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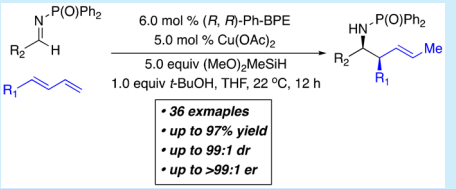
Cu-Catalyzed Enantioselective Reductive Coupling of 1,3-Dienes and Aldimines

Mingfeng Li, Jiping Wang, and Fanke Meng*

State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: Catalytic chemo- and enantioselective generation of 1,3-disubstituted allyl−Cu complexes from a Cu−H addition to 1,3-dienes followed by in situ reactions with aldimines to construct homoallylic amines is presented. The method is distinguished by an unprecedented pathway to generate enantiomerically enriched allyl−Cu species, allowing reactions with a wide range of aldimines in high chemo-, site-, diastereo-, and enantioselectivity. Functionalization provides useful building blocks that are otherwise difficult to access.



Homoallylic amines exist in structures of many biologically active molecules and serve as precursors for the preparation of a range of N-containing molecules.[1,2] Consequently, general methods for the synthesis of homoallylic amines in enantiomerically pure form have been considered to be an important goal in organic synthesis. Although approaches for catalytic enantioselective allylation of aldimines have significantly advanced,[3] the need to utilize stoichiometric quantities of an organometallic reagent is a limitation of these processes, and one or multiple additional synthetic operations are required to synthesize an organometallic reagent. In addition, the variety of allyl groups that can be introduced is limited due to the restriction of the available methods to prepare allyl reagents. In particular, synthesis of an enantioenriched allyl reagent and its utility in metal-catalyzed allylation of imines is rare. Therefore, catalytic generation of allyl nucleophiles from easily accessible alkenes and their in situ use for addition to imines could obviate these drawbacks. The utility of carbon-based nucleophiles formed from alkenes for addition to carbonyls promoted by noble metal catalysts (Rh, Ru, and Ir) has been pioneered by Krische.[4] While these processes have been successful for enantioselective addition to aldehydes,[5] only a few examples of enantioselective addition to imines have been reported.[6] Alternatively, the development of protocols using catalysts derived from earth-abundant metals attracts much attention. In particular, Cu-catalyzed enantioselective coupling of alkenes and imines represents an important method for the preparation of enantioenriched amines (Scheme 1a−c).[7] Although there are a few protocols on Cu-catalyzed enantioselective borylative allylation of imines using allenes or 1,3-dienes,[8] the generation of enantioenriched secondary allyl−Cu complexes from Cu−H addition to 1,3-dienes and their in situ use in imine addition remains undisclosed.[9−11]

Such a process allows the introduction of functionalized allyl groups that are otherwise difficult to access. The challenges include the following: (1) the catalyst has to control the chemoselectivity, as competitive Cu−H reduction of the aldimines can proceed rapidly; (2) the regioselectivity of Cu−H addition to 1,3-dienes (4,3-addition vs 4,1-addition) and the following addition to imines (which to participate in the addition, **I** or **II**) has to be well regulated by the catalyst; (3) the enantioselectivity of generation of the secondary allyl−Cu complex and subsequent addition to imines has to be controlled by the single catalyst; (4) the catalyst has to promote the imine addition rapidly enough to avoid possible racemerization (Scheme 1d).[12] Herein, we outline an

