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1,2-Boron Shifts of β-Boryl Radicals Generated from Bis-Boronic Esters using Photoredox Catalysis

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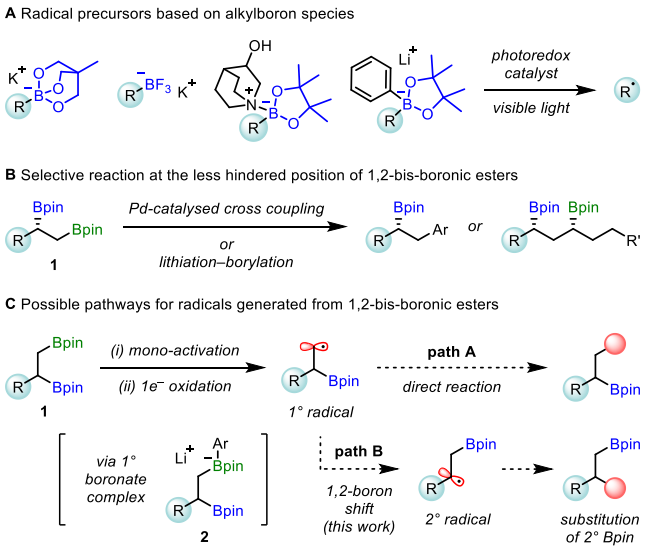
Supporting Information Placeholder

ABSTRACT: 1,2-Bis-boronic esters are versatile intermediates that enable the rapid elaboration of simple alkene precursors. Previous reports on their selective mono-functionalization have targeted the most accessible position, retaining the more hindered secondary boronic ester. In contrast, we have found that photoredox-catalyzed mono-deboronation generates primary β-boryl radicals that undergo rapid 1,2-boron shift to form thermodynamically favored secondary radicals, allowing for selective transformation of the more hindered boronic ester. The pivotal 1,2-boron shift, which has been demonstrated to be stereoretentive, enables access to a wide range of functionalized boronic esters and has been applied to highly diastereoselective fragmentation and transannular cyclization reactions. Furthermore, its generality has been shown in a radical cascade reaction with an allylboronic ester.

Photoredox chemistry enables radical species to be generated from a broad range of functional groups under exceptionally mild conditions.[1] We and others have shown that readily available alkylboron reagents, including boronic esters[2] and trifluoroborate salts,[3] undergo deboronative single-electron oxidation to give alkyl radical intermediates that engage in Giese-type additions,[2a–c,3a–d] hydrogen atom transfer,[2f] nickel-catalyzed cross couplings,[2e,3e–h] and radical-polar cross-over reactions (Scheme 1A).[2d,3l] Despite these diverse photoredox-catalyzed transformations of alkylborons, related reactions that use 1,2-bis-boron species as radical precursors have yet to be explored. However, such processes would be highly valuable since (i) 1,2-bis-boronic esters are easily prepared from alkenes, often with high enantioselectivity;[4] and (ii) following the deboronative radical reaction, a boronic ester is retained for use in further transformations.[5]

Previous reports of mono-functionalizations of 1,2-bis-boronic esters (**1**) have involved selective reaction at the primary boronic ester, which is due to favorable activation (boronate complex formation) of the sterically less hindered boron atom (Scheme 1B).[6] Based on this precedent, selective formation of boronate complex **2** followed by photoredox-catalyzed single-electron oxidation and reaction of the resulting primary radical would give a product bearing a secondary boronic ester (Scheme 1C, path A). However, given the instability of primary alkyl radicals, we considered the possibility of a radical 1,2-boron shift to provide the thermodynamically more stable secondary radical (Scheme 1C, path B). Thermodynamically driven 1,2-group transfers of alkyl radicals

Scheme 1. Alkylborons as radical precursors and functionalizations of 1,2-bis-boronic esters.



