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Copper-Catalyzed S_N2'-Selective Allylic Substitution Reaction of *gem*-Diborylalkanes

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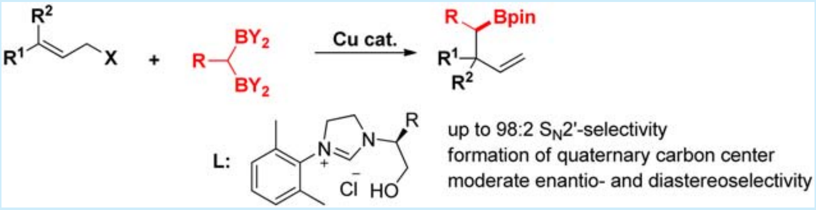
Supporting Information

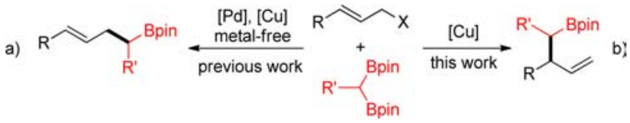


ABSTRACT: A Cu/(NHC)-catalyzed S_N2'-selective substitution reaction of allylic electrophiles with *gem*-diborylalkanes is reported. Different substituted *gem*-diborylalkanes and allylic electrophiles can be employed in this reaction, and various synthetic valuable functional groups can be tolerated. The asymmetric version of this reaction was initially researched with chiral N-heterocyclic carbene (NHC) ligands.

Copper-catalyzed cross-coupling reactions of allylic electrophiles are powerful methods for constructing C−C bonds, especially for the formation of saturated C−C bonds.[1] In the past few decades, a variety of organometallic reagents have been used in these reactions, such as Grignard, alkyllithium, alkylaluminum, alkylzirconium, and dialkylzinc.[2] Despite their high activity, their air and moisture sensitivity have limited their application in synthesis. In contrast, organoboronic acid derivatives are widely used because of their stability, availability, and good functional group tolerance.[3] To date, many studies in the field of coupling between allylic electrophiles with organoboron compounds have been reported,[4] which often employ aryl,[5] alkenyl,[6] and allyl boron reagents[7] and alkyl-9-BBN.[8] Among of them, allylboron reagents and alkyl-9-BBN applied in these methods can realize the alkylation of allylic electrophiles.

Recently, a series of novel alkylboron compounds, namely *gem*-diboryalkanes, attracted attention from chemists. In the field of construction of C−C bonds with *gem*-diboryalkanes,[9] Shibata et al. reported the pioneering work.[10] More and more attention focused on these interesting synthons due to their special activity and structure. Thereafter, Morken and co-workers developed the first Pd-catalyzed stereoselective Suzuki cross-coupling of 1,1-diborylalkanes,[11] and then Morken's[12] and our group[13] independently reported the coupling of alkyl (pseudo)halides with *gem*-diborylalkanes. Recently, Meek's group also reported the addition reaction of aldehydes and 1,1-diborylalkanes.[14] Despite many reaction types, allylic substitution reactions of allylic electrophiles with 1,1-diborylalkanes have rarely been reported (Scheme 1a).[10c,12,13] Furthermore, the γ-selective reaction of *gem*-diborylalkanes remains challenging. Herein, we describe copper-catalyzed S_N2'-selective alkylation reactions of allylic electrophiles with 1,1-diborylalkanes (Scheme 1b).[15] Through this method, we can obtain the branched γ-substitution products through the Cu/(NHC)-catalyzed system successfully. Various synthetic valuable functional groups could be tolerated with mild reaction conditions. Different side-chain-substituted *gem*-diborylalkanes and allylic electrophiles can be employed. Finally, the asymmetric version of this reaction was initially researched with chiral N-heterocyclic carbene (NHC) ligands.