Scheme 1. Cu-Catalyzed Enantioselective Reductive Coupling of Alkene and Imine

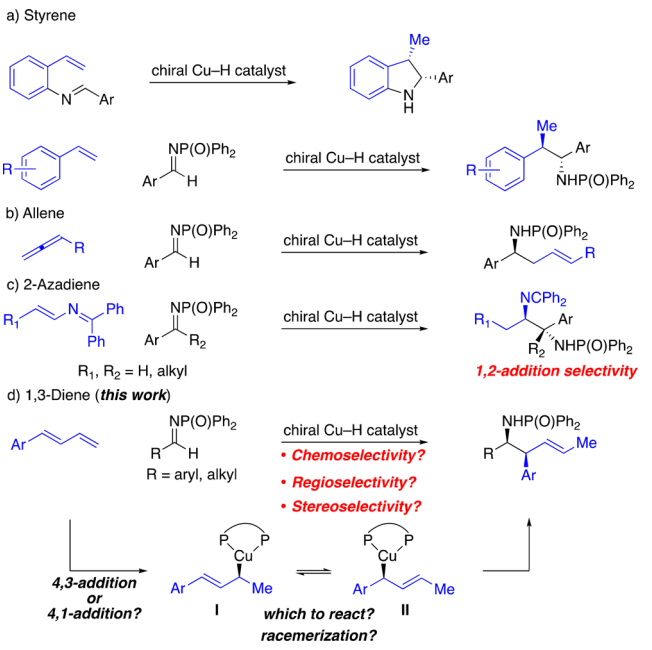


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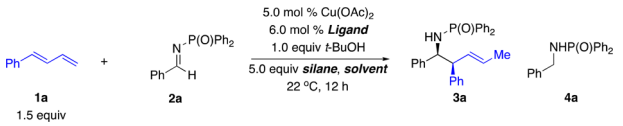
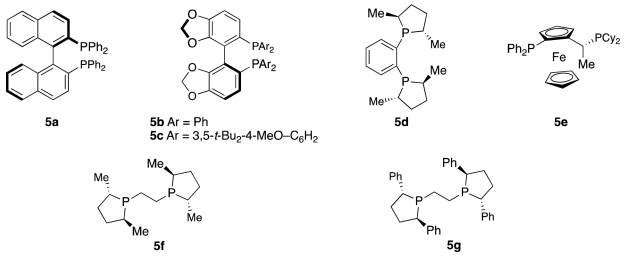
Table 1. Optimization of Conditions[a]



entry	ligand	solvent	silane	yield of **3a** (%)[a]	**3a**/**4a**[b]	dr[b]	er[c]
1	**5a**	THF	$(MeO)_2MeSiH$	<2	<2:98	NA	NA
2	**5b**	THF	$(MeO)_2MeSiH$	<2	<2:98	NA	NA
3	**5c**	THF	$(MeO)_2MeSiH$	30	32:68	>98:2	99:1
4	**5d**	THF	$(MeO)_2MeSiH$	40	60:40	79:21	87:13
5	**5e**	THF	$(MeO)_2MeSiH$	24	33:67	66:33	89:11
6	**5f**	THF	$(MeO)_2MeSiH$	<2	<2:98	NA[e]	NA[e]
7	**5g**	THF	$(MeO)_2MeSiH$	71	74:26	88:12	99:1
8	**5g**	CH_3CN	$(MeO)_2MeSiH$	<2	<2:98	NA[e]	NA[e]
9	**5g**	CH_2Cl_2	$(MeO)_2MeSiH$	34	38:62	82:18	99:1
10	**5g**	CyH	$(MeO)_2MeSiH$	47	47:53	80:20	99:1
11	**5g**	Et_2O	$(MeO)_2MeSiH$	23	31:69	81:19	98:2
12	**5g**	toluene	$(MeO)_2MeSiH$	51	58:42	81:19	99:1
13	**5g**	dioxane	$(MeO)_2MeSiH$	53	57:43	79:21	99:1
14	**5g**	THF	$(EtO)_2MeSiH$	53	55:45	80:20	99:1
15	**5a**	THF	PMHS	53	58:42	81:19	99:1
16[d]	**5g**	THF	$(MeO)_2MeSiH$	75	76:24	88:12	>99:1

[a]Yield of both isolated diastereomers from column chromatography. Further recrystallization can easily remove minor diastereomer in high yield. [b]Determined by analysis of ^1H NMR spectra of unpurified mixtures. [c]Determined by analysis of HPLC spectra. [d]2.0 equiv of diene were used. [e]Not available.



unprecedented protocol for catalytic enantioselective formation of a unique secondary allyl−Cu complex followed by an addition to aldimines to afford homoallylic amines that are otherwise difficult to access in high efficiency, chemo-, regio-, and stereoselectivity.

