ACS Catalysis

pubs.acs.org/acscatalysis Letter

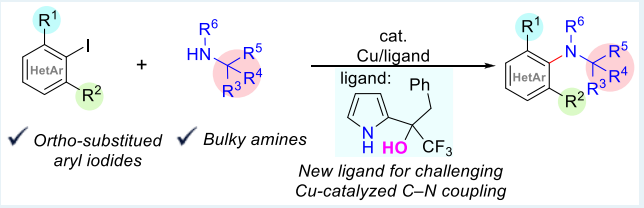
# Cu-Catalyzed C–N Coupling with Sterically Hindered Partners

Atanu Modak, Alex J. Nett, Elizabeth C. Swift, Michael C. Haibach, Vincent S. Chan, Thaddeus S. Franczyk, Shashank Shekhar,* and Silas P. Cook*

Cite This: *ACS Catal.* 2020, 10, 10495–10499 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** Copper, an earth-abundant metal, has reemerged as a viable alternative to the versatile Pd-catalyzed C–N coupling. Coupling sterically hindered reaction partners, however, remains challenging. Herein, we disclose the discovery and development of a pyrrole-ol ligand to facilitate the coupling of *ortho*-substituted aryl iodides with sterically hindered amines. The ligand was discovered through a library screening approach and highlights the value of mining heteroatom-rich pharmaceutical libraries for useful ligand motifs. Further evaluation revealed that this ligand is uniquely effective in these challenging transformations. The reaction enables the coupling of sterically hindered primary and secondary amines, anilines, and amides with broad functional group tolerance.




**KEYWORDS:** *copper, C–N coupling, aniline, ligand mining, sterically hindered partners*



Anilines represent a privileged class of amines in nature, as well as pharmaceuticals, agrochemicals, and other valuable organic materials.[1] Consequently, transition metal-catalyzed C–N-bond formation has become critically important to organic synthesis. While a number of d-block metals have been investigated for this reaction, the two most common metals remain palladium (Buchwald–Hartwig amination[2]) and copper (Ullmann–Goldberg-type[3] and Chan–Lam[4] amination). Exploration of palladium-catalyzed C–N-coupling reactions started almost 25 years ago concurrently by Buchwald and Hartwig.[5] Concentrated effort across a number of groups has positioned the Buchwald–Hartwig reaction as the dominant amination method with broad substrate scope and high selectivities.[6] While much progress has been made with the copper-catalyzed variants, the Ullmann-type amination has lagged in terms of both electrophile and amine scope.[7] Early advances came independently from Ma,[8] Goodbrand,[9] Buchwald,[10] and others.[11,12] Recently, the Ma group introduced oxalamide ligands that enable low catalyst loading and the use of aryl chlorides as electrophiles—addressing key challenges for copper-catalyzed amination.[13] Copper-catalyzed C–N-coupling reactions with hindered partners, however, remain an unsolved problem (Figure 1a).[12b] Currently, there exist only a few examples where an *ortho* methyl group can be tolerated on the electrophile (Figure 1a).[13,14] Furthermore, examples with *ortho,ortho′*-disubstituted electrophiles with sterically hindered amines have not been reported. Although alternative base metal-catalyzed approaches exist to synthesize sterically encumbered anilines (Figure 1b),[15] they rely on fundamentally different building blocks. Here, we describe a novel ligand that enables very challenging and previously unreported direct

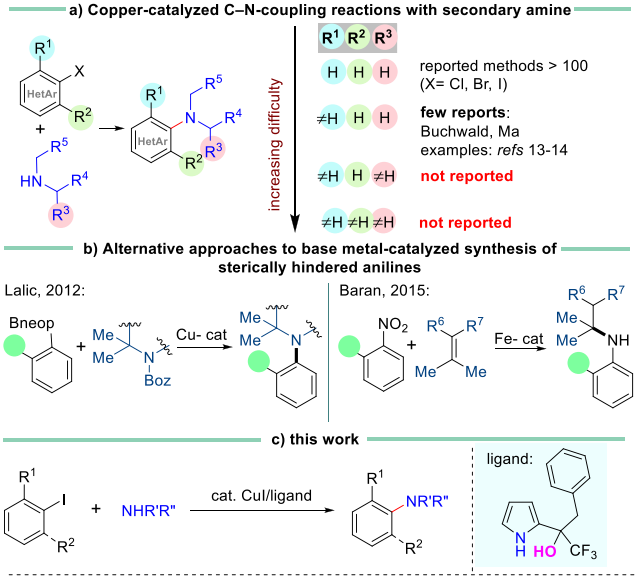



**Figure 1.** (a) Existing copper-catalyzed C–N-coupling reactions remain limited in sterically demanding environments. (b) Previous approaches for base metal-catalyzed aniline synthesis. (c) A novel pyrrole-ol ligand enables C–N coupling of sterically hindered partners.

