Copper-Catalyzed Asymmetric Formal Hydroaminomethylation of Alkenes with N,O-Acetals to Access Chiral β-Stereogenic Amines: Dual Functions of the Copper Catalyst

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Chiral amines are synthetically versatile intermediates used for the preparation of a wide range of biologically active compounds and drugs. Compared with the well-developed synthesis of α-stereogenic amines, the establishment of enantioselective protocols to access β-stereogenic amines are very limited. Herein, we report an asymmetric synthesis of β-stereogenic amines through copper-catalyzed enantioselective formal aminomethylation of alkenes with N,O-acetals of formaldehyde. We carried out series of reactions using a variety of vinylarenes and 1,3-dienes with N,O-acetals of formaldehyde to generate the corresponding chiral β-branched alkylamines and (E)-homoallylamine in high yields, and with excellent enantioselectivity. The copper catalyst promoted not only the formation of alkylcopper nucleophiles from alkenes but also the generation of methylene imine electrophiles from N,O-acetals of formaldehyde. Our experimental design provides an attractive approach for the synthesis of chiral β-stereogenic amines from readily available alkenes and N,O-acetals with a base-metal catalyst under mild conditions.

Keywords: alkene, aminomethylation, asymmetric catalysis, N,O-acetal, amine, copper

Introduction

β-Stereogenic chiral amines are privileged structures found in a variety of bioactive and pharmaceutically relevant molecules and drugs (Figure 1). Among numerous methods used to prepare chiral amines, the majority has focused on the synthesis of α-stereogenic amines, while attempts to prepare chiral β-stereogenic amines are rather limited. Asymmetric hydroamination of 1,1-disubstituted alkenes is an atom-economic approach to synthesize β-stereogenic amines, but the enantioselectivity of this reaction largely depends on the steric difference between two substituents on alkenes. Catalytic hydroformylation of alkenes with H₂/CO, followed by enantioselective reductive amination of aldehydes with amines, also yields β-stereogenic amines. However, this sequential reaction requires toxic CO gas and noble metal catalysts. Therefore, developing a practical enantioselective protocol, which could combine high enantioselectivity, base-metal catalysts, and easily
accessible starting materials to prepare chiral \(\beta\)-stereogenic amines remains a challenge.

Recently, chiral Cu–H complexes have been emerging as catalysts to convert alkenes to chiral amines via C–N or C–C bond-forming reactions.\(^{20-36}\) For example, chiral alkylcopper species, formed from alkenes, could react with ketimines and aldimines, derived from ketones or aryl-substituted aldehydes to yield chiral amines containing \(\alpha,\beta\)-stereogenic carbons.\(^{37-39}\) Due to their high reactivity toward polymerization and oligomerization, methylene imines have not been isolated in pure forms. Therefore, the reactions of chiral organometallic nucleophiles with formaldehyde imines, which could afford synthetically versatile chiral \(\beta\)-stereogenic amines, have not been studied. Very recently, Yu reported a Cu-catalyzed synthesis of \(\beta\)-stereogenic primary alcohols from alkenes\(^{40}\) and utilization of CO\(_2\) as a C\(_1\) building block as a key measure in achieving this transformation. In view of the synthetic importance of \(\beta\)-stereogenic amines, we took an interest to develop an enantioselective protocol for the synthesis of these \(\beta\)-stereogenic amines from alkenes. To study this asymmetric reaction, we rationalized that identifying a suitable N-containing C\(_1\) building block would be a critical step.

N,O-Acetals of formaldehyde are readily accessible via the reactions between paraformaldehyde and carbamates in the presence of acetic anhydride and acetic acid.\(^{41}\) Recently, Luo and co-workers\(^{42}\) used these N,O-acetals as C\(_1\) imine surrogates in Mannich reaction to prepare chiral \(\beta\)-amino carbonyl compounds. However, their applications as methylene imine surrogates in transition-metal-catalyzed C–C bond-forming reactions remain largely unexplored. During our efforts, in search to develop Cu-catalyzed hydrofunctionalization of olefins,\(^{43-45}\) we found that copper catalysts could promote the conversion of these N,O-acetals to carbamate methylene imines. Herein, we report the reactions between these in-situ-generated carbamate methylene imines and chiral alkylcopper species derived from vinylarenes and 1,3-dienes, which supported a practical and novel highly enantioselective approach to access synthetically versatile chiral \(\beta\)-stereogenic amines from readily available olefinic substrates.