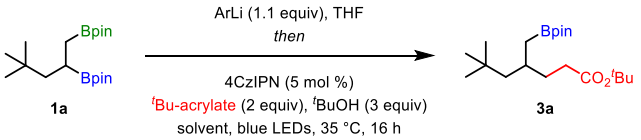
are mainly limited to migrations of π-systems, such as the well-established neophyl and Dowd-Beckwith rearrangements.[7] Related heteroatom-transfers are rare but have been proposed for halogen[8] and silicon groups.[9] There have been isolated reports of 1,2-boron migrations, including via cationic[10] or anionic intermediates,[11] and a single report by Batey in 1999 which showed that β-boryl radicals are capable of undergoing intramolecular homolytic substitution.[12] In our proposed strategy, a radical migration of the boronic ester group would enable a cascade sequence of 1,2-shift and subsequent reaction of the resulting thermodynamically favored secondary alkyl radical (Scheme 1C, path B). This would lead to a product in which it appeared as if the more hindered secondary boronic ester had been activated, providing the opposite selectivity to that typically observed for functionalizations of 1,2-bis-boronic esters.[6,13] We now report that, in photoredox-catalyzed deboronative Giese reactions of 1,2-bis-boronic esters, following activation of the less hindered primary boronic ester, the exclusive product obtained is that derived from substitution of the secondary boronic ester.

Our initial investigations of the reaction of 1,2-bis-boronic ester **1a** were based on our recent report of a deboronative cyclobutane synthesis, where phenyllithium was successfully employed to form a highly reducing boronate complex (Table 1).[2d] Thus, a

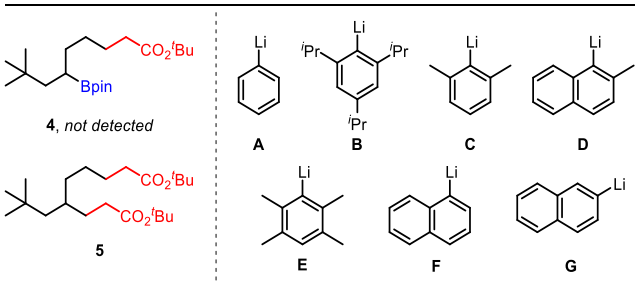
boronate complex was formed by reaction of **1a** with phenyllithium (**A**) in THF, and a solution of photoredox catalyst (4CzIPN), *tert*-butyl acrylate, and *tert*-butanol in DMF was added. The subsequent reaction under blue light irradiation afforded the product of functionalization at the secondary position (**3a**) in a promising 48% yield (entry 1). Two characteristics of this initial reaction are noteworthy: (i) no trace of regioisomeric product **4** was detected in the crude reaction mixture, confirming that a 1,2-boron shift occurred to form the more stable secondary radical; and (ii) we observed 12% of doubly functionalized product **5** and recovered 27% of **1a**. This suggested low selectivity between single and double addition of **A** to **1a**. Hoping to increase the selectivity, we turned to more sterically hindered aryllithium reagents (**B**–**G**, entries 2–7). Pleasingly, this approach proved successful, with *ortho*-substituted aryllithiums suppressing the formation of **5**. From this series of reactions, **B** emerged as the ideal reagent in terms of yield (68%), cost and reproducibility. A subsequent screen of solvents identified acetonitrile as optimal (entry 8).[14] Finally, a slight increase in concentration (compare entries 8–10) gave **3a** in 90% isolated yield, while the absence of ^{t}BuOH (required for protonation of the enolate intermediate; entry 11), light (entry 12) or photocatalyst (entry 13) led to dramatically diminished yields.

With the optimized conditions in hand, we investigated the scope of bis-boronic esters (Scheme 2A). Initially, we probed the effects of steric hindrance on the reaction efficiency and were pleased to see that products with α-secondary (**3b**) and α-tertiary centres (**3c**) were formed readily. Moreover, substrates containing a tertiary boronic ester (**3d**–**3f**) provided excellent yields of the products of tertiary functionalization. It should be noted that for substrates showing considerable steric bias between the two boronic ester groups (e.g., **3e**), using phenyllithium instead of **B** provided almost identical results (81% compared to 85% for **B**). Surprisingly, phenyl-containing **3g** was only isolated in moderate yield (35%) and an equimolar amount of starting material was recovered. We speculated that competitive addition of the transient radical intermediate to the aryl ring could (i) lead to unspecific degradation, as indicated by the low mass balance; and (ii) slow down turnover of the photocatalyst, thereby allowing the boronate complex intermediate to decompose over time.[14] When a homologated substrate was used, product **3h** was afforded in considerably increased yield (66%), suggesting the vicinity of the phenyl moiety was in fact inhibiting formation of **3g**. Unfortunately, styrene-derived bis-boronic esters failed to give the desired products.[14] In addition to substrates of varying steric demand, various functional groups were also tolerated, including esters (**3i**), nitriles (**3j**) and silyl ethers (**3k**)—the former two requiring the use of less hindered aryllithium **D** in order to suppress competing α-deprotonation. Additionally, using two equivalents of aryllithium allowed isolation of secondary carbamate **3l** in moderate yield. Bis-boronic esters derived from 3-carene and camphene were also competent substrates, affording the corresponding products **3m** and **3n** in good yields, with excellent diastereoselectivity observed for the latter product. The 1,2-bis-boronic ester derivative of β-pinene (**1o**) provided monocyclic product **3o** in 53% yield. This compound is the product of ring-opening of the strained cyclobutane moiety after 1,2-boron shift, highlighting the radical nature of this transformation.

