REPORT

ORGANIC CHEMISTRY

Radical-polar crossover reactions of vinylboron ate complexes

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Vinyl boronic esters are valuable substrates for Suzuki-Miyaura cross-coupling reactions. However, boron-substituted alkenes have drawn little attention as radical acceptors, and the radical chemistry of vinylboron ate complexes is underexplored. We show here that carbon radicals add efficiently to vinylboron ate complexes and that their adduct radical anions undergo radical-polar crossover: A 1,2-alkyl/aryl shift from boron to the α-carbon sp^2 center provides secondary or tertiary alkyl boronic esters. In contrast to the Suzuki-Miyaura coupling, a transition metal is not required, and two carbon-carbon bonds are formed. The valuable boronic ester moiety remains in the product and can be used in follow-up chemistry, enlarging the chemical space of the method. The cascade uses commercial starting materials and provides access to perfluoroalkylated alcohols, γ-lactones, γ-hydroxy alkylnitriles, and compounds bearing quaternary carbon centers.

Vinylboronic acid derivatives and their corresponding boron ate complexes are highly valuable substrates in organic synthesis. They are readily accessed at low cost, and some of them are commercially available. Such boron compounds have been intensively used in C–C bond formations. The most prominent such reaction is the Nobel prize–winning Suzuki-Miyaura coupling, in which the boron ate complexes engage in transition metal (initially palladium)–catalyzed cross-couplings with aryl, alkenyl, alkynyl, and alkyl halides (Fig. 1A) (*1*, *2*). The Suzuki-Miyaura coupling is a two-component process. Very recently, Morken and co-workers elegantly used in situ–generated vinylboron ate complexes in Pd-catalyzed three-component conjunctive cross-coupling reactions (Fig. 1B) (*3*). Electrophilic palladation of the vinyl group induces a 1,2-R migration (where R is an alkyl or aryl). Similar reactivity was noted in the Zweifel reaction, in which the 1,2-R shift is induced by initial electrophilic halogenation of the vinyl group (Fig. 1C) (*4*). That approach was recently extended further by Aggarwal and co-workers to the stereospecific alkylation of lithiated heteroarenes with boronic esters (*5*). Here we report the reaction of vinylboron ate complexes with alkyl radicals to induce 1,2-R shifts (Fig. 1D). Our approach is complementary to the Morken reaction: Whereas in the Pd variant, β-arylation of the vinyl group is achieved, the radical approach allows for β-alkylation of the alkene moiety. The radical process proceeds without transition metal catalysis, reducing the costs of the overall sequence. Radical chemistry on alkenyl boronic esters has been investigated (*6*–*8*); however, the corresponding boron ate complexes have not been applied as radical acceptors. Given the importance of fluorine substituents in medicinal and agrochemical research (*9*–*11*), we also focus here on the use of perfluoroalkyl radicals (*12*).

The reaction sequence required that the electron-rich double bond in the starting vinylboron ate complex react readily with electrophilic C radicals. We therefore planned to use perfluoroalkyl iodides (R_f–I) as C radical precursors in our initial studies. C radical generation can either be achieved by I abstraction from R_f–I or by single-electron reduction of R_f–I. Addition of the electrophilic perfluoroalkyl radical $R_f\cdot$ to the vinylboron ate complex would generate the corresponding adduct radical anion **I** that could further react via two different pathways (Fig. 2). In an electron-catalyzed process (*13*), single-electron oxidation of the adduct radical **I** by the perfluoroalkyl iodide would lead in a radical-polar crossover step to zwitterion **II**, along with the perfluoroalkyl radical, thereby sustaining the radical chain. Ionic 1,2-alkyl/aryl migration would eventually provide the target boronic ester **III** (Fig. 2A). Alternatively, adduct radical **I** could abstract the I atom of R_f–I to give the atom transfer product **IV**, which could further react in an ionic 1,2-alkyl/aryl migration substituting the iodide, likely assisted by the counter cation M^+, to give **III** (Fig. 2B). Whether reactions proceed by outer-sphere (**I** to **II**) or inner-sphere (**I** to **IV**) electron transfer depends on the reduction potential of the alkyl radical precursor and on the halogen atom transfer efficiency (*14*).

