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Vicinal Diboration of Alkyl Bromides via Tandem Catalysis

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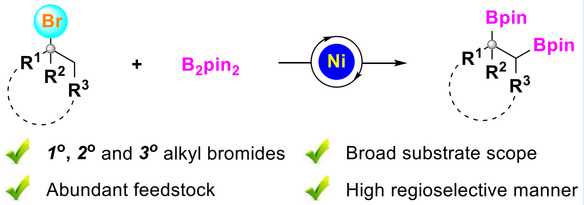
Supporting Information

ABSTRACT: Vicinal diboration of alkyl bromides via tandem catalysis is reported. The reported reaction exhibits a broad substrate scope, good functional group compatibility, and regioselectivity. Moreover, it shows good practicality due to the easy accessibility of alkyl bromides in combination with diverse transformations of diboronates. Mechanism study indicates that terminal alkenes are generated selectively through nickel-catalyzed dehydrohalogenation of alkyl bromides followed by base/MeOH promoted diboration process to provide 1,2-diboration products.



Organoboron compounds are fundamental and versatile intermediates in synthetic chemistry.[1] These compounds strike a good balance between stability and reactivity. They are easy to handle due to good air and moisture stability and can be conveniently transformed under mild reaction conditions.[2] Among boron family compounds, vicinal diboronates are indispensable, providing an efficient synthetic module for the expedient synthesis of complex molecules through C−B transformation approaches.[3] For the creation of vicinal diboronates, pioneer works focused on diboration of alkenes and alkynes catalyzed by diverse transition-metal catalysts.[4] Further, hydroxyl-directed diboration of alkenyl alcohols[5a] and unidirectional homologation of diborylmethane[5b] have also been reported. Recent progress was made by Fernández,[6a,b] Huang,[6c] and Song[6d] in base-catalyzed diboration of alkenes or alkynes. On the other hand, alkyl (pseudo)halides are also easily accessible and abundant feedstock starting materials and proved to be a good choice to access alkylboron compounds (Figure 1a, left).[7,8] Despite these successes, a new design principle capable of directly obtaining vicinal diboronates from alkyl (pseudo)halides would be practical (Figure 1a, right).

Over the past decade, nickel-catalyzed cross-coupling of alkyl electrophiles, especially alkyl halides, enjoyed great success in virtue of efficient retardation of undesired β-H elimination.[9] Most recently, such a previously avoided event was skillfully utilized as a desired process. For example, chain-walking functionalization was realized through dehydrohalogenation alkene generation, then successive insertion and migration of C−C double bond, and finally functionalization at a remote site (Figure 1b, pathway I).[10] As part of our ongoing interest in developing alkyl halide conversion reactions and alkene functionalization strategies,[11] we set out to achieve the regioselective vicinal diboration of alkyl halides, taking advantage of designed β-H elimination and alkene bisboronation (Figure 1b, pathway II). Herein, we report the vicinal diboration of alkyl bromides via tandem catalysis as an alternative method for preparing 1,2-diboronates. A variety of primary, secondary, and tertiary alkyl bromides could be easily diboronated with good regioselectivity. From the point of view of easy accessibility of alkyl bromides and diverse trans-

