Communication
DOI: 10.1002/bkcs.12212

BULLETIN OF THE
KOREAN CHEMICAL SOCIETY

Pd-Catalyzed Negishi Cross-Coupling of Vinyl Bromides with Diborylmethylzinc Chloride

Minjae Kim,[†] Jun Hee Lee,[‡,*] and Seung Hwan Cho[†,*]

*[†]Department of Chemistry, Pohang University of Science and Technology (POSTECH), Pohang 37673, Republic of Korea. *E-mail: seunghwan@postech.ac.kr*
*[‡]Department of Advanced Materials Chemistry, Dongguk University Gyeongju Campus, Gyeongju 38066, Republic of Korea. *E-mail: leejunhee@dongguk.ac.kr*

Received December 9, 2020, Accepted December 23, 2020, Published online January 4, 2021

Keywords: Palladium, Negishi coupling, Allylboronate ester, *gem*-diborylalkane, Cross-coupling

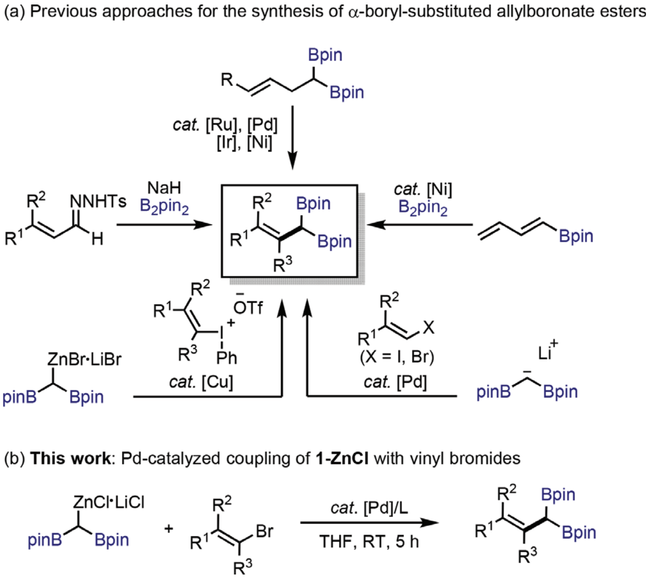
Allylboron compounds are valuable synthetic precursors during the synthesis of a variety of pharmaceuticals and biologically active compounds.[1] In particular, α-boryl-substituted allylic boronate esters have been considered promising reagents because they can chemoselectively react with aldehydes or aldimines to produce homoallylic alcohols or homoallylic amines that contain a vinyl boron unit.[2] Thus, the discovery of an efficient methodology that provides access to diverse α-boryl-substituted allylic boronate esters is desirable in organic synthesis.

In prior studies, such compounds have been prepared by the transition-metal-free insertion of B_2pin_2 into *N*-tosylhydrazone,[3b] by the metal–catalyzed alkene isomerization of *gem*-diborylalkanes containing an alkene moiety in the alkyl substituents,[4] or 1,4-diboration of dienylboronate ester.[2c] More recently, transition-metal-catalyzed cross-coupling approaches have also been disclosed (Scheme 1(a)). For example, our group reported Cu-catalyzed cross-coupling of diborylmethylzinc halides with various vinyl iodonium salts.[5a] Meek and co-workers developed Pd-catalyzed coupling of diborylmethyllithium with 2,2-disubstituted vinyl halides.[6] However, the former method required extra steps for the preparation of iodonium salts, and the latter approach typically showed low yields probably due to high reactivity of diborylmethyllithium.

In our continuing interest in the development of chemoselective transformations of *gem*-diborylalkanes,[7,8] we recently demonstrated that diborylmethylzinc halides served as useful multi-organometallic reagents in Pd-catalyzed, chemoselective cross-coupling with aryl (pseudo)halides.[5b,9] Based on this achievement, we envisaged that Pd-catalyzed coupling of diborylmethylzinc halides with vinyl halides would offer an attractive route for the preparation of α-boryl-substituted allylic boronate esters (Scheme 1(b)).

