Asymmetric Catalysis

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Enantio- and Diastereoselective Synthesis of Homopropargyl Amines by Copper-Catalyzed Coupling of Imines, 1,3-Enynes, and Diborons

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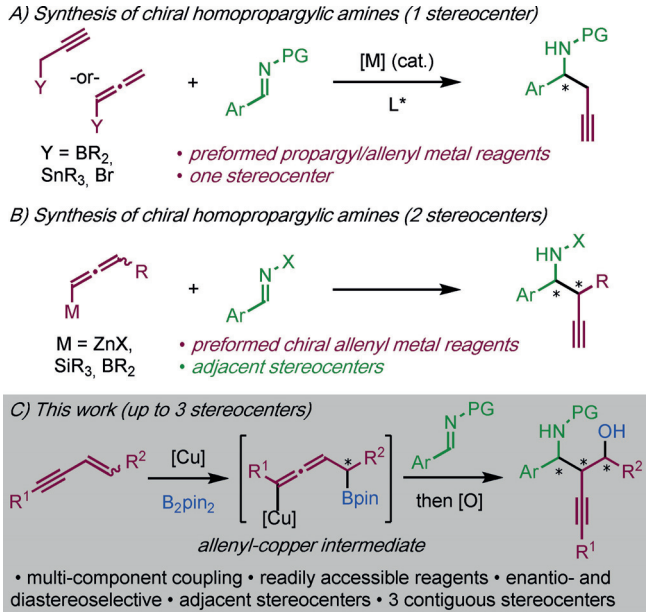
Abstract: *An efficient, enantio- and diastereoselective, copper-catalyzed coupling of imines, 1,3-enynes, and diborons is reported. The process shows broad substrate scope and delivers complex, chiral homopropargyl amines; useful building blocks on the way to biologically-relevant compounds. In particular, functionalized homopropargyl amines bearing up to three contiguous stereocenters can be prepared in a single step.*

Chiral homopropargyl amines are used in the synthesis of many natural products, and biologically and medicinally important molecules.[1–3] Most methods for homopropargyl amine synthesis involve the union of imines and propargylic or allenic substrates. These methods deliver racemic homopropargylic amines[4] and asymmetric variants selectively generate products with a stereocenter adjacent to the amino group (Scheme 1 A). In general, these methods use a transition metal catalyst and chiral ligand, or imines bearing a chiral auxiliary.[5] Constructing homopropargyl amines with more than one stereocenter, particularly if the stereocenters are adjacent, is a more challenging process (Scheme 1 B), few procedures address this goal and these require difficult-to-access reagents and/or chiral auxiliaries.[6] Thus, a general preparation of chiral homopropargylic amines, bearing multiple stereocenters, from readily-accessible substrates, remains an important challenge.

Copper-catalyzed borylative transformations are a powerful method for uniting unsaturated hydrocarbons and electrophiles.[7] Importantly, these methods produce densely functionalized, chiral molecules from simple, achiral substrates, and use cheap and non-toxic transition metal catalysts. We and others have described efficient routes to amines through the multicomponent coupling of imines with hydrocarbon pro-nucleophiles and boron reagents.[8–10] Krische pioneered the use of enynes as hydrocarbon pro-nucleophiles in transition metal-catalyzed transformations,[11–13] however, in both reductive and borylative coupling, the asymmetric union of imines and enynes remains an unmet challenge.[14]



Scheme 1. Enantioselective transition metal-catalyzed nucleophilic addition to imines for the synthesis of homopropargyl amines. PG = protecting group; X = PG or chiral auxiliary; Pin = pinacolato.

We envisaged a new approach to homopropargyl amines involving the copper-catalyzed enantio- and diastereoselective multicomponent coupling of imines, enynes, and diboron reagents (Scheme 1 C). Furthermore, through routine oxidation of the carbon–boron bond, biologically relevant 1,3-amino alcohols would be accessible.[15] Herein, we disclose an efficient method for obtaining functionalized chiral homopropargyl amines, bearing up to three stereocenters and various synthetic handles (amino, boron, alkynyl), using an inexpensive, non-toxic, and readily-available copper catalyst, and a commercial phosphine ligand.

