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# Hydrogen Atom Transfer Induced Boron Retaining Coupling of Organoboronic Esters and Organolithium Reagents

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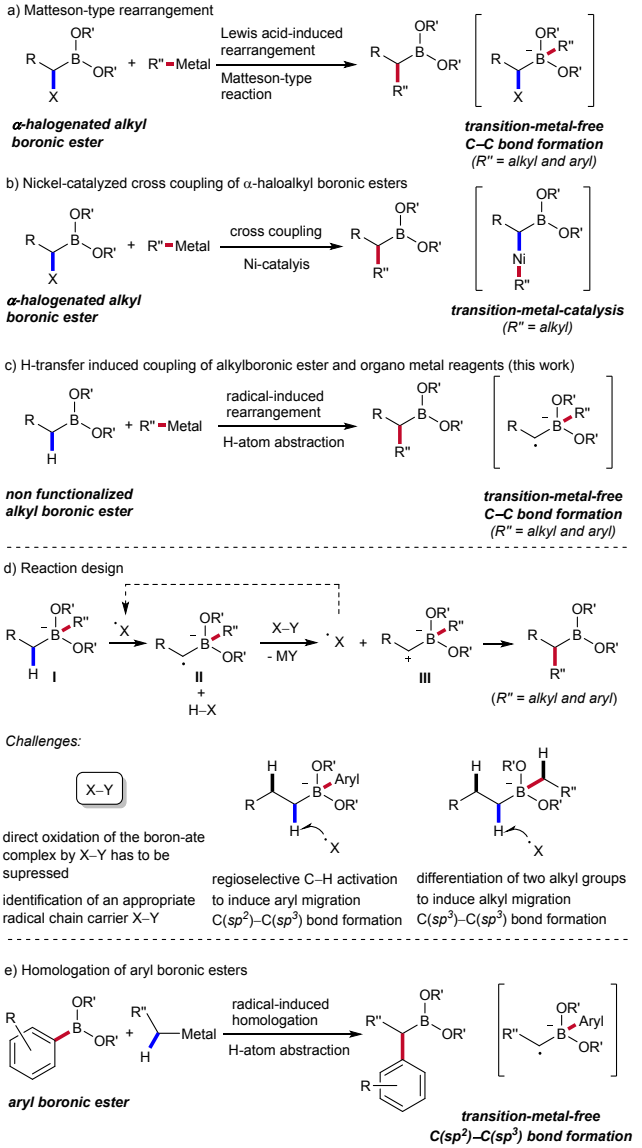
*Supporting Information Placeholder*

**ABSTRACT:** α-Functionalization of alkyl boronic esters and homologation of aryl boronic esters by regioselective radical C($sp^3$)–H activation in boron-ate complexes is reported. Reaction of commercial or readily accessed aryl boronic acid pinacol esters with alkyl lithium reagents provides boron ate complexes. Selective α-C–H abstraction by in situ generated trifluoromethyl radicals leads to radical anions that undergo electron transfer oxidation followed by 1,2-aryl/alkyl migration from boron to carbon to give the α-arylated/alkylated alkyl boronic esters. The valuable boronic ester functionality remains in the products and the cheap trifluoromethyl iodide acts as the oxidant in these C–C couplings. The 1,2-alkyl migration from boron to carbon is highly stereospecific allowing access to stereoisomerically pure boronic esters.

