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Synthesis of Borylcyclopropanes by Chromium-Promoted Cyclopropanation of Unactivated Alkenes

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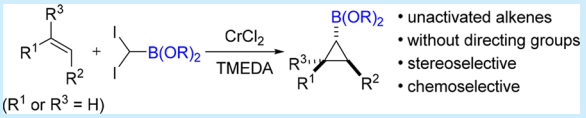
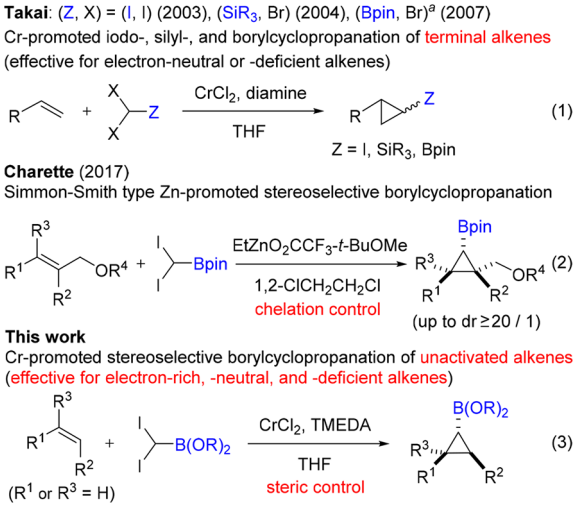
Supporting Information

ABSTRACT: The combination of diiodomethylboronate ester, $CrCl_2$ with TMEDA promoted borylcyclopropanation of unactivated alkenes under mild conditions. Compared with the typical Simmons–Smith cyclopropanation, the current protocol offers the following advantages: (1) the reaction proceeds stereoselectively with disubstituted alkenes even without hydroxy or alkoxy groups; (2) both electron-rich and electron-deficient alkenes can be applicable; and (3) the reaction does not require potentially flammable alkylzinc. These unique reactivity features result from the steric and electronic nature of the *gem*-dichromiomethane intermediates.



Cyclopropanes, the smallest carbocycles, are widely found in naturally occurring compounds, commercial medicines, and agrochemicals, and play indispensable roles as important substructures.[1] Due to the unique steric and electronic features that result from their distorted structure, appropriately substituted cyclopropanes are also useful building blocks for the synthesis of complex carbo- and heterocycles via ring-opening cycloaddition reaction with unsaturated bonds.[2] Therefore, methods to access them, such as catalytic cyclopropanation with diazo compounds, Simmons–Smith reaction using metal carbenoids (M–CH_2–X), the Kulinkovich reaction, and the Corey–Chaykovsky reaction, have been reported.[3] Although considerable success has been achieved, cyclopropanation of unactivated alkenes with high chemo- and stereoselectivity control remains a formidable challenge in organic synthesis. We focused on the early transition metals as promoters, and developed chromium-mediated selective cyclopropanation of unactivated terminal alkenes (Scheme 1, eq 1).[4,5] This method provided cyclopropanes containing synthetically useful iodo[4a] and silyl[4b,c] functionality in a single step from commercially available terminal alkenes. Recently, our mechanistic studies indicated that the reaction proceeded via generation of a *gem*-dichromiomethane (Cr–CHR–Cr) as a key reactive species from diiodomethane derivatives.[6,7] We envisioned that the use of diiodomethylboronate esters would provide borylcyclopropanes that could be utilized as efficient building blocks to incorporate a cyclopropyl ring into the target molecules through the Suzuki–Miyaura cross-coupling reaction.[8] Several methods for providing borylcyclopropanes have been reported, including cyclopropanation of alkenylboranes with metal carbenoids, hydroboration of cyclopropenes, direct borylation of cyclopropanes having heteroatom-containing directing groups, and cross-coupling reactions with cyclopropyl halides.[9] Some of these methods require reactive chemicals and/or are limited by a lack of control over stereochemistry. Thus, development of a more direct cyclopropanation with unactivated olefins is desirable. Our preliminary result for borylcyclopropanation was reported in 2007, in which two terminal alkenes (allyl benzyl ether and 1-dodecene) were demonstrated as substrates with $I_2CHBpin$ prepared in situ from the reaction of $Cl_2CHBpin$ and LiI, resulting in low stereoselectivity (up to 63:37).[4c] During a detailed study to clarify the reactive chromium species and reaction mechanism,[6] Charette and co-workers recently reported Simmons–Smith type borylcyclopropanation of olefins using a borylmethylzinc carbenoid (Scheme 1, eq 2).[10] As exemplified by this report, olefin substrates for most of the previously reported stereoselective cyclopropanation are limited to allylic ethers and aryl olefins.[3] Development of a novel protocol applicable to less reactive unactivated olefins without the use of potentially