Received: July 7, 2020
Revised: August 17, 2020

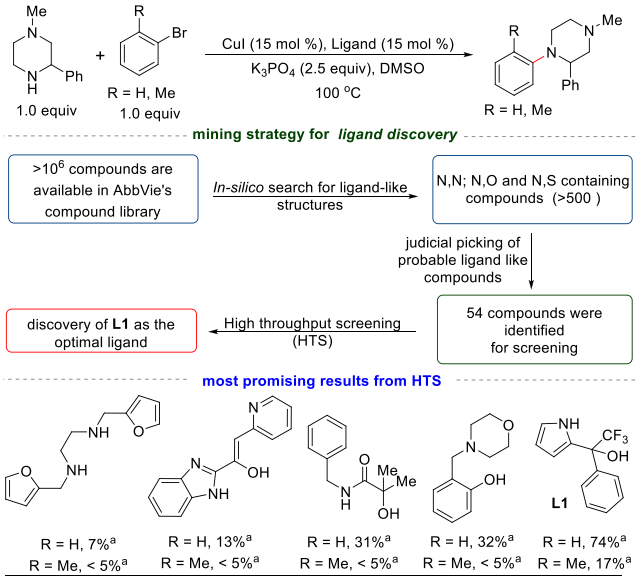



https://dx.doi.org/10.1021/acscatal.0c02965
*ACS Catal.* 2020, 10, 10495–10499

aminations with sterically hindered coupling partners using copper catalysis (Figure 1c).

We were interested in identifying a ligand for Cu to couple sterically hindered electrophiles and nucleophiles—a challenge even for Pd-based methods.[16] Despite several new ligands for Cu reported in the recent years, coupling of sterically hindered partners remains a formidable challenge. The discovery of a more effective ligand is critical to the success of this transformation. Given the recent success with evaluating pharmaceutical compound libraries as ligands for metal-catalyzed reactions,[17] AbbVie's internal compound library was screened as ligands for copper. The coupling of bromobenzene with 1-methyl-3-phenylpiperazine sought to evaluate 54 nonproprietary compounds that were previously examined for Cu-catalyzed C−O coupling (Scheme 1).[17b]

**Scheme 1. Discovery of Trifluoromethylated Pyrole-ol-Based Ligand**

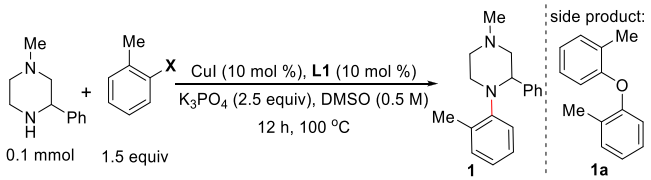



[a]Area% of the coupled products determined by HPLC is reported.

Interestingly, 2,2,2-trifluoro-1-phenyl-1-(1*H*-pyrrol-2-yl)ethan-1-ol (**L1**), a compound that had not been previously applied as a ligand, produced the highest yield of the coupled product (74 HPLC peak area%).[14d,18] Surprisingly, the more sterically hindered substrate combination, 2-bromotoluene and 1-methyl-3-phenylpiperazine, coupled to form product only in the presence of **L1**.

Ligand **L1** was chosen for further optimization (Table 1). Formation of an almost equal amount of the C−O coupled product **1a** was observed as a side-product in the reaction (entry 1). The addition of molecular sieves to the reaction mixture suppressed the C−O coupling product but failed to improve the yield of the desired product (entry 2). We speculated that base-mediated ligand degradation led to catalyst deactivation through the formation of phenyl(1*H*-pyrrol-2-yl)methanone **L1′**.[19] Further evaluation of both the target reaction and ligand stability demonstrated rapid, base-mediated decomposition to phenyl(1*H*-pyrrol-2-yl)methanone **L1′**, and it functions as an inhibitor for the reaction. Although lowering the reaction temperature suppressed ligand degradation, it also slowed the reaction. In an attempt to increase the lifetime of active catalyst and to block ligand degradation, a

