

Enantioselective Copper-Catalyzed Hydroamination of Vinylarenes with Anthranils

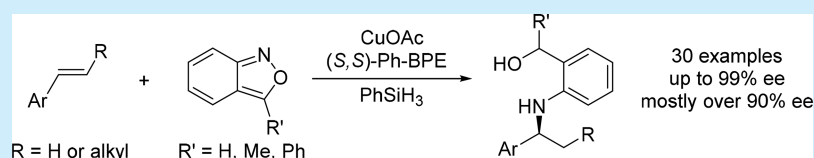
Fang Xie,^{†,§} Bingxue Shen,^{†,§,⊥} and Xingwei Li^{*,†,‡,⊥}

[†]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

[‡]School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China

[⊥]University of Chinese Academy of Sciences, Beijing 100049, China

S Supporting Information

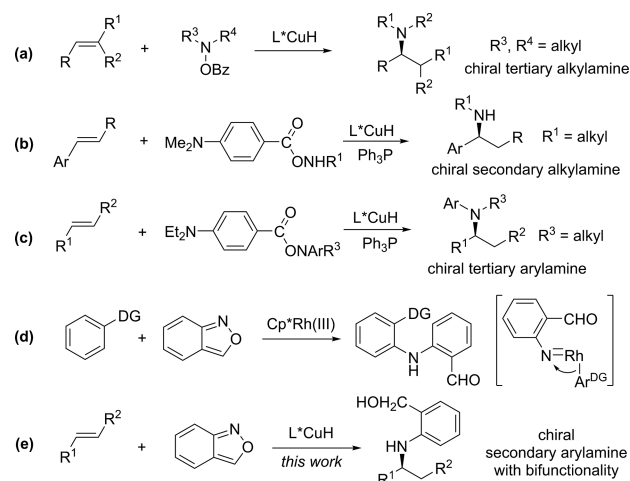


ABSTRACT: Copper hydride-catalyzed asymmetric hydroamination of olefins with anthranils has been realized in high efficiency and high enantioselectivity, affording enantioenriched secondary arylamines tethered to a benzylic alcohol. The bifunctionality of the product has been employed in diverse derivatization reactions.

Asymmetric catalytic synthesis of chiral amines is of considerable interest in both synthetic and medicinal chemistry since they are widely found in pharmaceuticals and bioactive products.¹ In 2013, Buchwald, Hirano, and Miura independently developed a general and highly efficient protocol of chiral amine synthesis by copper(I) hydride-catalyzed amination of olefins with an electrophilic aminating reagent.² The key step in these protocols involves the catalytic generation of an enantioenriched alkylcopper species via regioselective addition of a L^*CuH species across a $C=C$ bond. This alkylcopper species is then intercepted by an electrophilic aminating reagent such as dialkylaminobenzoate, leading to formal anti-Markovnikov hydroamination of the olefin (Scheme 1a). This system has been successfully

extended to alkynes³ and internal olefins.⁴ Other unsaturated substrates including vinylsilanes,⁵ boron-substituted alkenes,⁶ enals,⁷ and enones⁷ all proved applicable. However, the products are mostly limited to chiral tertiary alkyl amines due to the dominating applicability of dialkylamino benzoate reagents.^{2–7} Recently, Buchwald realized asymmetric synthesis of chiral secondary alkylamines and tertiary arylamines using meticulously designed amino benzoates with PPh_3 as a secondary ligand (Scheme 1b,c).^{8,9} However, a satisfactory protocol that utilizes related electrophilic aminating agents to deliver secondary arylamines still has not been realized, probably due to the challenge of the undesired direct reduction of the hydroxylamine ester by CuH . On the other hand, the atom economy of using hydroxylamine *O*-benzoates as aminating reagents is unsatisfactory. Therefore, the extension of this method to aminating reagents that allow the direct preparation of chiral secondary aryl amines would be of considerable interest.

