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Intramolecular Hydrogen Atom Transfer Induced 1,2-Migration of Boronate Complexes

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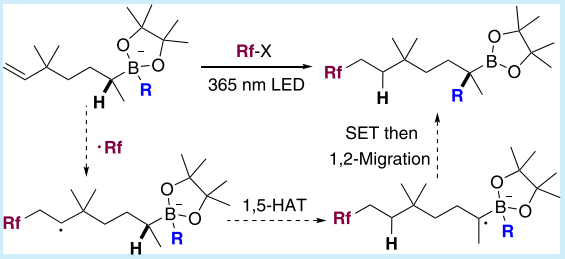
ABSTRACT: Radical α-C-H functionalization of alk-5-enyl boronic esters with concomitant functionalization of the alkene moiety is reported. These cascades comprise perfluoroalkyl radical addition to the alkene moiety of a boronate complex, intramolecular hydrogen atom transfer (HAT), single electron oxidation, and 1,2-alkyl/aryl migration. The boronate complexes are readily generated in situ by reaction of the alkenyl boronic esters with alkyl or aryl lithium reagents. Products are formed in a divergent approach by varying carbon radical precursors as well as alkyl/aryl lithium donors, and reactions proceed under mild conditions upon UV irradiation.

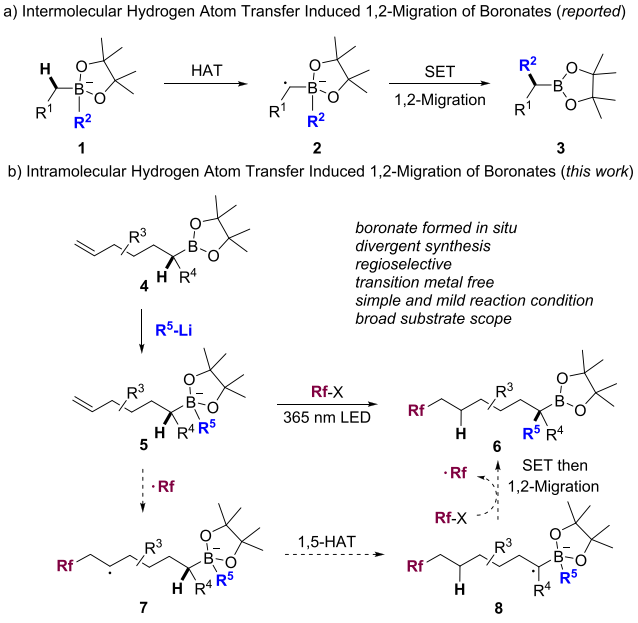


Organoboron compounds are important intermediates and valuable cross coupling partners in organic synthesis. Radical induced 1,2-migration of boronate complexes[1] is a highly efficient approach for the preparation of more complex organoboronic acid esters. In 2017, we[2,3] and Aggarwal and co-workers[3] reported radical addition induced 1,2-migration of vinyl boronate complexes to access α-arylated/alkylated alkyl boronic acid pinacol esters. This strategy was later applied to the construction of functionalized and diverse boron containing compounds by Renaud and co-workers,[4] Lovinger and Morken,[5] and Shi and co-workers.[6] In 2019, 1,2-migration induced by radical addition to highly strained σ-bonds of bicyclobutyl boronate complexes was achieved by Silvi and Aggarwal.[7]

Hydrogen atom transfer (HAT) represents an atom- and step-economic approach for C−H functionalization.[8] In 2019, α-functionalization of alkylboronic esters and homologation of arylboronic esters were developed by us, where regioselective α-C(sp^3)-H abstraction of a boronate complex **1** by an electrophilic trifluoromethyl radical is used as a key step to generate the corresponding radical anion intermediate **2**. Single electron transfer (SET) oxidation and boronate 1,2-migration eventually provide the α-functionalized boronic ester **3** (Scheme 1a).[9] Later, we found that synthetically versatile 1,1-bisborylalkanes can be accessed by intermolecular HAT induced 1,2-migration of diboronate complexes, applying the same strategy.[10] As a continuation of these studies, we wondered whether intramolecular HAT processes that generally occur with excellent regiocontrol can be used to induce a 1,2-migration in boronate complexes.