**Experimental Method**

In an argon (Ar)-filled dry box, cupric acetate \([\text{Cu(OAc)}_2]\) (1.8 mg, 10.0 \(\mu\)mol), (+)-1,2-Bis((2S,5S)-2,5-diphenylphospholano)ethane [(S,S)-Ph-BPE] (6.1 mg, 12.0 \(\mu\)mol), vinylarene (0.200 mmol), N,O-acetal (0.400 mmol), CH\(_3\)CN (0.2 mL), and \(^1\)BuOH (29.6 mg, 0.400 mmol) were added to a 4 mL screw-capped vial and stirred with a magnetic stirring bar for 10 min, followed by addition of dimethoxymethyl silane [(MeO)\(_2\)MeSiH] (106 mg, 1.00 mmol). Then, the vial was sealed with a cap containing a polytetrafluoroethylene (PTFE) septum and removed from the dry box, after which the reaction mixture was stirred at room temperature (RT) for 12 h, and the resultant solution was concentrated in vacuum. Subsequently, the crude product was purified by column chromatography on silica gel with a mixture of ethyl acetate (EtOAc) and hexane (1:9) as eluent. The enantiopurity of the purified products was analyzed by chiral high-performance liquid chromatography (HPLC). See the Supporting Information for more detailed experimental procedures and the characterization data of all the products.

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**Figure 1** | Examples of drugs and biologically active compounds containing a \(\beta\)-stereogenic amine moiety.
Results and Discussion

We initiated our studies by identifying selective copper catalysts and optimal conditions for the reaction between 4-chlorostyrene (1a) and methyl 2-(acetyl-amino)benzoate (AcOCH₂NHCbz), which is an N,O-acetal derived from formaldehyde. Copper catalysts, generated in situ by the combination of Cu(OAc)₂ and various bisphosphine ligands were employed in the reaction to test their effectiveness. The results from selected experiments are summarized in Scheme 1. In general, these reactions were conducted in acetonitrile (CH₃CN) at RT with 1a as a limiting reagent, (MeO)₂MeSiH was used as a hydride source and tert-butanol [(CH₃)₃C-OH] as a proton source in the presence of 5 mol % copper catalyst. We identified β-stereogenic amine 2a as the major product for these reactions, by our established optimal reaction conditions indicated below:

Reaction conditions: 1a (0.100 mmol), AcOCH₂NHCbz (0.150 mmol), (MeO)₂MeSiH (0.500 mmol), Cu(OAc)₂ (5.0 μmol), bisphosphine ligand (6.0 μmol), solvent (0.2 mL), RT, 12 h; aIsolated yields; b ee was determined by chiral HPLC analysis; c 1a (0.200 mmol) and AcOCH₂NHCbz (0.100 mmol) were employed; d AcOCH₂NHCbz (0.200 mmol); (MeO)₂MeSiH was added after all other reagents were stirred in acetonitrile (CH₃CN) at RT for 10 min.

Our results showed that (1) the copper catalysts generated from Cu(OAc)₂ and (R₉)-synphos, and (R₉)-DM-segphos were marginally active for this reaction (entries 1 and 2, Scheme 1). (2) The reactions catalyzed by the combination of Cu(OAc)₂ and (R₈)-DTBM-segphos or (R₉,R₉)-QuinoxP* occurred at low conversions of 1a, and the desired product 2a was obtained in low yields with modest enantioselectivity (entries 3 and 4 in Scheme 1). (3) To our delight, the reaction conducted with 5 mol % of Cu(OAc)₂ and 6 mol % (S,S)-Ph-BPE proceeded with high conversion of 1a, affording amine 2a in modest isolated yield, but with excellent enantioselectivity (97% ee, entry 5, Scheme 1).