Our investigations began with screening a variety of ligands for the reaction of 1,3-diene **1a** and aldimine **1b** in the presence of 5.0 mol % $Cu(OAc)_2$ and 5.0 equiv of $(MeO)_2MeSiH$ (Table 1). Cu complexes derived from bisphosphines **5a** and **5b** did not promote the reductive allylation (entries 1 and 2). Only a product **4a** from reduction of aldimine was observed. A reaction in the presence of a Cu complex formed from sterically congested bisphosphine **5c** afforded homoallylic amine **3a** in 30% yield, >98:2 dr, and 99:1 er, although the chemoselectivity was low (entry 3). Further studies revealed that no improvement was made on chemo-, diastereo-, and enantioselectivity by Cu complexes derived from phosphines **5d**−**f** (entries 4−6). Transformation of **1a** and **2a** promoted by a Cu complex generated from Ph-BPE **5g** delivered **3a** (CCDC 1859782) in 71% yield, 88:12 dr, and 99:1 er (entry 7). Optimization of solvents indicated that reaction that was performed in THF provided the best yield and stereoselectivity for **3a** (entries 8−13). Changing the silane to $(EtO)_2MeSiH$ or PMHS resulted in erosion of yield and stereoselectivity (entries 14−15). Increasing the equivalent of diene slightly improved the chemoselectivity (entry 16). It is noteworthy that, in contrast to previous work on borylative allylation of imines that resulted in only 4,3-addition products being formed,[8a] the 4,1-addition mode occurred exclusively to afford homoallylic amine **3a**, indicating that only allyl−Cu complex **I** participated in the imine addition step (Scheme 1d). In addition, the configuration of alkene in **3a** is exclusively *E*, which is different from those generated from reactions with CO_2.[10b]

With the optimal conditions in hand, we investigated the scope of aldimines. As shown in Scheme 2, reactions of aryl-substituted aldimines that contain electron-donating (**3b**, **3d**−**e**), electron-withdrawing (**3c**, **3f**−**j**), and halogen groups (**3e**−**h**) afforded exclusive 4,1-addition products in 60−85% yields, 86:14−99:1 dr, and 97:3−99:1 er. Aldimines substituted with sterically congested aryl groups were transformed in 71−77% yields, 92:8−97:3 dr, and 99:1−>99:1 er (**3k**−**m**). A variety of heterocycles were well tolerated (**3n**−**s**). Transformation of alkyl-substituted aldimines provided 4,1-addition products **3t**−**u** in 70−75% yields, 75:25−90:10 dr, and 98:2 er.

We further explored the scope of 1,3-dienes. As indicated in Scheme 3, reaction of dienes substituted with electron-rich (**6a**, **6e**), electron-deficient (**6b**−**d**, **6h**), halogen-containing (**6a**−**c**, **6f**−**g**), and sterically congested (**6i**−**j**) aryl groups afforded homoallyic amines in 71−97% yields, 80:20−99:1 dr, and 97:3−>99:1 er. A wide range of heterocycles were well tolerated (**6k**−**o**). When alkyl-substituted dienes were used in the reaction, only a product from the imine reduction was observed, probably due to the lower reactivity of alkyl-