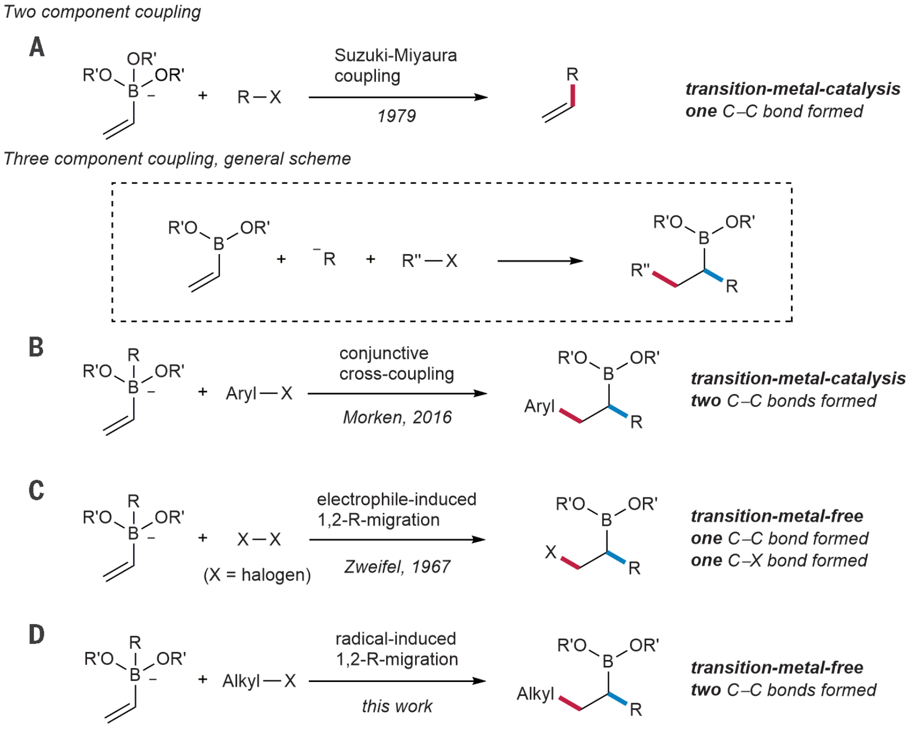

Fig. 1. Vinylboron ate complexes show diverse reactivity. (**A**) Transition metal–catalyzed Suzuki-Miyaura cross-coupling forms a single C–C bond. (**B**) Transition metal–catalyzed conjunctive cross-coupling forms two C–C bonds. (**C**) The Zweifel reaction forms a C–halogen and a C–C bond in the absence of transition metals. (**D**) Vinylboron ate complexes act as radical acceptors to form two C–C bonds in the absence of transition metals, via radical addition and a subsequent 1,2-R shift; as in (B) and (C), the valuable boron ester functionality remains in the product. An R indicates an alkyl or aryl group; X is a halogen. Red, first C–C or C–X bond formed; blue, second C–C bond formed via 1,2-R migration.

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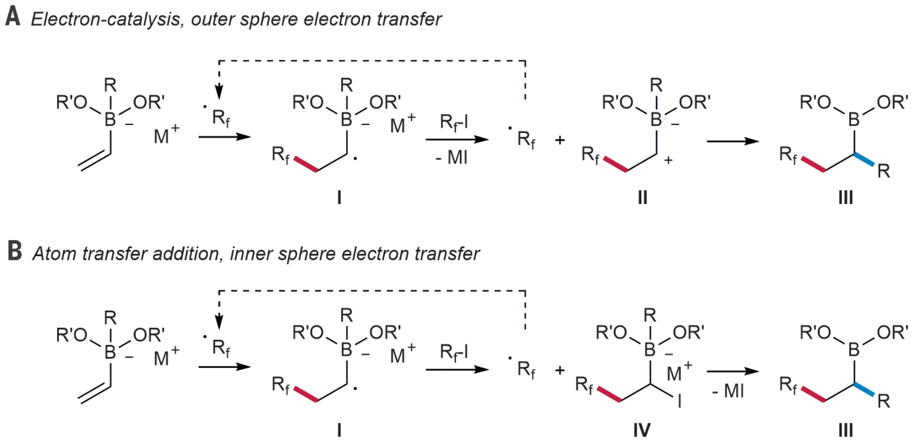

Fig. 2. Reaction design and mechanistic considerations. (**A**) Addition of the perfluoroalkyl radical $R_f\cdot$ generates radical anion **I** that further reacts with R_f–I via single-electron oxidation to give $R_f\cdot$ and zwitterion **II**. Ionic 1,2-alkyl/aryl migration leads to **III**. (**B**) R_f–I reacts in an atom transfer addition via **I** to iodide **IV** that undergoes M^+-mediated 1,2-alkyl/aryl migration to **III**. M, Li or MgBr.

