Communication

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Stereospecific Allylic Functionalization: The Reactivity of Allylboronate Complexes with Electrophiles

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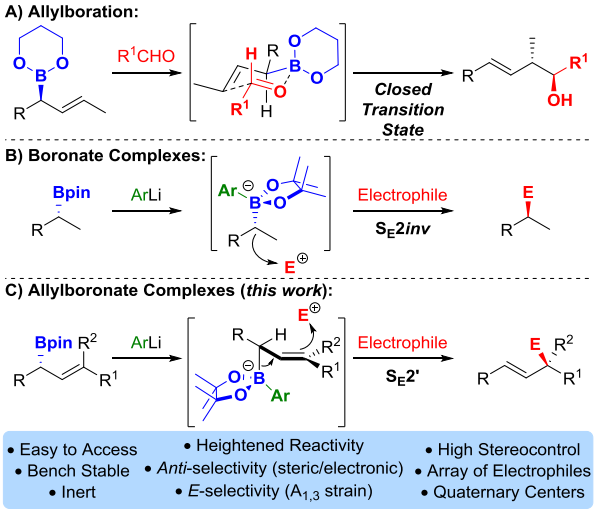
Supporting Information Placeholder

ABSTRACT: Allylboronic esters react readily with carbonyls and imines (π-electrophiles), but are unreactive towards a range of other electrophiles. By addition of an aryl organolithium, the corresponding allylboronate complexes display enhanced nucleophilicity, enabling addition to a range of electrophiles (tropylium, benzodithiolylium, activated pyridines, Eschenmoser's salt, Togni's reagent, Selectfluor, DIAD, MeSX) in high regio- and stereocontrol. This protocol provides access to key new functionalities, including quaternary stereogenic centers bearing moieties such as fluorine and the trifluoromethyl group. The allylboronate complexes were determined to be 7 to 10 orders of magnitude more reactive than the parent boronic ester.

The reaction of allylmetals with electrophiles represents a cornerstone in organic synthesis.[1] The field is dominated by reactions of allylborons with carbonyls and imines (π-electrophiles) because (i) it leads to synthetically useful products with high and predictable selectivity and (ii) enantioenriched allylborons are easily available or chiral catalysts have been developed to promote the reaction.[2,3] However, reactions of allylborons with a broader range of electrophiles are virtually unknown; their unique reactivity with π-electrophiles stems from the simultaneous activation of both the boron atom and the carbonyl group in the closed transition state (Scheme **1A**).[4] In order to address this shortcoming, more nucleophilic allylmetals have been explored, e.g. allylsilanes[5] and allylstannanes,[6] but the chiral versions are often difficult to prepare with high selectivity[7] and the latter are toxic and labile towards 1,3-transposition.

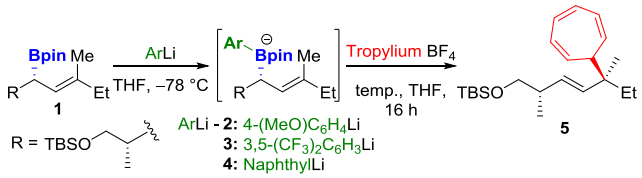
Allylborons would be ideal reagents since they are configurationally stable, easily accessible in high ee[3h,8] and unlike most other allylmetals do not undergo 1,3-transposition,[9] but their low nucleophilicity has limited their broader use. We considered separating the activation mode of boron by converting the allylic boronic ester into a more nucleophilic boronate complex. Previously, we have shown that the addition of an aryl organolithium to an alkylboronic ester creates a configurationally stable nucleophilic boronate complex which can react with electrophiles through an enantiospecific S_E2*inv* pathway (Scheme **1B**).[10] We reasoned that the addition of an organolithium to an allylboronic ester might also 'switch on' the reactivity of these species, enabling S_E2' reactions with a much more diverse array of electrophiles (Scheme **1C**). Herein, we report the successful realization of this strategy, providing access to an array of stereodefined tertiary and quaternary allylic products.

Scheme 1. Reactions of (A) Allylboronic esters and (B) Alkylboronate complexes. (C) This work – The reactivity of Allylboronate complexes.