We explored the copper-catalyzed coupling of imine **1a**, 1,3-enyne **2a** and bis(pinacolato)diboron (B_2pin_2). Using CuCl and (*S*,*S*)-Ph-BPE (**L1**), the desired product **3a′** (PG = PMP) was obtained in 70% yield and the major diastereoisomer was found to have an *ee* of 53% (Table 1, entry 1). After screening reaction conditions with imine **1a**, we turned our attention to *N*-phosphinoylimine **1b**. With this imine, the enantioselectivity and diastereoselectivity of the reaction increased (89% *ee*, > 95:5 dr), however, only 37% yield of the desired product was obtained (entry 2). By screening the copper salt, base, and solvent, we found that the use of CuOAc, KOMe, and THF was optimal; **3a** was obtained in high yield, with excellent diastereoselectivity and enantioselectivity (entry 3).[16] X-ray crystallographic analysis of **3d** revealed the relative and absolute stereochemistry of the

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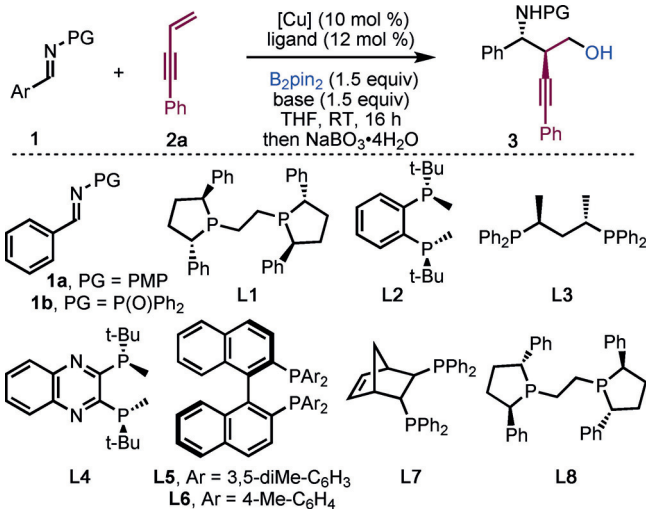
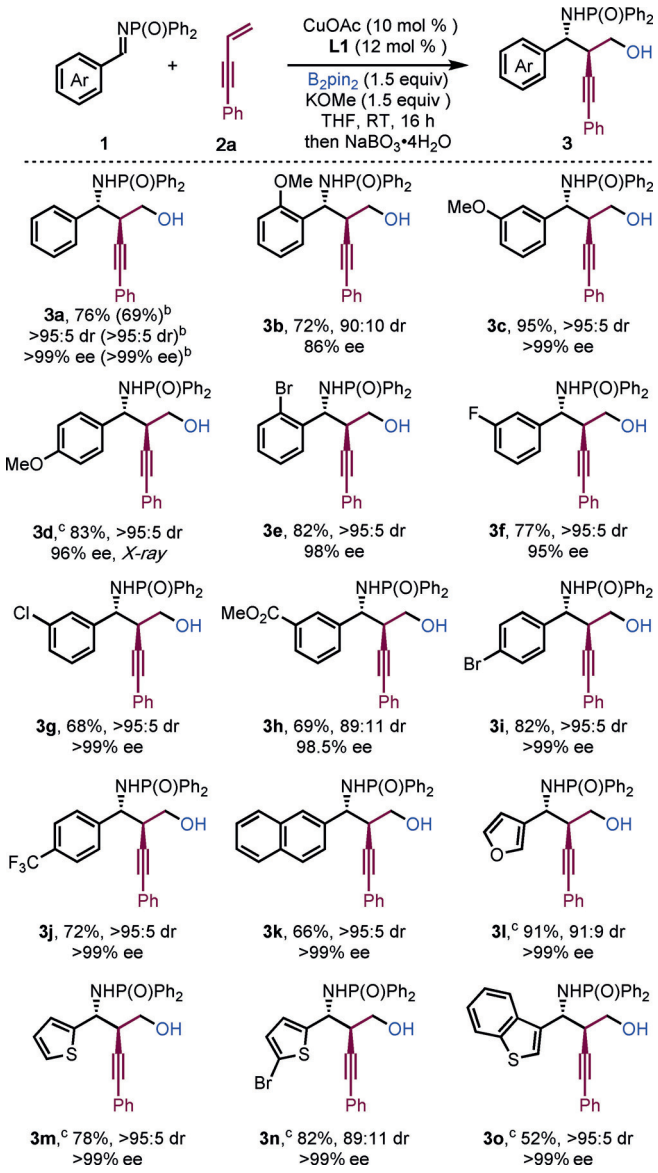
Table 1: Screening of reaction conditions[a]