**Table 1. Initial Reaction Optimization**




| entry | X | additive | 1(%)[a] | 1a (%)[a] | conversion (%)[b] |
|---|---|---|---|---|---|
| 1 | Br | - | 17 | 23 | 40 |
| 2 | Br | 100 mg MS (4 Å) | 18 | 1 | 20 |
| 3 | Br | 100 mg MS (4 Å), 0.5 equiv HE | 32 | 2 | 35 |
| 4[c] | I | - | 42 | 50 | 95 |
| 5[c] | I | 100 mg MS (4 Å) | 46 | 8 | 59 |
| 6[c] | I | 100 mg MS (4 Å), 0.5 equiv HE | 64 | 5 | 70 |
| 7 | I | 24 h, 100 mg MS (4 Å), 1 equiv HE 1.7 equiv amine, 4 equiv $K_3PO_4$ 90 °C | 86 | 7 | 98 |

[a]GC yield. [b]Based on unreacted aryl halide. [c]Reaction was conducted at 80 °C. MS = molecular sieves.

variety of mild reductants were evaluated. Interestingly, a stochiometric amount of Hantzsch ester (HE) increased the catalyst lifetime.[20] Conversely, ascorbic acid offered no improvement.[21] In the presence of one equivalent of Hantzsch ester, the desired product was obtained in 33% yield (entry 3). Next, the more reactive electrophile, 2-iodotoluene, was tested in the reaction. The desired product was obtained in a higher 42% yield along with 50% of **1a** (entry 4). As observed earlier, addition of molecular sieves suppressed the ether formation (entry 5). The higher yield of **1** (64%) was observed by conducting the reaction in the presence of 0.5 equiv of HE at 80 °C (entry 6). Fortunately, employing additional base (4 equiv) and amine (1.7 equiv) produced the desired product in 86% yield after 24 h (entry 7).

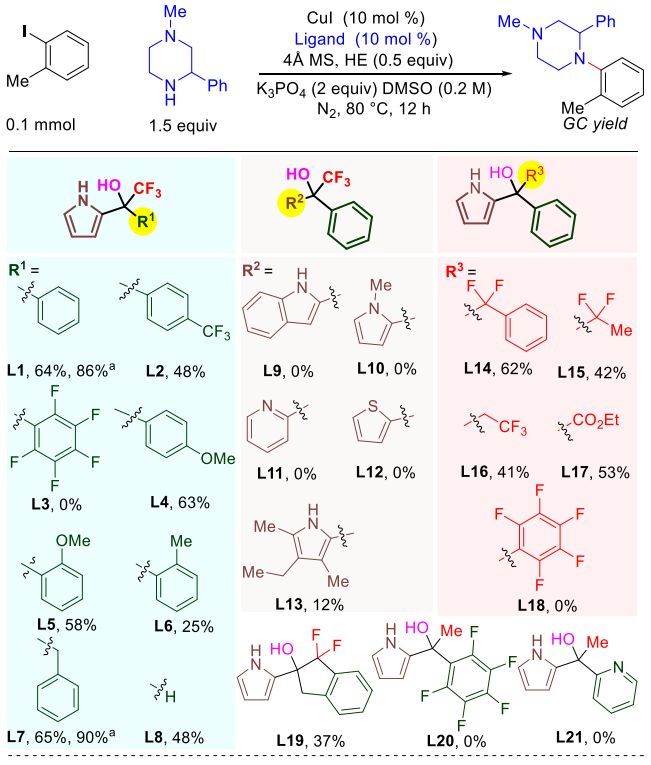
As discussed above, this type of sterically demanding coupling is unprecedented with a Cu catalyst. To better understand the catalyst landscape, we also screened 46 established ligands for Cu in this reaction using a high-throughput approach. To our surprise, none of the established ligands resulted in the formation of **1** in any appreciable yield (Table S1).[22] These results suggest that the catalyst derived from L1 and CuI may be unique in its reactivity for sterically demanding C−N couplings.