We began our study by investigating the tropylium cation as a model electrophile for addition to boronate complexes, selecting trisubstituted allylic boronic ester **1** to explore the formation of quaternary stereogenic centers, incorporating a reporter stereogenic center in order to assess the stereospecificity of the reaction. When the parent boronic ester **1** was subjected to the tropylium cation in THF, no reaction was observed (Table **1**, entry 1), demonstrating the low reactivity of allylboronic esters even with highly reactive electrophiles. However, after addition of aryllithium **2**, the allylboronate complex reacted readily to afford the allylation product **5**, albeit with moderate regiocontrol between γ- and α- addition (87:13), and poor diastereocontrol (56:44, entry 2). The selectivity was found to be improved by lowering the reaction temperature to –78 °C, although the dr was still moderate (88:12, entry 4). In all cases, the reaction gave complete *E*-selectivity (>95:5). In our previous studies of boronate complexes, we had observed that electron-deficient aryllithiums improved the stereospecificity of the reaction,[10a] and they were examined here too. Using the electron-deficient aryllithium **3** did indeed result in improved diastereocontrol (>95:5, entry 5). Interestingly, through screening various aryllithiums, we discovered that naphthyllithium (**4**) also gave very high

Table 1. Optimization of the Formation of Quaternary Stereogenic Centers with Tropylium Tetrafluoroborate[a]



Entry	ArLi	Temp. / °C	Yield[b] / %	γ/α[c]	*dr*[c] / %
1	None	25	0	–	–
2	**2**	25	62	87:13	56:44
3	**2**	0	48	86:14	55:45
4	**2**	–78	52	>95:5	88:12
5	**3**	–78	81[d]	>95:5	>95:5
6	**4**	–78	95	>95:5	93:7

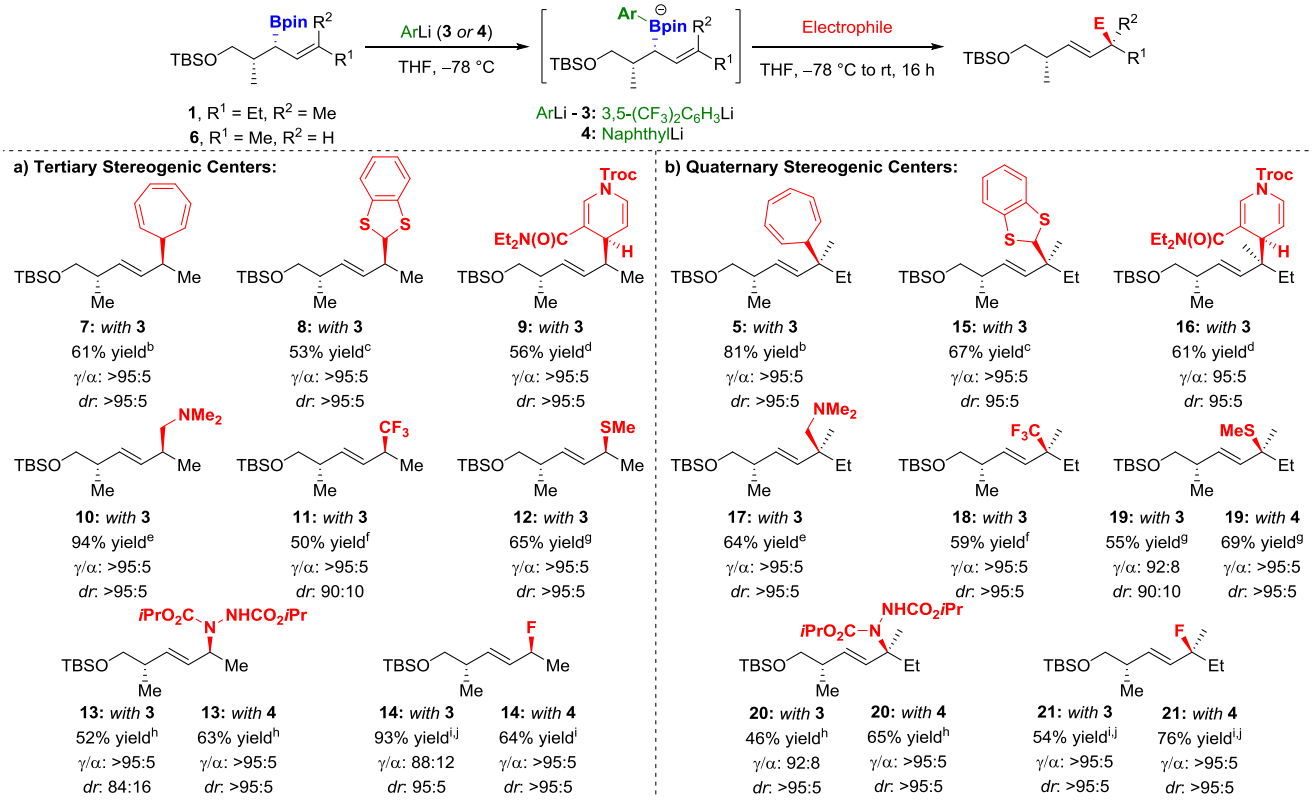
[a]Reactions conducted with 0.10 mmol **1**, 1.2 eq ArLi and 1.2 eq tropylium tetrafluoroborate. [b] ^{1}H NMR yield using 0.33 eq of 1,3,5-trimethoxybenzene as internal standard. [c]dr of γ-attack product **5**, determined by GCMS. [d]Isolated yield.