Subsequently, we tested this catalytic reaction in various solvents, such as cyclohexane, toluene, and tetrahydrofuran (THF). Nonetheless, these reactions proceeded with low conversions of 1a, with very low isolated yields (<5% to 21%) of 2a (entries 6–8, Scheme 1). In addition, when we performed the reaction with AcOCH₂NHCbz, as a limiting reagent, we found that the process occurred with a higher yield (72%), but with a slightly diminished enantioselectivity (92% ee; entry 9, Scheme 1). Thus to further improve the reaction conditions, we conducted the experiment by stirring Cu(OAc)₂, the ligand, 1a, N,O-acetel, and 'BuOH for 10 min to allow ligand coordination, prior to the addition of (MeO)₂MeSiH. This reaction proceeded with a full conversion of 1a to 2a, obtaining...
a 79% yield with excellent enantioselectivity (97%; entry 10, Scheme 1).

With the identified copper catalyst and optimal conditions in hand, we studied the scope of vinylarenes that undergo this Cu-catalyzed asymmetric transformation. The results of these reactions are summarized in Scheme 2. In general, we observed that a wide range of vinylarenes containing various substituted phenyl groups (1c–l) or polyaromatic groups (1m–p) reacted with AcOCH$_2$NHCbz readily in the presence of 5 mol % Cu(OAc)$_2$ and 6 mol % (S,S)-Ph-BPE at RT, yielding the corresponding enantioenriched-$eta$-stereogenic amines (2a–2p) in moderate to high yields (55–97%) with high enantioselectivities (92% to >99% ee). Noticeably, vinylarenes containing ortho-substituted aryl groups (1g and 1h) reacted to give amine products 2g and 2h in relatively lower yields (41–43%), but with high enantioselectivity (93–99% ee). These low yields occurred, possibly due to the incomplete conversions of vinylarenes 1g and 1h as we were able to recover the unreacted substrates. Besides, Boc- and Fmoc-protected N,O-acetals reacted with 1p under our standard conditions, affording the desired amines 2p' and 2p'' in high yields (95% and 83%) with excellent enantioselectivity (99% and 98%), respectively (Scheme 2).

(1) Reaction conditions with lower N,O-acetal derivative but higher tBuOH concentrations: Vinylarene (0.200 mmol), AcOCH$_2$NHR (0.400 mmol), (MeO)$_2$MeSiH (1.00 mmol), tBuOH (0.400 mmol), Cu(OAc)$_2$ (10.0 μmol), (S,S)-Ph-BPE (12.0 μmol), CH$_3$CN (0.2 mL),

Scheme 2 | Scope of vinylarenes for the Cu-catalyzed formal aminomethylation.
RT, 12 h, yields of isolated products; ee was determined by chiral HPLC analysis. \(^6\) The absolute configuration of 2b was assigned as \((S)\), see the Supporting Information for the details.

(2) Reaction conditions with higher N,O-acetal derivative but lower \(^{3}BuOH\) concentrations: Vinylarene (0.200 mmol), AcOCH\(_2\)NHR (0.400 mmol), (MeO)\(_2\)MeSiH (1.60 mmol), \(^{3}BuOH\) (0.200 mmol), Cu(OAc)\(_2\) (10.0 \(\mu\)mol), (S,S)-Ph-BPE (12.0 \(\mu\)mol), CH\(_3\)CN (0.2 mL), RT, 12 h, yields of isolated products; ee was determined by chiral HPLC analysis.

