Boron Chemistry Hot Paper

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# Synthesis of 1,3-Bis-(boryl)alkanes through Boronic Ester Induced Consecutive Double 1,2-Migration

*Cai You and Armido Studer**

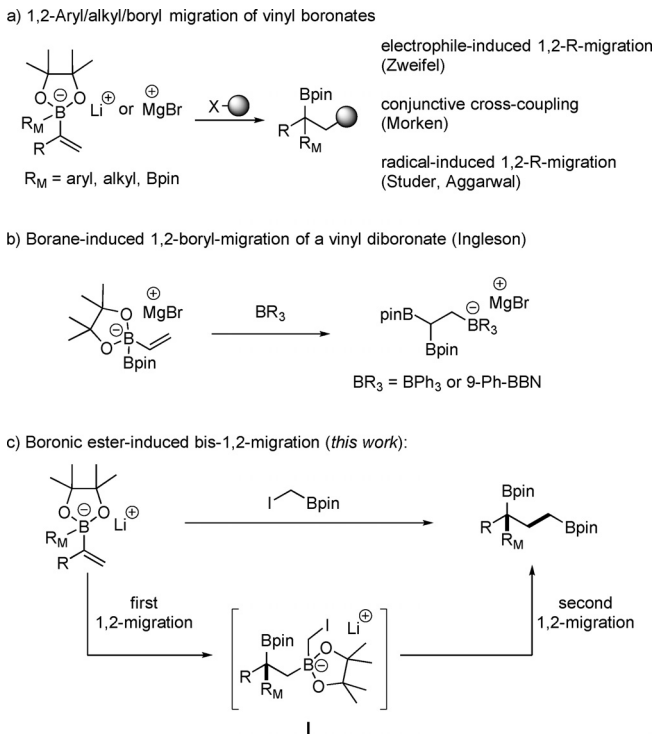
***Abstract:*** *A general and efficient approach for the preparation of 1,3-bis-(boryl)alkanes is introduced. It is shown that readily generated vinylboron ate complexes react with commercially available $ICH_2Bpin$ to valuable 1,3-bis-(boryl)alkanes. The introduced transformation, which is experimentally easy to conduct, shows broad substrate scope and high functional-group tolerance. Mechanistic studies reveal that the reaction does not proceed via radical intermediates. Instead, an unprecedented boronic ester induced sequential bis-1,2-migration cascade is suggested.*

Organoboron compounds are versatile intermediates in synthesis[1] that also play an important role in materials science and medicinal chemistry.[2] Bis-(boryl)alkanes, an interesting subclass, have attracted increasing attention as synthetic precursors in organic synthesis enabling multiple C–C and C–heteroatom bond construction.[3,4a,b] Although many methods for accessing 1,1- and 1,2-bis-(boryl)alkanes have been reported,[4] general methods for the synthesis of 1,3-bis-(boryl)alkanes are rare.[3b,5] Therefore, an efficient and general procedure for the preparation of 1,3-bis-(boryl)alkanes is demanded.

1,2-migrations of boron ate complexes have been shown to be highly reliable for C–C bond construction while retaining the valuable boron moiety in the product.[6,7] In 1967, Zweifel and co-workers first reported 1,2-alkyl/aryl migrations of vinylboron ate complexes induced by electrophilic halogenation (Scheme 1a).[8] In 2016, Morken and co-workers disclosed the electrophilic palladation-induced 1,2-alkyl/aryl migration of vinylboron ate complexes.[9] More recently, we,[10] Aggarwal,[11] and Renaud[12] developed radical polar crossover reactions, in which 1,2-alkyl/aryl migrations of vinylboron ate complexes are induced by alkyl radical additions. This radical approach was further extended by Shi and co-workers to the radical-induced 1,2-boron migration.[13]

In 2018, Ingleson and co-workers demonstrated that soft boron-based Lewis acids ($BPh_3$ and 9-Ph-BBN) induce 1,2-boron migration of a vinyl diboron ate complex to enable the one-pot synthesis of 1,1,2-triborylated alkanes (Scheme 1b).[14] Inspired by this reaction, we envisioned that commercially available $ICH_2Bpin$ would react with vinyl boron ate complexes to form 1,3-bis-(boryl)alkanes (Scheme 1c, pin = pinacolato). We considered that $ICH_2Bpin$ acting as a soft electrophile would induce a Zweifel-type 1,2-$R_M$-migration of a vinyl boron ate complex to form the 1,2-diborylated alkane intermediate **I** that might engage in a subsequent Matteson rearrangement[6b] to afford a 1,3-bis-(boryl)alkane. This strategy comprising two sequential 1,2-alkyl/aryl migration steps would offer a general and efficient approach for the synthesis of 1,3-bis-(boryl)alkanes, and first results are reported in this communication.

