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CuI/2-Aminopyridine 1-Oxide Catalyzed Amination of Aryl Chlorides with Aliphatic Amines

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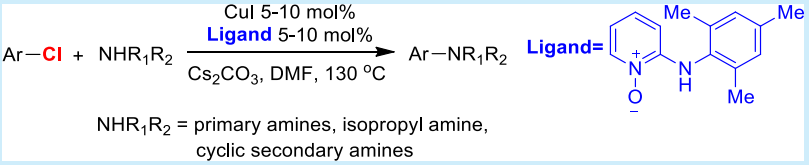

ABSTRACT: A class of 2-aminopyridine 1-oxides are discovered to be effective ligands for the Cu-catalyzed amination of less reactive (hetero)aryl chlorides. A wide range of functionalized (hetero)aryl chlorides reacted with various aliphatic amines to afford the desired products in good to excellent yields under the catalyst of CuI/2-aminopyridine 1-oxides. Furthermore, the catalyst system worked well for the coupling of cyclic secondary amines and *N*-methyl benzylamine with (hetero)aryl chlorides.

Cross-coupling of aryl halides with amines has been demonstrated to be a highly useful transformation for the preparation of important *N*-aryl amine moieties found in numerous natural products, pharmaceuticals, agrochemicals, and materials sectors.[1] The wide applications of this coupling reaction and advances in this area are largely due to the identification of improved supporting ligands.[1d,2] For example, the efficient palladium- and Ni-catalyzed aminations of aryl halides and sulfonates with amines have been accomplished by the use of sterically hindered phosphine, *N*-heterocyclic carbene ancillary ligands, or through the merger of photoredox/electrochemistry-nickel catalysis;[3,4] the classic copper-mediated aminations of aryl iodides/bromines with amines (Ullmann-type reaction) proceed smoothly under milder conditions when several classes of bidentate ligands are employed.[5−9] Despite all these achievements, further breakthroughs are still required to make the aminations more attractive. For example, a prominent limitation for years on Cu/ligand-catalyzed aryl amination reaction, in comparison with expensive Pd/ligand-catalyzed process, is that aminations of less expensive and less reactive aryl chlorides are still challenging.[10] Recently, one such highly active ligand, oxalic diamides discovered by Ma's group, has successfully enabled the Cu-catalyzed coupling of amines with aryl and heteroaryl chlorides.[11] Subsequently, Singer's group reported three examples of aryl chlorides reacted with amines efficiently with the use of 6-hydroxypicolinamide as supporting ligands in 2019.[11e] But the coupling reactions of steric hindrance primary amines and secondary amines with aryl chlorides are still rare.[11a,e] Herein, we wish to report the rational development of 2-aminopyridine *N*-oxide as powerful ligands to facilitate the CuI-catalyzed amination of (hetero)aryl chlorides. With these ligands, the *N*-arylation of cyclic secondary amines and *N*-methyl benzylamine also take place with good yields.

In 2014, we reported a ligand-free CuI-catalyzed coupling reaction between 2-aminopyridine with aryl halide even at low catalytic loadings and using the most hindered aryl iodides as substrates.[12] The excellent reactivity of 2-aminopyridine might be due to the chelating interaction of 2-aminopyridine with copper ion to form a transitional 4-membered ring, which may efficiently facilitate the coupling reaction. With the goal of discovering effective ligands for Cu-catalyzed aminations of aryl chlorides, we realized that 2-aminopyridine may be suitable as ligand for the C−N coupling reaction.[13] We then set up the coupling reaction of 4-chloroanisole and *n*-hexylamine with the use of 2-aminopyridine as ligand, but no desired product was detected. This might be ascribed to the transitional 4-membered ring of 2-aminopyridine with copper ion is not stable enough to promote the amination of aryl chlorides. Keeping in mind Jiang's previous report that 8-hydroxyquinolin-*N*-oxide was proved to be a highly efficient ligand for Ullmann coupling reaction,[14] we therefore hoped to attain our goal of finding 2-aminopyridine *N*-oxides ligands (Figure 1), in which the N and O atoms might provide ideal bidentate chelating centers for Cu ion to form a much more stable 5-membered ring.