Subsequently, we tested 1,3-dienes for this Cu-catalyzed asymmetric reaction. Different from vinylarenes, the presence of two double bonds in 1,3-dienes poses additional challenges to the study of formal hydroaminomethylation of 1,3-dienes, such as the control over 1,2-/1,4-regioselectivity and \(Z\)/\(E\)-stereochemistry of the remaining double bond. After modifying reaction conditions (entry 10 in Scheme 1) with 8-gram, instead of 5-gram equivalent of (MeO)\(_2\)MeSiH, we found that aryl-substituted 1,3-dienes reacted with N,O-acetals to yield chiral homoallylic amines with excellent 1,4-regioselectivity, \(E\)-selectivity, and enantioselectivity. Scheme 3 summarizes the scope of 1,3-dienes that undergo this Cu-catalyzed formal hydroaminomethylation reaction. Typically, a variety of 1,3-dienes containing electronically varied aryl groups reacted to afford the corresponding \((E\)-homoallylic amines (4a–4m) in high isolated yields with high enantioselectivity (95% to >99% ee). Our standardized reaction tolerated various aryl groups with substituents at para (4b–4g), meta (4h), and ortho (4i and 4j) positions, as well as oxygen- and sulfur-containing heteroaryl groups (4k–4m). The absolute configuration of 4b‘ was assigned as \((R)\) by comparison of optical rotation with a reported value.\(^{46}\)

The formal hydroaminomethylation reactions of vinylarene 1p and 1,3-diene 3a with AcOCH\(_2\)NHCbz were run on a gram scale with 1–2 mol % of Cu(OAc)\(_2\)/(S,S)-Ph-BPE, which occurred in good yields with excellent enantioselectivity (Scheme 4a,b). Thus these reactions could also be conducted on a scale that allows practical applications in synthesis. We also showed that the Cbz, Boc, and Fmoc groups in 2a, 2p’, and 2p” could be readily removed under neutral, acidic, and basic conditions.\(^{47-53}\)

Scheme 3 | Scope of 1,3-dienes for the Cu-catalyzed formal aminomethylation.

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respectively, yielding \( \beta \)-stereogenic primary amines 5 and 6 in high yields (87% and 92%), while maintaining excellent enantiopurity (95% and 98% ee), respectively (Scheme 4c).

Further, we conducted several experiments to elucidate the mechanism of this Cu-catalyzed reaction (Scheme 5). First, we showed that the N-Cbz methylene imine 6 was generated from AcOCH₂NHCbz in the presence of the copper catalyst, as indicated by gas chromatography–mass spectrometry (GC-MS) and high-resolution mass spectrometry (HRMS) analysis (Scheme 5a). Second, we demonstrated that in contrast to copper catalyst reaction, the corresponding reaction in the absence of the copper catalyst failed to yield the imine 6. Indeed, our results are consistent with previous studies which showed that N,O-acetals of formaldehyde could form imines in the presence of Lewis acids.³¹ Third, our study revealed that formal hydroaminomethylation of vinylarene 1p in the presence of biphenylhydrosilane (Ph₂SiD₂), instead of (MeO)₂MeSiH yielded the chiral amine 2p-d₁ in 51% yield with 98% ee, and the deuterium label localized in the methyl group of 2p (Scheme 5b). Similarly, deuterium incorporation was observed for 4a-d₁ when the reaction of 1,3-diene 3a was run with Ph₂SiD₂ (Scheme 5c).

Based on the results of the aforementioned experiments on imine detection, deuterium labeling, and previous studies on Cu–H-catalyzed reactions of alkenes,²³ we proposed a plausible catalytic cycle for this Cu-catalyzed hydroaminomethylation of alkenes (Scheme 5d), as follows: Activation of Cu(OAc)₂ with hydrosilane in the presence of (S,S)-Ph-BPE (L*) generates a chiral Cu–H species, (L*)Cu–H. Insertion of alkenes into (L*)Cu–H, in turn, formed chiral alkylcopper species A.⁵⁴ Intermediate A reacted with the N-Cbz imine 6, generated in situ from N,O-acetal, in the presence of a copper catalyst, to produce an amido-copper complex B. Consequently, B was protonated by 'BuOH to yield the chiral \( \beta \)-stereogenic amine product 2 and copper tert-butoxide (L*)CuO'Bu, which was reacted with hydrosilane to regenerate the catalytically active Cu–H species, (L*)Cu–H.