We began our investigations by exploring the reaction between the vinyl boron ate complex **2a** and $ICH_2Bpin$. To this end, **2a** was generated in situ by addition of *n*-butyllithium to the boronic ester **1a** in diethyl ether at 0 °C. The solvent was removed and crude **2a** was redissolved in acetonitrile. An excess (2 equivalents) of $ICH_2Bpin$ was added and the mixture was stirred at room temperature for 16 hours. To our delight, the desired 1,3-bis-(boryl)alkane **3a** was obtained in high yield (85 %, Table 1, entry 1). Solvent




***Scheme 1.*** 1,2-Group migrations of vinyl boron ate complexes.

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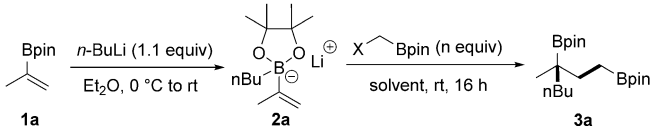
screening revealed acetonitrile to be superior to all other solvents tested (entries 1–4). Upon replacing $ICH_2Bpin$ by $BrCH_2Bpin$ or $ClCH_2Bpin$, the yield of **3a** significantly dropped (entries 5 and 6). However, in the presence of 1.0 equiv of NaI, the reaction with $ClCH_2Bpin$ delivered **3a** in 80% yield (entry 7). Increasing the amount of $ICH_2Bpin$ led to a further improvement and the best result was obtained when 3 equivalents were used (86% yield of isolated product; entries 8 and 9).

To investigate the substrate scope, various vinyl boron ate complexes were tested (Scheme 2). B-ate complexes **2a**–**2e** generated by treating the boronic ester **1a** with *n*-butyllithium, *n*-hexyllithium, isobutyllithium, isopropyllithium, or *tert*-butyllithium underwent this transformation smoothly to afford **3a**–**3e** in 73–86% yield, which demonstrates that the sequence tolerates different levels of steric hindrance with respect to the migrating alkyl group. By using PhLi for boronate formation, the tertiary benzylic boronic ester **3f** was obtained (73%). Other aryllithiums bearing various functional groups at the *para* position of the aryl moiety, such as methyl (**3g**), *tert*-butyl (**3h**), trifluoromethyl (**3i**), methoxyl (**3j**), trimethylsilyl (**3k**), and halides (**3l** and **3m**) are all compatible with this transformation. Aryl groups bearing *meta* or *ortho* substituents are tolerated, as documented by the successful preparation of **3n**–**3p**. We also tested a substrate containing a C=C bond at the phenyl ring, and **3q** was obtained in 72% yield with the less nucleophilic styrenic double bond unreacted. Substrates containing extended aromatic systems also engage in this cascade (see **3r** and **3s**). Isopropenylmagnesium bromide could be employed for boronate generation to afford **3t**, albeit in a slightly lower yield (46%). We also tested whether $ICH_2Bpin$ can be replaced by secondary borylated alkyl iodides. However, reaction of **2a** with $ICHCH_3Bpin$ under optimized conditions afforded only traces of the targeted compound.

Studies were continued by varying the R substituent at the vinyl boronic ester **1** with the *n*-butyllithium group as the migrating substituent $R_M$. When the unsubstituted vinyl boronate **2u** was employed (R = H), trace amounts of the targeted **3u** were formed, likely due to the lowered nucleophilicity of **2u** compared to the α-methyl congeners. However, upon using Ir photocatalysis, smooth reaction occurred and **3u** was obtained in 58% yield, likely through a different mechanism (see discussion below).