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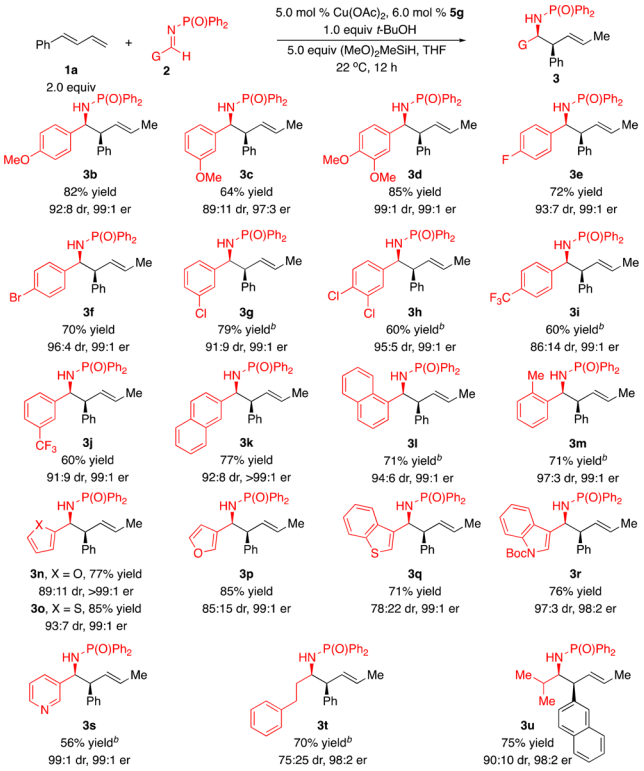
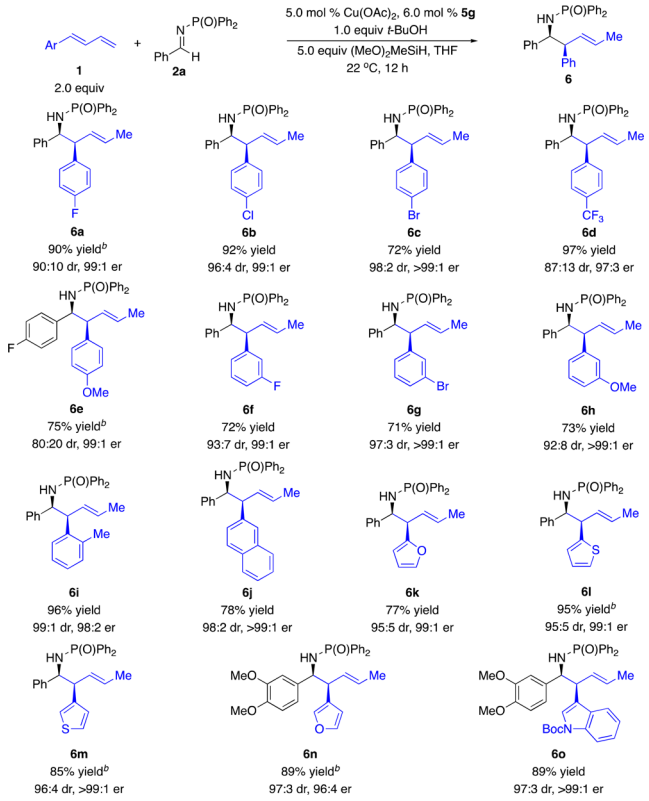
Scheme 2. Scope of Aldimines[a]



[a]The reactions were performed under a N_2 atmosphere. See Supporting Information (SI) for details. [b]3.0 equiv of diene were used.

Scheme 3. Scope of 1,3-Dienes[a]



