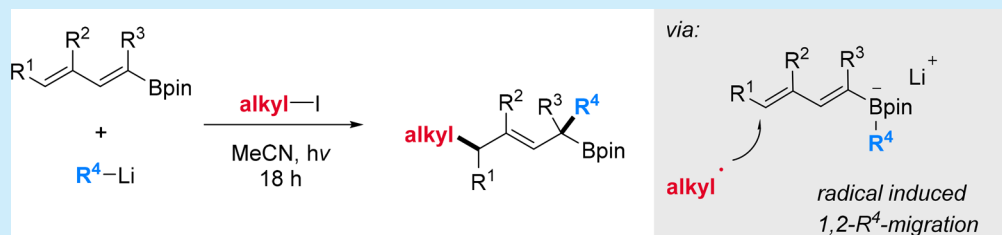


Radical-Polar Crossover Reactions of Dienylboronate Complexes: Synthesis of Functionalized Allylboronic Esters

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S Supporting Information



ABSTRACT: Radical-polar crossover reactions of dienylboronate complexes are applied to the synthesis of functionalized secondary and tertiary allylboronic esters. The transition-metal-free three-component coupling uses readily accessible dienylboronate esters as substrates in combination with various sp^3/sp^2 carbon nucleophiles and commercial alkyl iodides as radical precursors. In the visible light-initiated radical chain process, two new C–C bonds are formed, and the *E*-double bond geometry in the product allylboronic esters is controlled with good to excellent selectivity.

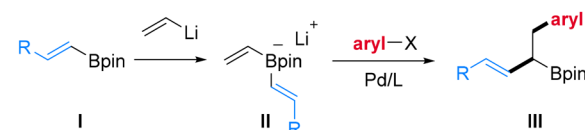
Allylboronic esters are highly useful building blocks in organic synthesis.¹ The great value of these reagents lies in their configurational and chemical stability.² They have been successfully applied to cross-coupling reactions,³ but most often they are used as nucleophiles for the stereoselective synthesis of homoallylic secondary alcohols and amines by an allyl transfer reaction to carbonyls and imines.⁴ Notably, functionalized allylboronic esters can also participate in tandem reactions with aldehydes,⁵ and it was demonstrated that allylboronate complexes can react with a range of other types of carbon as well as heteroatom electrophiles with high γ -selectivity.⁶ Although various direct or indirect methods for the synthesis of allylboronic esters have been introduced,⁷ the development of novel strategies for their preparation is still of importance.

Along these lines, Morcken and co-workers recently used bis(alkenyl)boronate complexes **II** in palladium-catalyzed three-component conjunctive cross-coupling reactions.⁸ Regioselective electrophilic aryl-palladation of the vinyl moiety induces a 1,2-alkenyl migration to provide, after reductive elimination, α -arylmethyl allylboronic esters of type **III** (Scheme 1, a).

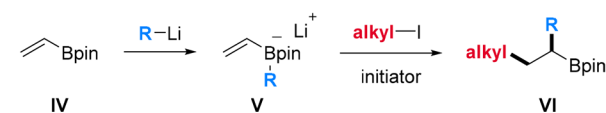
Our group and the Aggarwal laboratory have recently shown that electrophilic alkyl radicals add efficiently to *in situ* generated vinylboronate complexes **V** and that their corresponding radical anions undergo a radical polar crossover step, inducing a 1,2-R-migration to provide secondary and tertiary allylboronic esters **VI** (Scheme 1, b).^{9,10} Motivated by these studies, we considered using dienylboronate complexes in radical-polar crossover reactions for the synthesis of α -alkylated/arylated allylboronic esters. Importantly, the starting dienylboronic esters are readily accessible by hydrozirconation,¹¹ boron-Wittig reaction¹² or by Heck–Mizoroki cou-

Scheme 1. Synthesis of Allylboronic Esters in Three-Component Couplings

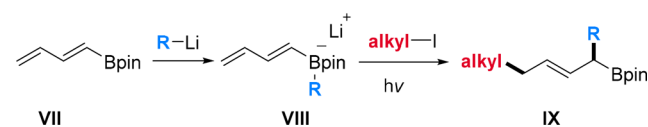
a) Conjunctive cross-coupling of bis(alkenyl)boronate complexes⁸



b) Radical induced 1,2-migration of vinylboronate complexes^{9,10a}



c) Radical induced 1,2-migration of dienylboronate complexes (this work)



pling.¹³ We assumed that a carbon radical would selectively add to the δ -position of the diene moiety in boronate complexes of type **VIII** (Scheme 1, c). The resulting allyl radical anion should then undergo a radical polar crossover step with concomitant 1,2 aryl- or alkyl-shift from boron to the α -carbon. During the R-migration, the double bond geometry of the targeted allylboronic ester gets installed. A challenge will therefore lie in the control of the *E/Z*-selectivity. Moreover, for

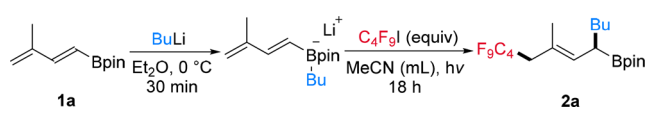
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more complex substituted dienylboronate complexes, regioselective δ -addition of the radical must be ensured. This novel transition-metal-free three-component strategy should enable the efficient construction of highly substituted and functionalized secondary and tertiary allylboronic esters IX.