Scheme 1. Borylcyclopropanation of Olefins



[a]LiI was added for in situ generation of Z-CHI_2.

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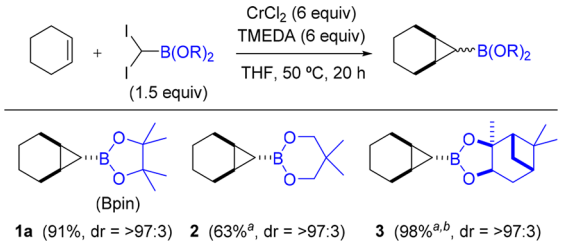
flammable alkylzinc and environmentally harmful dichloroalkanes as a solvent would be an innovative milestone, and provide novel insights into cyclopropanation chemistry. The present report describes the chromium-promoted borylcyclopropanation of unactivated alkenes (Scheme 1, eq 3) and new insights into the unique reactive nature of boryl-group substituted *gem*-dimetallomethanes.[7]

Treatment of cyclohexene with diiodomethylboronic acid pinacol ester ($I_2CHBpin$)[11] in the presence of $CrCl_2$ and TMEDA afforded the corresponding borylcyclopropane **1a** in 91% yield as a single diastereomer (Scheme 2). The NOESY

Scheme 2. Effect of the Structure of Boronate Esters



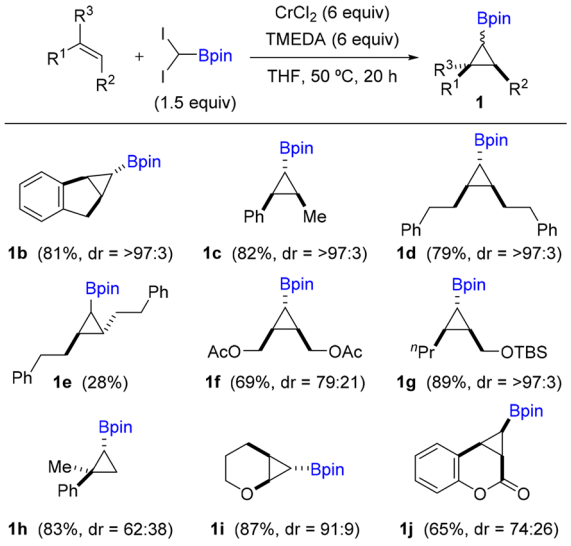
1a (91%, dr = >97:3) **2** (63%[a], dr = >97:3) **3** (98%[a,b], dr = >97:3)

[a]$I_2CHB(OR)_2$ were prepared in situ from reaction of $Cl_2CHB(OR)_2$ with NaI. [b](3a*S*,4*S*,6*S*,7a*R*)-2-(dichloromethyl)-3a,5,5-trimethylhexahydro-4,6-methanobenzo-1,3,2-dioxaborole was used for $Cl_2CHB(OR)_2$. Stereochemistry of the pinanediol moiety was retained during the borylcyclopropanation.

study indicated that a boryl group was situated *anti* to the fused cyclohexane ring. The use of nitrogen- and phosphine-based ligands, such as triethylamine, 2,2′-bipyridyl, and 1,2-bis(diphenylphosphino)ethane, decreased the yield, while the readily available and inexpensive TMEDA was particularly effective.[12] With the combination of $CrCl_2$ and TMEDA as a promoter, excellent stereoselectivity was observed for cyclopropanation with neopentylglycol and pinanediol boronate esters, leading to **2** and **3**, respectively.