Scheme 1. CuH -Catalyzed Hydroamination of Olefins and Metal-Catalyzed C–H Amination



We and others have recently demonstrated that anthranils are efficient nitrene-transfer reagents in Rh- and Co-catalyzed C–H activation of aryl and alkyl C–H bonds, leading to amination together with introduction of a proximal carbonyl group.¹⁰ In these systems, the key steps consist of formation of an electrophilic nitrene intermediate (owing to presence of a cleavable N–O bond) and subsequent interactions with a nucleophilic M–C bond (Scheme 1d). In addition, anthranils have also been applied as a nitrene source in other Au- and Cu-catalyzed transformations.¹¹ We reasoned that the M–C bond could be extended to a chiral alkyl copper reagent, which is generated via asymmetric hydrocuperation of an olefin. By this strategy, the CuH catalysis and the nitrene chemistry of

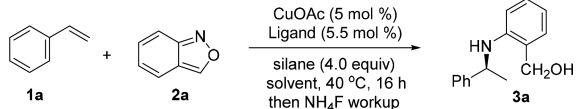
Received: September 27, 2018

Published: October 26, 2018

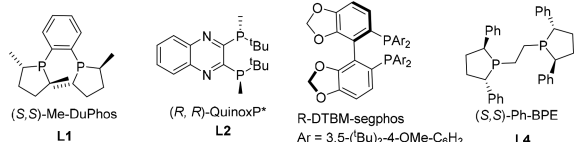
anthranils are integrated for asymmetric synthesis of chiral secondary aryl amines (Scheme 1e). The significance of this protocol could be elucidated as follows: (1) anthranils are efficiently used as new aryl amination reagents with 100% atom efficiency; (2) compared to *N*-aryl-*O*-acylhydroxylamines, anthranils are less susceptible to direct reaction with CuH and the decompositions like rearrangement reactions^{8,9} are not noticeable; thus, the efficiency and generality of the transformation is increased; (3) besides introduction of an amino group, the resulting skeleton contains an electrophilic formyl group which could be further reduced into an alcohol by L*CuH through a dual catalytic cycle, leading to eventual formation of a secondary aryl amine bearing a benzylic alcohol functionality. Such bifunctional products may act as key intermediates in chemical synthesis and as important precursors for medicines or other chiral nitrogen-containing bioactive compounds.

We initiated our investigation by examining the reactivity of styrene with anthranil (2a) using silane as a reductant. In conjunction of diphenylsilane, using ligands such as (*S,S*)-Me-DuPhos, (*R,R*)-QuinoxP*, and *R*-DTBM-segphos failed to yield the product in acceptable efficiency (Table 1, entries 1–

Table 1. Optimization of Reaction Conditions^a



entry	ligand	silane	solvent	yield ^b (%)	ee (%)
1	L1	Ph ₂ SiH ₂	CyH	trace	ND
2	L2	Ph ₂ SiH ₂	CyH	trace	ND
3	L3	Ph ₂ SiH ₂	CyH	trace	ND
4	L4	Ph ₂ SiH ₂	CyH	62	97
5 ^c	L4	Ph ₂ SiH ₂	CyH	35	97
6	L4	(MeO) ₂ MeSiH	CyH	13	88
7	L4	(EtO) ₃ SiH	CyH	trace	ND
8	L4	Et ₂ SiH ₂	CyH	trace	ND
9	L4	PhSiH ₃	CyH	66	97
10	L4	Ph ₂ SiH ₂	THF	33	89
11	L4	Ph ₂ SiH ₂	toluene	25	85
12	L4	Ph ₂ SiH ₂	dioxane	trace	ND
13 ^d	L4	PhSiH ₃	CyH	15	95
14 ^e	L4	PhSiH ₃	CyH	89	97