Next, we evaluated the structure−activity relationships for the pyrrole-ol-based N−O type ligands. Systematically replacing the phenyl ring of **L1** resulted in significant variations in yield (**L2**−**L8**, Table 2). Pentafluorobenzene-containing ligands (**L3**, **L18**, **L20**), for example, showed no reactivity possibly because of decreased ligand stability under the reaction conditions, ejecting $C_6F_5^-$ as a leaving group. The pyrrole-ol ligand bearing a benzyl substituent (**L7**), which is presumably less prone to elimination, provided a minor improvement in yield. The unprotected pyrrole moiety proved critical to afford a ligand which promote the overall reaction in reasonable yields (**L9**−**L13**, Table 2). Finally, evaluation of the $R^3$- substituent (**L14**−**L18**, Table 2) revealed that the trifluoromethyl group is crucial for the ligand reactivity—presumably due to its steric and electronic properties. On the basis of these results, **L7** was chosen for further reaction optimization, providing 90% of the desired product under the optimal conditions (described in Table 1, entry 7).

A diverse range of sterically crowded amines with varied N−H p$K_a$ values were explored for the coupling with *ortho*-substituted aryl iodide. Satisfyingly, the protocol was successful for amines with an N−H p$K_a$ window of ∼20 to ∼40.[23] Next,


https://dx.doi.org/10.1021/acscatal.0c02965
ACS Catal. 2020, 10, 10495−10499

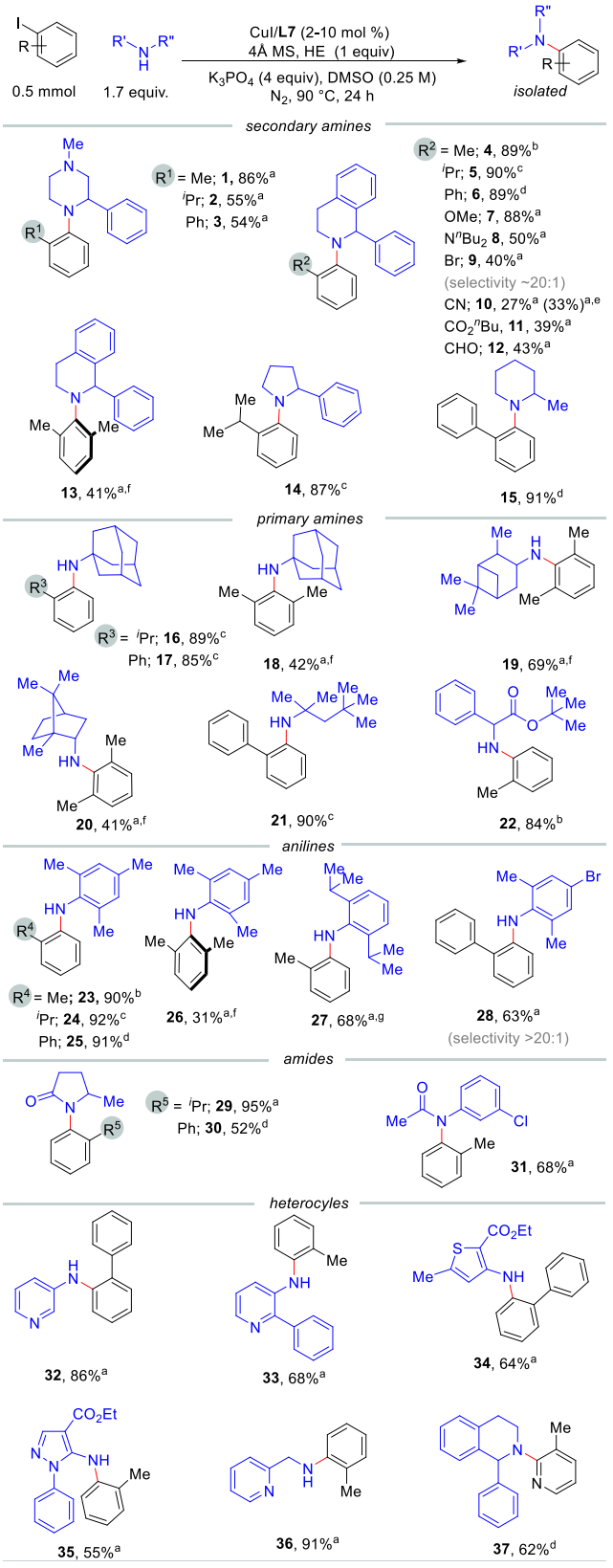
**Table 2. Screening of Pyrole-ol-Based Ligand**[a]




