ChemComm

Cu-Catalyzed Coupling of Vinylidene Cyclopropanes with Allyl and Allenyl Boronates

Journal:	*ChemComm*
Manuscript ID	CC-COM-07-2021-003823.R1
Article Type:	Communication

Journal Name

COMMUNICATION

Cu-Catalyzed coupling of vinylidene cyclopropanes with allyl and allenyl boronates

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

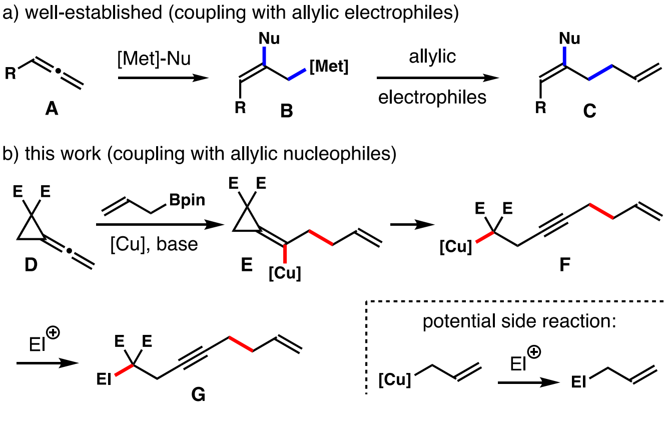
Ming Chen*

Abstract: The development of Cu-catalyzed coupling of vinylidene cyclopropanes with allyl and allenyl boronates is reported. The reaction forms a C-C bond at the terminal carbon atom of the allene moiety of vinylidene cyclopropanes with concurrent opening of the cyclopropane ring. In addition, the resulting Cu-enolate intermediate can be intercepted by external electrophiles.

Vinylidene cyclopropanes are versatile intermediates in chemical synthesis.[1] The cyclopropane and the appended allene moiety can undergo a variety of transformations either separately or in a concerted manner.[1,2] For instance, skeleton rearrangement and isomerization of vinylidene cyclopropanes can be induced by photo irradiation.[3] Cycloaddition of vinylidene cyclopropanes with unsaturated compounds can also be accomplished through photo chemistry.[4] Under Brønsted or Lewis acid conditions, they have been shown to participate in reactions to generate aromatic or poly-unsaturated molecules.[5] Moreover, vinylidene cyclopropanes can undergo various transition metal-catalyzed cyclopropane ring-opening transformations to give synthetically useful carbocycles or heterocycles.[6,7] Selective functionalization of the allene moiety can be achieved with the cyclopropyl group being intact.[2]

Transition metal-catalyzed functionalization of allene is an important approach to synthesize poly-unsaturated molecules.[8] As shown in Scheme 1a, conventional coupling of allene □ with allylic substrates involves the addition of nucleophilic organometallics to **A** to form allylic metal species **B** with the nucleophile adding to the central carbon of the allene. Subsequent interception of the resulting intermediate **B** with an allylic electrophile produces 1,5-diene adduct **C**. This process effectively accomplishes 1,2-functionalization of allene **A**. For instance, the reactions of allenes with Cu-based nucleophiles, including boron,[9] silicon[10] and hydrogen,[11] have been shown to proceed through this pathway.[12,13] By contrast, transition metal-catalyzed reactions of allenes with allyl or allenyl nucleophiles are rare. A single example of Pd-catalyzed coupling of an allene with allylic boronate was reported by the Dong group.[14] It is therefore valuable to develop novel transformations to fill this gap.

With our continuing research interest in developing catalytic transformations using organoboron compounds,[15] we envisioned that nucleophilic allylcopper, which can be generated via base-promoted transmetalation with the corresponding allylic boronate, could react with vinylidene cyclopropane **D** (Scheme 1b). In contrast to the reaction with allene **A**, the addition should proceed with the allyl group adding to the terminal carbon of the allene moiety of **D** to give vinyl copper species **E**.[16,17] Intermediate **E** should trigger subsequent opening of the cyclopropyl group via β-carbo elimination to produce intermediate **F**, with releasing ring strain as the thermodynamic driving force. Interception of **F** by an electrophile should give product **G**. However, to implement such a process, it is critical that the reactivities of the electrophile and nucleophilic allylic copper species need to be balanced in order to minimize direct coupling of these two species (Scheme 1b).



