, 1 equiv), phenyl boronic acid **2a** (10.2 mmol, 1.2 g, 2.5 equiv), $Cu(OAc)_2{\cdot}H_2O$ (0.8 mmol, 163 mg, 20 mol%), DMAP (0.8 mmol, 100 mg, 20 mol%), and KI (0.8 mmol, 136 mg, 20 mol%) were added to a dried Schlenk flask with a magnetic stir bar. Then DME (50 mL) was added with a syringe and the resulting mixture was allowed to stir for 48 h. After completion of the reaction (TLC monitored), it was transferred to a round-bottom flask after dilution with CH_2Cl_2 and extracted with saturated $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4. The solvent was evaporated to dryness and the crude reaction mixture was loaded directly on to silica gel column and purified to provide pure amide **3va** (1.15 g, 82%).

Sequential *N*-Arylation of the Tryptamine Derivative. In a dried Schlenk tube, the CsF (2 equiv) was taken inside the glovebox, the compound **3va** (0.15 mmol), aryl iodide derivatives (2 equiv), CuI (20 mol%) were added under nitrogen atmosphere. Then, DMSO (1.5 mL) was added with a syringe and allowed to stir at 130 °C for 24 h. After completion of the reaction (TLC monitored), it was extracted with saturated $NaHCO_3$ solution and EtOAc. The organic layer was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel with a gradient eluent of hexane and ethyl acetate to give the corresponding tryptamine derivatives.

*N-(2-(1-(4-Methoxyphenyl)-1H-indol-3-yl)ethyl)-N-phenylpicolinamide (**8**).* Yellow liquid (81 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1H), 7.65 (s, 1H), 7.53 (td, J^1 = 7.72 Hz, J^2 = 1.40 Hz, 1H), 7.42−7.33 (m, 5H), 7.19−6.98 (m, 10H), 4.29 (t, *J* = 6.76 Hz, 2H), 3.84 (s, 3H), 3.22 (t, *J* = 7.04 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7, 158.0, 154.5, 148.5, 143.0, 136.5, 136.2, 132.8, 129.0, 128.6, 127.7, 126.7, 126.2, 125.7, 123.8, 123.6, 122.3, 119.7, 119.2, 114.7, 113.3, 110.3, 55.6, 51.0, 23.4; HRMS (ESI/TOF-

DOI: 10.1021/acs.joc.7b00002
J. Org. Chem. 2017, 82, 2764−2771

Q) *m/z*: [M+H]+Calcd for $C_{29}H_{25}N_3O_2H$ 448.2025; Found 448.2032.

*N-Phenyl-N-(2-(1-(thiophen-2-yl)-1H-indol-3-yl) ethyl)-picolinamide (**9**).* Yellow solid (50 mg, 59%), mp (146−148 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1H), 7.65 (s, 1H), 7.57−7.54 (m, 2H), 7.40 (d, *J* = 8.12 Hz, 1H), 7.25−7.01 (m, 12H), 4.28 (t, *J* = 7.52 Hz, 2H), 3.20 (t, *J* = 6.96 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7, 154.5, 148.6, 141.8, 137.3, 136.2, 129.1, 128.8, 127.7, 127.1, 126.8, 126.1, 123.9, 123.7, 123.0, 121.2, 120.6, 119.8, 119.3, 114.7, 110.7, 50.8, 23.3; HRMS (ESI/TOF-Q) *m/z*: [M+Na]+Calcd for $C_{26}H_{21}N_3OSNa$ 446.1303; Found 446.1322.

Synthesis of Compound 10. The compound **3va** (0.29 mmol, 100 mg, 1 equiv), and NaOH (400 mg) were added to a dried Schlenk tube with a magnetic stir bar. Then EtOH (4 mL) was added with a syringe and the resulting mixture was allowed to stir at 80 °C for 8 h. After completion of the reaction (TLC monitored), it was diluted with DCM. The filtrate was evaporated to dryness and the crude reaction mixture was purified by silica gel column chromatography to provide product **10**.