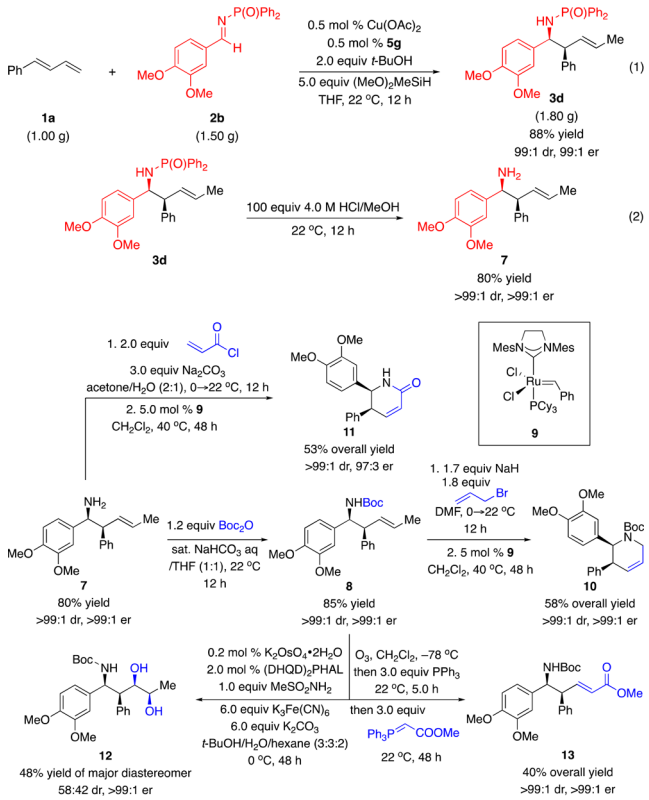
[a]The reactions were performed under a N_2 atmosphere. See SI for details. [b]3.0 equiv of dienes were used.

substituted dienes in the Cu−H addition step, resulting in domination of reduction of imine.

The reaction can be conducted on multigram scale with a 0.5 mol % catalyst loading without any erosion of yield and stereoselectivity (eq 1). One of the advantages of the phosphinoyl group is the ease of deprotection. The phosphinoyl group of the homoallylic amine **3d** was cleaved with 4.0 M HCl solution in MeOH (eq 2).[13] As shown in Scheme 4, the multifunctional homoallylic amine can be further transformed into useful building blocks (Scheme 4). Acylation of the amine with acryloyl chloride followed by ring closing metathesis promoted by Ru complex **9** afforded *δ*-lactam **11** in 53% overall yield.[14] Allylation of the Boc amide **8** followed by ring closing metathesis in the presence of Ru complex **9** delivered tetrahydropyridine **10** in 58% overall yield, >99:1 dr and >99:1 er.[15,16] Tetrahydropyridines and piperidines commonly exist in biologically active molecules.[17] The alkene moiety can be dihydroxylated to generate aminoalcohol **12** (CCDC 1859783) in 58:42 dr with 48% yield of the major diastereomer as a single enantiomer. The alkene moiety can be converted to other olefins.[18] Switching the methyl group on the alkene to a functionalizable ester moiety through a one-pot ozonolysis followed by a Wittig reaction led to **13** in 40% overall yield as a single enantiomer.[19]

The proposed catalytic cycle is shown in Scheme 5. The addition of Cu−H complex **III** to diene **1a** afforded allyl−Cu complex **IV**, which reacted with phosphinoyl imine **2a** directly without isomerization to **V**, probably due to the high affinity of the phosphonoyl group to the metal center.[3a] Once allyl−Cu complex **IV** was generated, a fast intramolecular C−C bond forming reaction occurred before possible isomerization and

Scheme 4. Gram Scale Reaction and Functionalization



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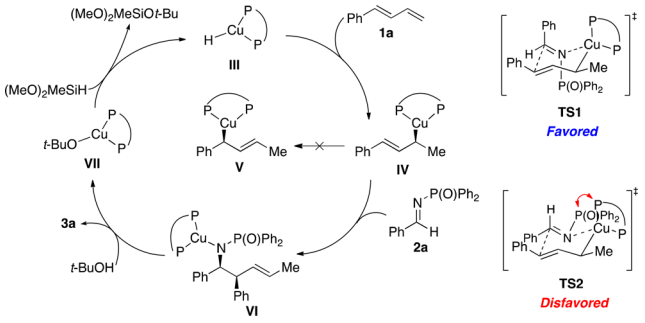
Scheme 5. Proposed Catalytic Cycle