[a]Reaction conditions: iodide 0.1 mmol, amine 1.7 equiv, CuI 10 mol %, ligand 10 mol %, 100 mg 4 Å MS, HE 1 equiv, $K_3PO_4$ 4 equiv, DMSO 0.2 M, 90 °C, 24 h. HE = Hantzsch ester

we explored the substrate scope with regard to various *ortho*-substituted aryl iodides and 1-methyl-3-phenylpiperazine. Not surprisingly, larger *ortho* substituents led to lower yields (**1**–**3**, Scheme 2). Next, we tested the scope of *ortho* substituted aryl iodides with the bioactive and sterically demanding 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**4**–**13**).[24] The catalyst demonstrated excellent reactivity with electron-neutral (**4**–**6**) or electron-donating (**7**) substituents at the *ortho* position of the aryl iodide. To our delight, a bulky *N*,*N*-di-*n*-butyl-amino group was well tolerated in the reaction (**8**). Importantly, 2-bromo-iodobenzene promoted the C–N coupling preferentially at the iodide with >20:1 chemoselectivity (**9**). Surprisingly, aryl iodides with electron-deficient substituents at the *ortho* position resulted in low-to-moderate yield (**10**–**12**) with significant halide-reduction product. Control reactions revealed that this unwanted side product was not due to hydride donation from the Hantzsch ester (**10**). Excitingly, hindered 2,6-dimethyl-iodobenzene reacted successfully to form **13**, a unprecedented reaction for copper catalysis. The ligand even enabled sterically demanding primary amines to couple with *ortho*-substituted iodides (**16**–**21**). As expected, 2,6-dimethyl-substituted aryl iodides provided satisfactory yield of the desired products (**18**–**20**, **26**). Additionally, this protocol offered excellent reactivity with 2,6-dimethylaniline (**23**–**26**, **28**). The reactivity with 2,6-diisopropylaniline further established the versatility of this catalyst system (**27**). Furthermore, this method is also applicable to cyclic amides (**29**–**30**), anilide (**31**), and an amino acid derivative (**22**). As an investigation into medicinally relevant heterocycles, a series of heteroaryl iodides

**Scheme 2. Substrate Scope for C–N Coupling Reaction**




[a]10 mol % Cu/**L7**; [b]2 mol % Cu/**L7**; [c]5 mol % Cu/**L7**; [d]8 mol % Cu/**L7**; [e]without HE; [f]48 h; [g]60 h. HE = Hantzsch ester

and amines were tested. Moreover, pyridine, thiophane, and pyrazole moieties were well tolerated by the catalyst (**32**–**37**).



https://dx.doi.org/10.1021/acscatal.0c02965
ACS Catal. 2020, 10, 10495–10499

The origin for the effectiveness of pyrrole-ol-based ligands for enabling the Cu-catalyzed coupling of sterically hindered coupling partners remains worthy of further mechanistic consideration. We expect **L7** to be deprotonated under the reaction conditions and act as either mono- or bis-anionic ligand for Cu.[25] Likely, **L7** forms a highly electron-rich Cu(I) or anionic Cu(I)-complex that promotes oxidative addition even with sterically hindered electrophiles.[26]

In summary, we have disclosed a new ligand that enables an unprecedented Cu-catalyzed method for coupling *ortho*- and *ortho,ortho'*-substituted aryl iodides with sterically hindered primary aliphatic amines, anilines, and amides. The unique reactivity and novel pyrrole-ol structural motif of ligand **L7** was discovered by mining AbbVie's internal compound library—demonstrating the value of screening pharmaceutical compound libraries for ligand discovery in challenging metal-catalyzed reactions. Complementary to the rational ligand design and optimization, this approach has the potential to identify previously unexplored and nonobvious compounds as ligands. Our future studies will focus on detailed mechanistic studies to elucidate the role of pyrrole-ol ligands in Cu-catalyzed reactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c02965.

Experimental details and spectroscopic data (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Authors

**Silas P. Cook** − *Department of Chemistry, Indiana University, Bloomington, Indiana 47405-7102, United States;* orcid.org/0000-0002-3363-4259; Email: sicook@indiana.edu

**Shashank Shekhar** − *Process Research and Development, AbbVie Inc., North Chicago, Illinois 60064, United States;* orcid.org/0000-0002-1903-5380; Email: shashank.shekhar@abbvie.com

### Authors

**Atanu Modak** − *Department of Chemistry, Indiana University, Bloomington, Indiana 47405-7102, United States*

**Alex J. Nett** − *Process Research and Development, AbbVie Inc., North Chicago, Illinois 60064, United States*

**Elizabeth C. Swift** − *Process Research and Development, AbbVie Inc., North Chicago, Illinois 60064, United States;* orcid.org/0000-0002-3207-4288