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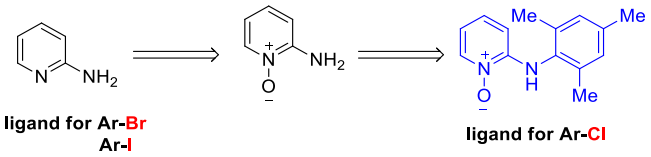
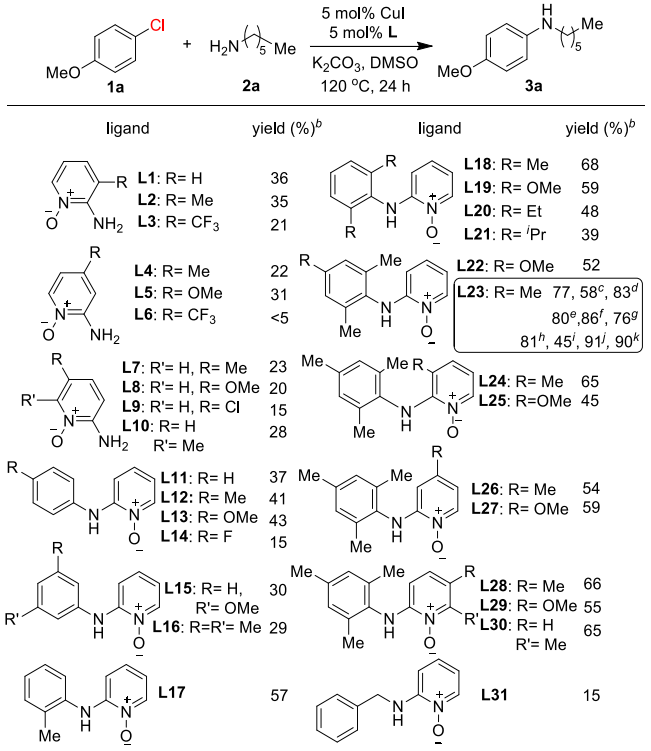


Figure 1. Rational design of 2-(*N*-aryl substituted amino)pyridine 1-oxide.

Then, 2-aminopyridine 1-oxide, a commercially available compound, was selected as the ligand for CuI-catalyzed C−N bond formation in the reaction between 4-chloroanisole and *n*-hexylamine. The reaction occurred with a low yield of 36% at 120 °C in DMSO using K_2CO_3 as base (Scheme 1, **L1**). This prompted us to test a variety of substituted 2-aminopyridine *N*-oxides. The results showed that changing the ligand with an electron-deficient group substituted (trifluoromethyl-)2-aminopyridine *N*-oxides gave poor yields (Scheme 1, **L3**, **L6**, **L9**), while the ligand with an electron-rich group substituted (methyl- or methoxy-)2-aminopyridine *N*-oxides gave a little better yields (Scheme 1, **L2**, **L4**−**L5**, **L7**−**L8**, **L10**). Unfortunately, none of substituted 2-aminopyridine 1-oxides screened showed high efficiency. Interestingly, after careful analysis of the reaction mixtures, we found that the ligands 2-aminopyridine *N*-oxides coupled with 4-chloroanisole during the reaction process to produce the corresponding 2-((4-methoxyphenyl)amino)-pyridine 1-oxides. When **L13** was directly used, target product *N*-hexyl-4-methoxyaniline was obtained in 43% yield (Scheme 1, **L13**), indicating that 2-(aryl amino)pyridine 1-oxide may be a real ligand for this reaction.

Scheme 1. CuI-Catalyzed Coupling of 4-Chloroanisole and *n*-Hexylamine: Evolution of Ligands[a]



[a]Typical conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), CuI (0.05 mmol), ligand (0.05 mmol), base (2.0 mmol), solvent (1.0 mL), Ar, 120 °C, 24 h. [b]Isolated yields. [c]Na_2CO_3 as the base. [d]Cs_2CO_3 as the base. [e]K_3PO_4 as the base. [f]DMF as the solvent. [g]DMAc as the solvent. [h]NMP as the solvent. [i]*t*BuOH as the solvent. [j]Cs_2CO_3, DMF, 130 °C. [k]**L23** (0.1 mmol).