Scheme 1. Regioselective Allylic Substitution Reactions of Allylic Electrophiles with *gem*-Diborylalkanes



Recently, we reported Cu-catalyzed/promoted alkylation of *gem*-diborylalkanes. We found that diborylmethane could react with cinnamyl phosphate to afford the linear α-substitution product.[13] On the basis of this finding, we attempted to achieve the synthesis of branched products by governing the catalyst system. Subsequently, we examined the allylic substitution of 1,1-diborylalkanes with allylic electrophiles. Diborylmethane (**1**) and cinnamyl electrophiles were selected as the model substrates (Table 1). At first, we repeated our previous conditions with cinnamyl phosphate (**1b**) (entry 1 and 2) and obtained major product **2a**. Then we tried THF and dioxane (entry 3 and 4) and found that **1a** was the major product and the selectivity of **1a** and **2a** was reversed. We next examined the ligand effect with SIMes, IMes, IPr, and L1

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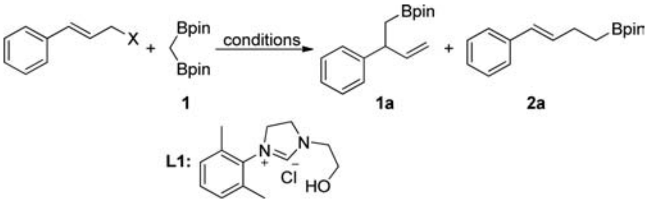
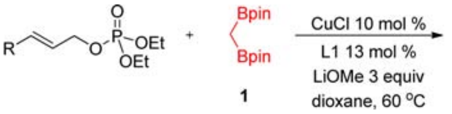
Table 1. Optimization of the Reaction Conditions[a]

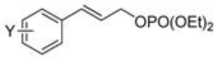
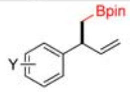
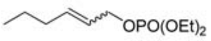
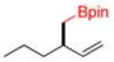
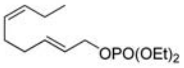
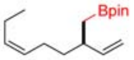
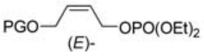
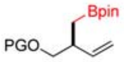
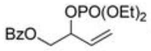
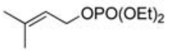


entry	X	solvent	ligand	yield (%)	1a/2a
1[b]	OPO(OEt)$_2$	DMF	–	88	8:92
2	OPO(OEt)$_2$	DMF	–	87	4:96
3	OPO(OEt)$_2$	THF	–	66	83:17
4	OPO(OEt)$_2$	dioxane	–	68	87:13
5	OPO(OEt)$_2$	dioxane	SIMesHCl	72	85:15
6	OPO(OEt)$_2$	dioxane	IMesHCl	67	80:20
7	OPO(OEt)$_2$	dioxane	IPrHCl	23	82:18
8	**OPO(OEt)$_2$**	**dioxane**	**L1**	**89**	**97:3**
9[b]	OPO(OEt)$_2$	dioxane	L1	64	96:4
10	Cl	dioxane	L1	79	90:10
11	OAc	dioxane	L1	trace	–
12	OCOOMe	dioxane	L1	22	75:25
13[c]	OPO(OEt)$_2$	dioxane	L1	0	–

[a] All reactions were carried out at 60 °C on a 0.15 mmol scale, and 10 mol % of CuCl, 3 equiv of LiOMe, 2 equiv of diborylmethane (**1**), and 1 mL of solvent were used. The yields and the ratios of **1a**/**2a** were determined by GC (average of two GC runs). [b] *t*-BuOLi was used instead of LiOMe. [c] The reaction was carried out without CuCl.