Scheme 1. Approaches for allyl-allene coupling

We commenced our studies by establishing suitable conditions for the reaction of vinylidene cyclopropane **1a** with allylboronate **2a**. As shown in Table 1, the initial experiments were performed with 10 mol % CuCl as the catalyst and 1.2 equiv base in THF at ambient temperature. The reaction with LiO^{t}Bu as the base gave product **3a** in 27% yield (entry 1). When NaO^{t}Bu was employed as the base, the reaction yield improved significantly,

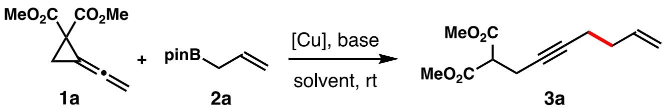
---

Departments of Chemistry and Biochemistry, Auburn University, Auburn, 36849
E-mail: mzc0102@Auburn.edu

Electronic Supplementary Information (ESI) available:
Financial support provided by Auburn University and National Science Foundation (CAREER Award CHE-2042353) is gratefully acknowledged.

and product **3a** was isolated in 85% yield (entry 2). The reaction performed with KO^{t}Bu as the base gave product **3a** in 54% yield (entry 3). Next, reactions with several methoxide bases were examined. In contrast to the case of LiO^{t}Bu, product **3a** was generated in a significantly higher yield (71% vs. 27%) with LiOMe as the base (entry 4). The yield of **3a** (80%, entry 5) in the reaction with NaOMe as the base is comparable to the one conducted with NaO^{t}Bu. A similar yield was obtained for the reaction with KOMe vs. KO^{t}Bu as the base (entry 6). Other copper catalysts, $CuCl_2$ for instance, can be employed for the reaction, and **3a** was isolated in 67% yield (entry 7). The reaction also proceeded in dioxane, albeit in a lower yield (63%, entry 8). When toluene was used as the solvent, the reaction only gave a trace amount of product **3a** (entry 9). The presence of a base is required for the reaction; the formation of product **3a** was not detected without the added base (entry 10). The same conclusion holds true for the copper catalyst, as the reaction did not proceed without the catalyst (entry 11). The results eliminate the potential pathway of a base-promoted direct addition of allyl boronate **2a** to vinylidene cyclopropane **1a** without the copper catalyst. In all cases, the allyl group added to the terminal carbon atom of the allene moiety of vinylidene cyclopropane **1a**. Product generated from allyl addition to the central carbon was not detected.

Table 1. Evaluation of the conditions for reactions of allylboronate **2a** with vinylidene cyclopropane **1a** ^{a,b}