We next synthesized a number of *N*-substituted 2-aminopyridine 1-oxides for the exploration of the structure−efficiency relationship so as to obtain highly effective ligands for Cu-catalyzed amination of aryl chlorides. Screening of **L11**−**L16** demonstrated that *N*-aryl with m-, and p-substituted derived 2-aminopyridine 1-oxides were less active to afford **3a** in low yields (15−43%), while improved yields (57%) were acquired by using *o*-methyl substituted ligands (Scheme 1, **L17**), stating that ligands with suitable substituents at the ortho-position of *N*-aryl might favor the coupling reaction. Thus, ligands **L18**−**L21**, in which the ortho-position of *N*-aryl have two substituents of Me, OMe, Et, and ^{i}Pr, respectively, were prepared for the coupling reaction. Consistent with our supposition, a good yield of 68% was obtained when two substituents of Me at the ortho-position of **L18** was used as ligand. Interestingly, changing the ortho-position substituents to OMe, Et, or ^{i}Pr led to formation of **3a** in decreased product yields (Scheme 1, **L19**−**L21**), which implied that larger substituents at the ortho-position of aromatic ring in ligands were less active. To our surprise, the best result (77%) achieved by **L23** in comparison with **L18** and **L22** showed that the appropriate electronic nature is important for the efficiency of ligands. In order to fully discover the potential efficiency of ligands, we tested **L24**−**L30**, in which the pyridine ring has several kinds of substitutes at different positions. The good results obtained by using **L24**, **L28**, and **L30** showed again that the appropriate electronic nature is necessary to explore the active ligands. Additionally, only 15% yield of desired product was isolated when utilizing **L31** as ligand, indicating that *N*-alkyl-substituted 2-aminopyridine 1-oxides were less active for the C−N coupling reactions. We next examined other bases using **L23** as the ligand. Changing the base to Na_2CO_3 led to a lower yield of 58%, while Cs_2CO_3 and K_3PO_4 gave much better yields of 83% and 80%, respectively. Then using Cs_2CO_3 as the base, DMF, DMAc, NMP, and ^{t}BuOH were also screened as the solvents, among which, DMF gave the best yield of 86%. To our delight, using Cs_2CO_3 as the base and DMF as the solvent, a 91% yield of **3a** was achieved when elevating the reaction temperature to 130 °C (Scheme 1, **L23**). In addition, a 90% isolated yield was obtained when increasing the loading of **L23** to 10 mol %, which showed that the increased relative stoichiometry of the ligand to Cu have little effect on the reaction. Noteworthy is that no coupling occurred under similar conditions using *N*-mesitylpyridin-2-amine as ligand, which implied again that 2-aminopyridine 1-oxides are real ligands for this reaction.

With the optimal conditions in hand, we began to explore the reaction scope. As summarized in Scheme 2, various *para*- and *meta*-substituted aryl chlorides bearing either electron-rich or electron-deficient groups reacted with *n*-hexylamine or benzylamine smoothly to produce the coupling products **3a**−**3f**, **3h**−**3l** in 81−93% yields. It should be noted that a 10 mmol scale reaction of **1a** with **2a** took place smoothly in excellent yield (Scheme 2, 3a). The coupling reaction of a methoxy ortho group in the aryl chloride with *n*-hexylamine occurred in 65% yields, but for *o*-chlorotoluene, poor yields (19%) were obtained (**3g**). The scope of the present method also includes the aminations of heteroaryl chlorides. Pyridyl (**3m**), benzothiophenyl (**3n**), and quinolyl (**3o**) chlorides underwent reaction with benzylamine in good to excellent yields.