We commenced our study by employing 1-bromo-2-methylprop-1-ene (**2a**) as an electrophile and diborylmethylzinc bromide **1-ZnBr** as a nucleophile in the presence of $Pd_2(dba)_3$ (1.0 mol%) as a catalyst and P(*o*-tolyl)$_3$ (2.0 mol%) as a ligand in THF at 60 °C (Table 1). However, we obtained the desired coupled product **3a** in a low yield of 24% (Table 1, entry 1). Further evaluation revealed that the halide source of diborylmethylzinc halides strongly affected the reaction efficiency. Pleasingly, we obtained product **3a** in a good yield of 83% using diborylmethylzinc chloride **1-ZnCl** (entry 2). Unfortunately, no reaction took place when diborylmethylzinc iodide **1-ZnI** was employed as a nucleophile (entry 3). Noteworthy is that the choice of a ligand is also critical to the success of the cross-coupling reaction in high efficiency. When a monophosphine such as P(*m*-tolyl)$_3$ or P(*p*-tolyl)$_3$ was used instead of P(*o*-tolyl)$_3$, the yield of the reactions decreased (entries 4 and 5). Interestingly, the employment of bidentate ligand such as 1,1′-bis(diphenylphosphino)ferrocene (dppf) as a ligand resulted in a negligible conversion (entry 6).

Having determined the optimal conditions, we investigated the substrate scope of vinyl bromides in Pd-catalyzed coupling with **1-ZnCl**. As depicted in Scheme 2, the coupling reactions of (*E*)-vinyl bromides bearing various alkyl substituents at the β-position proceeded without difficulties, giving α-boryl-substituted allylic boronate esters **3a**–**3e** in good-to-moderate yields. Reactions performed with (bromomethylene)cyclohexane and cycloheptane efficiently produced **3f** and **3g**, respectively, in good yields. When the monosubstituted vinyl bromides, such as (*E*)-(2-bromovinyl) trimethylsilane and (2-bromovinyl)trimethylsilane, were exposed to **1-ZnCl** at an elevated temperature of 80 °C in the presence of $Pd_2(dba)_3$ (2.0 mol%) and P(*o*-tolyl)$_3$ (4.0 mol%), we obtained the corresponding cross-coupling products **3h** and **3i** in moderate yields. We were pleased to find that a 1,2,2-trisubstituted vinyl bromide such as 2-bromo-3-methylbut-2-ene also underwent the coupling reaction to afford **3j** in good yield. Furthermore, the cross-couplings of the cyclic vinyl bromides, such as 3-bromo-1,2-dihydronaphthalene and 3-bromo-3-fluoro-1,2-dihydronaphthalene, with **1-ZnCl** also proceeded smoothly to yield the corresponding α-boryl-substituted allylic boronate esters **3k** and **3l** in 90% and 65% yields, respectively. Pleasingly, we found that a rather complicated vinyl bromide derived from estrone,[10,11] a female sex hormone,



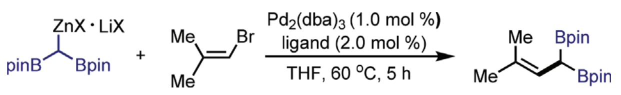
Scheme 1. Approaches for synthesizing α-boryl-substituted allylic boronate esters.

can also be successfully used in this cross-coupling reaction to afford **3m** in 40% yield.

Next, we sought to demonstrate the synthetic utility of α-boryl-substituted allylic boronates via their further transformations. To this end, as summarized in Scheme 3, the treatment of **3m** with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) generated the allylic (diboryl)lithium species *in situ*, which was then captured by CH_2I_2 to give the vinyl boronate ester **4** in 41% yield.[12] Subsequent oxidation of **4** with basic hydrogen peroxide provided the α,β-unsaturated ketone **5** in 77% yield.

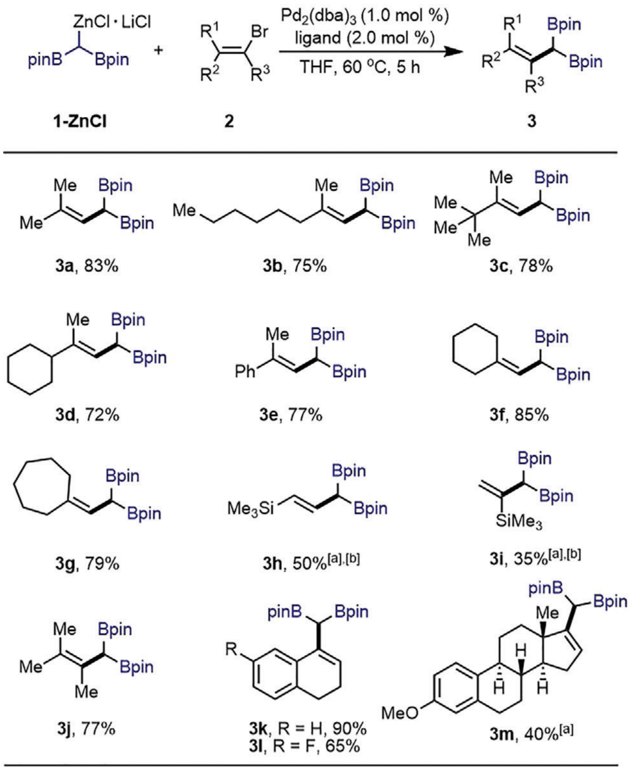
In conclusion, we have reported the Pd-catalyzed cross-coupling of vinyl bromides with diborylmethylzinc halides **1-ZnX**. The halide source of **1-ZnX** and the choice of a monophosphine ligand are critical to the success of the cross-coupling reactions. Hence, the coupling process proceeds efficiently by using diborylmethylzinc chloride **1-ZnCl** in the presence of $Pd_2(dba)_3$ as the catalyst along with P(*o*-tolyl)$_3$ as the ligand, providing various *α*-boryl-substituted allylboronate esters in good-to-moderate yields. Furthermore, we have also demonstrated that the obtained α-boryl-substituted allylboronate ester can be used as a synthetically useful synthon for the preparation of advanced derivatives.