**Michael C. Haibach** − *Process Research and Development, AbbVie Inc., North Chicago, Illinois 60064, United States*

**Vincent S. Chan** − *Process Research and Development, AbbVie Inc., North Chicago, Illinois 60064, United States*

**Thaddeus S. Franczyk** − *Process Research and Development, AbbVie Inc., North Chicago, Illinois 60064, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c02965


### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare the following competing financial interest(s): E.C.S., M.C.H., T.S.F., and S.S. are AbbVie employees and may own AbbVie stocks. A.J.N. and V.S.C. were employees of AbbVie and may own AbbVie stocks. A.J.N. is currently an employee of Dow Chemicals. V.S.C. is currently an employee of Seattle Genetics. A.M. is a postdoctoral associate, and S.P.C. is an Associate Professor at Indiana University and have no conflicts of interest to disclose. The authors wish to acknowledge Dr. Seble Wagaw and Dr. David M. Barnes for helpful discussions. S.W. and D.M.B. are AbbVie employees and may own AbbVie stocks.

## ■ ACKNOWLEDGMENTS

AbbVie contributed to the design, study conduct, and financial support for this research. AbbVie participated in the interpretation of data, writing, reviewing, and approving the publication. We acknowledge funds from Indiana University in partial support of this work. We also acknowledge the NIH (R01GM121840) for partial support of this work.

## ■ REFERENCES


(1) Kahl, T.; Schröder, K.-W.; Lawrence, F. R.; Marshall, W. J.; Höke, H.; Jäckh, R. Aniline. *Ullmann's Encyclopedia of Industrial Chemistry* **2011**, 465−478.

(2) Forero-Cortés, P. A.; Haydl, A. M. The 25th Anniversary of the Buchwald−Hartwig Amination: Development, Applications, and Outlook. *Org. Process Res. Dev.* **2019**, *23*, 1478−1483.

(3) (a) Ullmann, F.; Bielecki, J. Ueber Synthesen in der Biphenylreihe. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174−2185. (b) Ullmann, F.; Sponagel, P. Ueber die Phenylirung von Phenolen. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211−2212.

(4) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New N- and O-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **1998**, *39*, 2933−2936. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New aryl/heteroaryl C—N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation. *Tetrahedron Lett.* **1998**, *39*, 2941−2944.

(5) (a) Louie, J.; Hartwig, J. F. Palladium-catalyzed synthesis of arylamines from aryl halides. Mechanistic studies lead to coupling in the absence of tin reagents. *Tetrahedron Lett.* **1995**, *36*, 3609−3612. (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348−1350.

(6) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald−Hartwig Amination After 25 Years. *Angew. Chem., Int. Ed.* **2019**, *58*, 17118−17129.

(7) (a) Shaughnessy, K. H.; Ciganek, E.; DeVasher, R. B. Copper-Catalyzed Amination of Aryl and Alkenyl Electrophiles. *Org. React.* **2014**, 1−668. (b) Evano, G.; Blanchard, N.; Toumi, M. Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis. *Chem. Rev.* **2008**, *108*, 3054−3131.

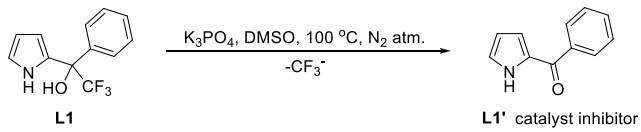
(8) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. Accelerating Effect Induced by the Structure of α-Amino Acid in the Copper-Catalyzed Coupling Reaction of Aryl Halides with α-Amino Acids. Synthesis of Benzolactam-V8. *J. Am. Chem. Soc.* **1998**, *120*, 12459−12467.

(9) Goodbrand, H. B.; Hu, N.-X. Ligand-Accelerated Catalysis of the Ullmann Condensation: Application to Hole Conducting Triarylamines. *J. Org. Chem.* **1999**, *64*, 670−674.

(10) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. A General and Efficient Copper Catalyst for the Amidation of Aryl Halides and the N-Arylation of Nitrogen Heterocycles. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729.