Table 1. Optimization Studies



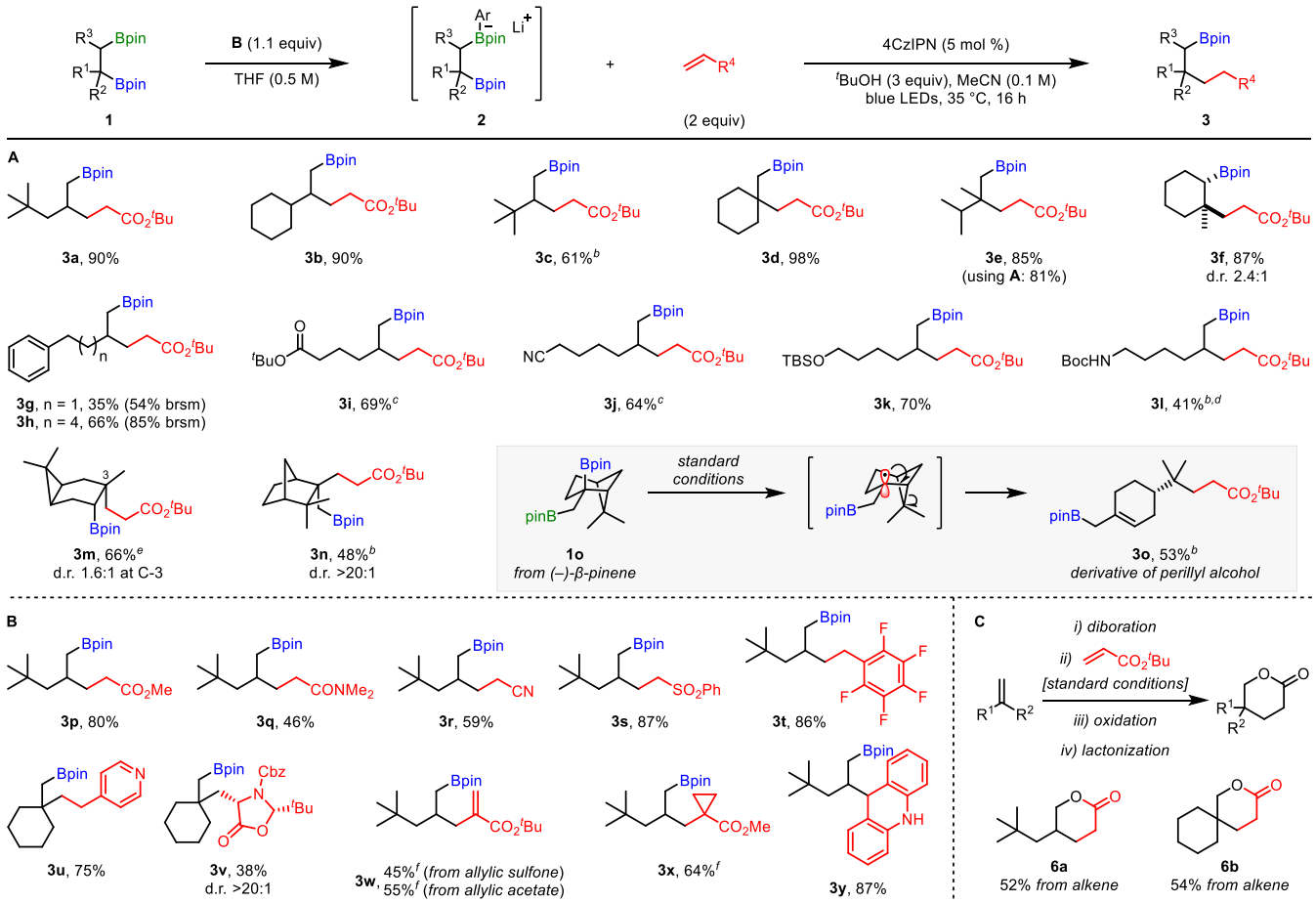
Entry[a]	ArLi	Solvent	c (M)	**3a** (%)[b]	**1a** (%)[b]
1	**A**	DMF	0.05	48	27
2	**B**	DMF	0.05	68	12
3	**C**	DMF	0.05	38	27
4	**D**	DMF	0.05	75	15
5	**E**	DMF	0.05	70	9
6	**F**	DMF	0.05	70	2
7	**G**	DMF	0.05	29	11
8	**B**	MeCN	0.05	88	2
9	**B**	MeCN	0.1	100 (90)	0
10	**B**	MeCN	0.2	89	5
11[c]	**B**	MeCN	0.1	11	37
12[d]	**B**	MeCN	0.1	0	17
13[e]	**B**	MeCN	0.1	<1	33