racemerization, delivering exclusive 4,1-addition product **VI**. Protonation of the Cu−N bond by *t*-BuOH released the product **3a** and generated Cu complex **VII**, which underwent σ-bond metathesis with silane to regenerate Cu−H complex **III**. Two transition states of allylation are shown in Scheme 5 to illustrate the stereoselectivity. In **TS2**, the proximity of the large phosphonoyl group and the phosphine ligand on Cu leads to the steric repulsion and raised the energy of such a pathway. In the absence of such a disadvantageous interaction, a pathway through **TS1** that led to the major diastereomer **3a** was favored.

In conclusion, we developed an unprecedented protocol of catalytic enantioselective generation of chiral secondary allyl−Cu complexes through Cu−H addition to 1,3-dienes followed by their in situ addition to aldimines, providing a wide range of homoallylic amines in high chemo-, regio-, diastereo-, and enantioselectivity. The reactions were performed with easily accessible starting materials in the presence of a readily available phosphine−Cu complex. Functionalization of the product afforded a variety of useful building blocks that are otherwise difficult to access. Further investigations on expanding the scope of alkenes to generate enantiomerically enriched organometallic complexes are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03216.

Experimental procedures, spectroscopic data, and NMR spectra for all products; X-ray structures and data for **3a** and **12** (PDF)

Accession Codes

CCDC 1859782−1859783 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mengf@sioc.ac.cn.

ORCID

Fanke Meng: 0000-0003-1009-631X

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ding, H.; Friestad, G. K. *Synthesis* **2005**, *2005*, 2815−2829. (b) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541−2569.

(2) For general reviews that discuss allyl additions to imines, see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. For recent reviews on Cu-catalyzed enantioselective nucleophilic addition to imines, see: (d) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853−2873. (e) Yamada, K.; Tomioka, K. *Chem. Rev.* **2008**, *108*, 2874−2886.

(3) For recent examples on catalytic enantioselective allylation of imines, see: (a) Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 3332−3335. (b) Gandhi, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2573−2576. (c) Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309−8313. (d) Hepburn, H. B.; Lam, H. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 11605−11610. (e) Ghosh, D.; Bera, P. K.; Kumar, M.; Abdi, S. H. R.; Khan, N. H.; Kureshy, R. I.; Bajaj, H. C. *RSC Adv.* **2014**, *4*, 56424−56433. (f) Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E. M.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216−221. (g) Alam, R.; Diner, C.; Jonker, S.; Eriksson, L.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 14417−14421. (h) Wu, L.; Shao, Q.; Yang, G.; Zhang, W. *Chem. - Eur. J.* **2018**, *24*, 1241−1245.

(4) For recent reviews, see: (a) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653−661. (b) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394−1401. (c) Feng, J.; Holmes, M.; Krische, M. J. *Chem. Rev.* **2017**, *117*, 12564−12580. (d) Kim, S. W.; Zhang, W.; Krische, M. J. *Acc. Chem. Res.* **2017**, *50*, 2371−2380. (e) Holmes, M.; Schwartz, L. A.; Krische, M. J. *Chem. Rev.* **2018**, *118*, 6026−6052. (f) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. *Science* **2016**, *354*, 300. (g) Holmes, M.; Schwartz, L. A.; Krische, M. J. *Chem. Rev.* **2018**, *118*, 6026−6052.

(5) For recent selected examples, see: (a) Holmes, M.; Nguyen, K. D.; Schwartz, L. A.; Luong, T.; Krische, M. J. *J. Am. Chem. Soc.* **2017**, *139*, 8114−8117. (b) Nguyen, K. D.; Herkommer, D.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 14210−14213. (c) Nguyen, K. D.; Herkommer, D.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 5238−5241. (d) Liang, T.; Nguyen, K. D.; Zhang, W.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 3161−3164. For additional references, see SI.