Alkyl boronic esters are valuable reagents in synthesis. They are readily accessed either from commercial sources or by using established chemistry. Such boron compounds engage in various coupling reactions.[1] However, the valuable boron moiety is mostly not retained in the product and chemical modification of alkyl boronic esters keeping the boron entity is not well investigated. An established and well investigated route for functionalization of alkyl boronic esters uses pre-functionalized α-halo derivatives as substrates (Scheme 1a). In these Matteson-type rearrangements, the boronic ester is first converted to its boron-ate complex upon reaction with an alkyl or aryl-metal compound. The ate-complex is then activated by a Lewis acid to induce a 1,2-alkyl/aryl migration with concomitant substitution of the halide anion (X) to give an α-alkylated/arylated boronic ester.[2] Alternatively, boron-ate complexes bearing an α-anionic leaving group can be generated by α-lithiation of alkyl carbamates and subsequent reaction with boronic esters, as developed by Aggarwal for the preparation of optically active alkyl boronic esters.[3]

α-Halo boronic esters have been used by Fu as substrates in Ni-catalyzed cross couplings to provide α-alkylated boronic esters (Scheme 1b). These formal halide substitution reactions proceed via dialkyl-Ni-complexes as intermediates.[4] Both strategies highlighted employ pre-functionalized alkyl boronic esters and correspond to formal substitution reactions. Considering step economy, the direct C–H functionalization[5] of alkyl boronic esters would be even more attractive. Herein we disclose our results on radical α-C–H functionalization of various alkyl boronic esters for the preparation of α-arylated and α-alkylated boronic esters (Scheme 1c).

**Scheme 1. Chemical modification of alkyl boronic esters at the α-C-atom with organometallic compounds and homologation of aryl boronic esters**



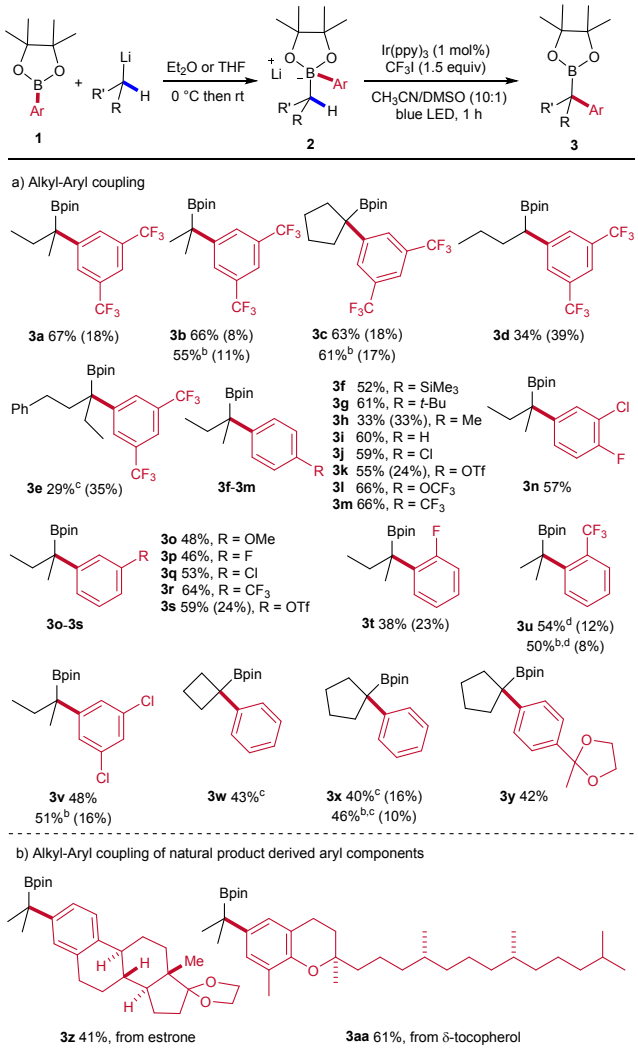

The suggested sequence commences with formation of a boron-ate complex of type **I** by reacting an alkyl boronic ester with an aryl or alkyl organometallic species (Scheme 1d).[6,7,8,9,10] A reactive radical X should then undergo regioselective H-abstraction at the α-position to give the radical anion **II**. Such radical anions are