[a] Reactions were run on 0.2 mmol scale. [b] Determined by GC/MS analysis; values in parentheses correspond to isolated yields. [c] Without ^{t}BuOH. [d] In the dark. [e] Without 4CzIPN.

Our interest subsequently shifted to investigation of the radical acceptor (Scheme 2B). Radical conjugate addition to a range of electron-deficient alkenes afforded the desired products (**3p**–**3s**) in good to excellent yields. Styrene derivatives were also found to be competent radical acceptors, with pentafluorostyrene efficiently affording **3t**. On the other hand, 4-vinylpyridine, a comparatively weaker acceptor, only reacted with more nucleophilic tertiary radicals, forming **3u** in 75% yield. Employing an enantiopure dehydroalanine derivative provided product **3v** in only moderate yield, but with complete diastereocontrol. While the aforementioned reactions all require protonation to form the corresponding products, we were interested in exploring alternative modes of termination. In this sense, enoate **3w** was synthesized via two mechanistically distinct addition-elimination sequences from either the allylic sulfone (radical elimination, 45%) or the allylic acetate (polar elimination, 55%). Following our recent report on radical addition-polar cyclization cascades,[2d] formation of cyclopropane **3x** was also shown to be a viable pathway for this transformation. Additionally, acridine reacted readily with the secondary radical generated from **1a**, providing **3y** in excellent yield.

Scheme 2. Reaction Scope.[a]

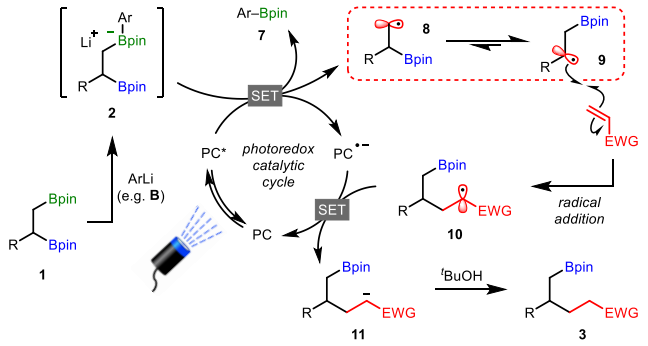


[a] Reactions were run on 0.2 mmol scale, unless otherwise noted. Yields are of isolated products. [b] Isolated as the corresponding alcohols after oxidation. [c] Using aryllithium **D**. [d] Using 2.0 equiv **B**. [e] Run on 0.15 mmol scale. [f] Without ^{t}BuOH.

As a demonstration of the synthetic utility of this methodology, we sought to highlight its application in the synthesis of valuable structures (Scheme 2C). By using a diboration/photoredox-catalyzed deboronative Giese reaction/oxidation/lactonization sequence, we were able to transform unfunctionalized alkenes into lactones **6a** and **6b** in good yields over four steps.