(6) For a Ni-catalyzed asymmetric reductive coupling of alkynes and imines, see: (a) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269−11276. (b) Skucas, E.; Kong, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242−7243. (c) Zhou, C.-Y.; Zhu, S.-F.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132*, 10955−10957. For nonenantioselective examples, see: (d) Chen, T.-Y.; Tsutsumi, R.; Montgomery, T. P.; Volchkov, I.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 1798−1801. (e) Oda, S.; Franke, J.; Krische, M. J. *Chem. Sci.* **2016**, *7*, 136−141. (f) Komanduri, V.; Grant, C. D.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 12592−12593.

(7) (a) Ascic, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 4666−4669. (b) Yang, Y.; Perry, I. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 9787−9790. (c) Liu, R. Y.; Yang, Y.; Buchwald, S. L.

DOI: 10.1021/acs.orglett.8b03216
Org. Lett. XXXX, XXX, XXX−XXX

Angew. Chem., Int. Ed. **2016**, *55*, 14077−14080. (d) Shao, X.; Li, K.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 7083−7087.
(8) (a) Jiang, L.; Cao, P.; Wang, M.; Chen, B.; Wang, B.; Liao, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 13854−13858. (b) Yeung, K.; Ruscoe, R. E.; Rae, J.; Pulis, A. P.; Procter, D. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 11912−11916.
(9) For reviews on CuH catalysis, see: (a) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916−2927. (b) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 498−504. (c) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 48−57.
(10) For generation of allyl−Cu complex from CuH addition to diene, see: (a) Iwasaki, T.; Shimizu, R.; Imanishi, R.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2015**, *54*, 9347−9350. (b) 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. For generation of allenyl−Cu complex from Cu−H addition to enyne, see: (c) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, *353*, 144−150.
(11) For Cu-catalyzed enantioselective reductive Mannich reactions, see: (a) Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146−16147. (b) Choi, B.; Saxena, A.; Smith, J. J.; Churchill, G. H. *Synlett* **2015**, *26*, 350−354.
(12) Cheng, F.; Lu, W.; Huang, W.; Wen, L.; Li, M.; Meng, F. *Chem. Sci.* **2018**, *9*, 4992−4998.
(13) Yan, W.; Mao, B.; Zhu, S.; Jiang, X.; Liu, Z.; Wang, R. *Eur. J. Org. Chem.* **2009**, *2009*, 3790−3794.
(14) Fiorelli, C.; Savoia, D. *J. Org. Chem.* **2007**, *72*, 6022−6028.
(15) Guo, R.; Lu, S.; Chen, X.; Tsang, C.-W.; Jia, W.; Sui-Seng, C.; Amoroso, D.; Abdur-Rashid, K. *J. Org. Chem.* **2010**, *75*, 937−940.
(16) Yang, X.-F.; Yu, W.-H.; Ding, C.-H.; Ding, Q.-P.; Wan, S.-L.; Hou, X.-L.; Dai, L.-X.; Wang, P.-J. *J. Org. Chem.* **2013**, *78*, 6503−6509.
(17) (a) Hayes, J. F.; Shipman, M.; Twin, H. *Chem. Commun.* **2001**, 1784−1785. (b) Urushima, T.; Sakamoto, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 4588−4591. (c) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712−7722. (d) Cuthbertson, J. D.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 1490−1493. (e) Viegas, C.; da S. Bolzani, V.; Furlan, M.; Barreiro, E. J.; Young, M. C. M.; Tomazela, D.; Eberlin, M. N. *J. Nat. Prod.* **2004**, *67*, 908−910. (f) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679−3681.
(18) Sprott, K. T.; Corey, E. J. *Org. Lett.* **2003**, *5*, 2465−2467.
(19) Quirin, C.; Kazmaier, U. *Synthesis* **2009**, *2009*, 1725−1731.

DOI: 10.1021/acs.orglett.8b03216
Org. Lett. XXXX, XXX, XXX−XXX