**Scheme 4** | Gram-scale reactions and deprotection of carbamates to access \( \beta \)-stereogenic primary amines.
Conclusion

We have developed an effective and highly enantioselective protocol for the synthesis of chiral β-stereogenic amines through Cu-catalyzed asymmetric formal hydroaminomethylation of alkenes with N,O-acetals. A wide range of vinylarenes and 1,3-dienes reacted with N,O-acetals of formaldehyde to afford the corresponding alkyamines and homoallylic amines in high yields with excellent enantioselectivity in the presence of a chiral copper catalyst generated in situ from Cu(OAc)₂ and (S,S)-Ph-BPE ligand. Mechanistic studies revealed dual functions of the copper catalyst, involving the formations of both the chiral alkycopper nucleophile from alkenes and the N-Cbz imine electrophile from N,O-acetals of formaldehyde. Further studies to determine the detailed mechanism of this transformation and to expand the scope of this aminoalkylation reaction is the focus of future work in our laboratory.

Supporting Information

Supplemental Information is available online.

Conflict of Interest

There is no conflict of interest to report.

Acknowledgment

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References

1. Davies, H. M. L.; Ni, A. Enantioselective Synthesis of β-Amino Esters and its Application to the Synthesis of the Enantiomers of the Antidepressant Venlafaxine. Chem. Commun. 2006, 3110–3112.
2. Harris, R. N.; Stabler, R. S.; Repke, D. B.; Kress, J. M.; Walker, K. A.; Martin, R. S.; Brothers, J. M.; Ilnicka, M.; Lee, S. W.; Mirzadegan, T. CHIPS Tends to the Phosphorylated N-Terminus of the C5a-Receptor. Bioorg. Med. Chem. Lett. 2010, 20, 3436–3440.

3. Huang, K.-C.; Gopula, B.; Kuo, T.-S.; Chiang, C.-W.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to β-Nitroolefins: Formal Synthesis of (S)-SKF 38393. Org. Lett. 2013, 15, 5730–5733.

4. Yeung, C.-T.; Chan, W. T. K.; Yan, S.-C.; Yu, K.-L.; Yim, K.-H.; Wong, W.-T.; Law, G.-L. Lanthanide Supramolecular Helical Diastereoselective Breaking Induced by Point Chirality: Mixture or P-Helix, M-Helix. Chem. Commun. 2015, 51, 592–595.

5. Wang, Z.; Bian, H.; Bartual, S. G.; Du, W.; Luo, J.; Zhao, H.; Zhang, S.; Mo, C.; Zhou, Y.; Xu, Y.; Tu, Z.; Ren, X.; Lu, X.; Brekken, R. A.; Yao, L.; Bullock, A. N.; Su, J.; Ding, K. Structure-Based Design of Tetrahydro-β-carboline-7-carboxamides as Selective Discoidin Domain Receptor 1 (DDR1) Inhibitors. J. Med. Chem. 2016, 59, 5911–5916.

6. Han, C.; Han, C.; Savage, S.; Al-Sayyah, M.; Yajima, H.; Remarchuk, T.; Reents, R.; Wirtz, B.; Iding, H.; Bachmann, S.; Fantasia, S. M.; Scalone, M.; Hell, A.; Hidber, P.; Gosselin, F. Asymmetric Synthesis of Akt Kinase Inhibitor Ipasertib. Org. Lett. 2017, 19, 4806–4809.

7. Ramesh, P.; Reddy, K. S. N. Asymmetric Synthetic Strategies of (R)-(−)-Baclofen: An Antispastic Drug. Synthetic 2018, 50, 211–226.

8. Smilovic, I. G.; Cluzeau, J.; Richter, F.; Nerdinger, S.; Schreiner, E.; Laus, G.; Schottenberger, H. Synthesis of Enantiopure Antibiotics by Copper-Catalyzed Hydroamination of Vinylsilanes. Bioorg. Med. Chem. 2016, 26, 2686–2690.

9. Nugent, T. C.; El-Shazly, M. Chiral Amine Synthesis—Recent Developments and Trends for Enamide Reduction, Reductive Amination, and Imine Reduction. Adv. Synth. Catal. 2010, 352, 753–819.

10. Nugent, T. C. Chiral Amine Synthesis; Wiley-VCH: Weinheim, 2010.

11. Patil, M. D.; Grogan, G.; Bommarius, A.; Yun, H. Oxidoreductase-Catalyzed Synthesis of Chiral Amines. ACS Catal. 2018, 8, 10985–11015.