Entry	Imine	Ligand	Cu[I]/base	dr	**3** Yield/*ee*[b] [%]
1	**1a**	**L1**	CuCl/NaO*t*Bu	87:13	70/53[c]
2	**1b**	**L1**	CuOAc/NaO*t*Bu	>95:5	37/89
3	**1b**	**L1**	CuOAc/KOMe	>95:5	92/99
4	**1b**	**L2**	CuOAc/KOMe	–	–
5	**1b**	**L3**	CuOAc/KOMe	–	–
6	**1b**	**L4**	CuOAc/KOMe	–	–
7	**1b**	**L5**	CuOAc/KOMe	>95:5	56/34
8	**1b**	**L6**	CuOAc/KOMe	–	–
9	**1b**	**L7**	CuOAc/KOMe	88:12	37/16
10	**1b**	**L8**	CuOAc/KOMe	>95:5	88/96[d]
11	**1b**	**L1**	CuOAc/KOMe	90:10	56/92[e]

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), B_2pin_2 (0.3 mmol), base (0.3 mmol), Cu[I] (10 mol%), ligand (12 mol%) in THF (2.0 mL) at RT for 16 h under nitrogen. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude product mixtures. NMR yields are given. [b] The *ee* values were determined by chiral HPLC after oxidation. [c] The *ee* values were measured by chiral HPLC analysis of the boron-containing product. [d] The enantiomer of **3a** was formed. [e] B_2neo_2 (0.3 mmol) was used. THF = tetrahydrofuran. PMP = 4-methoxyphenyl; Neo = neopentyl glycolato.

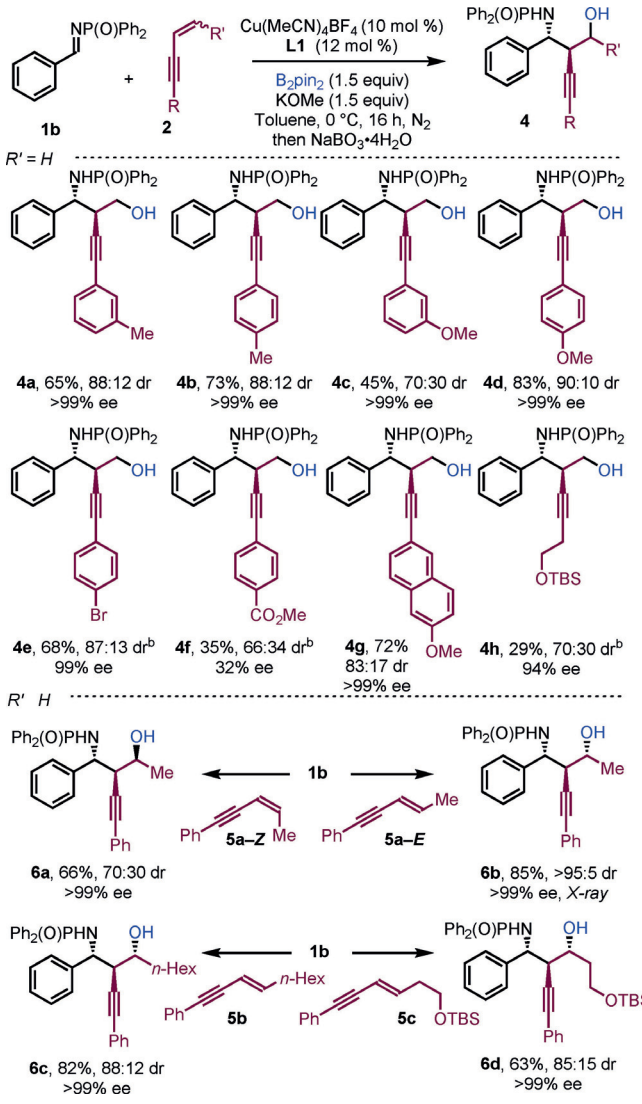


Scheme 2. Scope with respect to the imine. [a] Reaction conditions: See Table 1. Yields of isolated products are given. [b] Values in parentheses indicate the result of a 1 g scale reaction. [c] 0 °C in MTBE. MTBE = methyl-*t*-butyl ether.