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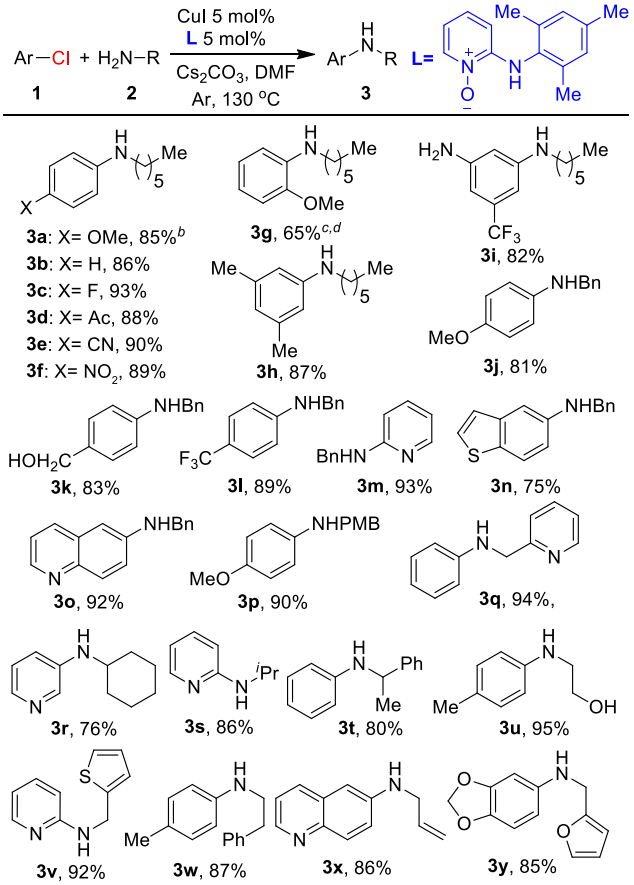
Scheme 2. CuI/L23 Catalyzed Amination of Aryl/Heteroaryl Chlorides with Primary Amines[a]



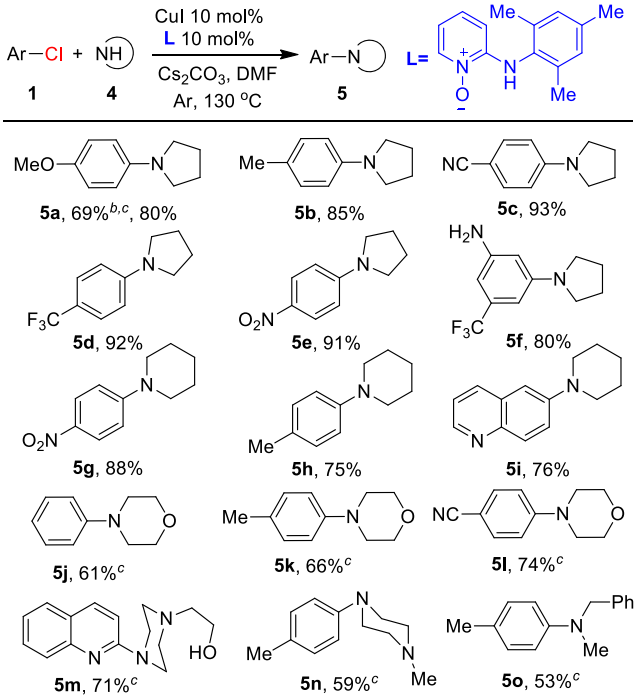
[a]Typical conditions: **1** (1.0 mmol), **2** (1.5 mmol), CuI (0.05 mmol), **L23** (0.05 mmol), Cs_2CO_3 (2.0 mmol), DMF (1.0 mL), Ar, 130 °C, 24 h. [b]Ten mmol scale. [c]Incomplete conversion was observed. [d]*O*-Chlorotoluene coupled with *n*-hexylamine in 19% yield.