Perfluoroalkyl groups are important pharmacophores,[11] and perfluoroalkyl radicals show a high reactivity in alkene addition reactions.[12] We therefore decided to apply such reactive C-radicals to induce a 1,2-boronate migration. Thus, an alkenyl boronate complex **5**, which is readily formed in situ by the reaction of an alkenyl boronic ester **4** with an alkyl/aryl lithium reagent, should react with a perfluoroalkyl halide under UV irradiation to give the remotely difunctionalized alkylboronic

Scheme 1. Hydrogen Atom Transfer Induced Boronate 1,2-Migration



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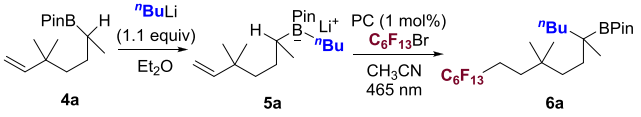
ester **6** (Scheme 1b). In this sequence, the perfluoroalkyl radical first adds to the alkene moiety of **5** to generate the distal radical anion intermediate **7**. Intramolecular 1,5-HAT will lead to an α-radical anion **8**, which is finally SET oxidized by perfluoroalkyl halide and transformed to **6** by a boronate 1,2-migration. Notably, intramolecular HAT to an alkyl radical is less common as compared to the heavily investigated HAT to an N-[13] or O-radical,[14] due to lower thermodynamic driving force and mismatched radical polarity[8d] in contrast with that to an alkenyl radical.[15]

We first tested the intramolecular 1,5-HAT induced boronate migration reaction of **5a**, which is in situ formed from 2-(5,5-dimethylhept-6-en-2-yl)boronic acid pinacol ester **4a** and *n*-butyl lithium in Et_2O. Since Et_2O is not compatible with HAT-mediated radical transformations, the ethereal solvent was replaced by acetonitrile. To our delight, upon 465 nm LED irradiation with Rhodamine B base as a smart photocatalyst[12] and perfluorohexanyl bromide as the carbon radical precursor in acetonitrile, **6a** was obtained in 61% yield (Table 1, entry 1). *n*-Butyl boronic acid pinacol ester (26%)

Table 1. Reaction Optimization[a]



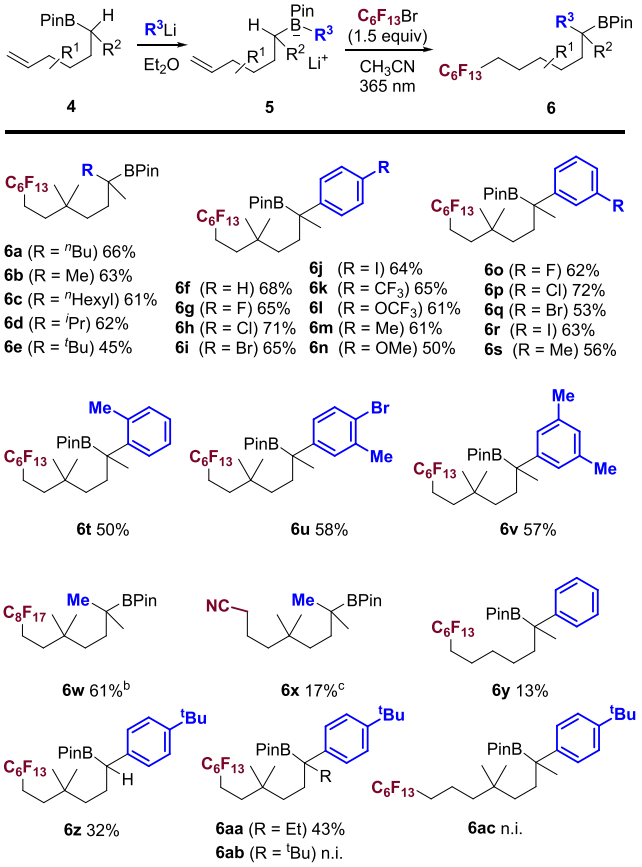
entry	PC	6a	^{n}Bu-Bpin	conv.
1	Rhodamine B base	61%	26%	100%
2	Eosin Y	56%	33%	100%
3	Rose Bengal	54%	35%	100%
4	$Ru(bpy)_3(PF6)_2$	40%	43%	100%
5[b]	Rhodamine B base	15%	40%	100%
6[c]	Rhodamine B base	60%	27%	100%
7[d]	Rhodamine B base	58%	25%	100%
8[e]		75% (66%[f])	14%	100%