known to be efficient single electron transfer (SET) reductants[6d, 7a, 8f, 10] which deliver in the reaction with a terminal oxidant X-Y the zwitter ion **III** along with the chain carrying radical X. **III** will further react in a 1,2-alkyl/aryl migration to provide the targeted α-functionalized boronic ester. However, there are several challenges associated with that reaction design: a) the terminal oxidant X-Y should be a mild SET-oxidant that does not directly react with the starting boron-ate complex **I** ($E_{p/2}$ = 0.31 V vs SCE in $CH_3CN$)[11]; b) X-Y must be readily SET reduced by a radical anion **II**; c) radical X derived from X–Y should be an efficient and selective H-abstractor. In case of the aryl migration process leading to C($sp^2$)-C($sp^3$) bond formation, regioselectivity of the H-abstraction step must be controlled, since only α-H-abstraction will lead to a reducing radical anion. For the alkyl migration culminating in C($sp^3$)-C($sp^3$) bond formation, along with the intra chain selectivity control, the two alkyl substituents at the boron-ate complex have to be differentiated by radical X.

Regarding the C($sp^2$)-C($sp^3$) bond formation, such a sequence can also be achieved upon starting with an aryl boronic ester in combination with an alkyl lithium species, since the same boron ate-complex is generated as an intermediate (Scheme 1e). This important fact allows the scientist to choose the starting materials/reagents depending on their availability and costs. By selecting aryl boronic esters as starting compounds, the sequence corresponds to an unprecedented homologation[12] using an alkyl lithium reagent. Considering the prerequisites of our design, we chose trifluoromethyl iodide as oxidant, since it is a weak oxidant ($E_p$ = -1.52 V vs SCE in DMF)[13] that is SET reduced by various radical anions. Moreover, the $CF_3$-radical is reactive[14] and should allow for exothermic H atom abstractions from boron-ate complexes.

We first studied radical-induced migration in boron-ate complexes bearing an alkyl and an aryl substituent (Scheme 1e) and commenced with aryl boronic esters **1** (arylBpin) in combination with alkyl lithium reagents targeting the homologated boronic esters **3**. Reaction optimization was conducted with 3,5-bistrifluoromethylphenylboronic acid pinacol ester and sec-butyl lithium (Supporting Information). The boron-ate complex **2** was generated by addition of sec-butyl lithium in diethylether at 0 °C. The solvent was removed and crude **2** was redissolved in acetonitrile. $CF_3I$ (1.5 equiv) was added as a solution in dimethylsulfoxide. Different radical initiators were screened and we found that the cascade works best with tris[2-phenylpyridinato-$C^2$,$N$]iridium(III) ($Ir(ppy)_3$, 1mol%) as a smart[15] photoinitiator. Blue light irradiation for 1 hour at room temperature provided **3a** in 67% yield (Scheme 2a). As a side product, aryl boronic ester **1a** was identified (18%), likely resulting from competing 2-butyl radical fragmentation of the SET-oxidized boron-ate complex **2a**. Initiation can also be achieved with Eosin Y, Rose Bengal and Rhodamine B base or with $Ru(bpy)_3Cl_2$ (Supporting Information) and for selected cases, we showed that initiation also works without any photocatalyst by simple LED irradiation (365 nm). As expected for a radical process, the cascade was fully inhibited in the presence of TEMPO (2 equivalents). Reaction proceeds also well on isopropyl boron-ate complexes (**3b**) but cyclic (**3c**,**v-x**), sterically more demanding secondary-alkyl (**3e**) and linear alkyl systems (**3d**) showed lower yields. Problems are direct SET-oxidation of the boron-ate complex **2** leading to alkyl radical fragmentation to give starting ester **1** that was identified as a side product (yields in bracket). More challenging C–H activation due to stronger and sterically more shielded C–H bonds also leads to a lowering of the yield. Trifluoromethylation at sterically accessible aryl rings was also observed (see SI for **3h**, **3x**) which suggested the generation of a $CF_3$ radical in the reaction.