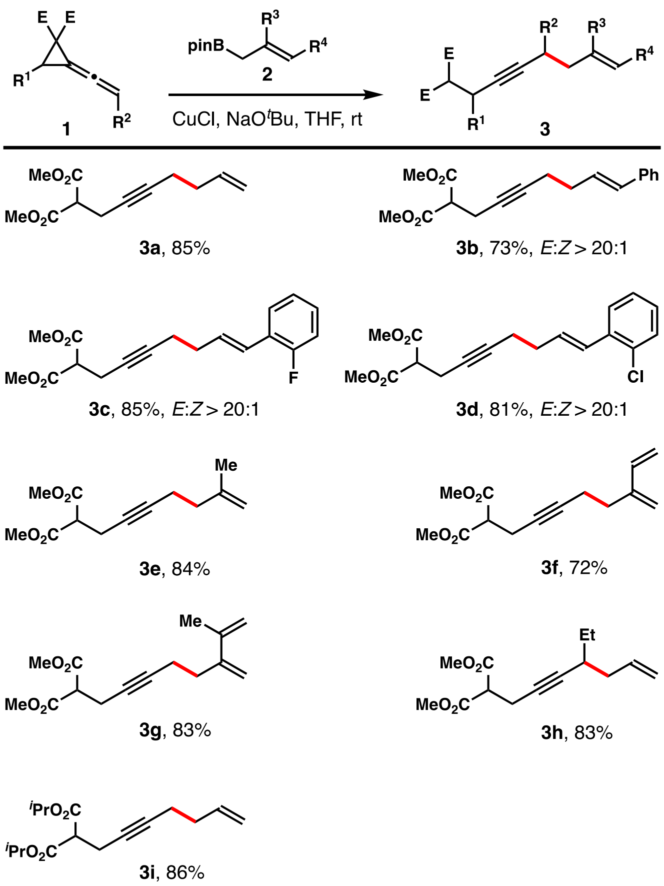


entry	[Cu]	base	solvent	yield (%)
1	CuCl	LiO*t*-Bu	THF	27
2	CuCl	NaO*t*-Bu	THF	85
3	CuCl	KO*t*-Bu	THF	54
4	CuCl	LiOMe	THF	71
5	CuCl	NaOMe	THF	80
6	CuCl	KOMe	THF	58
7	$CuCl_2$	NaO*t*-Bu	THF	67
8	CuCl	NaO*t*-Bu	dioxane	63
9	CuCl	NaO*t*-Bu	toluene	<5
10	CuCl	no base	THF	N.R.
11	no CuCl	NaO*t*-Bu	THF	N.R.

(a) vinylidene cyclopropane **1a** (0.1 mmol, 1 equiv), allylBpin **2a** (0.11 mmol, 1.1 equiv), [Cu] (10 mol %), base (0.12 mmol, 1.2 equiv), solvent (0.5 mL). (b) Yields of isolated products are listed.

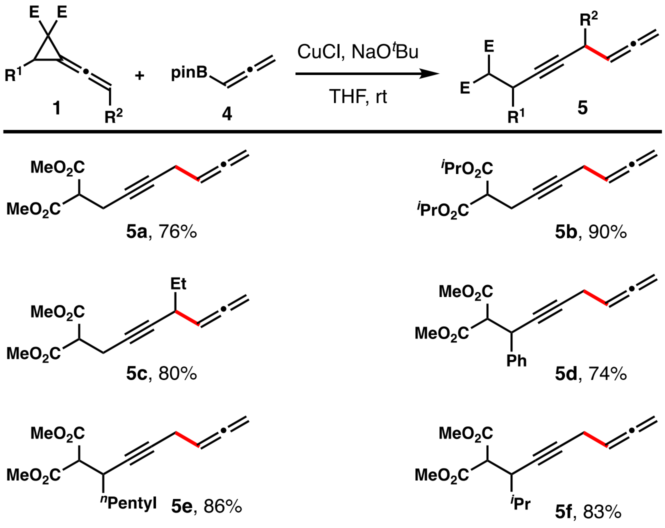
Table 2 summarizes the scope of vinylidene cyclopropane **1** and allylboronate **2** that participated in the reaction under the developed conditions. The reactions worked well with various allylboronates to give products **3a**-**i** in good yields. For instance, the reactions of γ-substituted allylboronates with **1a** occurred to give products **3b**-**d** in 73-85% yields with >20:1 *E*-selectivity. β-Substituted allylboronates reacted with **1a** to afford products **3e**-**g** in 72-84% yields. The developed conditions are also suitable for the reaction with an ethyl substituted vinylidene cyclopropane, and product **3h** was obtained in 83% yield. Vinylidene cyclopropane **1b** with *i*-Pr ester groups reacted with allylboronate **2a** to give product **3i** in 86% yield.