We commenced our investigations by treating the readily prepared γ -methyl substituted dienylboronic ester **1a** (see Supporting Information (SI)) with *n*-butyllithium at 0 °C in Et₂O to generate the corresponding dienylboronate complex. After removal of the solvent, the crude ate complex was redissolved in acetonitrile, and 1.5 equiv of perfluorobutyl iodide was added. Visible light irradiation¹⁴ for 18 h afforded the desired perfluorinated allylboronic ester **2a**, resulting from regioselective δ -addition in 63% isolated yield with moderate 4:1 *E/Z*-selectivity (Table 1, entry 1). The product derived

Table 1. Optimization Studies Using 1a as Substrate



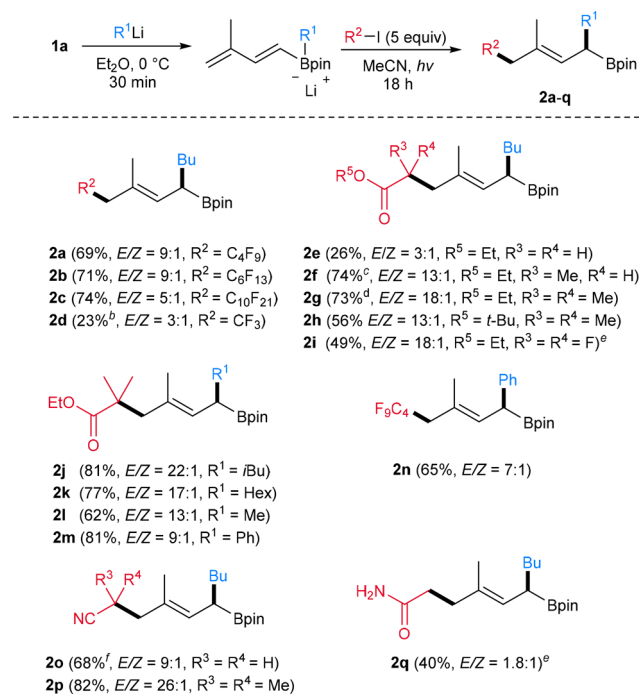
entry ^a	C4F9I (equiv)	solvent (mL)	yield (%) ^b	<i>E/Z</i> (ratio) ^c
1	1.5	MeCN (2)	63	4:1
2	2.0	MeCN (2)	67	5:1
3	5.0	MeCN (2)	69	9:1
4	10.0	MeCN (2)	69	12:1
5	5.0	MeCN (1)	66	8:1

^aReactions were conducted with **1a** (0.3 mmol). ^bYields provided represent isolated yields. ^cSelectivity was determined by ¹H NMR spectroscopy.

from β -addition was not identified. Increasing the amount of perfluoroalkyl iodide to 2.0 equiv resulted in a slightly higher yield (67%) and enhanced selectivity (5:1, Table 1, entry 2). A further increase of the amount of perfluorobutyl iodide significantly affected the double bond selectivity without altering the yield. While using 5.0 equiv of iodide resulted in a 9:1 *E/Z*-selectivity, 10.0 equiv led to an even further improvement of the stereoselectivity to 12:1 (Table 1, entries 3 and 4). However, increasing the concentration of the reaction mixture did not affect the selectivity, but led to a slightly decreased yield (Table 1, entry 5). Note that this positively influenced *E/Z*-selectivity, as a function of the amount of added radical precursor was found to be general and could be observed also in other transformations. Any time dependence of the *E/Z*-selectivity could be ruled out by varying the reaction time. Considering reaction economy and selectivity, we regarded 5.0 equiv of the radical precursor R–I as optimal (Table 1, entry 3). For comparative data on reactions conducted with 2.0 equiv of R–I and varied reaction times, we refer to the SI.