Based on previous reports on the oxidation of boronate complexes,[2,3] and the observed regioselectivity of our reaction, we propose the mechanism depicted in Scheme 3. Initial oxidation of primary boronate complex **2** by the excited state photoredox catalyst generates a primary radical with concomitant loss of an equivalent of arylboronic ester **7**.[15] Subsequent equilibration of the radical species through 1,2-boron shift of **8** affords thermodynamically favored secondary radical **9**. Addition of **9** to the radical acceptor forms electron deficient radical **10**, which accepts an electron from the reduced form of the photoredox catalyst. Finally, anion **11** is protonated to afford product **3**.

Scheme 3. Mechanistic Proposal.

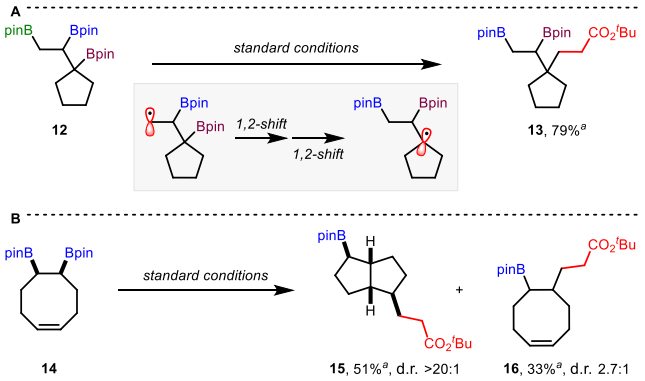


At this point, we were intrigued as to whether our approach could be extended to the selective functionalization of 1,2,3-trisboronic esters (Scheme 4A). We therefore subjected **12** to our reaction conditions and were pleased to isolate **13**, the product of sequential double 1,2-shift of two boronic esters in 79% yield. Notably, this product is formed with impeccable selectivity, highlighting the thermodynamic control that favors the most stabilized radical center as the site of reaction.

Given the ease in which 1,2-bis-boronic esters can be prepared from readily available alkenes, we were keen to explore substrates

derived from dienes, which could potentially undergo radical cascade reactions. We were attracted by cyclooctadiene derivatives, which could undergo transannular radical reactions (Scheme 4B). Pleasingly, under the standard conditions, diborated cyclooctadiene (**14**) reacted to give bicyclic product **15** in 51% yield and with excellent diastereoselectivity, alongside uncyclized product **16** (33%). This unusual radical cyclization can be viewed as both a *5-exo-* and *5-endo-trig* cyclization, accounting for its relatively low rate of ring closure ($k = 3.3 \times 10^4$ s^{-1}),[16] and consequently significant formation of the direct trapping product **16**.[17]

Scheme 4. Additional Studies.