12. Wang, C.-J.; Sun, X.; Zhang, X. Enantioselective Hydrogenation of Allylphthalimides: An Efficient Method for the Synthesis of β-Methyl Chiral Amines. Angew. Chem. Int. Ed. 2005, 44, 4933–4935.

13. Hoffmann, S.; Nicoletti, M.; List, B. Catalytic Asymmetric Reductive Amination of Aldehydes via Dynamic Kinetic Resolution. J. Am. Chem. Soc. 2006, 128, 13074–13075.

14. Otsuka, M.; Yokoyama, H.; Endo, K.; Shibata, T. Ru-Catalyzed β-Selective and Enantioselective Addition of Amines to Styrenes Initiated by Direct Arené-Exchange. Org. Biomol. Chem. 2012, 10, 3815–3818.

15. Reznichenko, A. L.; Hultsch, K. C. The Mechanism of Hydroaminoalkylation Catalyzed by Group 5 Metal Binaphtholate Complexes. J. Am. Chem. Soc. 2012, 134, 3300–3301.

16. Fuchs, C. S.; Hollauf, M.; Meissner, M.; Simon, R. C.; Besset, T.; Reek, J. N. H.; Riehwer, T.; Zepeck, F.; Kroutil, W. Dynamic Kinetic Resolution of 2-Phenylpropanal Derivatives to Yield β-Chiral Primary Amines via Bioamination. Adv. Synth. Catal. 2014, 356, 2257–2265.

17. Zhu, S.; Buchwald, S. L. Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes. J. Am. Chem. Soc. 2014, 136, 15913–15916.

18. Meng, J.; Li, X.-H.; Han, Z.-Y. Enantioselective Hydroamination of Olefins Enabled by Rh/Brensted Acid Relay Catalysis. Org. Lett. 2017, 19, 1076–1079.

19. Zhang, J.; Liu, C.; Wang, X.; Chen, J.; Zhang, Z.; Zhang, W. Rhodium-Catalyzed Asymmetric Hydrogenation of β-Branched Enamides for the Synthesis of β-Stereogenic Amines. Chem. Commun. 2018, 54, 6024–6027.

20. Shibasaki, M.; Kanai, M. Asymmetric Synthesis of Tertiary Alcohols and α-Tertiary Amines via Cu-Catalyzed C–C Bond Formation to Ketones and Ketimines. Chem. Rev. 2008, 108, 2853–2873.

21. Deutsch, C.; Krause, N.; Lipshutz, B. H. Cu-Catalyzed Reactions. Chem. Rev. 2008, 108, 2916–2927.

22. Sorádová, Z.; Šebesta, R. Enantioselective Cu-Catalyzed Functionalizations of Unactivated Alkenes. ChemCatChem 2016, 8, 2581–2588.

23. Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. Copper Hydride-Catalyzed Hydroamination of Alkenes and Alkynes. Angew. Chem. Int. Ed. 2016, 55, 48–57.

24. Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. Copper-Catalyzed Intermolecular Regioselective Hydroamination of Styrenes with Polymethylhydrosiloxane and Hydroxylamines. Angew. Chem. Int. Ed. 2013, 52, 10830–10834.

25. Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. Copper-Catalyzed Enantioselective Formal Hydroamination of Oxa- and Azabicyclic Alkenes with Hydroxilanes and Hydroxylamines. Org. Lett. 2014, 16, 1498–1501.

26. Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. Catalytic Asymmetric Hydroamination of Unactivated Internal Olefins to Aliphatic Amines. Science 2015, 349, 62–66.

27. Asci, E.; Buchwald, S. L. Highly Diastereo- and Enantioselective CuH-Catalyzed Synthesis of 2,3-Disubstituted Indolines. J. Am. Chem. Soc. 2015, 137, 4666–4669.

28. Nishikawa, D.; Hirano, K.; Miura, M. Asymmetric Synthesis of α-Aminoboronic Acid Derivatives by Copper-Catalyzed Enantioselective Hydroamination. J. Am. Chem. Soc. 2015, 137, 15620–15623.