*N-(2-(1H-Indol-3-yl)ethyl)aniline (**10**).* Yellow solid (45 mg, 95%), mp (114−116 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (brs, 1H), 7.60 (d, *J* = 7.88 Hz, 1H), 7.33−7.31 (m, 1H), 7.21−7.09 (m, 4H), 6.98 (d, *J* = 2.12 Hz, 1H), 6.71−6.67 (m, 1H), 6.61−6.59 (m, 2H), 3.45 (t, *J* = 6.82 Hz, 2H), 3.06 (t, *J* = 6.76 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.3, 136.5, 129.3, 127.5, 122.3, 122.1, 119.5, 118.9, 117.4, 113.5, 113.1, 111.3, 44.1, 25.2; HRMS (ESI/TOF-Q) *m/z*: [M+H]+Calcd for $C_{16}H_{16}N_2H$ 237.1392; Found 237.1383.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00002.

Complete experimental details, characterization data for the prepared compounds (PDF)
X-ray crystallographic data of compound **3aa** (CIF)
X-ray crystallographic data of compound **3va** (CIF)
X-ray crystallographic data of compound **5aa** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*mbaidya@iitm.ac.in

ORCID

Mahiuddin Baidya: 0000-0001-9415-7137

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge CSIR New Delhi for the financial support (02(0212)/14/EMR-II). H.S. thanks IITM for HTRA and G.S.G. thanks UGC New Delhi for a JRF. We also thank the Department of Chemistry, IIT-Madras for instrumental facilities.

■ REFERENCES

(1) (a) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science*; Wiley-Interscience: New York, 2000. (b) Buckheit, R. W., Jr; Kinjerski, T. L.; Fliakas-Boltz, V.; Russell, J. D.; Stup, T. L.; Pallansch, L. A.; Brouwer, W. G.; Dao, D. C.; Harrison, W. A.; Schultz, R. J. *Antimicrob. Agents Chemother.* **1995**, *39*, 2718. (c) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973. (d) Okubo, T.; Yoshikawa, R.; Chaki, S.; Okuyama, S.; Nakazato, A. *Bioorg. Med. Chem.* **2004**, *12*, 423. (e) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (f) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. (g) Cogo, J.; Kaplum, V.; Sangi, D. P.; Ueda-Nakamura, T.; Correa, A. G.; Nakamura, C. V. *Eur. J. Med. Chem.* **2015**, *90*, 107. (h) Sun, Y.-H.; Sun, T.-Y.; Wu, Y.-D.; Zhang, X.; Rao, Y. *Chem. Sci.* **2016**, *7*, 2229 and the references cited in..

(2) (a) Overman, L. E.; Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2587. (b) Shang, S.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 6216. (c) Cyr, P.; Règnier, S.; Bechara, W. S.; Charette, A. B. *Org. Lett.* **2015**, *17*, 3386. (d) Règnier, S.; Bechara, W. S.; Charette, A. B. *J. Org. Chem.* **2016**, *81*, 10348.

(3) (a) Arnold, K.; Davies, B.; Herault, D.; Whiting, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2673. (b) Charville, H.; Jackson, D.; Hodges, G.; Whiting, A. *Chem. Commun.* **2010**, *46*, 1813. (c) Allen, C. L.; Chhatwal, R. A.; Williams, J. M. J. *Chem. Commun.* **2012**, *48*, 666. (d) Ishihara, K.; Lu, Y. *Chem. Sci.* **2016**, *7*, 1276.

(4) (a) Yoo, W. J.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 13064. (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798. (c) Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. H.; Chai, C. L. L.; Chen, A. *J. Org. Chem.* **2012**, *77*, 8007.

(5) (a) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790. (b) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672. (c) Zweifel, T.; Naubron, J.-V.; Grutzmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559. (d) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667. (e) Soule, J. F.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2011**, *133*, 18550. (f) Yamaguchi, K.; Kobayashi, H.; Oishi, T.; Mizuno, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 544.

(6) (a) Yamaguchi, K.; Matsushita, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1576. (b) Ramon, R. S.; Marion, N.; Nolan, S. P. *Chem. - Eur. J.* **2009**, *15*, 8695. (c) Mitsu-dome, T.; Mikami, Y.; Mori, H.; Arita, S.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.* **2009**, 3258.

(7) (a) Cho, S.; Yoo, E.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (b) Chen, Z.-W.; Jiang, H.-F.; Pan, X.-Y.; He, Z.-J. *Tetrahedron* **2011**, *67*, 5920.