selectivity (entry 6), which proved beneficial in some cases with alternative electrophiles (*vide infra*).[11]

Having identified conditions under which the allylboronate complex derived from **1** reacted with high regio- and stereoselectivity, we explored the electrophile scope in the formation of both tertiary and quaternary stereogenic centers (Scheme **2**). We used **3** as the standard nucleophilic activator, but if lower selectivity was observed we also tested **4**. Pleasingly, the reactions of boronate complexes derived from **1** and **6** were successfully extended to benzodithiolylium (to afford **8** and **15**), activated pyridines (**9** and **16**)[10b] and Eschenmoser's salt (**10** and **17**). In all of these C–C bond forming cases, high regio- and stereospecificity and complete *E*-selectivity was observed.

The allylboronate complex derived from **6** could also be trifluoromethylated using Togni's reagent as an electrophilic source of CF_3, providing access to **11** in 50% yield, >95:5 γ/α and 90:10 dr. In comparison to alternative allylmetal species, Gouverneur and coworkers have reported the trifluoromethylation of analogous allylsilanes, which proceeds with similar selectivity under photoredox catalysis.[12] It is of particular note that the allylboronate complex from **1** could also be trifluoromethylated in 59% yield, >95:5 γ/α and >95:5 dr (**18**) – the trifluoromethylation of an allylmetal to form a quaternary stereogenic center has, to the best of our knowledge, not previously been reported.

Scheme 2. Scope of Electrophiles added to Allylboronate Complexes[a]

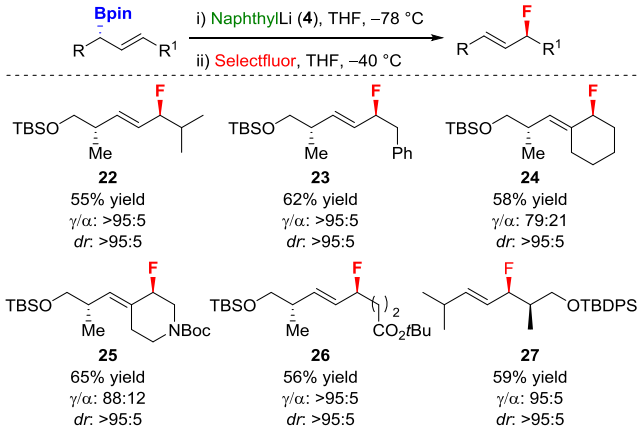


[a]See the Supporting Information for more details; yields of isolated material; γ/α ratio and dr determined by GCMS, ^{1}H NMR or ^{19}F NMR. [b]Tropylium tetrafluoroborate added at –78°C. [c]1,3-benzodithiolylium tetrafluoroborate added at –78°C. [d]*N*,*N*-diethylnicotinamide and Troc-Cl added at –78°C. Relative stereochemistry of dihydropyridine based on previous model,[10b] but not confirmed. [e]*N*,*N*-dimethylmethyleneiminium iodide added at –78°C. [f]Ate complex solution added to solution of 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one in THF at –78°C. [g]Dimethyl(methylthio)sulfonium tetrafluoroborate added at –78°C. [h]Diisopropyl azodicarboxylate added at –78°C, and the reaction maintained at –78°C for 16 h. [i]Ate complex solution in MeCN added to solution of Selectfluor in MeCN at –40°C, and the reaction maintained at –40°C for 16 h. [j] ^{1}H NMR yield using 0.33 eq of 1,3,5-trimethoxybenzene as internal standard due to product instability.