Next, the scope of olefins was investigated (Scheme 3). 1*H*-Indene reacted at the olefinic double bond to give **1b** in 81% yield. Not only cyclic olefins, but also linear olefins, such as (*Z*)-1-phenyl-1-propyne and (*Z*)-1,6-diphenyl-3-hexene, reacted smoothly to give **1c** and **1d**, respectively, in good yield without formation of the corresponding diastereomers. Cyclopropanation of (*E*)-1,6-diphenyl-3-hexene provided the expected adduct **1e**, albeit in low yield. These results indicate that the cyclopropanation occurred stereospecifically without isomerization of the starting alkenes. Note that the reaction proceeded smoothly and stereoselectively without a hydroxy or alkoxy group, which is used for general stereoselective Simmons–Smith type cyclopropanation with zinc carbenoids.[3a,10] The reaction occurred without loss of functional groups, such as acetoxy and silyloxy groups. However, (*Z*)-1,4-diacetoxy-2-butene gave the corresponding cyclopropane **1f** with decreased selectivity (dr = 79:21). The decrease in diastereoselectivity can be rationalized by considering the unfavorable interaction of oxygen with boron atoms in the transition state. This hypothesis was supported by the reaction result using the bulkier *N*,*N*,*N*′,*N*′-tetramethyl-1,3-diaminopropane as a ligand in place of TMEDA, which afforded **1f** with stereoselectivity of up to 87:13 albeit in low yield (20% yield). As expected, a single stereoisomer was obtained from borylcyclopropanation of allyl alcohol protected by the sterically hindered silyl group leading to **1g**. The *gem*-disubstituted alkene, such as α-methylstyrene, was also utilized as a substrate to give **1h**

Scheme 3. Chromium-Mediated Stereoselective Borylcyclopropantion of Internal Alkenes[a]

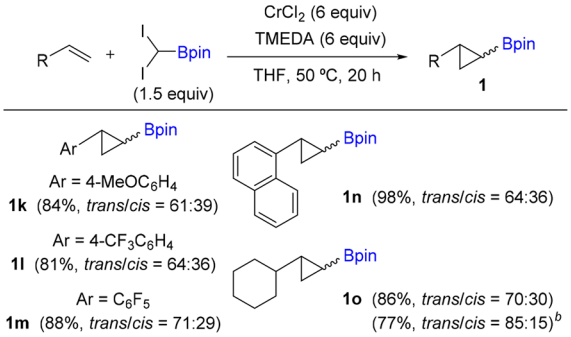


[a]Diastereomeric ratio was determined by ^{1}H NMR of the crude product.

in 83% yield. Bulkiness of alkenes affected the reactivity, and trisubstituted olefins, such as 2-methyl-5-phenyl-2-pentene, shut down the reaction. Note that borylcyclopropanation also underwent with both electron-rich 3,4-dihydro-2*H*-pyran and electron-deficient coumarin to give **1i** and **1j**, respectively, with high stereoselectivity. The stereochemistry of the major diastereomer of **1j** was opposite to that of the other borylcyclopropanes obtained in this study, and was unambiguously determined by X-ray crystallographic analysis (Figure S1 in Supporting Information (SI)). Note that disubstituted alkenes and/or electron-rich alkenes, such as 3,4-dihydro-2*H*-pyran, were not applicable to the previous iodo- and silylcyclopropanation in contrast to the current borylcyclopropantion.[4] Although the exact reason for this is not clear, these reactivity differences might be due to the compactness and electron-deficient nature of the pinacolylboryl group compared to the iodo and trimethylsilyl groups.

The current reagent system was also effective for cyclopropanation of monosubstituted olefins (Scheme 4). Both

Scheme 4. Chromium-Mediated Borylcyclopropanation of Terminal Alkenes[a]



[a]Diastereomeric ratio was determined by ^{1}H NMR of the crude product. [b]*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diaminopropane was used in place of TMEDA.