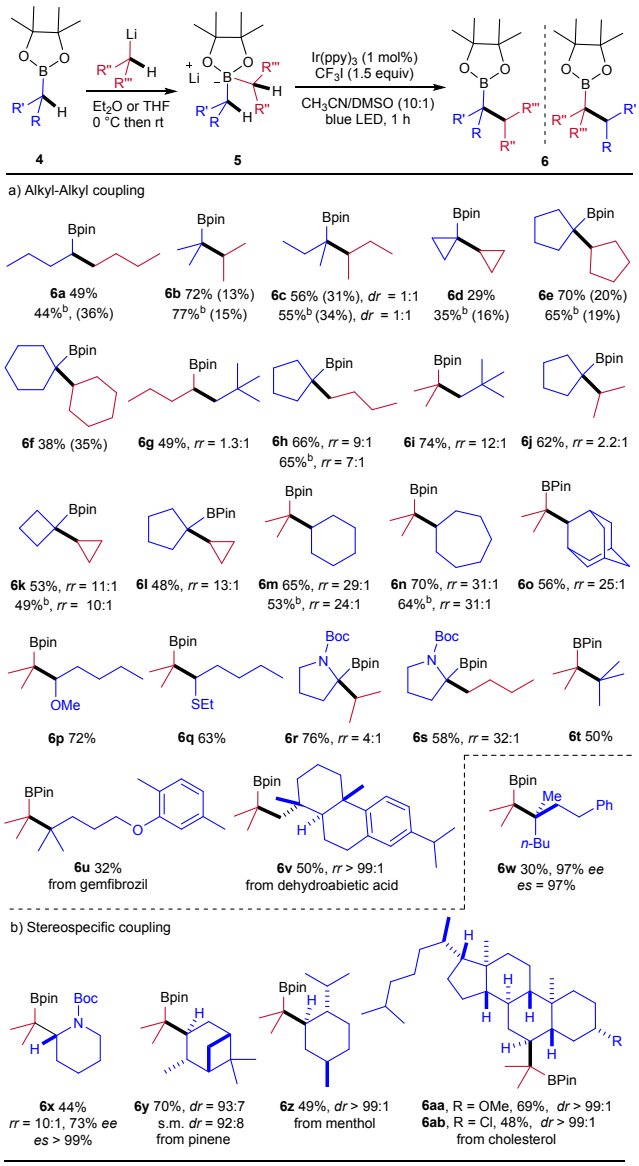
**Scheme 2. Substrate scope for C($sp^2$)-C($sp^3$) coupling [a]**




[a] Conducted at 0.2 mmol scale. Arylboronic ester identified as side product (GC-yield in bracket). [b] Conducted under 365 nm LED irradiation without photocatalyst. [c] The boron ate complexes were formed from the corresponding alkylboronic esters and aryl lithium reagents. [d] Isolated as alcohol after $H_2O_2$/NaOH oxidative work-up.

Keeping sec-butyl lithium we showed that differently substituted (*ortho*, *meta* and *para*) aryl boronic esters engage in the homologation and the esters **3f-3u** were isolated in 33-66% yields. Various functionalities such as trimethylsilyl, chloro, fluoro, trifluoromethylsulfonyl, trifluoromethyl, trifluoromethoxy and acetal are tolerated. The method is also applicable to the homologation of more complex natural product derived aryl boronic esters, as documented by the synthesis of the estrone derived **3y** and the δ-tocopherol derivative **3z** (Scheme 2b). The tocopherol system bears three additional activated methine C–H bonds and a benzylic methylene moiety that all did not react, showing that H-abstraction with the $CF_3$-radical occurs with excellent regioselectivity. Along these lines, the estrone derivative carries a benzylic methine H-atom that is not interfering.

**Scheme 3. Substrate scope for C($sp^3$)-C($sp^3$) coupling** [a]




[a] Conducted at 0.2 mmol scale. Alkylboronic ester identified as a side product (GC-yield in bracket). [b] Conducted under 365 nm LED irradiation without photocatalyst.