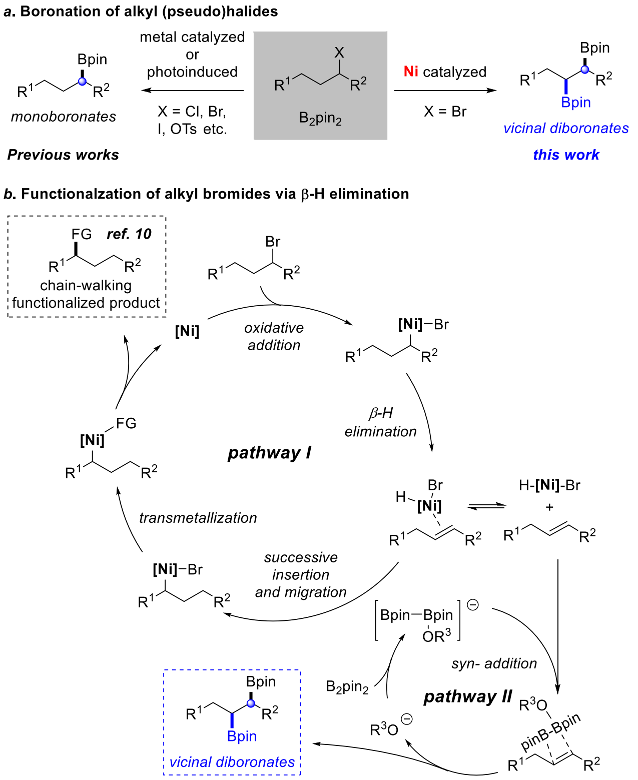


Figure 1. Boronation of alkyl (pseudo)halides and reaction design of vicinal diboration of alkyl bromides via tandem catalysis. FG = functional group. B$_2$pin$_2$ = bis(pinacolato)diboron. Ts = tosyl.

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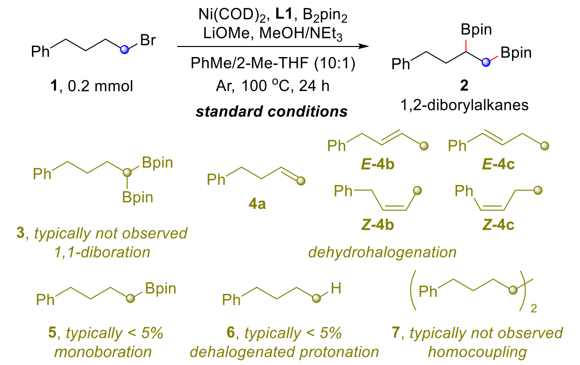
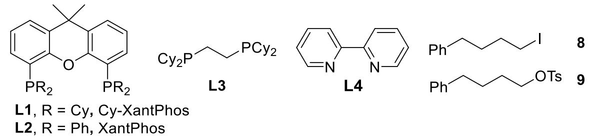
formations of diboronates, this reaction might find many applications in synthetic chemistry.

We commenced the study with the preparation of 1,2-diborylalkane **2** through proposed vicinal diboration of primary alkyl bromide **1** (Table 1). On the basis of our previously reported nickel-catalyzed synthesis of 1,1-diboronates,[11b] we were pleased to obtain the desired product **2** with 70% GC yield and 60% isolated yield in the presence of Ni(COD)$_2$ and Cy-XantPhos, modified with MeOH and NEt$_3$ (entry 1). In the absence of nickel catalysts, diboration could not proceed with 84% alkyl bromide recovered (entry 2). Ligand effects were systematically screened (see Supporting Information for more details), for example, monodentate phosphine (entry 3), other bidentate phosphines (entries 4 and 5), and nitrogen ligands (entry 6) were much less effective. Cy-XantPhos might be the only appropriate ligand, providing good reactivity and selectivity for terminal alkene generation.[12,13] Cesium carbonate showed high efficiency for diboration reactions in previous works;[6a,b] however, it showed almost complete loss of reactivity in our reaction system (entry 7). Without the addition of NEt$_3$ or MeOH, lower yields were provided (entries 8 and 9). Alkyl iodine **8** was also a good substrate in this transformation (entry 10), but alkyl tosylate **9** was unreactive under the current reaction conditions (entry 11). It should be pointed out that 1,1-diboration was not observed in most conditions (also see Scheme 5 for more explanation).

Table 1. Optimization of Reaction Conditions[a]