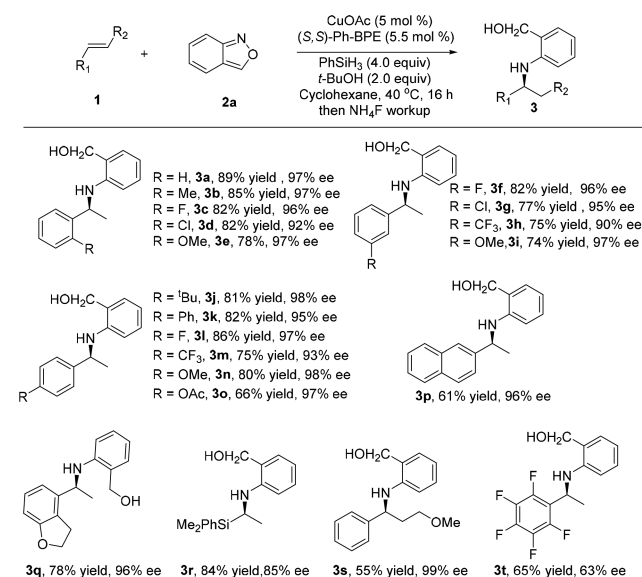
^aReaction conditions: 1a (0.2 mmol), 2a (0.3 mmol), CuOAc (5 mol %), Ligand (5.5 mol %), and silane (4.0 equiv) were stirred in a solvent (1.0 mL) under N₂ for 16 h. ^bIsolated yield after chromatography. ^cCu(OAc)₂ (5 mol %) was used. ^d25 °C. ^e*t*-BuOH (0.4 mmol) was added.

3). Alkyldiphosphine (*S,S*)-Ph-BPE (L4) proved to a promising ligand in terms of reactivity and stereoselectivity (entry 4). A series of silanes were then examined (entries 5–8), and PhSiH₃ afforded product 3a in better yield and high enantioselectivity. However, lowering the temperature or switching to other solvents all resulted in lower yields (entries 9–12). To our delight, when 2 equiv of *t*-BuOH was added,

the yield was raised to 89% without deterioration of the enantioselectivity (entry 13). The *t*-BuOH likely promotes the catalyst turnover by protonation of a Cu–O species (see Scheme 5).^{9,12} The absolute configuration of the amine product was determined to be (*S*) when (*S,S*)-Ph-BPE was used. Of note, no formyl-retentive hydroamination product was observed under any conditions screened, owing to the fact that the phosphine-ligated CuH species is a very active catalyst for the reduction of carbonyl.^{7,13}

With an optimized protocol in hand, we then explored the reaction scope with respect to the olefin substrates (Scheme 2). Introduction of a variety of alkyl, halo, aryl, CF₃, OMe, and

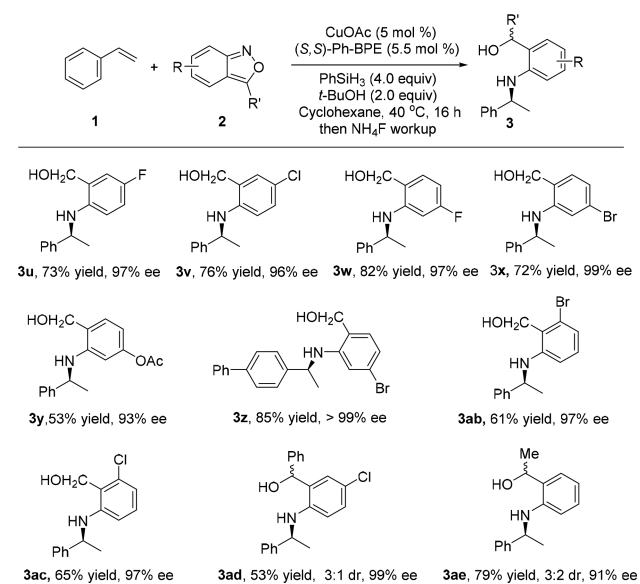
Scheme 2^a



^aReaction conditions: alkene (0.2 mmol), 2a (0.3 mmol), CuOAc catalyst (5 mol %), (*S,S*)-Ph-BPE (5.5 mol %), PhSiH₃ (0.8 mmol), *t*-BuOH (0.4 mmol) in cyclohexane (1.0 mL) under N₂ for 16 h; see the Supporting Information for details.

OAc groups to different positions of styrenes were fully tolerated, and the arylamine products were isolated in 61–89% yield and in consistently excellent enantioselectivities (3a–q). The reaction also worked smoothly for a vinylsilane to yield an α -aminosilane (3r) in 84% yield and 85% ee. Furthermore, styrene with β -methoxymethyl substitution was found to react with anthranil, giving 3s in good yield and excellent enantioselectivity. The olefin could be extended to C₆F₅CH=CH₂, affording product 3t in good yield and moderate ee. The diminished ee in 3r and 3t was not caused by postcoupling racemization, and it is related to the steric and electronic effects of the olefin substrates. This reaction failed for vinylpyridines under the standard conditions, likely due to strong coordination of the pyridine, thus inhibiting coordination of anthranils.