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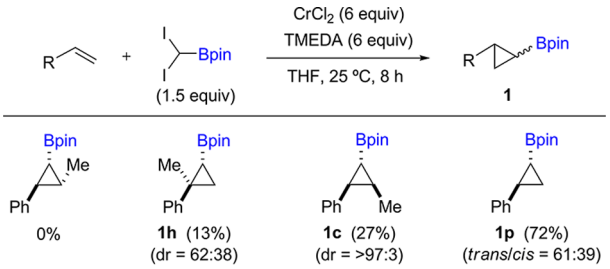
electron-rich 4-methoxystyrene and electron-deficient 4-(trifluoromethyl)styrene were applicable as substrates to form the corresponding **1k** and **1l**, respectively, in excellent yields. Even olefins having sterically congested substituents, including pentafluorostyrene and 1-vinylnaphthalene, underwent borylcyclopropanation to afford **1m** and **1n**, respectively. Aliphatic olefins, such as vinylcyclohexane, also provided the desired product **1o** in high yield. The wide substrate scope of the current reaction is advantageous because Simmons–Smith type cyclopropanation is generally sluggish with electron-deficient olefins.[3a,10] Although the stereoselectivity for the cyclopropanations was lower than that with disubstituted alkenes in Scheme 3, it can be increased up to 85:15 by using *N*,*N*,*N*′,*N*′-tetramethyl-1,3-diaminopropane as a ligand as demonstrated by the reaction with **1o** although the yield slightly decreased.

The current borylcyclopropanation possessed different chemoselectivity compared to typical Simmons–Smith type cyclopropanation, in which *gem*-disubstituted and trisubstituted olefins react preferentially to *cis*-disubstituted olefins.[3a] As exemplified with parallel reactions of *β*-methylstyrene, *α*-methylstyrene, (*Z*)-1-phenyl-1-propene, and styrene at 25 °C for 8 h, the terminal monosubstituted double bond was the most reactive in the present cyclopropanation (Scheme 5). This

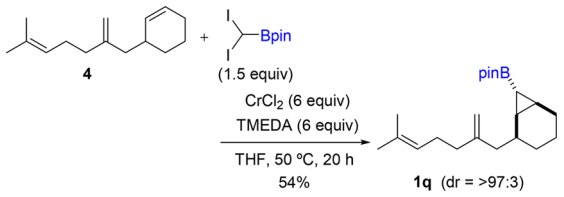
Scheme 5. Intermolecular Competitive Cyclopropanation[a]



[a]Yields and diastereoselectivity are determined by ^{1}H NMR.

unique reactivity enabled highly chemoselective cyclopropanation of the *cis*-disubstituted double bond of hydrocarbon **4**, even in the presence of *gem*-di- and trisubstituted double bonds without heteroatom coordination (Scheme 6).[13]

Scheme 6. Chemoselective Borylcyclopropanation of 4



A plausible reaction mechanism is shown in Figure 1, which shows the borylcyclopropanation of (*Z*)-disubstituted olefins. Reduction of diiodomethylboronate ester with 2 equiv of $[(tmeda)CrCl_2]_2$ **A** gave *gem*-dichromiomethylboronate ester **C**, along with $(tmeda)CrCl_2I$ **B**.[14] The stuctures of **A**, **B**, and the related complex of **C**, *gem*-(dichromiomethyl)trimethylsilane, were confirmed umambiguously by X-ray crystallographic analysis in our recent work.[6] Chromocarbene intermediate **D** was formed from **C**, which then converted into chromocyclobutane **E** via [2 + 2] cycloaddition with olefins. The carbene carbon of intermediate **D** is slightly electrophilic due to the

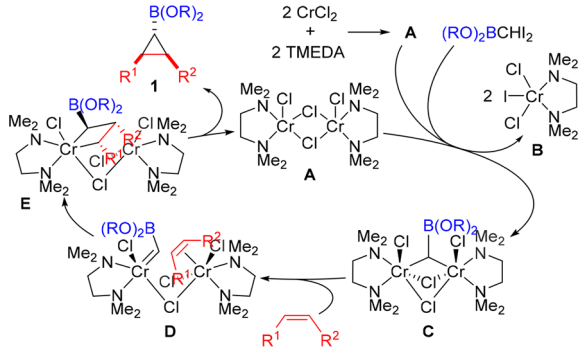


Figure 1. Plausible reaction mechanism for borylcyclopropanation of (*Z*)-disubstituted olefins.

attachment of the electron-withdrawing boryl group, which enables cyclopropanation, even with electron-rich olefins (Scheme 3 and 4). Formation of the unique structure of the chlorine-bridged dinuclear chromium complex **D** was supported by kinetic studies in our recent work.[6] Finally, reductive elimination of Cr furnishes borylcyclopropane **1** along with regeneration of **A**. The stereoselectivity of these reactions can be explained by considering that formation of **E** occurs preferentially to minimize the steric repulsion of the boryl group and substituents on the olefins in intermediate **D** (Figure 2).[15]