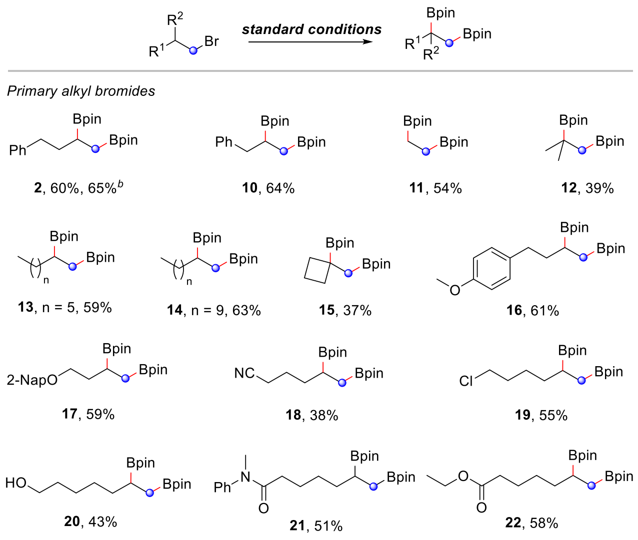
entry	deviation from standard conditions	yield of **2** (%)	recovery of **1** (%)	yield of **4** (%)
1[b]	none	70 (60[c])	8	12
2	w/o Ni(COD)$_2$	trace	84	trace
3	PCy$_3$ instead of **L1**	8	54	12
4	**L2** instead of **L1**	6	trace	47
5	**L3** instead of **L1**	15	43	7
6	**L4** instead of **L1**	5	trace	30
7	Cs$_2$CO$_3$ instead of LiOMe	trace	trace	43
8	w/o NEt$_3$	62	8	18
9	w/o MeOH	44	trace	36
10	**8** instead of **1**	73	2[d]	5
11	**9** instead of **1**	trace	77[e]	trace



[a] GC yield. 4,4′-Carbonylbis(toluene) was used as an internal standard. [b] Standard conditions: 5 mol % Ni(COD)$_2$, 5 mol % Cy-XantPhos, 2.0 equiv B$_2$pin$_2$, 1.0 equiv LiOMe, 0.5 equiv NEt$_3$, 5.0 equiv MeOH, 1.1 mL PhMe/2-Me-THF (v:v = 10:1) under Ar at 100 °C for 24 h. [c] Isolated yield. [d] Recovery of **8**. [e] Recovery of **9**. COD = *cis*,*cis*-1,5-cyclooctadiene. THF = tetrahydrofuran. Cy = cyclohexyl.

With the optimized reaction conditions, we sought to examine the substrate scope of alkyl bromides with different functional groups. As shown in Scheme 1, a variety of unactivated primary alkyl bromides could be easily diboronated with moderate to good isolated yields (37−65%). Although there are remote π-system in substrates, terminal vicinal diboranates were obtained as single products (**2**, **10**). Substrates with different chain lengths also performed well in this transformation (**11**−**14**). Further, the four-membered ring was well-tolerated, and no ring opening side product was observed (**15**). A variety of functional groups could be readily accommodated, including ether (**16**, **17**), cyano (**18**), alkyl chloride (**19**), and even unprotected alcoholic hydroxyl group (**20**). In addition, the toleration of amide (**21**) and ethoxycarbonyl group (**22**) indicated that the diboration reaction could be conducted without unexpected trans-esterification.[14]

Scheme 1. Substrate Scope of Primary Alkyl Bromides[a]

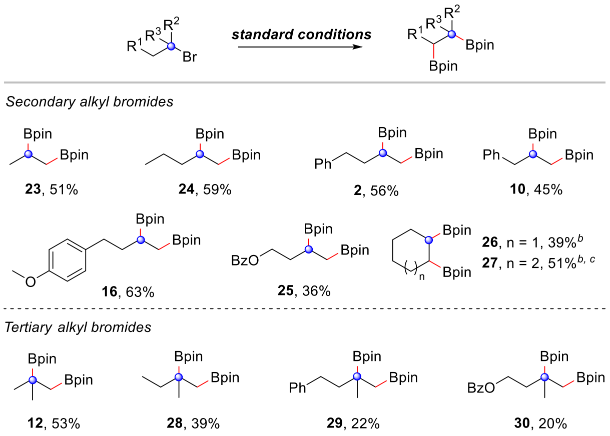


[a] Isolated yield for 0.2 mmol scale reaction. [b] Isolated yield for 0.5 mmol scale reaction. Nap = naphthyl.

Subsequent studies revealed that this diboration reaction has broad substrate scope with respect to the alkyl bromides. As illustrated in Scheme 2, a wide range of secondary and tertiary alkyl bromides was successfully converted to the desired products. Substrates with different chain lengths (**2**, **10**, **12**, **16**, **23**−**25**, **28**−**30**) smoothly delivered the desired products in moderate to good yields. Cyclic alkyl bromides, such as six- and seven-membered rings (**26**, **27**) also performed well in this transformation and produced vicinal diboronates in onefold *syn*-configuration. In addition, representative substrate (**27**) was conveniently prepared in gram-scale (see the Supporting Information for more details).