To document the substrate scope, **1a** was reacted under optimized conditions, varying the C-nucleophile and also the radical precursor to give the allylboronic esters **2b–2q** (Scheme 2). We first tested the ate complex derived from **1a** and *n*-butyllithium in combination with various perfluoroalkyl iodides. With the exception of the volatile trifluoromethyl iodide, all other congeners performed well in this sequence, and the resulting perfluoroalkylated allylboronic esters **2b–2d** were isolated in good yields and good *E/Z* selectivities. α -Iodo ethyl esters are eligible C-radical precursors for this cascade, and higher *E/Z* selectivity was achieved upon increasing the degree

Scheme 2. Radical-Polar Crossover Reaction of Various Dienylboronate Complexes^a

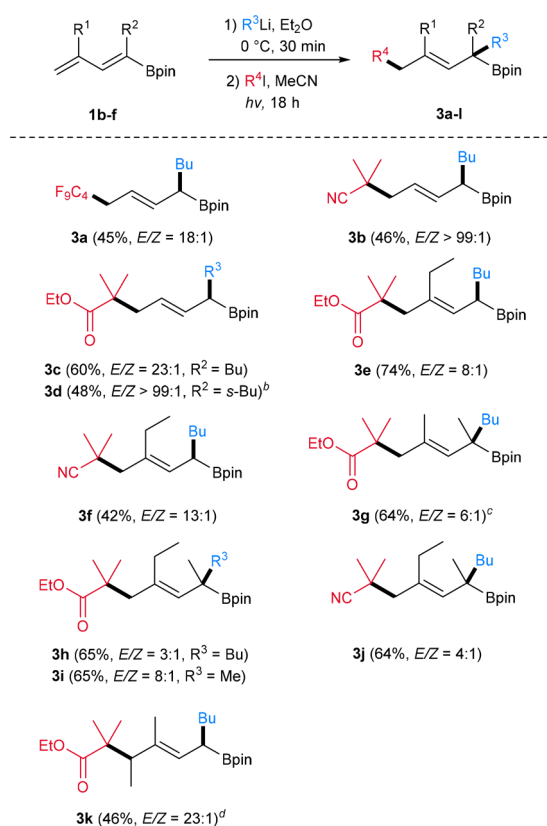


^aIsolated yields. ^b10.0 equiv of CF₃I were used. ^cdr = 1.4:1. ^dReaction was conducted on a 2.5 mmol scale. ^e2.0 equiv of R²–I was used. ^fYield refers to isolated *E* isomer.

of α -substitution in the ester moiety (**2e–2g**). As expected, low diastereoselectivity was noted for the reaction with α -iodo ethyl propanoate. Replacing the ethyl by a *tert*-butyl ester group led to slightly lower *E/Z*-selectivity (**2h**). The α -iodo- α -difluorinated ester is a suitable C-radical precursor, and **2i** was isolated in good yield and high selectivity. The migrating alkyl group can be readily varied by replacing *n*-butyllithium with *i*-butyl-, *n*-hexyl-, and methyl-lithium (**2j–2l**). Importantly, the cascade also works efficiently for aryllithium reagents, as documented by the successful preparation of the secondary benzylic allylboronic esters **2m** and **2n**. We next investigated α -iodo acetonitrile and α -iodo isobutyronitrile as radical precursors. Both nitriles worked well, and in analogy to the reaction with the α -iodo esters, the *E/Z* selectivity was increased by switching to the bulkier α -dimethyl substituted system (from 9:1 to 26:1). Notably, unprotected α -iodo amides are tolerated in the radical-polar crossover reaction, as documented by the successful preparation of **2q**.

We next varied the dienylboronic ester moiety using *n*-butyllithium as the nucleophilic reaction component (Scheme 3). Starting with the unsubstituted boronic ester **1b**, perfluorobutyl iodide, α -iodo isobutyronitrile, and ethyl dimethyl α -iodo ester provided the targeted allylboronic esters **3a–3c** in good yields and excellent *E/Z* selectivities (up to >99:1). The radical induced 1,2-migration also allows the introduction of secondary alkyl chains, as demonstrated by the successful preparation of the allylboronic ester **3d**. Replacing the methyl with a γ -ethyl substituent at the diene acceptor leads to lower *E/Z* selectivity, as shown for the synthesis of α -iodo ester **3e** and the nitrile analogue **3f**. Of note, γ -substituted tertiary allylboronic esters also could be accessed (**3g–3j**). We further demonstrated that the reaction also proceeds on a δ -

Scheme 3. Radical-Polar Crossover Reaction of Dienylboronate Complexes: Variation of the Diene Moiety^a

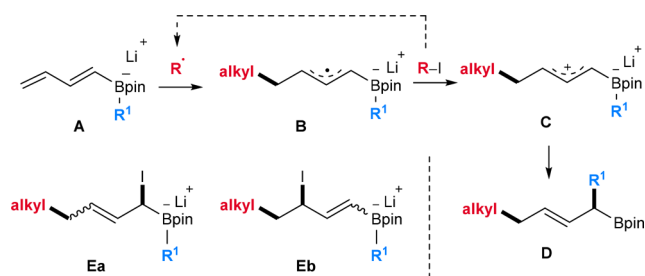


^aIsolated yields. ^bdr = 1.4:1. ^c2.0 equiv of R²-I was used. ^ddr = 1.7:1.

substituted dienylboronate complex, and the resulting boronic ester **3k** was isolated as a diastereomeric mixture in moderate yield and excellent *E/Z* selectivity. The corresponding product resulting from β -addition was not identified showing the high intrinsic δ -reactivity of these radical diene acceptors.