[a]Reactions conducted on a 0.2 mmol scale with $C_6F_{13}Br$ (1.5 equiv) in CH_3CN (2 mL); conversion determined on the basis of recovered **4a**, and yields were determined by GC analysis with *n*-tetradecane as internal standard. [b]$C_6F_{13}I$ used instead of $C_6F_{13}Br$. [c]Irradiated at 0 °C. [d]Irradiated at 50 °C. [e]Irradiated at r.t. under 365 nm (3W) without a photocatalyst. [f]Isolated yield.

was identified as side product via GC analysis on the crude reaction mixture. *n*-BuBPin was likely formed by direct SET oxidation of **5a** by oxidizing species such as the C_6F_{13} radical, $C_6F_{13}Br$, or the photocatalyst. With other photocatalysts as smart initiators, lower yields were noted (entries 2−4). Upon using perfluorohexyl iodide in place of the corresponding bromide as the C-radical precursor, a significantly lower yield was obtained (15%, entry 5). A decrease in the reaction temperature to 0 °C or an increase in the temperature to 50 °C did not influence the reaction outcome to a large extent (entries 6 and 7). The best result was achieved in the absence of any photocatalyst under simple UV LED (365 nm) irradiation (75% GC yield and 66% isolated yield). In this setup, radical chain initiation proceeds by light-mediated C−Br bond homolysis.

With the optimized reaction condition in hand, we first tested the scope with respect to the alkyl/aryl lithium reagent, keeping **4a** as the acceptor and $C_6F_{13}Br$ as the carbon radical precursor (Table 2). Methyl (**6b**), primary (**6a** and **6c**), and secondary (**6d**) alkyl lithium reagents could be used, and the

Table 2. Substrate Scope for the 1,5-HAT/Migration Reaction[a]



[a]Reactions conducted on 0.2 mmol scales with $C_6F_{13}Br$ (1.5 equiv) in CH_3CN (2 mL). n.i. = not identified. [b]$C_8F_{17}Br$ (1.5 equiv) used. [c]Bromoacetonitrile (1.5 equiv) used.

corresponding perfluoroalkylated migration products were isolated in 61−66% yields. Sterically bulky *tert*-butyl lithium also engaged in the cascade; albeit, a lower yield was obtained (**6e**, 45%). Boronate complexes derived from para-substituted aryl lithium reagents reacted with moderate to good yields (50−71%). In this series, along the parent unsubstituted system (see **6f**), various para-substituents were tolerated, such as fluorine (**6g**), chlorine (**6h**), bromine (**6i**), iodine (**6j**), trifluoromethyl (**6k**), trifluoromethoxy (**6l**), methyl (**6m**), and methoxy (**6n**). Meta-substituted aryl lithium compounds also worked well, and the migration products **6o**−**s** were formed in 53−73% yields. The HAT/migration reaction of the ortho-tolyl boronate complex **5t** was less efficient, likely due to steric reasons, and **6t** was isolated in 50% yield. Reactions of boronate complexes generated by multisubstituted aryl lithium reagents also worked (**6u** and **6v**).

Next, the C-radical precursor was varied, and perfluorooctyl bromide afforded the corresponding HAT/migration product **6w** in 61% yield with methyl lithium as the alkyl group donor. With bromoacetontrile, the yield dropped (**6x**). Considering the skeleton of boronic ester **4**, the gem-dimethyl substitution pattern in the backbone is important; as for **5y**, which does not express any Thorpe−Ingold effect, only 13% of the target **6y** was obtained.[16] We found that an R^2-substituent stabilizing the C-radical is required to get a good yield (**6z**). The replacement of the R^2-methyl substituent by an ethyl group led to a lower