Table 2. Reaction scope of vinylidene cyclopropanes **1** and allylic boronates **2** ^{a,b}



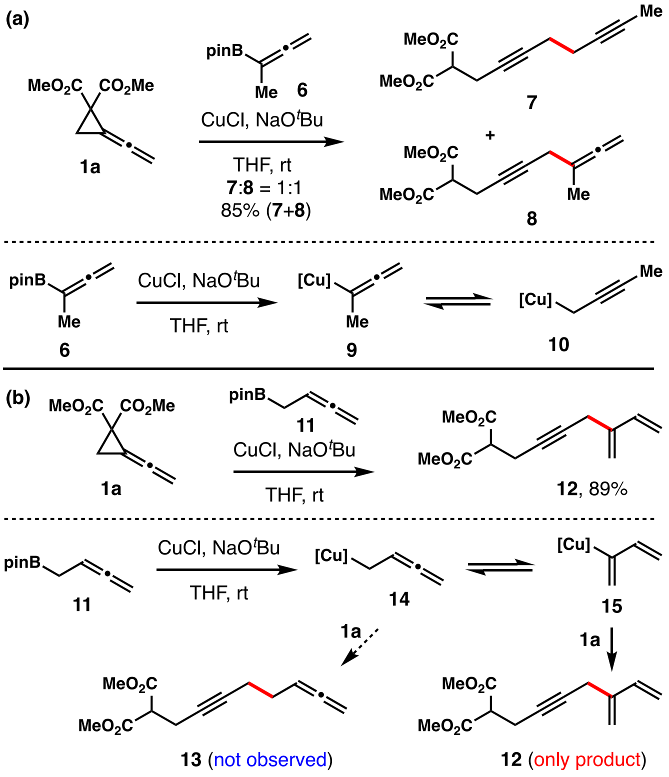
(a) vinylidene cyclopropane **1a** (0.1 mmol, 1 equiv), CuCl (10 mol %), allylBpin **2** (0.11 mmol, 1.1 equiv), NaO^{t}Bu (0.12 mmol, 1.2 equiv), THF (0.5 mL). (b) Yields of isolated products are listed.

Table 3. Reactions of vinylidene cyclopropanes **1** with allenyl boronate **4** ^{a,b}



(a) vinylidene cyclopropane **1** (0.1 mmol, 1 equiv), CuCl (10 mol %), NaO^{t}Bu (0.12 mmol, 1.2 equiv), allenylboronate **4** (0.11 mmol, 1.1 equiv), THF (0.5 mL). (b) Yields of isolated products are listed.

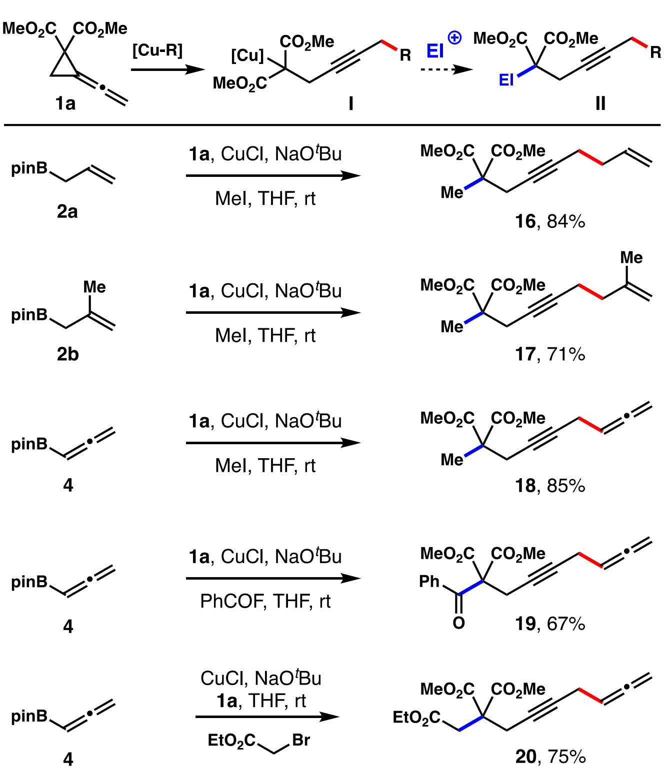
Allenyl boronate **4** also participated in reactions with a variety of vinylidene cyclopropanes under the developed conditions. As shown in Table 3, the reactions of boronate **4** with vinylidene cyclopropanes bearing different ester groups proceeded smoothly to give products **5a**-**b** in 76-90% yields. Vinylidene cyclopropanes with different substitution patterns are also suitable substrates for reactions with allenyl boronate **4**. For instance, the reaction between **4** and vinylidene cyclopropane with an ethyl group at the terminal olefin unit of the allene (R^1 = H, R^2 = Et) gave product **5c** in 80% yield. Different substitution groups on the cyclopropane ring are tolerated. Reactions of **4** with vinylidene cyclopropanes substituted with a Ph-, ^{n}Pentyl, or ^{i}Pr-group occurred to give products **5d**-**f** in 74-86% yields. Notably, the reaction occurred only at the allene moiety of vinylidene cyclopropanes **1**. Addition of nucleophilic allenyl copper species to allene **4** or the allene group of products **5** was not observed.