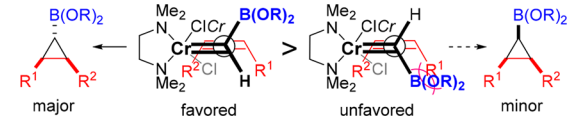
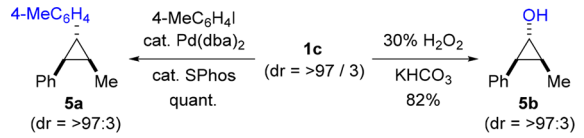


Figure 2. Rationale for determination of stereochemistry in intermediate **D**.

Furthermore, intermolecular competition experiments using 4-trifluoromethylstyrene and 4-methoxystyrene revealed that the reactivity rate of the current borylcyclopropanation is independent of the electron density of the alkenes, indicating that [2 + 2] cycloaddition of chromocarbene **D** with olefins was not involved in the rate-determining step.

The resulting borylcyclopropanes underwent further transformations to illustrate their synthetic utility (Scheme 7). The

Scheme 7. Transformation of the Borylcyclopropanes[a]



[a]See SI for the details.

pinacolylboryl group of **1c** could be converted to aryl and hydroxy groups by palladium-catalyzed Suzuki–Miyaura cross-coupling reaction and oxidation, respectively.[16] Both transformations proceeded with complete retention of stereochemistry to provide functionalized cyclopropane derivatives as a single stereoisomer.

In conclusion, the present study describes the operationally simple borylcyclopropanation of unactivated alkenes. In contrast to the typical Simmons–Smith cyclopropanation, this reaction proceeded even with alkenes, which do not have heteroatom-containing directing groups. Furthermore, disubstituted and/or

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electron-rich olefins, which were not applicable to iodo- and silylcyclopropanation in our previous work, reacted smoothly to provide the corresponding borylcyclopropanes in good yield. The compactness and electron-deficient nature of the pinacolylboryl group attached to the chromocarbene intermediate was key for clarifying the novel reactivity of the *gem*-dimetallomethanes. The current reaction proceeds under mild conditions with good stereoselectivity and functional group tolerance, and therefore will be useful in the total synthesis of natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02956.

X-ray crystallographic data of complex **1j** (CIF)

Experimental procedures, spectroscopic data for all new compounds, copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) de Meijere, A.; Kozhushkov, S. I. *Chem. Rev.* **2000**, *100*, 93. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (c) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251. (d) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603. (e) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625. (f) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631. (g) Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712.

(2) (a) *Small Ring Compounds in Organic Synthesis VI*; de Meijere, A., Ed.; Springer: Berlin, 2000; Vol. *207*. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504.

(3) (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. (c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (d) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041. (e) Chen, D. Y. K.; Pouwer, R. H.; Richard, J. A. *Chem. Soc. Rev.* **2012**, *41*, 4631. (f) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, *46*, 979. (g) Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651.

(4) (a) Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R. *J. Am. Chem. Soc.* **2003**, *125*, 12990. (b) Takai, K.; Hirano, M.; Toshikawa, S. *Synlett* **2004**, 1347. (c) Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R.; Hirano, M. *J. Organomet. Chem.* **2007**, *692*, 520.

(5) Although Cr^{VI} salts are highly toxic, $Cr^{II}Cl_2$ possesses lower toxicity than $MnCl_2$, $FeCl_2$, $NiCl_2$, and $PdCl_2$. See: (a) Steib, A. K.; Kuzmina, O. M.; Fernandez, S.; Flubacher, D.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 15346. For reviews on the transformation using organochromium reagents, see: (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (c) Takai, K. *Org. React.* **2004**, *64*, 253. (d) Yamamoto, H.; Xia, G. *Chem. Lett.* **2007**, *36*, 1082. (e) Takai, K. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G. A.; Knochel, P., Eds.; Elsevier: Oxford, 2014; Vol. *1*, p 159.

(6) Murai, M.; Taniguchi, R.; Hosokawa, N.; Nishida, Y.; Mimachi, H.; Oshiki, T.; Takai, K. *J. Am. Chem. Soc.* **2017**, *139*, 13184.