To better highlight the practicability of our diboration protocol, we exploited its application in the modification of natural products. Lithocholic acid **31** was esterified, reduced by

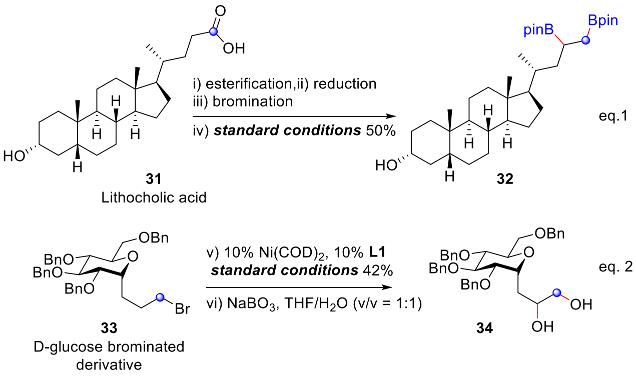
Scheme 2. Substrate Scope of Secondary and Tertiary Alkyl Bromides[a]



[a] Isolated yield for 0.2 mmol scale reaction. [b] *syn-/anti-* > 20:1. [c] Isolated yield for 8.0 mmol scale. Bz = benzoyl.

lithium aluminohydride, brominated, and then followed by our diboration reaction under standard conditions, after which **32** was obtained with a moderate yield (50%) (Scheme 3, eq 1).

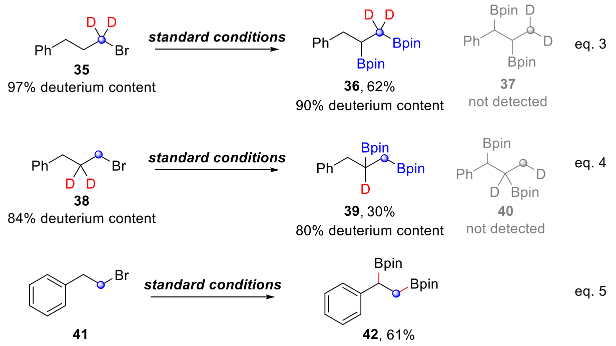
Scheme 3. 1,2-Diboration of Natural Products[a]



[a] Isolated yield for 0.2 mmol scale reaction. (i) $SOCl_2$, MeOH; (ii) $LiAlH_4$, THF; (iii) NBS, PPh_3, CH_2Cl_2; (iv) standard conditions. (v) Standard conditions, 10 mol % $Ni(COD)_2$, 10 mol % **L1**; vi) $NaBO_3 \cdot 4H_2O$, THF/H_2O (v/v = 1:1). Bn = benzyl.

Another example was the synthesis of C-alkyl glycoside. Our new reaction was used to modify glycoside to produce diboron-containing derivative. Brominated *C*-allyl-D-glucose derivative **33** was synthesized from tetrabenzyl-protected D-glucose (see the Supporting Information for more synthetic details). Under standard conditions, the desired diboration product was obtained in 42% yield. Using oxidation with sodium perborate tetrahydrate in a mixture of H_2O and THF, polyhydroxy sugar derivative **34** was delivered with good yield (81%) (Scheme 3, eq 2). Notably, the two enantiomers could be well-separated by normal silica gel workup. These transformations demonstrated high synthetic value of this newly developed reaction.

Scheme 4. Mechanistic Experiments[a]



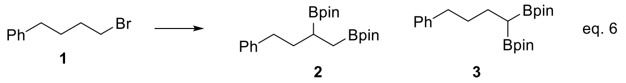
[a] Isolated yield for 0.2 mmol scale reaction.

A series of experiments was carried out to support our proposed catalytic cycle (Scheme 4). Deuterated alkyl bromide **35** (97% deuterium content) was employed as starting material and provided product **36** in 62% yield with 90% deuterium content (Scheme 4, eq 3), while isomers **37** were not detected. As a comparison, deuterated compound **38** (84% deuterium content) was used to furnish single diboration product **39** in 30% yield with 80% deuterium content (Scheme 4, eq 4). The formation of single diboronates **36** and **39** indicates that β-H of alkylnickel species eliminates in a regioselective manner to generate terminal alkene. Followed by *syn*-addition of bisboronates to terminal alkene, vicinal diboronate was obtained. The different yields might be rationalized in terms of isotope effects. Finally, (2-bromoethyl)benzene (**41**) could also be converted to the desired product (**42**) smoothly under our standard reaction conditions, in which a styrene intermediate might be formed (Scheme 4, eq 5).