Electrophiles which create new carbon–heteroatom bonds could also be utilized in conjunction with the allylboronate complexes, enabling the formation of C–S, C–N and C–F bonds at tertiary (**12**–**14**) and quaternary stereocenters (**19**–**21**). The electrophilic fluorination of boronate complexes[10c] provides access to medicinally relevant chiral allylic fluorides which are otherwise challenging to obtain from allylmetals.[13] Whilst allylsilanes undergo successful stereospecific fluorination,[14] access to enantioenriched acyclic tertiary allylfluorides from an allylmetal has not previously been reported. Pleasingly, the reaction of **1** with aryllithium **4**, and subsequent fluorination with Selectfluor in MeCN at –40 °C, was found to afford allylfluoride **21** in 76% yield, >95:5 γ/α and >95:5 dr. To determine the absolute configuration and demonstrate that there were no matched/mismatched effects in operation, we also synthesized the alternative diastereomer of fluoride **14** from the opposite *anti* diastereomer of **6**.[15]

We next chose to develop the fluorination of allylboronate complexes because of the importance of incorporating fluorine stereoselectively into organic molecules (Scheme **3**). It was found that changing the alkyl substituent at R^1 to either a sterically bulky *iso*propyl (**22**) or a benzyl group (**23**) afforded the desired allylfluorides in high yield and selectivity. Fluorination of allylboronates derived from cyclic alkenes also occurred in good yield, albeit with slightly reduced regioselectivities (**24** and **25**). Pleasingly, the reaction tolerated a range of functional groups including carbamates (**25**), *tert*-butyl esters (**26**) and *tert*-butyldiphenylsilyl protected alcohols (**27**). Owing to the facile synthesis of the starting allylboronic esters through lithiation–borylation between a vinylboronic ester and alkylbenzoate,[3k,16] an array of allylfluorides can now be formed with high selectivity.

Scheme 3. Scope of the Fluorination Reaction[a]



[a]All boronic esters have dr > 95:5. Yields of isolated material; γ/α ratio and dr determined by GCMS or ^{19}F NMR.

In order to quantify the change of nucleophilicity of the allyl moiety upon addition of an organolithium to an allylboronic ester (**28**), we measured the kinetics of the reactions of allylboron compounds **28**–**32** with benzhydrylium ions **33**, following previously published methods (Figures **1** and **2**).[17] Figure **1** demonstrates that the measured second-order rate constants correlate linearly with the electrophilicity parameters *E* of the reference benzhydrylium ions, which allows us to employ eq. (1) for calculating the nucleophilicity parameters *N* and susceptibilities s_N of **28**–**32**.

$$\log k_2\ (20\ ^\circ\mathrm{C}) = s_N(N + E) \qquad (1)$$

Although Figure **1** shows that the relative reactivities of the allylboron compounds somewhat depend on the nature of the electrophiles (because of the different slopes (s_N) of the correlation lines), a rough ordering of the nucleophilic reactivities is given by their *N* parameters (Figure **2**), which correspond to the negative

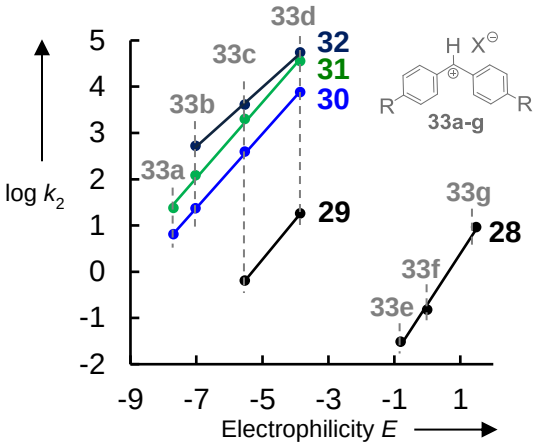


Figure 1. Correlation of the second-order rate constants k_2 for the reactions of allylboron compounds **28**–**32** (for structures, see Fig. **2**) with benzhydrylium ions **33** (see Supporting Information) toward the electrophilicity parameters *E* of the benzyhdrylium ions.