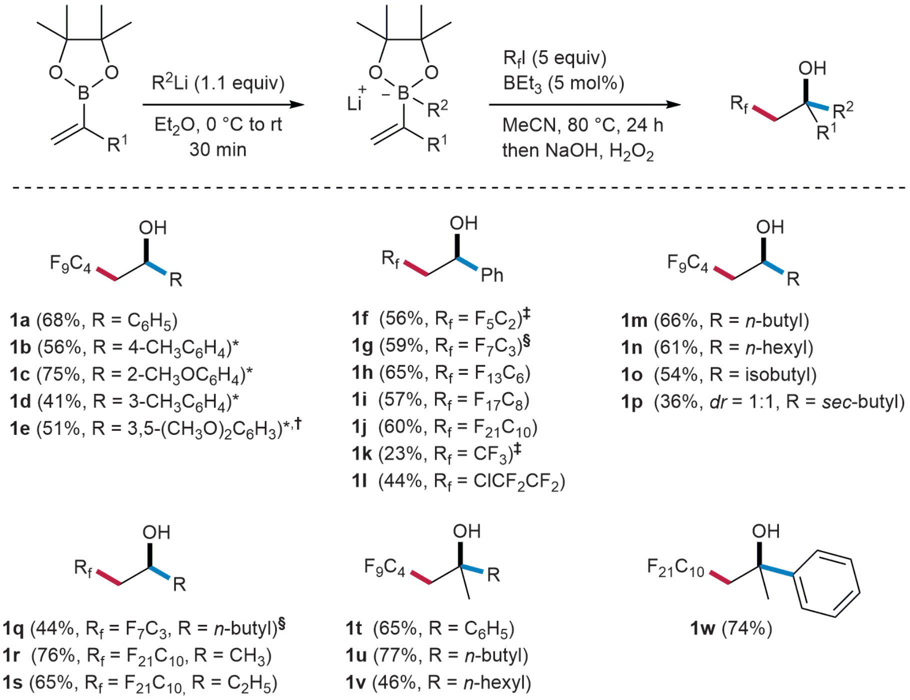

Fig. 3. Scope of the radical-polar crossover reaction of vinylboron ate complexes. The vinylboronic acid pinacol ester, organolithium compound, and perfluoroalkyl iodide were varied. Isolated yields are given in parentheses, and newly formed bonds are highlighted in bold. rt, room temperature; h, hours; dr, diastereomeric ratio. *Organolithium compound generated in situ from aryl bromide [1.3 equivalents (equiv)] by Br-Li exchange (supplementary materials). †Boron ate complex generated in THF. ‡Radical cascade run with 10 equiv of the perfluoroalkyl iodide and 20 mol % of BEt_3 at 60°C. §Radical cascade run with 20 mol % of BEt_3.

We commenced our investigations by using vinylboronic acid pinacol ester (vinylBpin), perfluorobutyl iodide, and phenyl lithium as the three reaction components. All these reagents are commercially available. Optimization studies revealed that generation of the boron ate complex is best achieved by treatment of vinylBpin in Et_2O (Et, ethyl) with PhLi (Ph, phenyl) at 0°C (Fig. 3). Complete formation of the boron ate complex under these conditions was unambiguously confirmed by ^{11}B nuclear magnetic resonance spectroscopy [in deuterated tetrahydrofuran (THF–d_8)], in which only one characteristic boron ate signal at δ = 9.6 parts per million was identified. The boron ate complex can be isolated by simple removal of the solvent and used for the radical sequence without any further purification. We combined the boron ate complex with perfluorobutyl iodide in acetonitrile at 80°C for 24 hours, using BEt_3 (5 mol %) as a radical initiator. For convenience, the resulting product boronic ester was directly oxidized by treatment with NaOH-H_2O_2 mixture. We found that the target sequence proceeded smoothly, and the desired alcohol **1a** was obtained in 68% isolated yield. Chain initiation can occur via reaction of BEt_3 with traces of air or via single-electron oxidation of the vinylboron ate complex. As a side product, phenol was obtained, derived from NaOOH oxidation of PhBpin, which was generated by direct oxidation of the boron ate complex. These conditions were applied to all other experiments in this series. Organolithium compounds that are not commercially available were readily generated in situ by Br-Li exchange from the corresponding bromides (supplementary materials). Other vinyl boronic esters that we tested provided lower yields (supplementary materials), and replacing PhLi with PhMgBr led to nearly complete suppression of the target three-component reaction. In these reactions, phenol was formed as the major product.