To expand the utility of this method, the substrate scope of the amine coupling partners was investigated. Various kinds of primary aliphatic amines with pyridyl (**3q**), hydroxyl (**3u**), thiophenyl (**3v**), vinyl (**3x**), and furanyl (**3y**) groups were arylated to give the desired products in good to excellent yields. It should be noted that the copper-catalyzed coupling of steric hindered primary amines proved to be difficult with aryl chlorides;[11a] we were pleased to find that alpha-branched primary alkylamines (**3r**−**3t**) coupled with (hetero)aryl chlorides successfully to afford the corresponding products in satisfactory yields (76−86%).

Given our success in *N*-arylation of alpha-branched primary alkylamines with aryl chlorides, we further examined the arylation of more steric hindrance of cyclic secondary amines (Scheme 3). To our pleasure, the good yield (80%) of **5a** could be obtained when coupling of 4-chloroanisole with pyrrolidine, a rather reactive secondary amine, by elevating CuI and ligand loadings to 10 mol %, although only moderate yield (69%) of **5a** was observed when using 5 mol % CuI and 5 mol % ligand.

Under these new reaction conditions, other aryl chlorides coupled well with five-membered cyclic secondary amines in good to excellent yields (**5b**−**5f**). The results also showed that electron-poor aryl chlorides were more reactive to couple with pyrrolidine than electron-rich aryl chlorides (compare **5a**, **5b** with **5c**−**5e**).

Scheme 3. CuI/L23 Catalyzed Amination of Aryl/Heteroaryl Chlorides with Cyclic Secondary Amines[a]



[a]Typical conditions: **1** (1.0 mmol), **4** (1.5 mmol), CuI (0.10 mmol), **L23** (0.10 mmol), Cs_2CO_3 (2.0 mmol), DMF (1.0 mL), Ar, 130 °C, 24 h. [b]CuI (0.05 mmol), **L23** (0.05 mmol). [c]Incomplete conversion was observed.

In terms of cyclic secondary amines coupling partners, the use of six-membered ring secondary amines, including piperidine, morpholine, *N*-(2-hydroxyethyl)piperazine, and *N*-methylpiperazine, also provided moderate to good yields of coupled products (**5g**−**5n**). Furthermore, the arylation of *N*-methylbenzylamine, a linear secondary amine which has more steric hindrance than cyclic secondary amines, with 4-chlorotoluene occurred in an acceptable yield of 53% (**5o**). These examples are significant because many biologically interesting (hetero)aryl amines could be assembled utilizing the presented method, and, to the best of our knowledge, the coupling of six-membered ring secondary amines or linear secondary amine with unactivated aryl chlorides is rare.[11a,e,15]

In summary, a class of effective ligands, 2-aminopyridine 1-oxides, are discovered for the Cu-catalyzed amination of less reactive (hetero)aryl chlorides. A wide range of functionalized (hetero)aryl chlorides reacted with various amines to afford the desired products in good to excellent yields under the present reaction conditions. Furthermore, the catalyst system worked well for the *N*-arylation of isopropyl amines and cyclic secondary amines with (hetero)aryl chlorides. The identification of 2-aminopyridine 1-oxides as supporting ligands might bring new opportunities in the development of highly active ligands for copper-catalyzed arylation reactions. The exploration of these ligands in other coupling reactions are currently underway in our laboratory, and the results will be disclosed in due course.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, NMR spectra data, and HRMS of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) For selected books and reviews, see: Craig, P. N. In *Comprehensive Medicinal Chemistry*; Drayton, C. J., Ed.; Pergamon Press: New York, 1991. (b) Lawrence, S.; Amines, A. *Synthesis: Properties and Application*; Cambridge University Press: Cambridge, 2004. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930. (d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337−2364. (e) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054−3131. (f) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450−1460. (g) Lygaitis, R.; Getautis, V.; Grazulevicius, J. V. *Chem. Soc. Rev.* **2008**, *37*, 770−788. (h) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177−2250. (i) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451−3479. (j) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825−1864. (k) Liang, M.; Chen, J. *Chem. Soc. Rev.* **2013**, *42*, 3453−3488. (l) Tekale, S.; Jadhav, V.; Pagore, V.; Kauthale, S.; Gaikwad, D.; Pawar, R. *Mini-Rev. Org. Chem.* **2013**, *10*, 281−301. (m) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564−12649. (n) Devendar, P.; Qu, R.-Y.; Kang, W.-M.; He, B.; Yang, G.-F. J. *J. Agric. Food Chem.* **2018**, *66*, 8914−8934.