intercepts on the abscissa of the correlation lines in Fig. **1**. Addition of an aryllithium to allylboronic ester **28** increases the nucleophilicity by 7 to 10 orders of magnitude.[18] Thus, the anionic allylboronate complexes **30**–**32** are significantly more nucleophilic than allylsilanes, allylstannanes and allyltrifluoroborate **29**, all of which are more nucleophilic than the parent boronic ester **28**. The previously reported *N* parameter of benzylboronate complex **34**,[19] which reacts in an S_E2 mode with electrophiles, is two logarithmic units smaller than of **30**. In line with this ordering, allylboronates **30**–**32** react with high γ-selectivity (S_E2'), in preference to reaction at the α-position (S_E2).

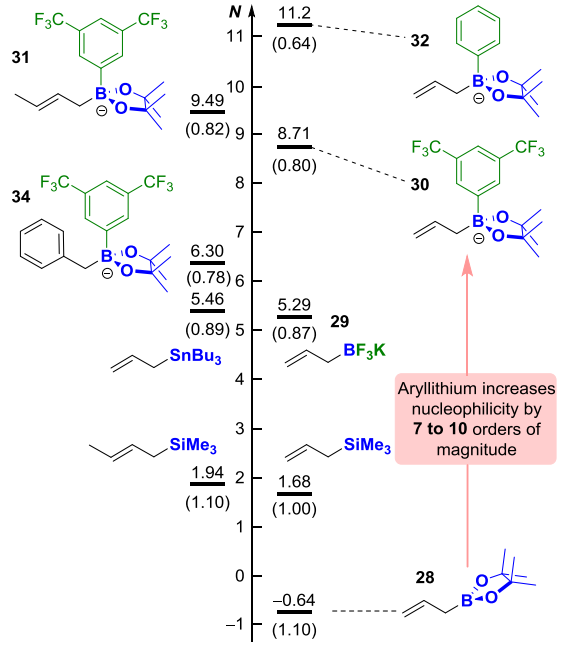


Figure 2. Comparison of nucleophilicity parameters *N* (susceptibility parameters s_N in parentheses) of allylmetal reagents. Boronate complexes and allyltrifluoroborate determined in CH_3CN, other nucleophiles in CH_2Cl_2.

In conclusion, by addition of an organolithium we have converted weakly nucleophilic allylic boronic esters into potent nucleophiles which now react with a broad range of carbon- and heteroatom-based electrophiles with very high γ-selectivity and essentially

complete stereospecificity. Indeed, the addition of an organolithium to form a boronate complex increases the nucleophilicity of the stable boronic ester by 7 to 10 orders of magnitude. Importantly, this process provides access to a broad array of functionalities, including quaternary all-carbon stereocentres and allylic fluoro- and trifluoromethyl moieties. We envisage that the continued application of boronate complexes[10e] will provide access to an array of new enantioenriched functionalities which are otherwise difficult to obtain.

ASSOCIATED CONTENT

Supporting Information

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

Detailed experimental procedures, kinetics data, and characterization data for new compounds (PDF).

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Notes

The authors declare no competing financial interests.

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(15) See Supporting Information for full details of alternative diastereomers, and analytical determination of γ/α and dr selectivities.

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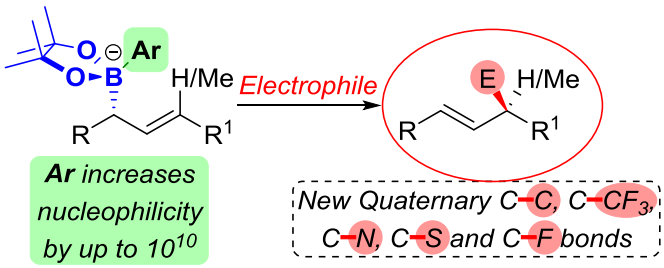
Ar
H/Me
R
R1
Electrophile
E
H/Me
R
R1
Ar increases nucleophilicity by up to 10^10
New Quaternary C–C, C–CF3, C–N, C–S and C–F bonds