(7) For representative reviews on *gem*-dimetallomethanes, see: (a) Marek, I.; Normant, J.-F. *Chem. Rev.* **1996**, *96*, 3241. (b) Marek, I. *Chem. Rev.* **2000**, *100*, 2887. (c) Matsubara, S.; Oshima, K.; Utimoto, K. *J. Organomet. Chem.* **2001**, *617–618*, 39. (d) Marek, I.; Normant, J. F. *Organozinc Reagents—A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford University Press: Oxford, 1999; pp 119–137. (e) Normant, J. F. *Acc. Chem. Res.* **2001**, *34*, 640.

(8) (a) Zhou, S.-M.; Deng, M.-Z.; Xia, L.-J.; Tang, M.-H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2845. (b) Wallace, D. J.; Chen, C. *Tetrahedron Lett.* **2002**, *43*, 6987. (c) Pietruszka, J.; Witt, A.; Frey, W. *Eur. J. Org. Chem.* **2003**, *2003*, 3219.

(9) For representative examples, see: (a) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198. (b) Charette, A. B.; Mathieu, S.; Fournier, J.-F. *Synlett* **2005**, 1779 and references therein. (c) Shimizu, M.; Schelper, M.; Nagao, I.; Shimono, K.; Kurahashi, T.; Hiyama, T. *Chem. Lett.* **2006**, *35*, 1222. (d) Kurahashi, T.; Kozhushkov, S. I.; Schill, H.; Meindl, K.; Rühl, S.; de Meijere, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6545. (e) Fujioka, Y.; Amii, H. *Org. Lett.* **2008**, *10*, 769. (f) Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7424. (g) Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516. (h) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 528. (i) Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 3375. (j) Bose, S. K.; Fucke, K.; Liu, L.; Steel, P. G.; Marder, T. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 1799. (k) Murakami, R.; Tsunoda, K.; Iwai, T.; Sawamura, M. *Chem. - Eur. J.* **2014**, *20*, 13127. (l) Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; Ruano, J. L. G.; Tortosa, M. *J. Am. Chem. Soc.* **2014**, *136*, 15833. (m) Miyamura, S.; Araki, M.; Suzuki, T.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 846. (n) Spencer, J. A.; Jamieson, C.; Talbot, E. P. A. *Org. Lett.* **2017**, *19*, 3891.

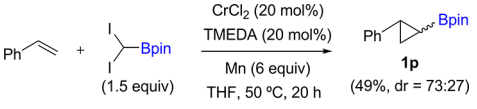
(10) Benoit, G.; Charette, A. B. *J. Am. Chem. Soc.* **2017**, *139*, 1364. Our work was reported in March 2017 (97th CSJ Annual Meeting 2017, Yokohama, 1E2–18).

(11) Wuts, P. G. M.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137.

(12) Effect of ligands (monodentate 12 equiv, and bidentate 6 equiv) with 6 equiv of $CrCl_2$ in THF at 50 °C for 20 h: **1a** was not obtained with Et_3N, 2,2′-bipyridyl, 1,2-bis(diphenylphosphino)ethane, or without ligands. Yield of **1a** was 39% with *N*,*N*,*N*′,*N*′-tetramethyl-1,3-diaminobutane.

(13) Due to electronic and steric effects, reactivity of alkenes in the Simmons–Smith reaction is known to diminish in the order of *gem*-disubstituted > trisubstituted > tetrasubstituted > *cis*-disubstituted > *trans*-disubstituted > monosubstituted alkenes.

(14) Although yield decreased, a preliminary result for the borylcyclopropanation of styrene indicated that the amount of $CrCl_2$ could be reduced to 20 mol% using 6 equiv of manganese powder as a reductant for the (tmeda)$CrCl_2$I **B** back to (tmeda)$CrCl_2$ **A** (unreacted styrene was recovered). A control experiment revealed cyclopropanation did not occur with only manganese in the absence of $CrCl_2$.



(15) The stereochemistry of **1j** was opposite to that of the other borylcyclopropanes, probably due to the interaction of the carbonyl group with boron atoms in the transition state.

(16) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

DOI: 10.1021/acs.orglett.7b02956
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