(2) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449. (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13−31. (c) Beletskaya, I. P.; Cheprakov, A. V. *Organometallics* **2012**, *31*, 7753−7808. (d) Lundgren, R. J.; Stradiotto, M. *Chem. - Eur. J.* **2012**, *18*, 9758−9769. (e) Amal Joseph, P. J.; Priyadarshini, S. *Org. Process Res. Dev.* **2017**, *21*, 1889−1924. (f) Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2017**, *56*, 16136−16179. (g) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. *Chem. Rev.* **2018**, *118*, 2249−2295. (h) Marín, M.; Rama, R. J.; Nicasio, M. C. *Chem. Rec.* **2016**, *16*, 1819−1832. (i) Ritleng, V.; Henrion, M.; Chetcuti, M. J. *ACS Catal.* **2016**, *6*, 890−906. (j) Lavoie, C. M.; Stradiotto, M. *ACS Catal.* **2018**, *8*, 7228−7250.

(3) For recent Pd-catalyzed C−N coupling, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (d) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768−2813. (e) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361. (f) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534−1544. (g) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027−3043. (h) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4071−4074. (i) Lundgren, R. J.; Sappong-Kumankumah, A.; Stradiotto, M. *Chem. - Eur. J.* **2010**, *16*, 1983−1991. (j) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27−50. (k) Alsabeh, P. G.; Lundgren, R. J.; McDonald, R.; Johansson Seechurn, C. C. C.; Colacot, T. J.; Stradiotto, M. *Chem. - Eur. J.* **2013**, *19*, 2131−2141. (l) Wheaton, C. A.; Bow, J.-P. J.; Stradiotto, M. *Organometallics* **2013**, *32*, 6148−6161. (m) Lemen, G. S.; Wolfe, J. P. *Top. Organomet. Chem.* **2012**, *46*, 1−54. (n) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283−9303.

(4) For recent Ni-catalyzed C−N coupling, see: (a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058. (b) Martin, A. R.; Makida, Y.; Meiries, S.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2013**, *32*, 6265−6270. (c) Zhu, F.; Wang, Z.-X. *Adv.*