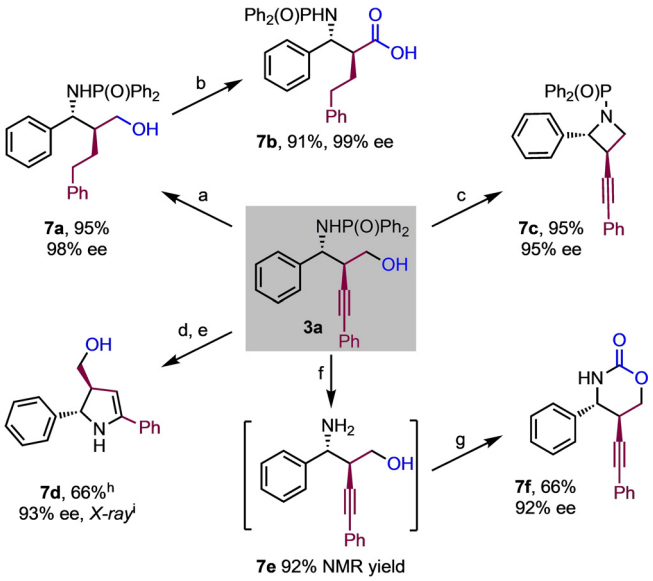
product.[16] Other diboron reagents are applicable in the reaction; the use of bis(neopentyl glycolato)diboron (B_2neo_2) gave **3a** in moderate yield but with high diastereo- and enantiocontrol (entry 11).

The reaction tolerated electron-donating and electron-withdrawing substituents on the aryl ring of the aldimine; the desired products were obtained in high yield and with excellent enantio- and diastereoselectivity (Scheme 2). For example, electron-rich aldimines were well tolerated in the reaction and only a slight decrease in enantioselectivity was observed when an *ortho*-methoxy substituent was used (**3b**). Similarly, imines bearing electron-withdrawing groups at the *ortho*-, *meta*-, and *para*-positions (**3e–3j**), including halogen (**3e–3g**, **3i**), ester (**3h**), and trifluoromethyl (**3j**) substituents, also performed well. The reaction also proceeded efficiently when heteroaryl-aldimines were used (**3l–3o**). The reaction could be executed on a gram scale without significant detriment to the yield or selectivity (**3a**). Attempts to use an aliphatic aldimine in the process were unsuccessful (See Supporting Information).

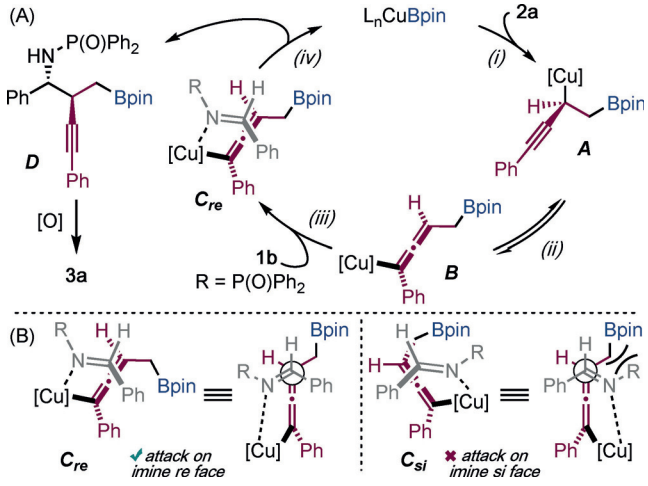
Aryl-substituted 1,3-enynes bearing electron-donating groups delivered the corresponding products in good to excellent yield and with high enantioselectivities (Scheme 3, **4a–4d**). Mixed results were obtained when using electron-deficient enynes; for example, whereas the bromo-substituted product **4e** was prepared in good yield, with high selectivity, an ester substituent severely affected the efficiency of the coupling (**4f**). The use of an alkyl substituted enyne gave **4h** in low yield but with high enantiocontrol. Substitution at the terminal position of the alkene was investigated: *E*-enynes gave products **6b–6d** in good to high yield, with good diastereoselectivity and excellent enantioselectivity. The structure of **6b** was confirmed by X-ray crystallography.[16] The use of *Z*-enyne **5a**-*Z* gave alternative diastereoisomeric product **6a**. Thus, the process delivers amino alcohols bearing three contiguous stereocenters with essentially complete enantiocontrol.