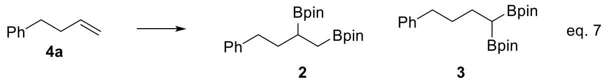
In our reaction design, alkene intermediate **4a** would be generated, followed by diboration process to access 1,2-diboronate. The transformation of **4a** with or without nickel catalysts supported our hypothesis (entries 3 and 4, Scheme 5). The approximate results indicated that nickel might not be involved in diboration process. Previously, we reported the nickel-catalyzed synthesis of 1,1-diborylalkanes from terminal alkenes (entry 5, Scheme 5).[11b] However, new transformation with alkyl halides shows almost entirely 1,2-diboration selectivity under very similar reaction conditions and went

Scheme 5. Mechanism Studies on Regioselectivity[a]

standard conditions	*conditions in ref. 11b*
5% $Ni(COD)_2$, 5% **L1**, 2.0 eq. B_2pin_2	5% $Ni(COD)_2$, 5% **L1**, 2.0 eq. B_2pin_2
1.0 eq. LiOMe, 0.5 eq. NEt_3	1.0 eq. LiOMe, 0.5 eq. NEt_3
1.0 eq. alkyl bromide (**1**), 5.0 eq. MeOH	1.0 eq. alkene (**4a**)
PhMe/2-Me-THF (10:1), Ar, 100 °C, 24 h	PhMe/THF (10:1), Ar, 130 °C, 1 h



		2	3
Entry 1	*standard conditions*	70%	trace
Entry 2	*conditions in ref. 11b* 2 eq. LiOMe, 1 eq. NEt_3 24h	40%	trace



		2	3
Entry 3	*standard conditions*	52%	trace
Entry 4	*standard conditions* w/o Ni cat., w/o **L1**	46%	trace
Entry 5	*conditions in ref. 11b*	trace	78%[b]
Entry 6	*conditions in ref. 11b* w 1.0 eq. LiBr	20%	37%
Entry 7	*conditions in ref. 11b* w 5.0 eq. MeOH	35%	trace

[a] GC yield. 4,4′-Carbonylbis(toluene) was used as an internal standard. [b] Literature yield.

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through the same alkene intermediate **4a** (entry 1, Scheme 5). To fully understand the nature of these transformations, more mechanism studies on regioselectivity were carried out. Conditions in ref 11b were performed on alkyl bromide substrate **1**, and we obtained 1,2-diboronate **2** but not the 1,1-diboronate **3** (entry 2, Scheme 5). We considered that the influence of in situ formed LiBr or MeOH must be taken into account. Under the conditions in ref 11b with LiBr as additive, a mixture of 1,1-diboronate **3** (37%) and 1,2-diboronate **2** (20%) was obtained from alkene **4a** (entry 6, Scheme 5). When MeOH was used as an additive, 1,2-diboronate **2** was formed as single product (entry 7, Scheme 5). These observations indicated that the added or in situ formed MeOH likely enables the alkoxide-promoted 1,2-diboration of alkenes which favors the 1,2- over the 1,1-product.

In conclusion, we report the regioselective diboration of primary, secondary, and tertiary alkyl bromides to furnish a variety of vicinal diboronates using tandem catalysis. This reaction presents a broad substrate scope and could be successfully performed in the presence of many synthetic useful functional groups. This diboration process is of practical value due to both the easy accessibility of starting material alkyl bromides and broad applications of product diboronates with various transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01481.

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

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Notes

The authors declare no competing financial interest.

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(13) We analyzed the reaction mixture in entries 4 and 7, Table 1. Under the conditions of entry 7, where Cy-XantPhos was used as the ligand, **4a** was obtained in a large amount as a diboration reaction intermediate. However, under the conditions of entry 4, where XantPhos was used as the ligand, inert **4c** was obtained predominantly. Moreover, we also carried out control experiments without the addition of B_2pin_2, and >80% starting material **1** was recovered. See the Supporting Information for more details.

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