Scheme 2. Reactions of substituted allenyl boronate **6** and homo-allenyl boronate **11** with vinylidene cyclopropane **1a**

Scheme 2a shows the results from the reaction of vinylidene cyclopropane **1a** with methyl substituted allenyl boronate **6** under the standard conditions. The reaction generated a 1:1 mixture of products **7** and **8**. It is known that allenyl boronate **6** can undergo base-promoted transmetalation with CuCl to form allenyl copper intermediate **9**, which can equilibrate with propargylic copper species **10** at ambient temperature.[18] It is apparent that the reactivities of the two copper intermediates, **9** and **10**, toward the addition to vinylidene cyclopropane **1a** are similar to each other. Therefore, an equal amount of products **7** and **8** were formed. Intriguingly, under the same reaction conditions, the reaction of vinylidene cyclopropane **1a** with homoallenyl boronate **11** gave 1,3-diene **12** as the only product in 89% yield (Scheme 2b). The formation of allene product **13** was not detected. It is conceivable that the initially formed homoallenyl copper intermediate **14** equilibrates with 2-dienyl copper species **15**.[19] However, in this case, the reactivity of 2-dienyl copper **15** must be much higher than that of homoallenyl copper **14** toward the addition to **1a**. Given the fast rates for 1,3-metallo shifts at ambient temperature, the reaction likely proceeded through the more reactive intermediate **15** to give product **12** as the only product, regardless of the thermodynamic stability of **14** and **15**.

On the basis of the proposed reaction pathway (Scheme 1), we suspect that it might be possible to intercept the nucleophilic Cu-[C]-enolate intermediate (or a Cu-[O]-enolate). For instance, when the reaction is conducted in the presence of an alkyl halide, we anticipate Cu-enolate **I** should react with the electrophile to give product **II** (Scheme 3). However, implementation of such a reaction requires balanced chemical reactivities of the nucleophilic copper species (Cu-R) and the electrophile to prevent premature termination of the catalytic cycle due to their direct coupling.



Scheme 3. Three-component reactions of boronates, vinylidene cyclopropane **1a** and electrophiles

To evaluate the feasibility of the proposed three-component coupling, we conducted the reaction of vinylidene cyclopropane **1a** with allylboronate **2a** in the presence of MeI (Scheme 3). Gratifyingly, the reaction afforded product **16** in 84% yield. Any product generated from other potential side-reaction pathways was not detected. Similar results were obtained when the reactions were conducted with allylboronate **2b** or allenyl boronate **4**; products **17** and **18** were isolated in 71% and 85% yield, respectively. In addition to MeI, other electrophiles can also be used to intercept Cu-enolate **I**. For example, when benzoyl fluoride was used, acylated product **19** was formed in 67% yield. Trapping the copper enolate with ethyl bromoacetate gave product **20** in 75% yield. As such, vinylidene cyclopropane **1a** serves as a linchpin to join a nucleophile and an electrophile by forming two carbon–carbon bonds sequentially (highlighted in red and blue in compounds **16**–**20**, Scheme 3).