Synth. Catal. **2013**, *355*, 3694−3702. (d) Park, N. H.; Teverovskiy, G.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 220−223. (e) Kampmann, S. S.; Sobolev, A. N.; Koutsantonis, G. A.; Stewart, S. G. *Adv. Synth. Catal.* **2014**, *356*, 1967−1973. (f) Borzenko, A.; Rotta-Loria, N. L.; MacQueen, P. M.; Lavoie, C. M.; McDonald, R.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 3773−3777. (g) Lavoie, C. M.; MacQueen, P. M.; Rotta-Loria, N. L.; Sawatzky, R. S.; Borzenko, A.; Chisholm, A. J.; Hargreaves, B. K. V.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *Nat. Commun.* **2016**, *7*, 11073−11084. (h) Zhou, Y.-P.; Raoufmoghaddam, S.; Szilvasi, T.; Driess, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 12868−12872. (i) Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C. *Science* **2016**, *353*, 279−283. (j) Tassone, J. P.; MacQueen, P. M.; Lavoie, C. M.; Ferguson, M. J.; McDonald, R.; Stradiotto, M. *ACS Catal.* **2017**, *7*, 6048−6059. (k) Lavoie, C. M.; McDonald, R.; Johnson, E. R.; Stradiotto, M. *Adv. Synth. Catal.* **2017**, *359*, 2972−2980. (l) Li, C.; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Chen, J.; Yan, M.; Baran, P. S. *Angew. Chem., Int. Ed.* **2017**, *56*, 13088−13093. (m) Harada, T.; Ueda, Y.; Iwai, T.; Sawamura, M. *Chem. Commun.* **2018**, *54*, 1718−1721. (n) Lavoie, C. M.; Stradiotto, M. *ACS Catal.* **2018**, *8*, 7228−7250. (o) Gatien, A. V.; Lavoie, C. M.; Bennett, R. N.; Ferguson, M. J.; McDonald, R.; Johnson, E. R.; Speed, A. W. H.; Stradiotto, M. *ACS Catal.* **2018**, *8*, 5328−5339. (p) Kim, T.; McCarver, S. J.; Lee, C.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2018**, *57*, 3488−3492. (q) McGuire, R. T.; Paffile, J. F. J.; Zhou, Y.; Stradiotto, M. *ACS Catal.* **2019**, *9*, 9292−9297. (r) Tassone, J. P.; England, E. V.; MacQueen, P. M.; Ferguson, M. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2019**, *58*, 2485−2489. (s) Clark, J. S. K.; Ferguson, M. J.; McDonald, R.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2019**, *58*, 6391−6395. (t) Kawamata, Y.; Vantourout, J. C.; Hickey, D. P.; Bai, P.; Chen, L.; Hou, Q.; Qiao, W.; Barman, K.; Edwards, M. A.; Garrido-Castro, A. F.; de Gruyter, J. N.; Nakamura, H.; Knouse, K.; Qin, C.; Clay, K. J.; Bao, D.; Li, C.; Starr, J. T.; Garcia-Irizarry, C.; Sach, N.; White, H. S.; Neurock, M.; Minteer, S. D.; Baran, P. S. *J. Am. Chem. Soc.* **2019**, *141*, 6392−6402. (u) Clark, J. S. K.; McGuire, R. T.; Lavoie, C. M.; Ferguson, M. J.; Stradiotto, M. *Organometallics* **2019**, *38*, 167−175. (v) Park, B. Y.; Pirnot, M. T.; Buchwald, S. L. J. *J. Org. Chem.* **2020**, *85*, 3234−3244. (w) Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2020**, *142*, 4500−4507. (x) McGuire, R. T.; Simon, C. M.; Yadav, A. A.; Ferguson, M. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2020**, *59*, 8952−8956. (y) Han, D.; Li, S.; Xia, S.; Su, M.; Jin, J. *Chem. - Eur. J.* **2020**, DOI: 10.1002/chem.202002800.

(5) (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459−12467. (b) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453−2455. (c) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (d) Guo, X.; Rao, H.; Fu, H.; Jiang, Y.; Zhao. *Adv. Synth. Catal.* **2006**, *348*, 2197−2202. (e) Zou, B.; Yuan, Y. Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598−2601. (f) Jiang, L.; Lu, X.; Zhang, H.; Jiang, Y.; Ma, D. J. *J. Org. Chem.* **2009**, *74*, 4542−4546. (g) Zhang, Y.; Yang, X.; Yao, Q.; Ma, D. *Org. Lett.* **2012**, *14*, 3056−3059.

(6) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428. (c) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581−584. (d) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684−11688. (e) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796. (f) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742−8743. (g) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490−3491. (h) Altman, R. A.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5167−5169. (i) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779−2782. (j) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190−6199. (k) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284−286. (l) Ueda, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 10364−10367.

(7) (a) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. - Eur. J.* **2004**, *10*, 5607−5622. (b) Cristau, H.-J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, *2004*, 695−709. (c) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337−339. (d) Racine, E.; Monnier, F.; Vors, J.-P.; Taillefer, M. *Org. Lett.* **2011**, *13*, 2818−2821. (e) Abdine, R. A. A.; Kurpik, G.; Walczak, A.; Aeash, S. A. A.; Stefankiewicz, A. R.; Monnier, F.; Taillefer, M. *J. Catal.* **2019**, *376*, 119−122.