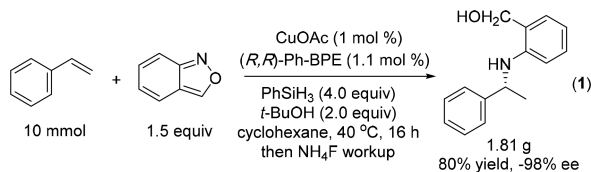
The scope of the anthranil coupling reagent was next explored (Scheme 3). Anthranils bearing halogen and OAc groups at different positions all reacted smoothly with styrene in good yields (53–85%) and excellent enantioselectivities (91–99% ee, 3u–ac). The amination reaction was also extended to 3-substituted anthranils, where the corresponding ketone is a putative intermediate. Subsequent hydrosilylation yielded the eventual alcohol products in good yield and high

Scheme 3^a

^aReaction conditions: alkene (0.2 mmol), anthranil (0.3 mmol), CuOAc (5 mol %), (S,S)-Ph-BPE (5.5 mol %), PhSiH₃ (0.8 mmol), *t*-BuOH (0.4 mmol) in cyclohexane (1.0 mL) under N₂ for 16 h.

enantioselectivities (3ad and 3ae) for the major product but with low diastereomeric ratio.

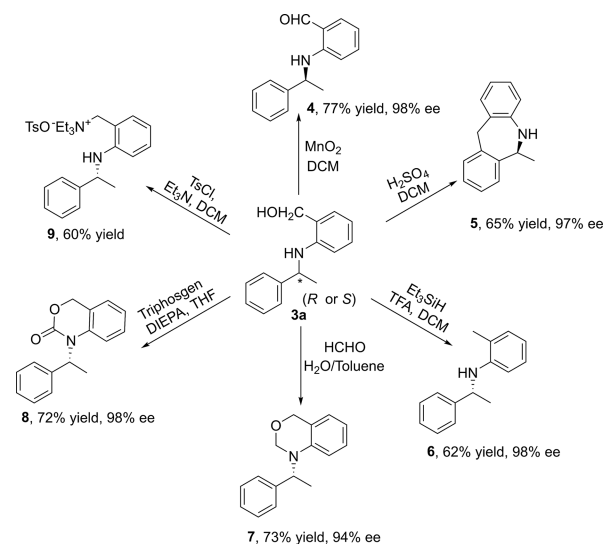
To demonstrate the scalability of this enantioselective protocol, a 10 mmol scale reaction of styrene and 2a was performed by simply using 1 mol % loading of CuOAc together with 1.1 mol % of (R,R)-Ph-BPE (eq 1). The reaction proceeded with full conversion to afford the (R)-3a isomer in 80% yield and -98% ee, which are comparable to those on a smaller scale reaction.