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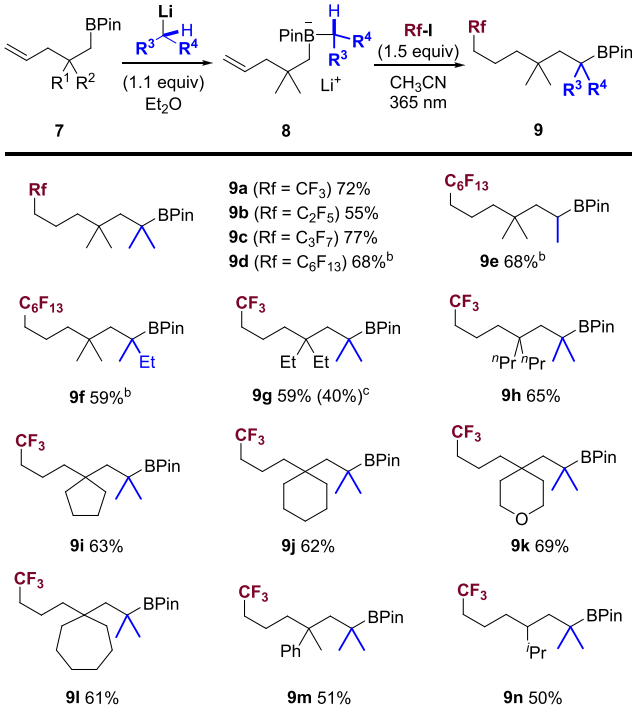
yield (see **6aa**), and with the bulky *tert*-butyl group, the targeted product **6ab** was not identified. We also studied a higher homologue of **4**, where the sequence would proceed via a 1,6-HAT. However, for the tested substrate, that cascade did not work and **6ac** was not identified. The 1,6-HAT is obviously too slow for this substrate type, and a radical chain reaction does not proceed since the feasible Br transfer is also too slow.

Further focusing on the 1,6-HAT/migration cascade, we decided to change the skeleton of the boronic ester (Table 3).

Table 3. Hydroperfluoroalkylation and Homologation via a 1,6-HAT/Migration Cascade[a]



[a]Reactions conducted on 0.2 mmol scales with perfluoroalkyl iodide (1.5 equiv) in CH_3CN (2 mL). [b]$C_6F_{13}Br$ (1.5 equiv) used. [c]Run at 1 mmol scale.

Pleasingly, with 2-(2,2-dimethylpent-4-en-1-yl)boronic acid pinacol ester **7a** as the radical acceptor and isopropyl lithium as the alkyl donor, the derived boronate complex **8** reacted with different perfluoroalkyl halides to form the 1,6-HAT/migration products **9a**–**9d** in 55–77% yields. The corresponding 1,4-HAT/migration products were not formed. Note that, in contrast to the previous examples presented in Table 2, the alkyl lithium component acts as both the alkyl donor and the H atom donor. Hence, the formed products, **9**, are the hydroperfluoroalkylated homologation products of the starting alkenylboronic esters **7**. Perfluoroalkyl iodides and also bromides worked well, indicating that the 1,6-HAT in these systems are efficient. Boronate complexes derived from ethyl lithium and *sec*-butyl lithium provided **9e** (68%) and **9f** (59%). We finally tested the scope of the alkenyl boronic acid pinacol ester component, keeping CF_3I as the C-radical precursor and isopropyl lithium reagent as the alkyl donor. The 2,2-diethyl and 2,2-dipropyl alkenyl boronic esters delivered the hydrotrifluoromethylated homologation products **9g** and **9h** in 59% and 65% yields, respectively. A 1 mmol scale experiment provided **9g** in 40% isolated yield. Substrates leading to boronic esters **9i**–**9l** bearing 5–7 membered rings also showed good reactivity (61–69%). 2-Methyl-2-phenyl substituted alkenyl boronic ester worked rather well (**9m**, 51%), and also for the monoalkyl substituted alkenyl boronic ester, the targeted homologation product **9n** was formed in 50% yield.

In summary, the 1,2-boronate migration reaction was introduced as an efficient route to alkylate and arylate secondary and tertiary alkyl radicals that were generated by perfluoroalkyl radical addition to pending double bonds of boronate complexes followed by intramolecular 1,5- and 1,6-HAT. The alkenylboronate complexes can be readily formed in situ by the reaction of the corresponding alkenyl boronic esters with alkyl/aryl lithium reagents. A broad range of highly functionalized organoboronic esters can be obtained by varying the perfluoroalkyl radical precursors and alkyl/aryl lithium donors, allowing for divergent chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01998.

Experimental details and characterization data; NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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