Table 2. Substrate Scope for the Reaction of Allylic Phosphates with Diborylmethane[a]



entry	substrates	product	yield (%)	S$_N$2′:S$_N$2 [b]
				
1	Y = 2-Br **2b**	**2c**	77	96:4
2	Y = 4-Br **3b**	**3c**	83	97:3
3	Y = 2-Cl **4b**	**4c**	79	95:5
4	Y = 3-Cl **5b**	**5c**	77	97:3
5	Y = 4-Cl **6b**	**6c**	76	96:4
6	Y = 4-NO$_2$ **7b**	**7c**	82	93:7
7	Y = 4-F **8b**	**8c**	88	98:2
8	Y = 3-CF$_3$ **9b**	**9c**	85	97:3
9	Y = 4-CN **10b**	**10c**	66	92:8
				
10	(*E*)- **11b**	**11c**	58	98:2
11	(*Z*)- **12b**	**12c**	52	97:3
				
12	**13b**	**13c**	57	98:2
				
13	PG = Benzoyl **14b**	**14c**	45	96:4
14	PG = 2-Thenoyl **15b**	**15c**	75	98:2
15	PG = 2-furoyl **16b**	**16c**	54	93:7
16	PG = Bn **17b**	**17c**	77	95:5
17	PG = TBS **18b**	**18c**	62	98:2
				
18	**19b**	**19c**	68	97:3
				
19[c]	**20b**	**20c**	72	85:15

[a] Reactions were carried out under the conditions shown, using allylic phosphates as substrates, and all yields are isolated yields. [b] The ratios of S$_N$2′/S$_N$2 were determined by ^{1}H NMR analysis of the reaction mixture. [c] When L1 was used as ligand, the S$_N$2′/S$_N$2 was low (68:32). When L2 was used, the regioselectivity ratio was improved to 85:15.

(entries 5–8; for details, see the Supporting Information). Significantly, ligand L1 not only improved the yield to 89% but also gave excellent regioselectivity (entry 8, **1a**/**2a** = 98:2). In addition to cinnamyl phosphate, we also tried some other cinnamyl electrophiles (Cl, OAc, OCOOMe); however, all these attempts failed to give better regioselectivity or yield. With control experiments, we found that this reaction could not be processed without copper catalysts (entry 13).

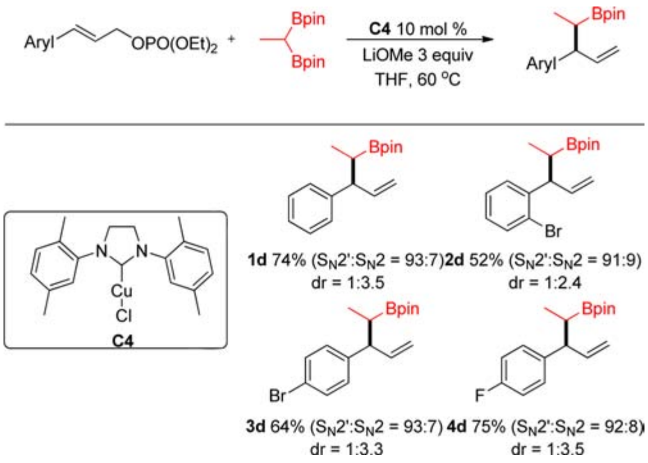
With the optimized conditions in hand, we investigated the scope of this newly developed reaction. As shown in Table 2, diborylmethane can react with both aromatic and aliphatic allylic phosphates. A variety of halogen-substituted cinnamyl phosphates can successfully afford the corresponding products in good yields and S$_N$2′ selectivity. Different substituted positions on the cinnamyl phosphates posed no problem with these reaction conditions (**2c**–**6c** and **8c**). Many important functional groups were also compatible, such as NO$_2$ (**7c**), CF$_3$ (**9c**), CN (**10c**), and vinyl (**13c**). Both (*Z*)- and (*E*)-allylic phosphates (**12b** and **11b**) have similar reactivity and afforded the same product (**11c**). Substrates with commonly used hydroxyl protecting groups can also be employed and give *γ*-selective product in high yields (**14c**, **17c**, and **18c**). The heterocyclic compounds (**15c** and **16c**) survived under our reaction conditions with good yields. In addition to primary allylic phosphates, the secondary ones also can be used in this reaction (**19c**). Finally, we examined the allylic phosphates which can afford quaternary carbon center (**20b**). The desired product (**20c**) was obtained with moderate yield and regioselectivity.