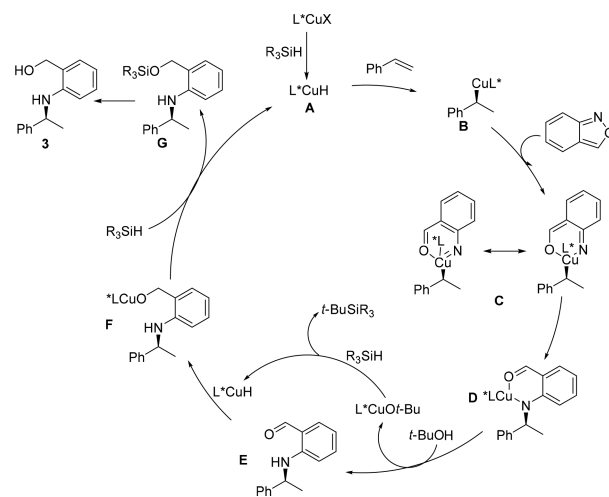
The synthetic utility of the coupled product was then demonstrated for preparation of diverse structures (Scheme 4). The benzyl alcohol was easily oxidized to the aldehyde 4 by MnO₂ (98% ee). Treatment of 3a with H₂SO₄ led to a Friedel–Crafts-type dehydrative cyclization to afford a seven-membered heterocycle 5 in 65% yield. Reduction of hydroxyl with Et₃SiH and TFA generated a known compound 6 (98% ee), which allowed assignment of the absolute configuration of 3a by measurement of its optical rotation. Derivatization of the product could also be achieved by taking advantage of the nucleophilicity of both the amino and hydroxyl groups. Thus, condensation of 3a with aqueous formaldehyde afforded a 1,4-dihydro-2*H*-benzo[*d*][1,3]oxazine 7 in 73% yield (94% ee). In another experiment, treatment of 3a with triphosgene afforded the heterocyclic carbamate 8 in 72% yield. Notably, in the presence of TsCl and triethylamine, the hydroxyl group was not tosylated but was instead converted to quaternary ammonium tosylate 9. In all cases, essentially no erosion of the enantiopurity was observed.

A plausible mechanism is proposed in Scheme 5 to account for this hydroamination system. Based on the previous

Scheme 4. Synthetic Applications of Aminated Product



Scheme 5. Plausible Catalytic Cycle



literature of related CuH-catalyzed hydrofunctionalization systems,¹⁴ an active L*CuH species A is generated from CuOAc bearing a chiral phosphine and a hydrosilane via σ -bond metathesis. Styrene then readily inserts into the Cu–H bond of A in a highly enantioselective and regioselective fashion to give the alkylcopper intermediate B. This intermediate undergoes oxidative insertion of the N–O bond of anthranil to afford C, which is essentially a copper nitrene species. Following migratory insertion of the alkyl group, intermediate D was generated. Protonolysis of D by *t*-BuOH provides the aldehyde intermediate E and the L*CuOt-*t*-Bu species. The latter would rapidly regenerate the active L*CuH by σ -bond metathesis with hydrosilane. The reformed L*CuH undergoes reduction of the aldehyde E to produce a silyl ether G, which is readily converted to the final product 3 upon hydrolysis.

In summary, we have developed a CuH-catalyzed hydroamination of alkenes using anthranil as a novel bifunctional aminating reagent with 100% atom economy. Diverse chiral arylamines functionalized with a benzylic alcohol were accessed in excellent enantioselectivity and regioselectivity. The reaction proceeded under mild conditions with good functional group tolerance. The chiral arylamino alcohols have

been demonstrated to be useful precursors for the synthesis of various chiral nitrogen containing compounds. Efforts toward expanding this methodology to a broader alkene scope and other aminating reagents are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03093.

Experimental details and chemical compound information (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xwli@dicp.ac.cn.

ORCID

Xingwei Li: 0000-0002-1153-1558

Author Contributions

§F.X. and B.S. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the NSFC (21525208 and 21472186) is gratefully acknowledged.

■ REFERENCES

- (1) (a) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420. (b) Huang, L.; Arndt, M.; Goossen, K.; Heydt, H.; Goossen, L. *Chem. Rev.* **2015**, *115*, 2596–2697. (c) *Stereoselective Formation of Amines. Topics in Current Chemistry*; Li, W., Zhang, X., Eds.; Springer: Berlin, 2014; Vol. 243. (d) *Chiral Amine Synthesis*; Nugent, T.C., Ed.; Wiley: Weinheim, 2010.
- (2) (a) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10830–10834. (b) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746–15749.
- (3) (a) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2013**, *42*, 1128–1130. (b) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015**, *7*, 38–44. (c) Tobisch, S. *Chem. Sci.* **2017**, *8*, 4410–4423.
- (4) (a) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62–66. (b) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *Nat. Chem.* **2016**, *8*, 144–150. (c) Miki, Y.; Hirano, k.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1498–1501. (d) Xi, Y.; Butcher, T. W.; Zhang, J.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 776–780.
- (5) (a) Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 1638–1641. (b) Kato, K.; Hirano, K.; Miura, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 14400–14404. (c) Takata, T.; Nishikawa, D.; Hirano, K.; Miura, M. *Chem. - Eur. J.* **2018**, *24*, 10975–10978. (d) Thomas, A. A.; Speck, K.; Kevlishvili, I.; Lu, Z.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, DOI: 10.1021/jacs.8b09565.
- (6) Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620–15623.
- (7) Shi, S.-L.; Wong, Z. L.; Buchwald, S. L. *Nature* **2016**, *532*, 353–356.
- (8) Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 9716–9721.
- (9) Ichikawa, S.; Zhu, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2018**, *57*, 8714–8718.
- (10) (a) Yu, S.; Tang, G.; Li, Y.; Zhou, X.; Lan, Y.; Li, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 8696–8700. (b) Zou, M.; Liu, J.; Tang, C.; Jiao, N. *Org. Lett.* **2016**, *18*, 3030–3033. (c) Tang, C.; Zou, M.; Liu, J.; Wen, X.; Sun, X.; Zhang, Y.; Jiao, N. *Chem. - Eur. J.* **2016**, *22*,