(11) Bernhardson, D. J.; Widlicka, D. W.; Singer, R. A. Cu-Catalyzed Couplings of Heteroaryl Primary Amines and (Hetero)aryl Bromides

with 6-Hydroxypicolinamide Ligands. *Org. Process Res. Dev.* **2019**, *23*, 1538−1551.
(12) (a) Wang, D.; Ding, K. 2-Pyridinyl β-ketones as new ligands for room-temperature CuI-catalysed C−N coupling reactions. *Chem. Commun.* **2009**, 1891−1893. (b) Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. Selected Copper-Based Reactions for C-N, C-O, C-S, and C-C Bond Formation. *Angew. Chem., Int. Ed.* **2017**, *56*, 16136−16179.
(13) (a) Gao, J.; Bhunia, S.; Wang, K.; Gan, L.; Xia, S.; Ma, D. Discovery of N-(Naphthalen-1-yl)-N′-alkyl Oxalamide Ligands Enables Cu-Catalyzed Aryl Amination with High Turnovers. *Org. Lett.* **2017**, *19*, 2809−2812. (b) De, S.; Yin, J.; Ma, D. Copper-Catalyzed Coupling Reaction of (Hetero)Aryl Chlorides and Amides. *Org. Lett.* **2017**, *19*, 4864−4867.
(14) (a) Job, G. E.; Buchwald, S. L. Copper-Catalyzed Arylation of β-Amino Alcohols. *Org. Lett.* **2002**, *4*, 3703−3706. (b) Antilla, J. C.; Klapars, A.; Buchwald, S. L. The Copper-Catalyzed N-Arylation of Indoles. *J. Am. Chem. Soc.* **2002**, *124*, 11684−11688. (c) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. Copper-Diamine-Catalyzed N-Arylation of Pyrroles, Pyrazoles, Indazoles, Imidazoles, and Triazoles. *J. Org. Chem.* **2004**, *69*, 5578−5587. (d) Altman, R. A.; Anderson, K. W.; Buchwald, S. L. Pyrrole-2-carboxylic Acid as a Ligand for the Cu-Catalyzed Reactions of Primary Anilines with Aryl Halides. *J. Org. Chem.* **2008**, *73*, 5167−5169. (e) Altman, R. A.; Buchwald, S. L. 4,7-Dimethoxy-1,10-phenanthroline: An Excellent Ligand for the Cu-Catalyzed N-Arylation of Imidazoles. *Org. Lett.* **2006**, *8*, 2779−2782.
(15) (a) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. Synthesis of Hindered Anilines: Copper-Catalyzed Electrophilic Amination of Aryl Boronic Esters. *Angew. Chem., Int. Ed.* **2012**, *51*, 3953−3956. (b) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. Practical olefin hydroamination with nitroarenes. *Science* **2015**, *348*, 886.
(16) (a) Ruiz-Castillo, P.; Blackmond, D. G.; Buchwald, S. L. Rational Ligand Design for the Arylation of Hindered Primary Amines Guided by Reaction Progress Kinetic Analysis. *J. Am. Chem. Soc.* **2015**, *137*, 3085−3092. (b) Park, N. H.; Vinogradova, E. V.; Surry, D. S.; Buchwald, S. L. Design of New Ligands for the Palladium-Catalyzed Arylation of α-Branched Secondary Amines. *Angew. Chem., Int. Ed.* **2015**, *54*, 8259−8262. (c) Khadra, A.; Mayer, S.; Mitchell, D.; Rodriguez, M. J.; Organ, M. G. A General Protocol for the Broad-Spectrum Cross-Coupling of Nonactivated Sterically Hindered 1° and 2° Amines. *Organometallics* **2017**, *36*, 3573−3577. (d) Hill, L. L.; Moore, L. R.; Huang, R.; Craciun, R.; Vincent, A. J.; Dixon, D. A.; Chou, J.; Woltermann, C. J.; Shaughnessy, K. H. Bulky Alkylphosphines with Neopentyl Substituents as Ligands in the Amination of Aryl Bromides and Chlorides. *J. Org. Chem.* **2006**, *71*, 5117−5125.
(17) (a) Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. New ligands for nickel catalysis from diverse pharmaceutical heterocycle libraries. *Nat. Chem.* **2016**, *8*, 1126−1130. (b) Chan, V. S.; Krabbe, S. W.; Li, C.; Sun, L.; Liu, Y.; Nett, A. J. Identification of an Oxalamide Ligand for Copper-Catalyzed C-O Couplings from a Pharmaceutical Compound Library. *ChemCatChem* **2019**, *11*, 5748−5753.
(18) (a) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. Copper-Catalyzed Arylation of Amines Using Diphenyl Pyrrolidine-2-phosphonate as the New Ligand. *J. Org. Chem.* **2005**, *70*, 8107−8109. (b) Zhang, H.; Cai, Q.; Ma, D. Amino Acid Promoted CuI-Catalyzed C-N Bond Formation between Aryl Halides and Amines or N-Containing Heterocycles. *J. Org. Chem.* **2005**, *70*, 5164−5173.
(19) Probable path for ligand degradation and catalyst poisonings:




(20) (a) Andersen, J.; Madsen, U.; Björkling, F.; Liang, X. Rapid Synthesis of Aryl Azides from Aryl Halides under Mild Conditions. *Synlett* **2005**, *2005*, 2209−2213. (b) Jin, Z.; Xue, P.; Fu, E. Application of Hantzsch Dihydropyridine in Copper-Catalyzed [3 + 2] Cycloaddition of Terminal Alkynes with Azides. *Synth. Commun.* **2014**, *44*, 68−75.
(21) Knöpfel, T. F.; Carreira, E. M. The First Conjugate Addition Reaction of Terminal Alkynes Catalytic in Copper: Conjugate Addition of Alkynes in Water. *J. Am. Chem. Soc.* **2003**, *125*, 6054−6055.
(22) See Supporting Information for details.
(23) Bordwell, F. G. Equilibrium acidities in dimethyl sulfoxide solution. *Acc. Chem. Res.* **1988**, *21*, 456−463.
(24) (a) Minor, D. L.; Wyrick, S. D.; Charifson, P. S.; Watts, V. J.; Nichols, D. E.; Mailman, R. B. Synthesis and Molecular Modeling of 1-Phenyl-1,2,3,4-tetrahydroisoquinolines and Related 5,6,8,9-Tetrahydro-13bH-dibenzo[a, h]quinolizines as D1 Dopamine Antagonists. *J. Med. Chem.* **1994**, *37*, 4317−4328. (b) Bolchi, C.; Pallavicini, M.; Fumagalli, L.; Straniero, V.; Valoti, E. One-Pot Racemization Process of 1-Phenyl-1,2,3,4-tetrahydroisoquinoline: A Key Intermediate for the Antimuscarinic Agent Solifenacin. *Org. Process Res. Dev.* **2013**, *17*, 432−437. (c) Chen, K.-X.; Xie, H.-Y.; Li, Z.-G.; Gao, J.-R. Quantitative structure−activity relationship studies on 1-aryl-tetrahydroisoquinoline analogs as active anti-HIV agents. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5381−5386.
(25) (a) Royappa, A. T.; Royappa, A. D.; Moral, R. F.; Rheingold, A. L.; Papoular, R. J.; Blum, D. M.; Duong, T. Q.; Stepherson, J. R.; Vu, O. D.; Chen, B.; Suchomel, M. R.; Golen, J. A.; André, G.; Kourkoumelis, N.; Mercer, A. D.; Pekarek, A. M.; Kelly, D. C. Copper(I) oxalate complexes: Synthesis, structures and surprises. *Polyhedron* **2016**, *119*, 563−574. (b) Hsu, S. C. N.; Chang, Y.-L.; Chuang, W.-J.; Chen, H.-Y.; Lin, I. J.; Chiang, M. Y.; Kao, C.-L.; Chen, H.-Y. Copper(I) Nitro Complex with an Anionic [HB(3,5-Me2Pz)3]- Ligand: A Synthetic Model for the Copper Nitrite Reductase Active Site. *Inorg. Chem.* **2012**, *51*, 9297−9308. (c) Ahmad, K.; Khan, B. A.; Akram, B.; Khan, J.; Mahmood, R.; Roy, S. K. Theoretical investigations on copper catalyzed CN cross-coupling reaction between aryl chlorides and amines. *Comput. Theor. Chem.* **2018**, *1134*, 1−7.
(26) Giri, R.; Brusoe, A.; Troshin, K.; Wang, J. Y.; Font, M.; Hartwig, J. F. Mechanism of the Ullmann Biaryl Ether Synthesis Catalyzed by Complexes of Anionic Ligands: Evidence for the Reaction of Iodoarenes with Ligated Anionic CuI Intermediates. *J. Am. Chem. Soc.* **2018**, *140*, 793−806.


https://dx.doi.org/10.1021/acscatal.0c02965
*ACS Catal.* 2020, 10, 10495−10499