We next investigated the more challenging α-C–H alkylation of alkyl boronic esters **4** (Scheme 3) first focusing on symmetrical dialkyl boron ate complexes **5**, where the two alkyl substituents do not need to be differentiated. Pleasingly, α-butylation of butyl boronic ester with butyl lithium worked and **6a** was isolated in 49% yield. Moderate to good yields were noted for cyclic and non-cyclic α-branched alkyl boronic esters (**6b-6f,** 35-77% yield). For unsymmetrical dialkyl boron-ate complexes **5**, in selected cases, excellent site selectivity was achieved. For the cyclopentyl-butyl ate-complex, H-abstraction occurred with a 9:1 selectivity at the cyclopentyl moiety (66%, **6h**). The selectivity is understood considering that the secondary-alkyl C–H bond is weaker than the methylene C–H bond, as also observed for **6i** (74%, *rr* = 12:1). Cyclopropane has stronger C–H bonds than other alkanes.[16] This reactivity trend is well reflected by the regioselectivities obtained, where the three-membered ring does preferably act as the migrating moiety (**6k**,**l**). Considering secondary-alkyl C–H activation, the non-strained and sterically least hindered iso-propyl group in most cases gets selectively activated (**6m**,**n**,**o**). To our surprise, the isopropyl substituent outcompeted an α-methoxy-alkyl group and an α-ethylthiyl-alkyl group, although the methoxy and ethylthiyl groups are known to stabilize C-radicals (**6p**, 72%; **6q**, 63%). However, for the 5-membered ring analogue, H-abstraction by the $CF_3$-radical occurred preferably next to the N-atom (**6r**, 76%, *rr* = 4:1; **6s**, 58%, *rr* = 32:1). For the sterically hindered primary alkylboronic ester **4v**, H-abstraction selectivity at the isopropyl group was exclusive (**6v**, *rr* > 99:1). These results indicate, that along with C–H bond strength, conformational effects and steric shielding play an important role. α-Functionalization also works with *tert*-alkyl groups as migrating substituents (**6t,u**).

Studies were continued by investigating stereospecific reactions (Scheme 3b). With readily accessed[17] enantioenriched tertiary alkyl boronic esters, isopropyl insertion was achieved in good yields and excellent stereospecificity (*es* = 97%) under retention of absolute configuration (**6w**). tert-Butyloxycarbonyl (Boc)-protected piperidine was stereoselectively α-borylated using established methodology.[18] The corresponding isopropyl lithium derived ate-complex reacts with the $CF_3$-radical with high chemoselectivity (*rr* = 10:1) at the isopropyl group. Subsequent stereospecific migration affords **6x** in excellent stereoselectivity (44%, *es* > 99%). Enantiopure boronic esters can also be prepared from chiral alkenes via diastereoselective hydroboration or borylation of a chiral alkyl halide. Boron-ate complex formation with isopropyl lithium followed by radical-mediated α-C–H-activation leads to the homologation products conserving the initial stereochemistry, as documented for natural product derived terpenes and steroids (48-70%, **6y-6ab**). For **6y-6ab,** regioselectivity was complete.

To better understand the regioselectivities for the α-C–H abstraction, DFT calculations were conducted for two representative compounds. Energies were obtained with the PWPB95-D3 double hybrid functional[19], and take solvent effects implicitly into account with the CPCM model[20] (Figure 1). The thermodynamic driving force of H-abstraction from the benzylic position of ethyl benzene is larger by 5.9 kcal/mol than for the boron-ate complex. However, the free energy barrier of H-transfer from the anionic complex is lower by 4 kcal/mol (13.2 kcal/mol) which corresponds to a selectivity of around $10^3$:1 over ethyl benzene. Due to the electrophilicity of the $CF_3$-radical, polar effects operate. This confirms the both extremely facile and regioselective reaction of the $CF_3$-radical next to the B-atom. We have already shown[7a] that electron transfer from the radical anion **II** (see Scheme 1d) to $CF_3I$ is highly exothermic. In the complex, the σ*-orbital of $CF_3I$ overlaps with the SOMO of the radical anion **II** and hence a nearly barrier less SET is expected generating the zwitter ion **III** which rearranges without barrier to the product **IV**.[7a]