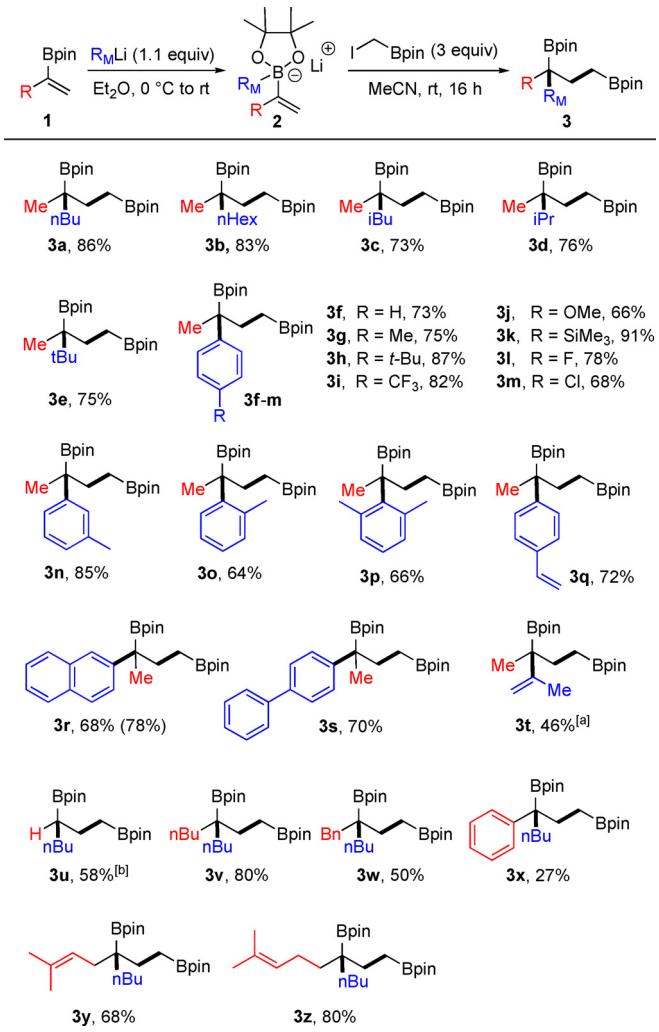
In contrast, vinylboron ate complexes bearing an activating R group at the α-position of the double bond engaged in the cascade without the necessity of using an Ir photocatalyst. Hence, various α-substituents R, such as *n*-butyl (**3v**), benzyl (**3w**), prenyl (**3y**), and homoprenyl (**3z**) serve as activating groups and the corresponding products were obtained in 50–80% yields. However, the α-styrenyl boronate **2x** gave

***Table 1:*** Reaction optimization.[a]




| Entry | Solvent | X | *n* | Yield [%][b] |
|---|---|---|---|---|
| 1 | MeCN | I | 2 | 85 |
| 2 | DMSO | I | 2 | 43 |
| 3 | THF | I | 2 | 26 |
| 4 | DMF | I | 2 | 44 |
| 5 | MeCN | Br | 2 | 64 |
| 6 | MeCN | Cl | 2 | 5 |
| 7[c] | MeCN | Cl | 2 | 80 |
| 8 | MeCN | I | 3 | 92 (86) |
| 9 | MeCN | I | 4 | 90 |

[a] Reaction conditions: **1a** (0.20 mmol), *n*-BuLi (0.22 mmol), in $Et_2O$ (2 mL), 0°C to rt, 1 h, under Ar. After boronate complex formation, solvent exchange to the selected solvent (2 mL) was performed. [b] GC yield using *n*-$C_{14}H_{30}$ as an internal standard; yield of isolated product is given in parentheses. [c] 0.20 mmol NaI was added.