Meanwhile, we also investigated the substituted *gem*-diborylalkanes under the reaction conditions. Unfortunately, the yield (52%, S$_N$2′/S$_N$2 = 82:18) and dr value (1.2:1) were very low when 1,1-diborylalkane (**2**) was used. Modifications to lead to improvements were carried out, and we determined newly optimized conditions. We examined several allylic phosphates to afford the corresponding products (**1d**–**4d**) with good yield, S$_N$2′-selectivity, and moderate diastereoselectivity. (Scheme 2; for details, see the Supporting Information).

Allylic epoxide could be recognized as a special allylic electrophile; thus, we also tried to employ it in this reaction and found it can indeed react with different *gem*-diborylalkanes to generate S$_N$2′-selective products (Scheme 3).

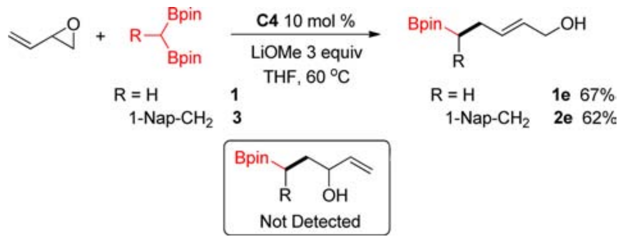
The asymmetric version of this reaction was initially researched with chiral N-heterocyclic carbene (NHC) ligands.

Scheme 2. Substrate Scope for the Reaction of Allylic Phosphates with Substituted *gem*-Diborylalkanes[a]



[a]Reactions were carried out under the conditions shown, all yields were isolated yields, and the ratios of S_N2'/S_N2 were determined by ^1H NMR analysis of the reaction mixture.

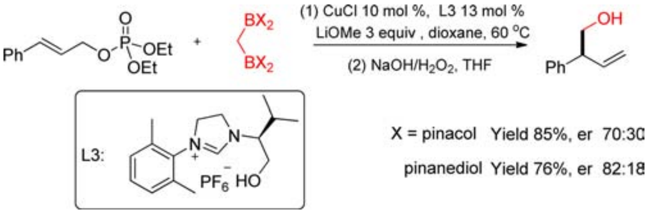
Scheme 3. Reaction of Allylic Epoxide with Substituted *gem*-Diborylalkanes[a]



[a]Reactions were carried out under the conditions shown, all yields are isolated yields, and the ratios of S_N2'/S_N2 were determined by ^1H NMR analysis of the reaction mixture.

We found that the ee value can be governed when diborylmethanes are used with different steric hindrance (X = pinacol, 40% ee, X = pinanediol, 64% ee) (Scheme 4; for details, see the Supporting Information).

Scheme 4. Asymmetric Selectivity of the Reaction of Allylic Phosphates with Diborylmethane[a]



[a]Reactions were carried out under the conditions shown, all yields are isolated yields, and the ee value were determined by HPLC analysis.

In summary, we have reported a copper-catalyzed S_N2'-selective allylic alkylation reaction of allylic electrophiles with substituted *gem*-diborylalkanes.[16] A variety of synthetically important functional groups can be compatible under these conditions. The asymmetric version of this reaction was initially researched with chiral N-heterocyclic carbene (NHC) ligands, and further efforts to improve the enantio- and diastereoselectivity of this reaction 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.5b03692.