(8) (a) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670−674. (b) Zhu, D.; Wang, R.; Mao, J.; Xu, L.; Wu, F.; Wan, B. *J. Mol. Catal. A: Chem.* **2006**, *256*, 256−260. (c) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672−674. (d) Zeng, L.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2009**, *351*, 1671−1676. (e) Lu, Z.; Twieg, R. J.; Huang, S. D. *Tetrahedron Lett.* **2003**, *44*, 6289−6292. (f) Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* **2005**, *46*, 2997−3001. (g) Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, *61*, 903−918. (h)) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863−3867. (i) Liu, L.; Frohn, M.; Xi, N.; Dominguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2005**, *70*, 10135−10138. (j) Wang, D.; Cai, Q.; Ding, K. *Adv. Synth. Catal.* **2009**, *351*, 1722−1726. (k) Wang, D.; Ding, K. *Chem. Commun.* **2009**, 1891−1893. (l) Wang, D.; Zhang, F.; Kuang, D.; Yu, J.; Li, J. *Green Chem.* **2012**, *14*, 1268−1271. (m) Wang, D.; Kuang, D.; Zhang, F.; Yang, C.; Zhu, X. *Adv. Synth. Catal.* **2015**, *357*, 714−718. (n) Ding, X.; Huang, M.; Yi, Z.; Du, D.; Zhu, X.; Wan, Y. *J. Org. Chem.* **2017**, *82*, 5416−5423. (o) Lo, Q. A.; Sale, D.; Braddock, D. C.; Davies, R. P. *ACS Catal.* **2018**, *8*, 101−109.

(9) For recent books and reviews, see refs 1e, 2b, 2f, and the following: (a) Shaughnessy, K. H.; Ciganek, E.; Devasher, R. B. *Organic Reactions*; Hoboken, NJ, 2014; Vol. *85*, pp 1−668. (b) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014**, *43*, 3525−3550. (c) Jiang, Y.; Ma, D. In *Copper-Mediated Cross-Coupling Reactions*; Evano, G., Blanchard, N., Eds.; John Wiley & Sons Inc.: Hoboken, NJ, 2013; pp 589−642. (d) Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G. *Dalton Trans.* **2010**, *39*, 10338. (e) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954−6971.

(10) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062. (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096−3099. (c) Monnier, F.; Taillefer, M. *Top. Organomet. Chem.* **2013**, *46*, 173−204.

(11) (a) Zhou, W.; Fan, M.; Yin, J.; Jiang, Y.; Ma, D. *J. Am. Chem. Soc.* **2015**, *137*, 11942−11945. (b) Fan, M.; Zhou, W.; Jiang, Y.; Ma, D. *Org. Lett.* **2015**, *17*, 5934−5937. (c) De, S.; Yin, J.; Ma, D. *Org. Lett.* **2017**, *19*, 4864−4867. (d) Chen, Z.; Ma, D. *Org. Lett.* **2019**, *21*, 6874−6878. (e) Bernhardson, D. J.; Widlicka, D. W.; Singer, R. A. *Org. Process Res. Dev.* **2019**, *23*, 1538−1551.

(12) Wang, D.; Kuang, D.; Zhang, F.; Liu, Y.; Ning, S. *Tetrahedron Lett.* **2014**, *55*, 7121−7123.

(13) For 2-aminopyridine as ligand promoted Cu-catalyzed Ullmann ether formation with Ar−Br, see: Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043−5051.

(14) (a) Yang, K.; Qiu, Y.; Li, Z.; Wang, Z.; Jiang, S. *J. Org. Chem.* **2011**, *76*, 3151−3159. (b) Yang, K.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. *Org. Lett.* **2011**, *13*, 4340−4343. (c) Zeng, X.; Huang, W.; Qiu, Y.; Jiang, S. *Org. Biomol. Chem.* **2011**, *9*, 8224−8227. (d) Chen, D.; Yang, K.; Xiang, H.; Jiang, S. *Tetrahedron Lett.* **2012**, *53*, 7121−7124.

(15) Bhunia, S.; Kumar, S. V.; Ma, D. *J. Org. Chem.* **2017**, *82*, 12603−12612.

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Org. Lett. XXXX, XXX, XXX−XXX