Table 1. Optimization study.

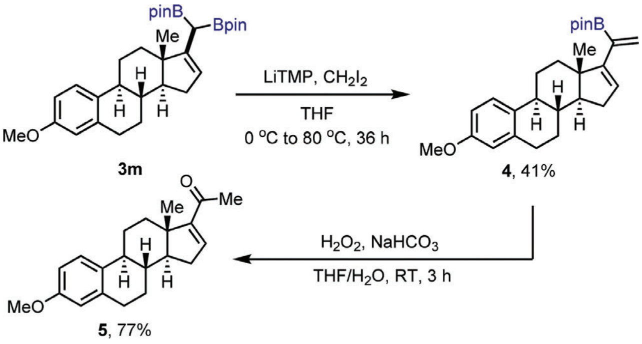


Entry	[M]X	Ligand]	Yield (%)[a]
1	ZnBr·LiBr (**1-ZnBr**)	P(*o*-tolyl)$_3$	24
2	ZnCl·LiCl (**1-ZnCl**)	P(*o*-tolyl)$_3$	83
3	ZnI·LiI (**1-ZnI**)	P(*o*-tolyl)$_3$	<1
4	ZnCl·LiCl (**1-ZnCl**)	P(*m*-tolyl)$_3$	44
5	ZnCl·LiCl (**1-ZnCl**)	P(*p*-tolyl)$_3$	17
6	ZnCl·LiCl (**1-ZnCl**)	dppf	<1

[a] The reaction was conducted using $Pd_2(dba)_3$ (1.0 mol%), ligand (2.0 mol%), **2a** (0.20 mmol), **1-ZnX** (1.5 equiv), and THF (1.0 mL) at 60 °C for 5 h. ^{1}H-NMR was determined using 1,1,2,2-tetrachloroethane as an internal standard.



Scheme 2. Scope of vinyl bromides. The reaction was conducted using $Pd_2(dba)_3$ (1.0 mol%), P(*o*-tolyl)$_3$ (2.0 mol%), vinyl bromide (0.20 mmol), **1-ZnCl** (1.5 equiv), and THF (1.0 mL) at 60 °C for 5 h. [a]$Pd_2(dba)_3$ (2.0 mol%) and P(*o*-tolyl)$_3$ (4.0 mol%). [b]Runs at 80 °C. In all cases, isolated yields were indicated.



Scheme 3. Further transformations of α-boryl-substituted allylic boronate ester **3m**.

Acknowledgments. This work was supported by the National Research Foundation of Korea (NRF-2019R1A2C2004925). J.H.L. is grateful for the Dongguk University Research Fund of 2020.

Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

References

1. For representative reviews on the preparation of allylboron reagents, see: (a) J. W. J. Kennedy, D. G. Hall, *Angew. Chem. Int. Ed.* **2003**, *42*, 4732. (b) D. G. Hall, *Synlett* **2007**, *2007*, 1644. (c) M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774. (d) H. X. Huo, J. R. Duvall, M. Y. Huang, R. Hong, *Org. Chem. Front.* **2014**, *1*, 303. (e) E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott, T. B. Marder, *Chem. Rev.* **2016**, *116*, 9091. (f) C. Diner, K. J. Szabo, *J. Am. Chem. Soc.* **2017**, *139*, 2.
2. (a) J. M. Zanghi, S. J. Meek, *Angew. Chem. Int. Ed.* **2020**, *59*, 8451.(b) M. Z. Liang, S. J. Meek, *J. Am. Chem. Soc.* **2020**, *142*, 9925. (c) M. Wang, S. Gao, M. Chen, *Org. Lett.* **2019**, *21*, 2151.
3. (a) H. Abu Ali, I. Goldberg, D. Kaufmann, C. Burmeister, M. Srebnik, *Organometallics* **2002**, *21*, 1870. (b) H. Li, X. Shangguan, Z. Zhang, S. Huang, Y. Zhang, J. Wang, *Org. Lett.* **2014**, *16*, 448. (c) A. J. Wommack, J. S. Kingsbury, *Tetrahedron Lett.* **2014**, *55*, 3163. (d) H. Zhao, M. Tong, H. Wang, S. Xu, *Org. Biomol. Chem.* **2017**, *15*, 3418.
4. (a) T. Miura, J. Nakahashi, M. Murakami, *Angew. Chem. Int. Ed.* **2017**, *56*, 6989. (b) T. Miura, J. Nakahashi, W. Zhou, Y. Shiratori, S. G. Stewart, M. Murakami, *J. Am. Chem. Soc.* **2017**, *139*, 10903. (c) J. Park, S. Choi, Y. Lee, S. H. Cho, *Org. Lett.* **2017**, *19*, 4054. (d) S. Gao, J. Chen, M. Chen, *Chem. Sci.* **2019**, *10*, 3637. (e) T. Miura, N. Oku, M. Murakami, *Angew. Chem. Int. Ed.* **2019**, *58*, 14620.
5. (a) M. Shin, M. Kim, C. Hwang, H. Lee, H. Kwon, J. Park, E. Lee, S. H. Cho, *Org. Lett.* **2020**, *22*, 2476. (b) H. Lee, Y. Lee, S. H. Cho, *Org. Lett.* **2019**, *21*, 5912.
6. J. C. Green, J. M. Zanghi, S. J. Meek, *J. Am. Chem. Soc.* **2020**, *142*, 1704.
7. For recent reviews, see: (a) N. Miralles, R. J. Maza, E. Fernández, *Adv. Synth. Catal.* **2018**, *360*, 1306. (b) R. Nallagonda, K. Padala, A. Masarwa, *Org. Biomol. Chem.* **2018**, *16*, 1050. (c) C. Wu, J. Wang, *Tetrahedron Lett.* **2018**, *59*, 2128. (d) K. D. Kim, J. H. Lee, *Bull. Kor. Chem. Soc.* **2018**, *39*, 5.
8. (a) J. Kim, S. Park, J. Park, S. H. Cho, *Angew. Chem. Int. Ed.* **2016**, *55*, 1498. (b) J. Park, Y. Lee, J. Kim, S. H. Cho, *Org. Lett.* **2016**, *18*, 1210. (c) W. Jo, J. Kim, S. Choi, S. H. Cho, *Angew. Chem. Int. Ed.* **2016**, *55*, 9690. (d) C. Hwang, W. Jo, S. H. Cho, *Chem. Commun.* **2017**, *53*, 7573. (e) J. Kim, K. Ko, S. H. Cho, *Angew. Chem. Int. Ed.* **2017**, *56*, 11584. (f) Y. Lee, S. Baek, J. Park, S. T. Kim, *J. Am. Chem. Soc.* **2017**, *139*, 976. (g) J. Kim, C. Hwang, Y. Kim, S. H. Cho, *Org. Process. Res. Dev.* **2019**, *23*, 1663. (h) J. Kim, S. H. Cho, *ACS Catal.* **2019**, *9*, 230. (i) J. Kim, M. Shin, S. H. Cho, *ACS Catal.* **2019**, *9*, 8503. (j) W. Jo, S. Baek, C. Hwang, J. Heo, M. H. Baik, S. H. Cho, *J. Am. Chem. Soc.* **2020**, *142*, 13235.
9. For the application of bis[(pinacolato)boryl]methylzinc halides in an asymmetric allylic substitution reaction, also see: Y. Lee, J. Park, S. H. Cho, *Angew. Chem. Int. Ed.* **2018**, *57*, 12930.
10. P. Yu, B. Morandi, *Angew. Chem. Int. Ed.* **2017**, *56*, 15693.
11. J. Pan, X. Wang, Y. Zhang, S. L. Buchwald, *Org. Lett.* **2011**, *13*, 4974.
12. J. R. Coombs, L. Zhang, J. P. Morken, *Org. Lett.* **2015**, *17*, 1708.