Detailed experimental procedures and spectra data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For allylic substitution reactions, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779. (c) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435. (d) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (e) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (f) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545. (g) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, *2008*, 3765. (h) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (i) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486. (j) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(2) For recent examples, see: (a) Falciola, C. A.; Alexakis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2619. (b) Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913. (c) Selim, K. B.; Yamada, K.; Tomioka, K. *Chem. Commun.* **2008**, 5140. (d) Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8733. (e) Selim, K. B.; Nakanishi, H.; Matsumoto, Y.; Yamamoto, Y.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2011**, *76*, 1398. (f) Lölsberg, W.; Ye, S.; Schmalz, H.-G. *Adv. Synth. Catal.* **2010**, *352*, 2023. (g) Magrez, M.; Le Guen, Y.; Baslé, O.; Crévisy, C.; Mauduit, M. *Chem. - Eur. J.* **2013**, *19*, 1199. (h) Hornillos, V.; Pérez, M.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. - Eur. J.* **2013**, *19*, 5432. (i) Li, H.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 1055. (j) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554. (k) Yoshikai, N.; Miura, K.; Nakamura, E. *Adv. Synth. Catal.* **2009**, *351*, 1014. (l) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446. (m) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419. (n) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8370. (o) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315. (p) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778. (q) You, H.; Rideau, E.; Sidera, M.; Fletcher, S. P. *Nature* **2015**, *517*, 351.

(3) Hall, D. G. In *Boronic Acids*; Wiley−VCH, 2006; p 1.

(4) For a review of transition-metal-catalyzed allylic substitution reactions with organoboron reagents, see: Pigge, F. C. *Synthesis* **2010**, *2010*, 1745.

(5) For some examples of Cu-catalyzed allylic substitution reactions with arylboronic acid derivatives, see: (a) Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216. (b) Ohmiya, H.; Yokokawa, N.; Sawamura, M. *Org. Lett.* **2010**, *12*, 2438. (c) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656. (d) Takeda, M.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2014**, *79*, 2354.

(6) For some examples of Cu-catalyzed allylic substitution reactions with alkenylboronic acid derivatives, see: (a) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6613. (b) Gao, F.; Carr, J. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 2149.

(7) For some examples of metal-catalyzed allylic substitution reactions with allylic boronic acid derivatives, see: (a) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778. (b) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716. (c) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686.

(8) For some examples of Cu-catalyzed allylic substitution reactions with alkyl-9-BBN, see: (a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895. (b) Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 18573. (c) Nagao, K.; Yokobori, U.; Makida, Y.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 8982. (d) Hojoh; Shido, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 4954.

(9) For reviews of reactions with *gem*-diborylalkanes, see: Xu, L.; Zhang, S.; Li, P. *Chem. Soc. Rev.* **2015**, *44*, 8848.

(10) (a) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033. (b) Endo, K.; Ohkubo, T.; Shibata, T. *Org. Lett.* **2011**, *13*, 3368. (c) Endo, K.; Ohkubo, T.; Ishioka, T.; Shibata, T. *J. Org. Chem.* **2012**, *77*, 4826.

(11) (a) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534. (b) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 17918.

(12) Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581.

(13) Zhang, Z.-Q.; Yang, C.-T.; Liang, L.-J.; Xiao, B.; Lu, X.; Liu, J.-H.; Sun, Y.-Y.; Marder, T. B.; Fu, Y. *Org. Lett.* **2014**, *16*, 6342.

(14) (a) Joannou, M. V.; Moyer, B. S.; Goldfogel, M. J.; Meek, S. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14141. (b) Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176.

(15) While our manuscript was in preparation, Cho et al. described a Cu-catalyzed S_N2'-selective substitution reaction of 1,1-diborylalkanes. In their work, *gem*-diborylalkanes can react with allyl chlorides smoothly by IMesCuCl catalysis. However, the reaction was mainly applied to allyl chlorides, and the diastereoselectivity of substituted 1,1-diborylalkyanes is very low. The asymmetric version of this reaction was not investigated. See: Kim, J.; Park, S.; Park, J.; Cho, S. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1498.

(16) According to the following references, we assume that the mechanism of this reaction involved an alkylalkoxycuprate complex generated by these bidentate NHC ligands as an active species. See ref 5c and: Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490.