In summary, we developed a Cu-catalyzed coupling of vinylidene cyclopropanes with allyl or allenyl boronates. These reactions proceeds through a pathway that is distinct from the well-established pathway of allene with allylic electrophiles. Poly-unsaturated molecules were generated in good yields from vinylidene cyclopropanes and allyl/allenyl boronates. In addition, the Cu-enolate intermediate, which is generated from the initial addition of the copper species to vinylidene cyclopropane, can be intercepted by external electrophiles. Therefore, the vinylidene cyclopropane serves as a linchpin to link a nucleophile and an electrophile by sequentially forming two carbon-carbon bonds to rapidly generate molecular complexity.

Notes and references

1 For selected reviews on vinylidene cyclopropanes, see: (a) H. Maeda and K. Mizuno, *J. Syn. Org. Chem., Japan,* 2004, **62**, 1014; (b) M. Shi, L.-X. Shao, J.-M. Lu, Y. Wei, K. Mizuno and H. Maeda, *Chem. Rev.*, 2010, **110**, 5883; (c) D.-H. Zhang, X.-Y. Tang and M. Shi, *Acc. Chem. Res.*, 2014, **47**, 913; (d) S. Yang and M. Shi, *Acc. Chem. Res.*, 2018, **51**, 1667.

2 M. J. Campbell, P. D. Pohlhaus, G. Min, K. Ohmatsu and J. S. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 9180.

3 (a) K. Mizuno, H. Sugita, K, Isagawa, M. Goto and Y. Otsuji, *Tetrahedron Lett.*, 1993, **34**, 5737; (b) K. Mizuno, H. Maeda, H. Sugita, S. Nishioka, T.Hirai and A. Sugimoto, *Org. Lett.*, 2001, **3**, 581.

4 (a) Mizuno, K.; Nire, K.; Sugita, H.; Otsuji, Y. *Tetrahedron Lett.*, 1993, **34**, 6563; (b) Mizuno, K.; Sugita, H.; Hirai, T.; Maeda, H.; Otsuji, Y.; Yasuda, M.; Hashiguchi, M.; Shima, K. *Tetrahedron Lett.*, 2001, **42**, 3363.

5 (a) D. J. Pasto and M. F. Miles, *J. Org. Chem.*, 1976, **41**, 425; (b) G.-C. Xu, L.-P. Liu, J.-M. Lu, and M. Shi, *J. Am. Chem. Soc.*, 2005, **127**, 14552; (c) J.-M. Lu and M. Shi, *Org. Lett.*, 2006, **8**, 5317; (d) Y.-P. Zhang, J.-M. Lu, G.-C. Xu and M. Shi, *J. Org. Chem.*, 2007, **72**, 509.

6 For selected recent references on transition metal-catalyzed reactions with vinylidene cyclopropanes, see: (a) W. Yuan, X. Dong, M. Shi, P. McDowell and G. Li, *Org. Lett.*, 2012, **14**, 5582; (b) C. Ji, Q. Xu and M. Shi, *Adv. Synth. Catal.*, 2017, **359**, 974; (c) S. Yang, K.-H. Rui, X.-Y. Tang, Q. Xu and M. Shi, *J. Am. Chem. Soc.*, 2017, **139**, 5957.