Scheme 3. Scope with respect to 1,3-enyne. [a] Reaction conditions: **1b** (0.2 mmol), **2** (0.3 mmol), B_2pin_2 (0.3 mmol), KOMe (0.3 mmol), $Cu(MeCN)_4BF_4$ (10 mol%), (*S,S*)-Ph-BPE **L1** (12 mol%) in toluene (2.0 mL) at 0 °C for 16 h under nitrogen. Yields of isolated products. [b] THF at RT with CuOAc.



Scheme 4. Manipulation of product **3a**. [a] Pd/C (10 mol%), H_2 (1 atm), MeOH, 40 °C, 24 h. [b] $RuCl_3$ (5 mol%), $NaIO_4$ (1.5 equiv), CCl_4:MeCN:H_2O = 1:1:1.2, 3 h, RT. [c] TsCl (1.5 equiv), NaH (6 equiv), THF, 40 °C, 8 h. [d] From borylated/non-oxidized form of **3a**: Ph_3PAuCl (10 mol%), AgOTf (10 mol%), DCE, 8 h, 80 °C. [e] $NaBO_3·4H_2O$ (5 equiv), THF:H_2O = 1:1, 6 h, RT. [f] 4 N HCl, MeOH, RT, 3 h, RT. [g] Triphosgene (1.0 equiv), Et_3N (2 equiv), THF, 3 h, 0 °C. [h] 4:1 Mixture of tautomers. [i] X-ray of minor tautomer of **7d**.



Scheme 5. Proposed catalytic cycle for the enantioselective coupling.

Amine **3a** was readily hydrogenated, to give the branched chain alkane **7a**, and the β-amino acid derivative **7b** was accessed by oxidation of **7a** (Scheme 4). Biologically- and medicinally-relevant *N*-containing heterocycles were also prepared, for example, azetidine **7c**, or 2,3-dihydropyrrole **7d** through π-activation of the alkyne bond using a Au–Ag catalyst system.[17] The phosphinoyl group could be removed to reveal the free amine **7e**,[9a] which was subjected to urethanation to give oxazinone **7f**.

Regioselective borocupration provides intermediate **A** (1),[12a,13a] which is proposed to undergo propargyl-to-allenyl isomerization to **B** (2) (Scheme 5 A).[12d] We propose that intermediate **B** is the major allenyl–copper isomer in the reaction.[12d] Coupling of the allenyl–copper intermediate **B** with imine **1b** ($\mathbf{C}_{re}$, 3) gives chiral homopropargylic amine **D** and closes the catalytic cycle (4).[12b–d] Scheme 5 B provides an explanation for the *anti*-diastereoselectivity observed in the reaction. Coupling (3) between allenyl intermediate **B** and imine **1b** can occur from attack at either the *re* face ($\mathbf{C}_{re}$) or the *si* face ($\mathbf{C}_{si}$) of the imine. However, reaction at the *si* face ($\mathbf{C}_{si}$) incurs unfavorable interactions between the *N*-phosphinoyl group and the -CH_2Bpin group and is disfavored.

In conclusion, a highly enantio- and diastereoselective coupling of imines, 1,3-enynes, and diborons using an inexpensive copper catalyst and a commercial ligand, delivers chiral homopropargyl amines with up to three contiguous stereocenters. The products provide access to important targets, including β-amino acids and *N*-heterocycles.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · borylative coupling · copper · 1,3-enynes · homopropargyl amines

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[1] a) G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541–2569; b) M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2013**, *113*, 5595–5698.

[2] For total synthesis, see: a) C. Kim, H. J. Bae, J. H. Lee, W. Jeong, H. Kim, V. Sampath, Y. H. Rhee, *J. Am. Chem. Soc.* **2009**, *131*, 14660–14661; b) W. Rao, D. Susanti, P. W. H. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 15248–15251; c) X. Zhou, T. Xiao, Y. Iwama, Y. Qin, *Angew. Chem. Int. Ed.* **2012**, *51*, 4909–4912; *Angew. Chem.* **2012**, *124*, 4993–4996.