29. Niljanskul, N.; Zhu, S.; Buchwald, S. L. Enantioselective Synthesis of α-Aminosilanes by Copper-Catalyzed Hydroamination of Vinylsilanes. Angew. Chem. Int. Ed. 2015, 54, 1638–1641.

30. Xi, Y.; Butcher, T. W.; Zhang, J.; Hartwig, J. F. Regioselective, Asymmetric Formal Hydroamination of Unactivated Internal Alkenes. Angew. Chem. Int. Ed. 2016, 55, 776–780.

31. Han, J. T.; Jung, W. J.; Kim, N.; Yun, J. Asymmetric Synthesis of Borylalkanes via Copper-Catalyzed Enantioselective Hydroallylation. J. Am. Chem. Soc. 2016, 138, 15146–15149.

32. Wang, H.; Yang, J. C.; Buchwald, S. L. CuH-Catalyzed Regioselective Intramolecular Hydroamination for the Synthesis of Alkyl-Substituted Chiral Aziridines. J. Am. Chem. Soc. 2017, 139, 8428–8431.
33. Ichikawa, S.; Zhu, S.; Buchwald, S. L. A Modified System for the Synthesis of Enantioenriched N-Arylamines Through Copper-Catalyzed Hydroamination. Angew. Chem. Int. Ed. 2018, 57, 8714–8718.

34. Xu-Xu, Q.-F.; Liu, Q.-Q.; Zhang, X.; You, S.-L. Copper-Catalyzed Ring Opening of Benzofurans and an Enantioselective Hydroamination Cascade. Angew. Chem. Int. Ed. 2018, 57, 15204–15208.

35. Xie, F.; Shen, B.; Li, X. Enantioselective Copper-Catalyzed Hydroamination of Vinylarenes with Anthranils. Angew. Chem. Int. Ed. 2017, 56, 15896–15900.

36. Yu, S.; Sang, H. L.; Ge, S. Copper-Catalyzed Asymmetric Hydroboration of 1,3-Enynes with Pinacolborane to Access Chiral Allenylboronates. Org. Chem. Front. 2018, 5, 1284–1287.

37. Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. Asymmetric Reductive Mannich Reaction to Ketimines Catalyzed by a Cu(I) Complex. J. Am. Chem. Soc. 2016, 138, 8718.

38. Yang, Y.; Perry, I. B.; Buchwald, S. L. Copper-Catalyzed Enantioselective Addition of Styrene-Derived Nucleophiles to Imines Enabled by Ligand-Controlled Chemoselective Hydrocupration. J. Am. Chem. Soc. 2016, 138, 9787–9790.

39. Liu, R. Y.; Yang, Y.; Buchwald, S. L. Regiodivergent and Diastereoselective Cu(i)-Catalyzed Allylation of Imines with Terminal Allenes. Angew. Chem. Int. Ed. 2016, 55, 14077–14080.

40. Gui, Y.-Y.; Hu, N.; Chen, X.-W.; Liao, L. L.; Ju, T.; Ye, J.-H.; Zhang, Z.; Li, J.; Yu, D.-G. Highly Regio- and Enantioselective Copper-Catalyzed Reductive Hydroxymethylation of Styrenes and 1,3-Dienes with CO2. J. Am. Chem. Soc. 2017, 139, 17011–17014.

41. Hartman, A. E.; Brophy, C. L.; Cupp, J. A.; Hodge, D. K.; Peelen, T. J. Addition of Carbon-Based Nucleophiles to Fmoc-Protected Acyl Iminium Ions. J. Org. Chem. 2009, 74, 3952–3954.

42. You, Y. E.; Zhang, L.; Cui, L.; Mi, X.; Luo, S. Catalytic Asymmetric Mannich Reaction with N-Carbamoyl Imine Surrogates of Formaldehyde and Fluroxylate. Angew. Chem. Int. Ed. 2017, 56, 13814–13818.

43. Yu, S.; Sang, H. L.; Ge, S. Enantioselective Copper-Catalyzed Alkylation of Quinoline N-Oxides with Vinylarenes. Angew. Chem. Int. Ed. 2017, 56, 15896–15900.