7 For selected recent references on reactions with vinylidene cyclopropanes bearing electron-withdrawing groups, see: (a) L. Wu and M. Shi, *Chem. Eur. J.*, 2010**, 16**, 1149; (b) L. Wu and M. Shi, *J. Org. Chem.*, 2010, **75**, 2296; (c) L. Wu and M. Shi, *Chem. Eur. J.*, 2011, **17**, 13160; (d) L. Wu and M. Shi, *Eur. J. Org. Chem.*, 2011, **2011**, 1099; (e) J. Chen, S. Gao and M. Chen, *Chem. Sci.*, 2019, **10**, 10601; (f) J. Chen, S. Gao and M. Chen, *Org. Lett.*, 2019, **21**, 8800.

8 For selected reviews: (a) S. Yu and S. Ma, *Angew. Chem., Int. Ed.* 2012, **51**, 3074; (b) K. Semba, T. Fujihara, J. Terao and Y. Tsuji, *Tetrahedron*, 2015, **71**, 2183; (c) A. P. Pulis, K. Yeung and D. J. Procter, *Chem. Sci.*, 2017, **8**, 5240; (d) M. Holmes, L. A. Schwartz and M. J. Krische, *Chem. Rev.*, 2018, **118**, 6026; (e) T. Fujihara and Y. Tsuji, *Synthesis*, 2018 **50**, 1737; (f) G. J. P. Perry, T. Jia and D. J. Procter, *ACS Catal.*, 2020, **10**, 1485.

9 For selected recent references: (a) K. Semba, T. Fujihara, J. Terao and Y. Tsuji, *Angew. Chem., Int. Ed.*, 2013, **52**, 12400; (b) K. Semba, M. Shinomiya, T. Fujihara, J. Terao and Y. Tsuji, *Chem. Eur. J.*, 2013, **19**, 7125; (c) W. Yuan, X. Zhang, Y. Yu and S. Ma, *Chem. Eur. J.*, 2013, **19**, 7193; (d) F. Meng, X. Li, S. Torker, Y. Shi, X. Shen and A. H. Hoveyda, *Nature*, 2016, **537**, 387; (e) W. Zhao and J. Montgomery, *J. Am. Chem. Soc.*, 2016, **138**, 9763; (f) J. Zhao and K. J. Szabó, *Angew. Chem., Int. Ed.*, 2016, **55**, 1502; (g) K. Yeung, R. E. Ruscoe, J. Rae, A. P. Pulis and D. J. Procter, *Angew. Chem., Int. Ed.*, 2016, **55**, 11912; (h) Y. Huang, S. Torker, X. Li, J. del Pozo and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2019, **58**, 2685.

10 For selected recent references: (a) Y. Tani, T. Fujihara, J. Terao and Y. Tsuji, *J. Am. Chem. Soc.*, 2014, **136**, 17706; (b) J. Rae, Y. C. Hu and D. J. Procter, *Chem. Eur. J.*, 2014, **20**, 13143; (c) Z.-T. He, X.-Q. Tang, L.-B. Xie, M. Cheng, P. Tian and G.-Q. Lin, *Angew. Chem., Int. Ed.*, 2015, **54**, 14815; (d) T. Fujihara, A. Sawada, T. Yamaguchi, Y. Tani, J. Terao and Y. Tsuji, *Angew. Chem., Int. Ed.*, 2017, **56**, 1539.

11 For selected recent references: (a) D. Zhao, K. Oisaki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 14440; (b) Y. Tani, K. Kuga, T. Fujihara, J. Terao and Y. Tsuji, *Chem. Commun.*, 2015, **51**, 13020; (c) R. Y. Liu, Y. Yang and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2016, **55**, 14077; (d) M. Lee, M. Nguyen, C. Brandt, W. Kaminsky and G. Lalic, *Angew. Chem., Int. Ed.*, 2017, **56**, 15703; (e) E. Y. Tsai, R. R. Liu, Y. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2018, **140**, 2007; (f) R. R. Liu, Y. Zhou, Y. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2019, **141**, 2251.

12 For a Cu-catalyzed reaction with carbon nucleophiles, see: T. Itoh, Y. Shimizu and M. Kanai, *Org. Lett.*, 2014, **16**, 2736.