[3] For heterocycle synthesis, see: a) Y.-F. Yu, C. Shu, T.-D. Tan, L. Li, S. Rafique, L.-W. Ye, *Org. Lett.* **2016**, *18*, 5178–5181; b) S. Tong, C. Piemontesi, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 7958–7962; *Angew. Chem.* **2017**, *129*, 6699–6703.

[4] a) P. Quinodoz, K. Wright, B. Drouillat, O. David, J. Marrot, F. Couty, *Chem. Commun.* **2016**, *52*, 10072–10075; b) J. Zhao, S. J. T. Jonker, D. N. Meyer, G. Schulz, C. D. Tran, L. Eriksson, K. J. Szabó, *Chem. Sci.* **2018**, *9*, 3305–3312.

[5] a) H. M. Wisniewska, E. R. Jarvo, *Chem. Sci.* **2011**, *2*, 807–810; b) Y.-Y. Huang, A. Chakrabarti, N. Morita, U. Schneider, S. Kobayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 11121–11124; *Angew. Chem.* **2011**, *123*, 11317–11320; c) E. M. Vieira, F. Haeffner, M. L. Snapper, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2012**, *51*, 6618–6621; *Angew. Chem.* **2012**, *124*, 6722–6725; d) X.-Y. Bai, Z.-X. Wang, B.-J. Li, *Angew. Chem. Int. Ed.* **2016**, *55*, 9007–9011; *Angew. Chem.* **2016**, *128*, 9153–9157.

[6] a) S. J. T. Jonker, C. Diner, G. Schulz, H. Iwamoto, L. Eriksson, K. J. Szabó, *Chem. Commun.* **2018**, *54*, 12852–12855; b) S. Yu, R. Hua, X. Fu, G. Liu, D. Zhang, S. Jia, H. Qiu, W. Hu, *Org. Lett.* **2019**, *21*, 5737–5741.

[7] a) A. P. Pulis, K. Yeung, D. J. Procter, *Chem. Sci.* **2017**, *8*, 5240–5247; b) K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Tetrahedron* **2015**, *71*, 2183–2197; c) Y. Shimizu, M. Kanai, *Tetrahedron Lett.* **2014**, *55*, 3727–3737.

[8] For borofunctionalization of unsaturated hydrocarbons with imines and related electrophiles, see: a) J. Rae, K. Yeung, J. J. W. McDouall, D. J. Procter, *Angew. Chem. Int. Ed.* **2016**, *55*, 1102–1107; *Angew. Chem.* **2016**, *128*, 1114–1119; b) D. Li, Y. Park, J. Yun, *Org. Lett.* **2018**, *20*, 7526–7529; c) H.-M. Wang, H. Zhou, Q.-S. Xu, T.-S. Liu, C.-L. Zhuang, M.-H. Shen, H.-D. Xu, *Org. Lett.* **2018**, *20*, 1777–1780; d) T. Jia, Q. He, R. E. Ruscoe, A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2018**, *57*, 11305–11309; *Angew. Chem.* **2018**, *130*, 11475–11479; e) Y.-P. Bi, H.-M. Wang, H.-Y. Qu, X.-C. Liang, Y. Zhou, X.-Y. Li, D. Xu, M.-H. Shen, H.-D. Xu, *Org. Biomol. Chem.* **2019**, *17*, 1542–1546; f) K. Yeung, F. J. T. Talbot, G. P. Howell, A. P. Pulis, D. J. Procter, *ACS Catal.* **2019**, *9*, 1655–1661; g) S. Zhang, J. del Pozo, F. Romiti, Y. Mu, S. Torker, A. H. Hoveyda, *Science* **2019**, *364*, 45–51.