The aryl group in the product alcohol is readily varied by changing the aryl lithium component, as documented by the successful preparation of **1b** to **1e** (41 to 75%). The modest yields obtained in some transformations of this series and in subsequent reactions can be explained by problems encountered during product isolation related to the volatility of the fluorinated alcohols. In addition, side products were formed by direct oxidation of the vinylboron ate complex. Keeping PhLi as the aryl donor and vinylBpin as the acceptor, we also demonstrated that other perfluoroalkyl iodides ($F_{2n+1}C_nI$) perform well in this three-component reaction (**1f** to **1j**; 56 to 65%). The cascade also works efficiently when using alkyl lithium reagents, as documented by the successful preparation of secondary alcohols **1m** to **1p** (36 to 66%). We further varied both the perfluoroalkyl iodide and the alkyl lithium component to access alcohols **1q** to **1s**. The method can also be used for the preparation of tertiary alcohols. To this end, we switched to isopropenylboronic acid pinacol ester (R^1 = Me, methyl) as a precursor of the radical acceptor. Reaction with perfluoroalkyl iodides in combination with several different organolithium compounds provided the corresponding tertiary alcohols **1t** to **1w**.

We next investigated whether the α-fluoro substituent in the C radical was essential for the radical-polar crossover reaction and found α-iodoesters to be suitable substrates for the three-component cascade (Fig. 4A). Reaction of vinylboronic acid pinacol ester with PhLi and subsequent radical-polar crossover reaction with ethyl α-iodoacetate provided γ-butyrolactone **2a** after oxidation of the boronic ester and acid-catalyzed lactonization. In analogy, the γ-lactones **2b** to **2f** were obtained in 40 to 94% isolated yield. Furthermore, iodoacetonitrile could be used in the radical-polar crossover sequence to prepare the γ-hydroxy nitriles **3a** and **3b** (Fig.