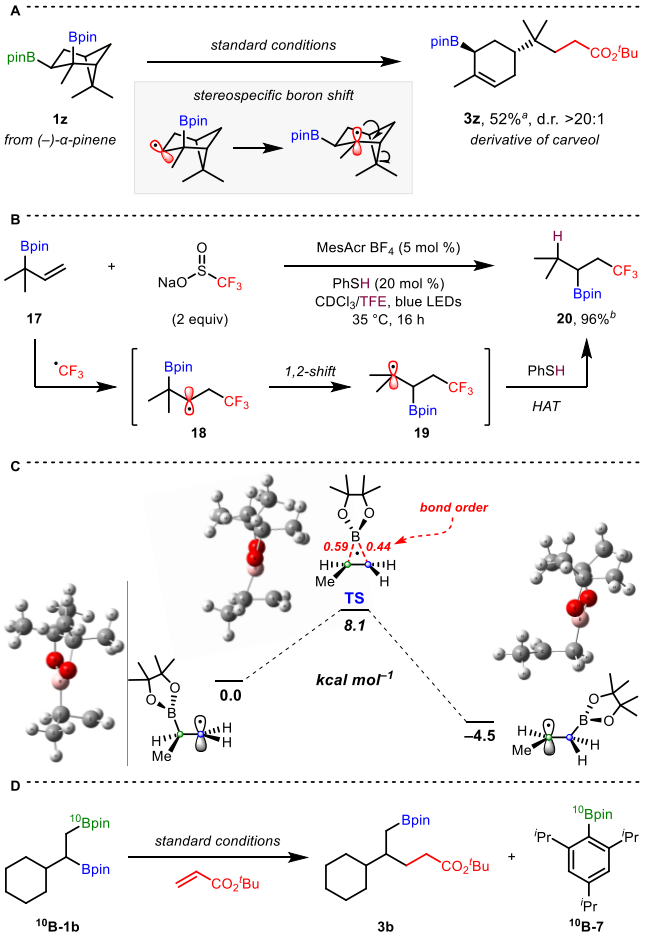


[a] Isolated as the corresponding alcohols after oxidation.

We subsequently turned our attention to the 1,2-boron shift. If this occurs via an intramolecular homolytic substitution, we reasoned that it could proceed with high stereospecificity. Thus, we investigated the stereochemical outcome of the reaction using diastereomerically pure **1z**, derived from α-pinene (Scheme 5A). The expected product of 1,2-shift and subsequent ring opening (**3z**) was obtained in 52% yield and with >20:1 d.r., in which the boronic ester migrated with high stereochemical fidelity. Further support for this was provided by the formation of **3m** from diborated 3-carene (Scheme 2A), in which boron migration occurred with complete stereospecificity but subsequent reaction of the resulting tertiary radical proceeded with poor diastereoselectivity.

Unequivocal proof for the 1,2-boron shift was obtained by treatment of allylboronic ester **17** with Langlois' reagent under Nicewicz's hydrotrifluoromethylation conditions, which gave **20** in 96% yield (Scheme 5B).[18]. This reaction proceeds via addition of a trifluoromethyl radical to **17** to provide secondary β-boryl radical **18**. 1,2-Transposition of the boronic ester affords the thermodynamically favored tertiary radical **19**, which undergoes hydrogen atom transfer (HAT) with thiophenol to form **20**. The high regioselectivity observed implies that 1,2-boron shift from a tertiary (**18**) to a secondary position (**19**) is much more rapid than HAT with thiophenol, which has a rate of $k = 1 \times 10^8$ M^{-1} s^{-1} for secondary alkyl radicals.[19] Further insight into the facile nature of the 1,2-shift was provided by modelling the process using DFT, which revealed a barrier of only 8.1 kcal mol^{-1} for migration of a secondary boronic ester to a primary radical (Scheme 5C). Finally, boron-isotope labelling studies using mono-labelled 1,2-bis-boronic ester **^{10}B-1b** yielded unlabelled product **3b** and labelled arylboronic ester **^{10}B-7**, confirming that boronate complex formation with aryllithium **B** occurs exclusively at the primary boronic ester (Scheme 5D).

Scheme 5. Investigations into the 1,2-Boron Shift.



[a] Isolated as the corresponding alcohols after oxidation. [b] Determined by ^{1}H NMR analysis.

In conclusion, we have described the use of boronate complexes derived from 1,2-bis-boronic esters in photoredox-catalyzed radical transformations. This reaction demonstrates, for the first time, a radical 1,2-boron shift under thermodynamic control, allowing for counter-intuitive selective functionalization of the more hindered position of 1,2-bis-boronic esters. We have demonstrated a broad substrate scope and highlighted the diversity of the method in ring fragmentation and transannular reactions. Furthermore, the stereoretentive nature of the 1,2-boron shift was shown and we have showcased the application of this approach in different settings by extending it to radical cascades with allylboronic esters.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interests.

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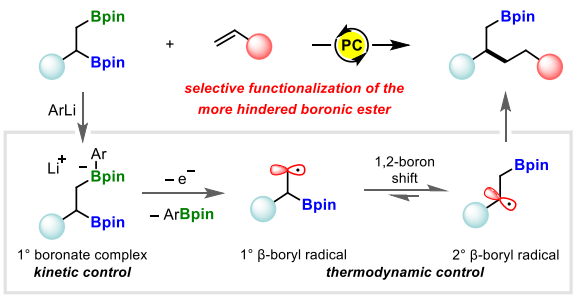
Bpin
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selective functionalization of the
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Bpin
1,2-boron
shift
Bpin
1° boronate complex
kinetic control
1° β-boryl radical
2° β-boryl radical
thermodynamic control