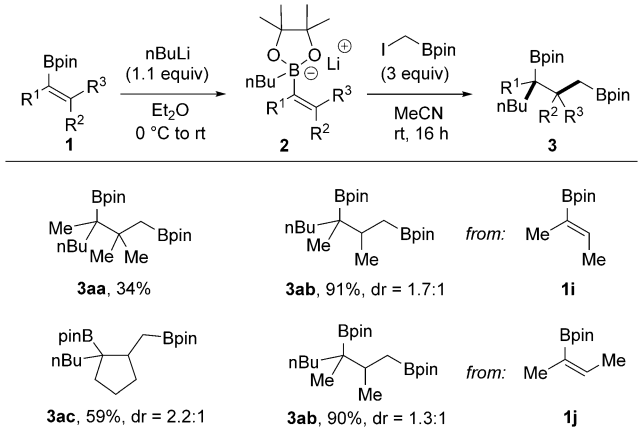

***Scheme 2.*** Substrate scope. Reaction conditions: **1** (0.20 mmol, 1.0 equiv), $R_M$Li (0.22 mmol, 1.1 equiv), in $Et_2O$ (2 mL), 0°C to rt, 1 h, under Ar; then $ICH_2Bpin$ (0.60 mmol, 3 equiv), rt, 16 h, in MeCN (2 mL). Yields given correspond to isolated products. Yield in parentheses for 1.2 mmol scale experiment. [a] α-Substituted alkenyl Grignard reagent isopropenylmagnesium bromide was used. [b] Vinylboronic acid pinacol ester (0.30 mmol), *n*-BuLi (0.33 mmol, 1.1 equiv), in $Et_2O$ (2 mL), 0°C to rt, 1 h, under Ar; then 1 mol% $Ir(ppy)_3$, $ICH_2Bpin$ (0.60 mmol, 2 equiv), rt, 16 h, in MeCN (1 mL), blue LEDs. ppy = 2-phenylpyridine.

a significantly lower yield of **3x** (27%). This is in our eyes not a serious limitation, since an α-phenyl group in the product boronic ester can be installed through phenyl-group migration (see **3f**). Notably, upon running the reaction on a larger scale (1.2 mmol), an increase in yield was obtained (**3r**, 78%).

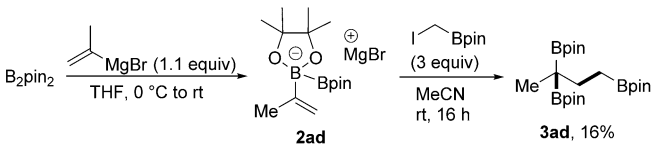
We also tested whether β-substituents at the vinylic double bond of the boron ate complexes are tolerated (Scheme 3). The sterically highly hindered trimethyl derivative **2aa** engaged in the cascade with nBuLi as reaction partner, although a drop in the yield was noted (**3aa**, 34%). Better yields were achieved with α,β-disubstituted alkenylboron ate complexes. However, reactions were not stereospecific and the *cis* complex **2ab** derived from **1i** reacted with a 1.7:1 diastereoselectivity to bisboronic ester **3ab**. The isomeric ate complex *trans*-**2ab′** derived from **1j** provided **3ab** with 1.3:1 diastereoselectivity. The relative configuration was not assigned but the same major isomer was formed in both transformations. 1-Cyclopentenylboronic ester reacted with a 2.2:1 selectivity to **3ac**.

We next tested whether our strategy enables the preparation of triborylated alkanes. Reaction of $B_2pin_2$ with the propenyl Grignard gave bisboronate complex **2ad** that was reacted with $ICH_2Bpin$ to give the targeted **3ad**, albeit in a low yield (Scheme 4). Regarding the mechanism, we first explored the possibility of a radical-based process[15] by performing radical-probe experiments[16] (Scheme 5). Typical scavengers such as 2,2-6,6-tetramethyl piperidine-N-oxyl (TEMPO) or 3,5-di-*tert*-4-butylhydroxytoluene (BHT) did not suppress the reaction and radical trapping products could not be identified. Furthermore, the reaction of the radical probes **2ae** and **2af** gave the bisboronic esters **3ae** and **3af** in high yields. Ring-opening products (in case of **2ae**) or any products derived from a 5-*exo*-cyclization (in case of **2af**) were not identified. These results indicate that the cascade does not occur through a radical process. Considering these findings and Ingleson's work,[14] we suggest the following mechanism (Scheme 5c). $ICH_2Bpin$ acts as soft Lewis acid, which triggers the first 1,2-migration of the boron ate complex **2**. Since this initial 1,2-migration does not proceed stereoselectively, the reaction likely proceeds via intermediate **A**, where the $R_M$ group can migrate in a non-concerted process to both sites of the carbenium ion. This is in agreement with the findings of Aggarwal and co-workers, who showed that Zweifel-type processes occur stereospecifically if induced by electrophiles that can form closed three-membered-ring intermediates with alkenes (onium ions).[17] The $R_M$-1,2-migration leads to the intermediate ate complex **B** that further reacts in a Matteson 1,2-migration[6b] to give the 1,3-bis-(boryl)alkane **3**. However, for the less-nucleophilic boronic ester **1u**, where an Ir photocatalyst and light were required, the cascade likely proceeds via radical intermediates[18] in analogy to the previously suggested radical/polar cross over additions to boronate complexes.[10–12]