13 For selected references on coupling of allenes with allylic electrophiles, see: (a) F. Meng, K. P. McGrath and A. H. Hoveyda, *Nature*, 2014, **513**, 367; (b) K. Semba, N. Bessho, T. Fujihara, J. Terao and Y. Tsuji, *Angew. Chem., Int. Ed.*, 2014, **53**, 9007; (c) T. Fujihara, K. Yokota, J. Terao and Y. Tsuji, *Chem. Commun.*, 2017, **53**, 7898; (d) G. Xu, B. Fu, H. Zhao, Y. Li, G. Zhang, Y. Wang, T. Xiong and Q. Zhang, *Chem. Sci.*, 2019, **10**, 1802.

14 For a single example of Pd-catalyzed hydroallylation of allene with allylic boronate: D.-W. Ji, Y.-C. Hu, H. Zheng, C.-Y. Zhao, Q.-A. Chen and V. M. Dong, *Chem. Sci.*, 2019, **10**, 6311.

15 (a) M. Wang, S. Khan, E. Miliordos and M. Chen, *Org. Lett.,* 2018, **20**, 3810; (b) M. Wang, S. Khan, E. Miliordos and M. Chen, *Adv. Synth. Catal.,* 2018, **360**, 4634; (c) S. Gao and M. Chen, *Org. Lett.,* 2018, **20**, 6174; (d) S. Gao, M. Wang and M. Chen, *Org. Lett.,* 2018, **20**, 7921; (e) S. Gao, J. Chen and M. Chen, *Chem. Sci.,* 2019, **10**, 3637; (f) M. Wang, S. Gao and M. Chen, *Org. Lett.,* 2019, **21**, 2151; (g) J. Chen, S. Gao, J. D. Gorden and M. Chen, *Org. Lett.,* 2019, **21**, 4638; (h) J. Chen, S. Gao and M. Chen, *Org. Lett.,* 2019, **21**, 9893; (i) S. Gao and M. Chen, *Chem. Sci.*, 2019, **10**, 7554; (j) S. Gao and M. Chen, *Chem. Commun.*, 2019, **55**, 11199; (k) S. Gao and M. Chen, *Org. Lett.,* 2020, **22**, 400; (l) J. Chen and M. Chen, *Org. Lett.*, 2020, **22**, 7321; (m) J. Liu and M. Chen, *Org. Lett.*, 2020, **22**, 8967; (n) S. Gao, M. Duan, K. N. Houk and M. Chen, *Angew. Chem. Int. Ed.,* 2020, **59**, 10540; (o) S. Gao, M. Duan, Z. Shao, K. N. Houk and M. Chen, *J. Am. Chem. Soc* 2020, **142**, 18355; (p) J. Chen, E. Miliordos and M. Chen, *Angew. Chem. Int. Ed* 2021, **60**, 840.

16 For selected references on allyl-metalation of allenes, see: (a) J. F. Normant, J. C. Quirion, Y. Masuda and A. Alexakis, *Tetrahedron Lett.*, 1990, **31**, 2879; (b) T. Nishikawa, H. Shinokubo and K. Oshima, *Org. Lett.*, 2003, **5**, 4623; (c) S. Kim and P. H. Lee, *Eur. J. Org. Chem.*, 2008, 2262.

17 For an example of reaction with allene to form a vinyl copper intermediate due to steric factors, see: W. Yuan, L. Song and S. Ma, *Angew. Chem. Int. Ed.*, 2016, **55**, 3140.

18 (a) D. R. Fandrick, K. R. Fandrick, J. T. Reeves, Z. Tan, W. Tang, A. G. Capacci, S. Rodriguez, J. J. Song, H. Lee, N. K. Yee and C. H. Senanayake, *J. Am. Chem. Soc.*, 2010, **132**, 7600; (b) B. Jung and A. H. Hoveyda, *J. Am. Chem. Soc.,* 2012, **134**, 1490.

19 Direct generation of copper species **15** via base-promoted transmetalation of **11** with the catalyst is also possible.