We further addressed the regioselectivity of the H-abstraction for the cyclopentyl isopropyl complex **5j** and the cyclohexyl isopropyl homologue **5m** where a surprising reversal of the regioselectivity was experimentally observed. In agreement with the experiment, calculations revealed the H-abstraction in **5m** at the isopropyl group to be favored by 3 kcal/mol. For the ate complex **5j**, where the experiment showed a slight preference for H-abstraction at the cyclopentyl group, calculations revealed similar activation barriers for the two competing processes with a barrier leading to the preferred product which is 0.3 kcal/mol lower (see SI). Of note, intermolecular H-transfer reactions to C-radicals are rarely used in organic chemistry, since such HAT-processes are generally too slow. Due to its high reactivity as H-abstracting species, the $CF_3$-radical is unique in that sense.[21]

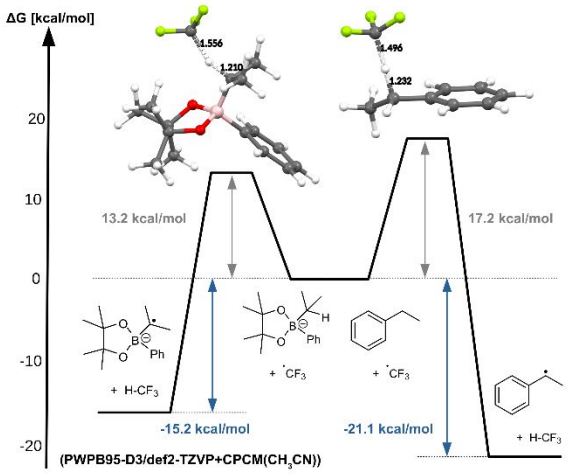



**Figure 1. DFT studies.** Transition states, activation barriers and free energies of hydrogen atom transfer of phenyl isopropyl boronate complex (left) and ethyl benzene (right) with the $CF_3$-radical.

Finally, we studied the initiation step of the cascade and found the trifluoromethyl iodide to be efficiently reduced by the photoexcited Ir-complex, as analyzed by Stern-Volmer quenching (Supporting Information). As an alternative initiation step, the boron ate complex can be oxidized by the photoexcited Ir-complex, albeit less efficiently. The quantum yield of the process[22] was determined to be 8.8, showing that the Ir-complex mainly acts to initiate the radical chain (see Scheme 1d) and is best described as a smart initiator.[15] This is in line with the observation that various organic and inorganic redox systems initiate the chain with similar efficiency and that initiation also proceeds in the absence of any photocatalyst. For reactions run without any smart redox initiator, initiation likely proceeds by direct reduction of the $CF_3I$/DMSO complex with the boron-ate complex upon irradiation.

We are confident that the herein introduced radical C–C couplings will significantly enlarge the portfolio of boron chemistry. The starting materials are easily accessed and special equipment is not required to run these valuable sequences.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx.

Experimental details and characterization data (PDF)
NMR spectrum of new compounds (PDF)
DFT calculations (PDF)

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### Notes

The authors declare no competing financial interests.

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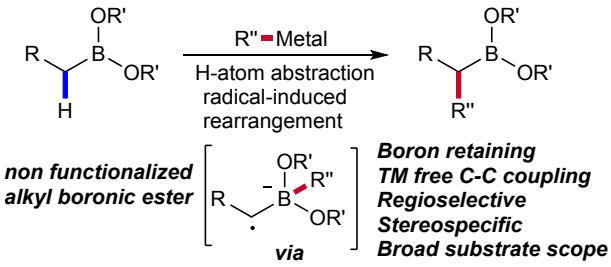
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Stereospecific
Broad substrate scope

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