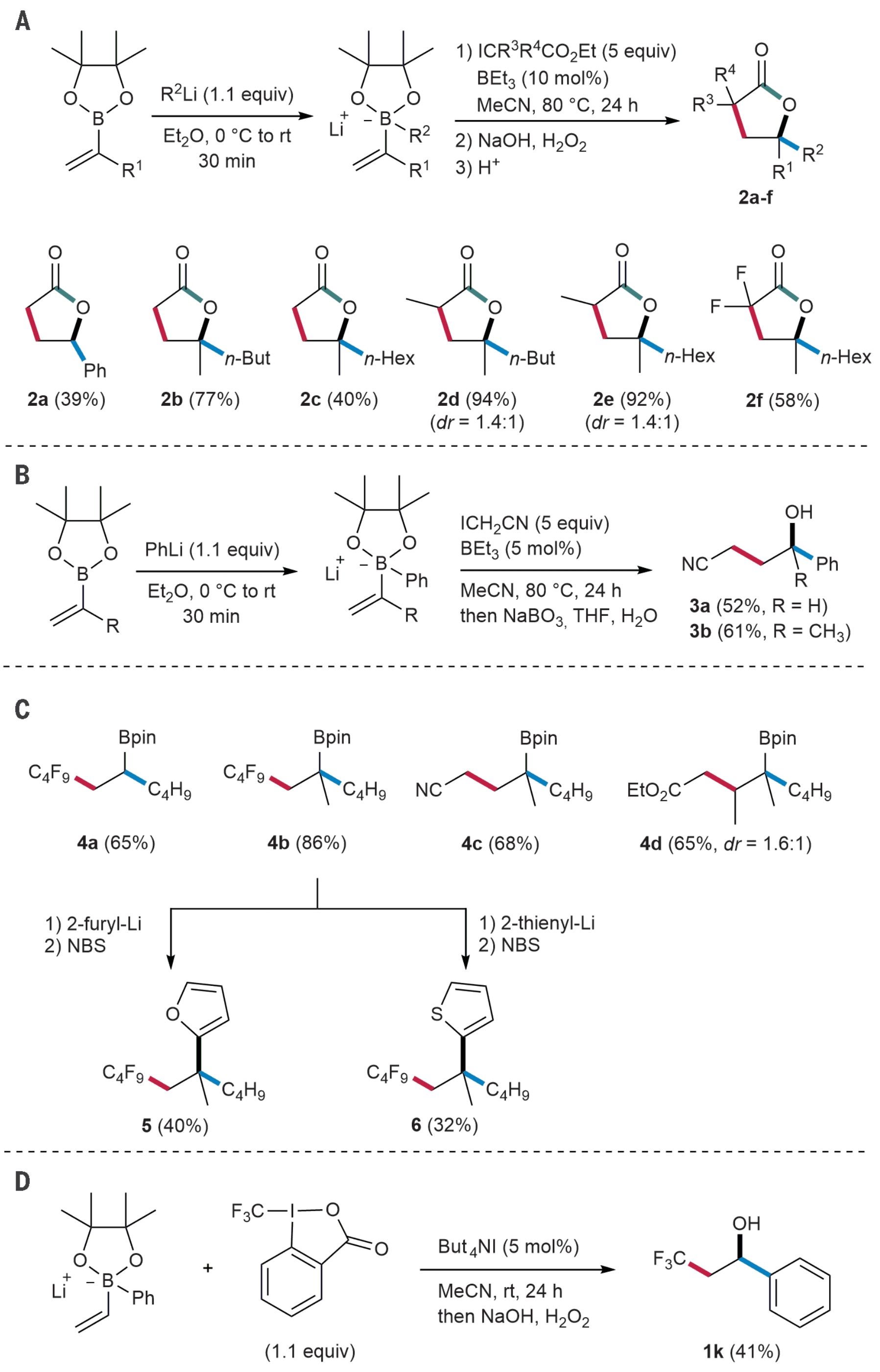

Fig. 4. Reaction with nonfluorinated halides to form γ-butyrolactones. Newly formed bonds are highlighted in bold. (**A**) α-Iodoesters act as radical precursors for the preparation of γ-butyrolactones. Green, C–O bond formed via acid-catalyzed lactonization. (**B**) Iodoacetonitrile provides nitriles **3a** and **3b**. (**C**) Alkylboronic esters can be isolated and used as substrates in follow-up chemistry. (**D**) Togni's reagent can also be applied as a trifluoromethyl radical precursor to prepare compounds such as alcohol **1k**. *n*-But, *n*-butyl; *n*-Hex, *n*-hexyl; NBS, *N*-bromosuccinimide.

4B). Alkylboronic esters can be isolated if the reaction sequence is stopped after the radical-polar crossover process, as documented by the successful preparation of **4a** to **4d** (Fig. 4C). Product **4d** showed that radical addition also works on β-substituted vinylboron ate complexes.

Alkylboronic esters are highly valuable substrates for diverse follow-up chemistry. Along these lines, we prepared compounds **5** and **6** bearing quaternary C centers (Fig. 4C) (*5*). In a proof-of-concept experiment for the enantioselective version of the cascade, we showed that alcohol **1a** could be obtained with 52% enantiomeric excess by running the reaction with the commercially available chiral (+)-vinylboronic acid pinanediol ester as starting material (see the supplementary materials).

To shed light on the possible mechanism of the radical cascade, we also tested Togni's reagent (*15*) as a CF_3 radical precursor. This reagent cannot react via iodine atom transfer but cleanly provides a CF_3 radical upon single-electron reduction. We combined Togni's reagent with vinyl phenyl pinacolboronate in acetonitrile at room temperature in the presence of tetrabutylammonium iodide as an initiator and obtained (after NaOOH oxidation) alcohol **1k** in 41% yield (Fig. 4D). Thus, at least for this process, it is highly likely that the radical-polar crossover proceeds via an outer-sphere electron transfer according to the mechanism in Fig. 2A. We also favor the outer-sphere process for the reactions conducted with the alkyl iodides for the following reasons. Successful transformations were observed with electron-poor alkyl halides that are readily reduced via a single-electron transfer process. Moreover, cyclohexyl iodide and 1-iodoadamantane, which are generally reactive substrates in atom transfer reactions, did not engage in the three-component reaction, although in these two cases, reactivity of the *sec*- and *tert*-alkyl radical toward the vinylboron ate complex might also be lowered. In addition, we computationally investigated the reaction between a radical anion of type **I** ($R_f = CF_3$, R = Ph, R' = CH_3; Fig. 2) and CF_3I (supplementary materials). Electron removal from **I** directly leads to the phenyl migration product **III** in a strongly exothermic process. However, formation of the corresponding I atom transfer product **IV** is also kinetically viable, and **IV** has a low free-energy barrier for 1,2-phenyl migration (formation of **III**). We are confident that readily generated alkenylboron ate complexes have great potential as radical acceptors in radical-polar crossover reactions.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
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Editor's Summary

Boron choreographs a double reaction

In the widely used Suzuki coupling reaction, boron surrenders an olefinic substituent to a metal catalyst en route to carbon-carbon bond formation. Kischkewitz *et al.* report a metal-free alternative pathway, wherein the boron stays bound to one end of the olefin while a carbon radical attacks the other end. Charge transfer then prompts migration of an alkyl or aryl group from the boron to form a second carbon-carbon bond. The boron can subsequently be displaced, generating a versatile array of alcohols, lactones, and quaternary carbon centers from simple precursors.

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