The suggested mechanism for the radical-polar crossover reaction is presented in Scheme 4. The cascade is initiated by

Scheme 4. Proposed Mechanism

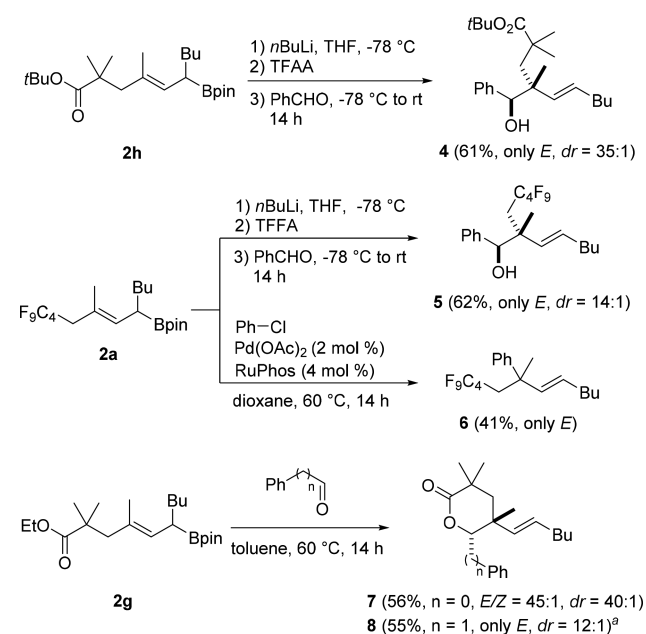


light-mediated C–I homolysis. The thus generated electrophilic C-radical selectively adds to the δ -position of the dienylboronate complex **A**, leading to the corresponding allyl radical anion **B**, which undergoes single electron oxidation by an alkyl iodide to generate the corresponding zwitterion **C**. Thereby an alkyl radical is cogenerated, sustaining the radical chain. Hence, the radical cascade belongs to an electron-catalyzed process.¹⁵ The zwitterion **C** further reacts in an ionic 1,2-R-migration to provide the isolated allylboronic ester **D**. Currently, we cannot fully exclude that the allyl radical anion **B** reacts via iodine atom

abstraction from the alkyl iodide to generate atom-transfer products **Ea** and/or **Eb**, which further react in a Matteson-type rearrangement¹⁶ to **D**. However, a mechanistic experiment, where the dienylboronate complex derived from **1a** and *n*-butyllithium was treated with the Togni reagent,¹⁷ revealed formation of the trifluoromethylated allylboronic ester **2d**. Since this reagent cannot undergo an iodine transfer process, we regard the I atom-transfer/rearrangement sequence as less likely for these transformations.

To highlight the synthetic potential of the functionalized allylboron reagents, we conducted a series of allylation reactions (Scheme 5). The secondary allylboron reagents **2h**

Scheme 5. Diverse Functionalization of Allylboron Reagents



^aIn the presence of 10 mol % Sc(OTf)₂.

and **2a** were successfully used in highly diastereoselective benzaldehyde allylations¹⁸ (see **4** and **5**). In addition, **2a** was applied to a Pd-catalyzed γ -selective cross-coupling with chlorobenzene to give **6**.¹⁹ To harvest the potential of the ethyl ester functional group, we used boronic ester **2g** as substrate for a one-pot allylation/lactonization sequence²⁰ and obtained **7** and **8** with excellent *E* selectivity and very good diastereoselectivities. Hence, our method also represents a conceptually novel approach toward biologically valuable δ -lactones.

In summary, we have developed a transition-metal-free three-component coupling of dienylboronic esters, alkyl/aryllithium compounds, and R–I radical precursors for the synthesis of functionalized secondary and tertiary allylboronic esters with good to excellent *E/Z* selectivity. The method is based on a visible light-initiated radical-polar crossover reaction of *in situ* generated dienylboronate complexes and works with a variety of commercial alkyl radical precursors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01459.

Experimental details and characterization data for the starting material and products ([PDF](#))

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Notes

The authors declare no competing financial interest.

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