11165–11169. (d) Debbarma, S.; Sudan Maji, M. *Eur. J. Org. Chem.* **2017**, 3699–3706. (e) Kim, S.; Han, S. H.; Mishra, N. K.; Chun, R.; Jung, Y. H.; Kim, H. S.; Park, J. S.; Kim, I. S. *Org. Lett.* **2018**, *20*, 4010–4014. (f) Li, L.; Wang, H.; Yu, S.; Yang, X.; Li, X. *Org. Lett.* **2016**, *18*, 3662–3665.

(11) (a) Jin, H.; Huang, L.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 794–797. (b) Sahani, R. L.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2017**, *56*, 12736–12740. (c) Biswas, A.; Karmakar, U.; Nandi, S.; Samanta, R. *J. Org. Chem.* **2017**, *82*, 8933–8942. (d) Tiwari, D. K.; Phanindrudu, M.; Wakade, S. B.; Nanubolu, J. B.; Tiwari, D. K. *Chem. Commun.* **2017**, *53*, 5302–5305.

(12) For examples of *t*-BuOH-accelerated CuH-catalyzed reactions, see: Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153–2166. (b) Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789–2798. (c) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253–11258. (d) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352–8353. (e) Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5821–5823. (f) Rupnicki, L.; Lam, H. W.; Saxena, A. *J. Am. Chem. Soc.* **2009**, *131*, 10386–10387. (g) Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 4666–4669.

(13) (a) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927. (b) Bandar, J. S.; Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5821–5824.

(14) CuH-catalyzed aminations: (a) Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D. S.; Buchwald, S. L.; Liu, P. *J. Am. Chem. Soc.* **2017**, *139*, 16548–16555. (b) Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812–14818. (c) Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 15913–15916. (d) Yang, Y.; Perry, I. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 9787–9790. (e) Tobisch, S. *Chem. - Eur. J.* **2016**, *22*, 8290–8300 For CuH-catalyzed types of functionalizations, see: (f) Gui, Y.-Y.; Hu, N.; Chen, X.-W.; Liao, L.-L.; Ju, T.; Ye, J.-H.; Zhang, Z.; Li, J.; Yu, D.-G. *J. Am. Chem. Soc.* **2017**, *139*, 17011–17014. (g) Zhou, Y.; Engl, O. D.; Bandar, J. S.; Chant, E. D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2018**, *57*, 6672–6675. (h) Han, J. T.; Jang, W. J.; Kim, N.; Yun, J. *J. Am. Chem. Soc.* **2016**, *138*, 15146–15149. (i) Xu, G. X.; Zhao, H.; Fu, B.; Cang, A.; Zhang, G.; Zhang, Q.; Xiong, T.; Zhang, Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 13130–13134. (j) Yu, S.; Sang, H.; Ge, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 15896–15900. (k) Sommer, H.; Marek, I. *Chem. Sci.* **2018**, *9*, 6503–6508. (l) Huang, Y.; del Pozo, J.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2018**, *140*, 2643–2655. (m) Lee, J.; Radomkit, S.; Torker, S.; del Pozo, J.; Hoveyda, A. H. *Nat. Chem.* **2017**, *10*, 99–108.