(8) (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27. (c) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2047. (d) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.

(9) (a) Handbook of "Synthetic Methods in Drug Discovery" Lam, P. Y. S. *RSC* **2016**, *1*, 242. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (c) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (e) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, *2011*, 829. (f) Vantourout, J. C.; Law, R. P.; Isidro-Llobet, A.; Atkinson, S. J.; Watson, A. J. B. *J. Org. Chem.* **2016**, *81*, 3942. (g) Roy, S.; Sarma, M. J.; Kashyap, B.; Phukan, P. *Chem. Commun.* **2016**, *52*, 1170.

(10) (a) Gnanaprakasam, B.; Milstein, D. *J. Am. Chem. Soc.* **2011**, *133*, 1682. (b) Zhang, M.; Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3905. (c) Rao, S. N.; Mohan, D. C.; Adimurthy, S. *Org. Lett.* **2013**, *15*, 1496. (d) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162.

(11) Efficient protocol on *N*-arylation of amides with aryl iodides at elevated temperature using copper-chelating ligand catalytic system, see: (a) Racine, E.; Monnier, F.; Vors, J.-P.; Taillefer, M. *Org. Lett.* **2011**, *13*, 2818. (b) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. - Eur. J.* **2004**, *10*, 5607.

(12) For recent reviews, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (b) Liu, J.; Chen, G.; Tan, Z. *Adv. Synth. Catal.* **2016**, *358*, 1174 and references cited therein..

(13) For selective example for C−N bond formation under copper catalysis: (a) Roane, J.; Daugulis, O. *J. Am. Chem. Soc.* **2016**, *138*, 4601. (b) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354. (c) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610 and references cited therein..

(14) (a) Urones, B.; Martınez, A. M.; Rodrıguez, N.; Arrayas, R. G.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 11044. (b) Li, Q.; Zhang,

DOI: 10.1021/acs.joc.7b00002
J. Org. Chem. 2017, 82, 2764−2771

S.-Y.; He, G.; Ai, Z.; Nack, W. A.; Chen, G. *Org. Lett.* **2014**, *16*, 1764. (c) Martınez, A. M.; Rodrıguez, N.; Arrayas, R. G.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 2801. (d) Zhao, S.; Liu, B.; Zhan, B.-B.; Zhang, W.-D.; Shi, B.-F. *Org. Lett.* **2016**, *18*, 4586. (e) Gui, Q.; Chen, X.; Hu, L.; Wang, D.; Liu, J.; Tan, Z. *Adv. Synth. Catal.* **2016**, *358*, 509. (f) Selvakumar, J.; Grandhi, G. S.; Sahoo, H.; Baidya, M. *RSC Adv.* **2016**, *6*, 79361.

(15) Kathiravan, S.; Ghosh, S.; Hogarth, G.; Nicholls, I. A. *Chem. Commun.* **2015**, *51*, 4834.

(16) Improvement of reaction yields in the presence of halide additives: (a) Hu, X. *Chem. Sci.* **2011**, *2*, 1867. (b) Lin, C.; Li, D.; Wang, B.; Yao, J.; Zhang, Y. *Org. Lett.* **2015**, *17*, 1328. (c) Ackerman, L. K. G.; Lovell, M. M.; Weix, D. J. *Nature* **2015**, *524*, 454.

(17) CCDC numbers of the crystal structures, **3aa**: 1502266; **3va**: 1502267; **5aa**: 1502268.

(18) (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233. (b) Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 1691. (c) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (d) Rao, D. N.; Rasheed, S.; Kumar, K. A.; Reddy, A. S.; Das, P. *Adv. Synth. Catal.* **2016**, *358*, 2126.

(19) (a) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2013**, *78*, 11045. (b) Martínez, Á.; Rodríguez, N.; Arrayás, R.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 2801. (c) Li, Q.; Zhang, S.-Y.; He, G.; Ai, Z.; Nack, W. A.; Chen, G. *Org. Lett.* **2014**, *16*, 1764.

(20) See reference 14f.

DOI: 10.1021/acs.joc.7b00002
J. Org. Chem. 2017, 82, 2764−2771