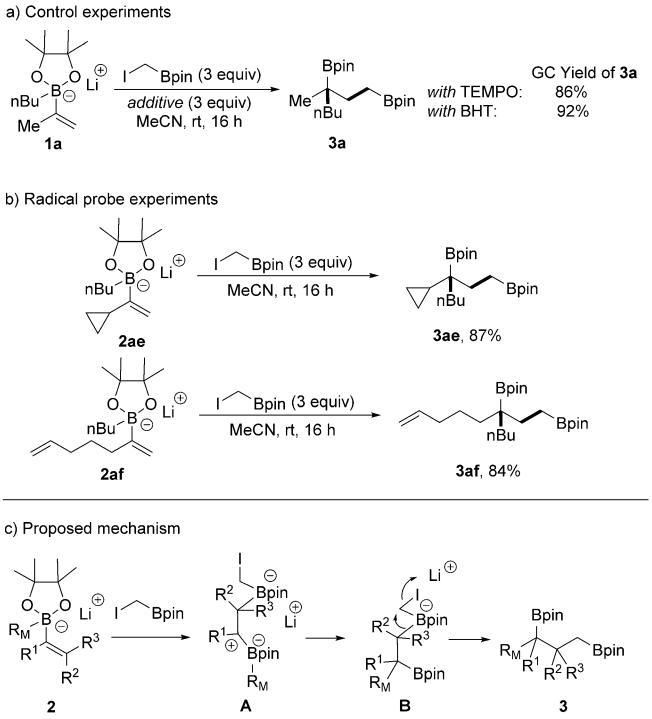
To demonstrate the synthetic utility, three follow-up transformations were conducted on the product bisboronic esters (Scheme 6). Under Matteson conditions, 1,3-bis-(boryl)alkane **3r** was successfully converted in a double homologation sequence into the 1,5-bis-(boryl)alkane **4** (63%). Treatment of **3r** with a $NaOH\text{-}H_2O_2$ mixture provided the 1,3-




***Scheme 3.*** Reaction with β-substituted boron ate complexes. Reaction conditions: **1** (0.20 mmol, 1.0 equiv), nBuLi (0.22 mmol, 1.1 equiv), in $Et_2O$ (2 mL), 0°C to rt, 1 h, under Ar; then $ICH_2Bpin$ (0.60 mmol, 3 equiv), rt, 16 h, in MeCN (2 mL).

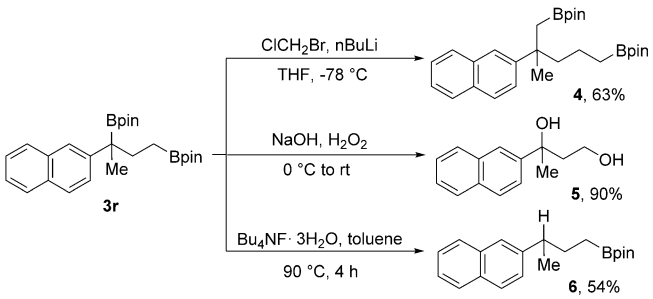



***Scheme 4.*** Synthesis 1,1,3-triborylated alkanes through boronic ester induced consecutive double 1,2-migration. Reaction conditions: $B_2pin_2$ (0.20 mmol, 1.0 equiv), isopropenylmagnesium bromide (0.22 mmol, 1.1 equiv), in THF (2 mL), 0°C to rt, 1 h, under Ar; then $ICH_2Bpin$ (0.60 mmol, 3 equiv), rt, 16 h, in MeCN (2 mL).




***Scheme 5.*** Mechanistic studies and suggested mechanism.




***Scheme 6.*** Synthetic transformations.

diol **5** in 90% yield. Selective protodeboronation[19] of **3r** was achieved with *n*-butylammonium fluoride trihydrate and the boronic ester **6** was obtained in 54% yield.

In summary, we have developed a process for the preparation of 1,3-bis-(boryl)alkanes. Commercially available $ICH_2Bpin$ reacts with readily prepared vinyl boron ate complexes to afford the corresponding valuable 1,3-bisboronic esters. The cascade is operationally easy to conduct and features broad substrate scope and high functional-group tolerance. Mechanistic investigations revealed that that the process does not proceed via radical intermediates. An ionic unprecedented boronic ester $ICH_2Bpin$-induced bis-1,2-migration mechanism is suggested. The value of the method was documented by successful follow-up reactions.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** 1,2-migration · 1,3-bis-(boryl)alkanes · reaction mechanisms · synthetic methods · vinylboron ate complexes

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