[9] For asymmetric borofunctionalization of unsaturated hydrocarbons with imines and related electrophiles, see: a) L. Jiang, P. Cao, M. Wang, B. Chen, B. Wang, J. Liao, *Angew. Chem. Int. Ed.* **2016**, *55*, 13854–13858; *Angew. Chem.* **2016**, *128*, 14058–14062; b) K. Yeung, R. E. Ruscoe, J. Rae, A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2016**, *55*, 11912–11916; *Angew. Chem.* **2016**, *128*, 12091–12095; c) H. Jang, F. Romiti, S. Torker, A. H. Hoveyda, *Nat. Chem.* **2017**, *9*, 1269–1275; d) T. Itoh, Y. Kanzaki, Y. Shimizu, M. Kanai, *Angew. Chem. Int. Ed.* **2018**, *57*, 8265–8269; *Angew. Chem.* **2018**, *130*, 8397–8401; e) D. Li, J. Kim, J. W. Yang, J. Yun, *Chem. Asian J.* **2018**, *13*, 2365–2368; f) G. Zhang, A. Cang, Y. Wang, Y. Li, G. Xu, Q. Zhang, T. Xiong, Q. Zhang, *Org. Lett.* **2018**, *20*, 1798–1801; g) T. Jia, M. J. Smith, A. P. Pulis, G. J. P. Perry, D. J. Procter, *ACS Catal.* **2019**, *9*, 6744–6750; h) H. Deng, Z. Meng, S. Wang, Z. Zhang, Y. Zhang, Y. Shangguan, F. Yang, D. Yuan, H. Guo, C. Zhang, *Adv. Synth. Catal.* **2019**, *361*, 3582–3587.

[10] For related copper-catalyzed functionalizations of imines, see: a) Y. Du, L.-W. Xu, Y. Shimizu, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 16146–16147; b) E. Ascic, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 4666–4669; c) R. Y. Liu, Y. Yang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 14077–14080; *Angew. Chem.* **2016**, *128*, 14283–14286; d) Y. Yang, I. B. Perry, S. L. Buchwald, *J. Am. Chem. Soc.* **2016**, *138*, 9787–9790; e) X. Shao, K. Li, S. J. Malcolmson, *J. Am. Chem. Soc.* **2018**, *140*, 7083–7087; f) M. Li, J. Wang, F. Meng, *Org. Lett.* **2018**, *20*, 7288–7292.

[11] M. Holmes, L. A. Schwartz, M. J. Krische, *Chem. Rev.* **2018**, *118*, 6026–6052.

[12] For borofunctionalizations of enynes, see: a) Y. Sasaki, Y. Horita, C. Zhong, M. Sawamura, H. Ito, *Angew. Chem. Int. Ed.* **2011**, *50*, 2778–2782; *Angew. Chem.* **2011**, *123*, 2830–2834; b) F. Meng, F. Haeffner, A. H. Hoveyda, *J. Am. Chem. Soc.* **2014**, *136*, 11304–11307; c) H. L. Sang, S. Yu, S. Ge, *Org. Chem. Front.* **2018**, *5*, 1284–1287; d) Y. Huang, J. del Pozo, S. Torker, A. H. Hoveyda, *J. Am. Chem. Soc.* **2018**, *140*, 2643–2655; e) D.-W. Gao, Y. Xiao, M. Liu, Z. Liu, M. K. Karunananda, J. S. Chen, K. M. Engle, *ACS Catal.* **2018**, *8*, 3650–3654; f) X.-C. Gan, Q. Zhang, X.-S. Jia, L. Yin, *Org. Lett.* **2018**, *20*, 1070–1073; g) X.-C. Gan, L. Yin, *Org. Lett.* **2019**, *21*, 931–936.

[13] For related copper-catalyzed functionalizations of enynes, see: a) Y. Yang, I. B. Perry, G. Lu, P. Liu, S. L. Buchwald, *Science* **2016**, *353*, 144–150; b) X.-F. Wei, X.-W. Xie, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.* **2017**, *139*, 4647–4650; c) X. Zhu, W. Deng, M.-F. Chiou, C. Ye, W. Jian, Y. Zeng, Y. Jiao, L. Ge, Y. Li, X. Zhang, H. Bao, *J. Am. Chem. Soc.* **2019**, *141*, 548–559.

[14] a) J.-R. Kong, C.-W. Cho, M. J. Krische, *J. Am. Chem. Soc.* **2005**, *127*, 11269–11276; b) M. Callingham, B. M. Partridge, W. Lewis, H. W. Lam, *Angew. Chem. Int. Ed.* **2017**, *56*, 16352–16356; *Angew. Chem.* **2017**, *129*, 16570–16574.

[15] S.-L. Shi, Z. L. Wong, S. L. Buchwald, *Nature* **2016**, *532*, 353–356.

[16] See Supporting Information for optimization studies and X-ray data.

[17] Y.-F. Yu, C. Shu, B. Zhou, J.-Q. Li, J.-M. Zhou, L.-W. Ye, *Chem. Commun.* **2015**, *51*, 2126–2129.

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