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Highly Diastereoselective Strain-Increase Allylborations: Rapid Access to Alkylidenecyclopropanes and Alkylidenecyclobutanes

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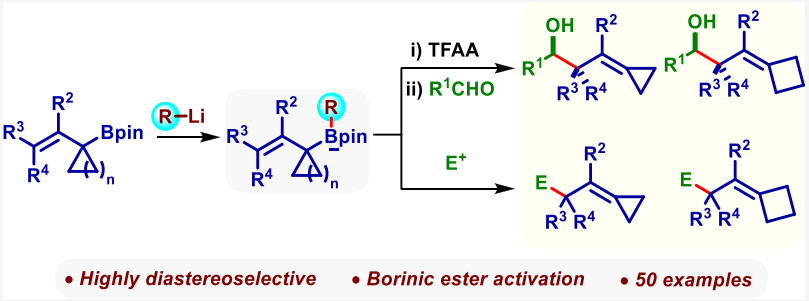

ABSTRACT: Allylboration of carbonyl compounds is one of the most widely used methods in the stereoselective synthesis of natural products. However, these powerful transformations are so far limited to allyl- or crotylboron reagents; ring-strained substituents in the α-position have not been investigated. Such substrates would lead to an increase in strain energy upon allylboration and as such cause a significant increase in the activation barrier of the reaction. Indeed, no reaction was observed between an α-cyclopropyl allylboronic ester and an aldehyde. However, by converting the boronic ester into the much more reactive borinic ester, the allylboration proceeded well giving alkylidenecyclopropanes in high yield. This process was highly diastereoselective and gives rapid access to versatile alkylidenecyclopropanes and alkylidenecyclobutanes. The chemistry shows a broad substrate scope in terms of both the range of vinylcycloalkyl boronic esters and aldehydes that can be employed. The intermediate boronate complexes were also found to be potent nucleophiles, reacting with a range of non-carbonyl-based electrophiles and radicals, leading to an even broader range of alkylidenecyclopropanes and alkylidenecyclobutanes. Using ^{11}B NMR experiments, we were able to track the intermediates involved, and DFT calculations supported the experimental findings.

INTRODUCTION

Allylboration is one of the most reliable and important C−C bond forming transformations in organic synthesis (Scheme 1A).[1−9] Since Hoffmann's first report on controlling relative stereochemistry by the olefin geometry of crotylboronates[10−13] and Brown's discovery of enantioselective allylboration using pinane-derived reagents,[14,15] this reaction has found numerous applications in the synthesis of stereochemically complex natural products.[16−19] Furthermore, this reaction has several advantages over other allyl metalations because it leads to (i) products with high and predictable selectivity via a six-membered boracyclic transition state and (ii) nontoxic boric acid byproducts, in contrast to other classes of allylmetal reagents. However, these powerful transformations are so far limited to allyl or crotylboron reagents; substituents carrying ring-strain in the α-position such as cyclopropyl groups have not been investigated. A major issue of concern with such substrates is that the products are significantly more strained (12−14 kcal/mol) than the starting materials (Scheme 1B),[20] which would substantially raise the activation energy for the reaction (vide infra). However, such processes would be highly valuable since they would give rapid access to versatile alkylidenecyclopropanes (ACPs). Not only are these interesting moieties present in several naturally occurring and biologically active compounds (Scheme 2A), but owing to their high ring-strain energy and unique reactivity, they also participate in a variety of ring-expansion or ring-cleavage reactions leading to highly valuable heterocycles, carbocycles, and ring-opened products (Scheme 2B).[21−28] The broad synthetic utility of alkylidenecyclopropanes has stimulated a number of synthetic approaches, the most common being the addition of cyclopropyl ylides to carbonyl compounds.[29−31] However, this strategy requires protecting groups to access functionalized ACPs.[32] Another method to access ACPs involves the

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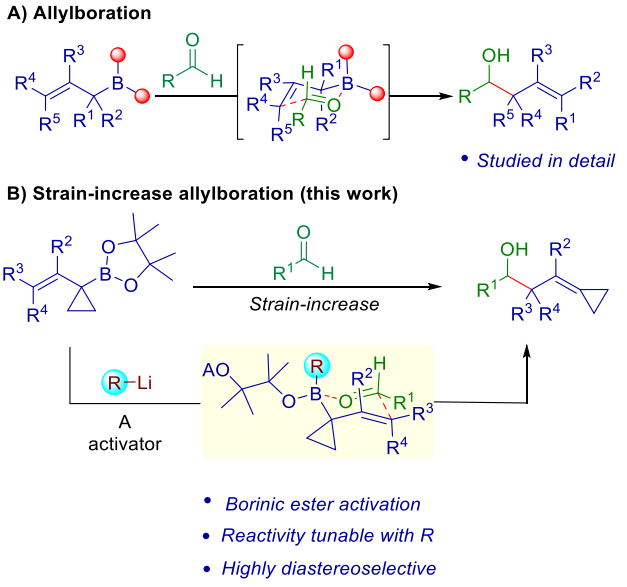
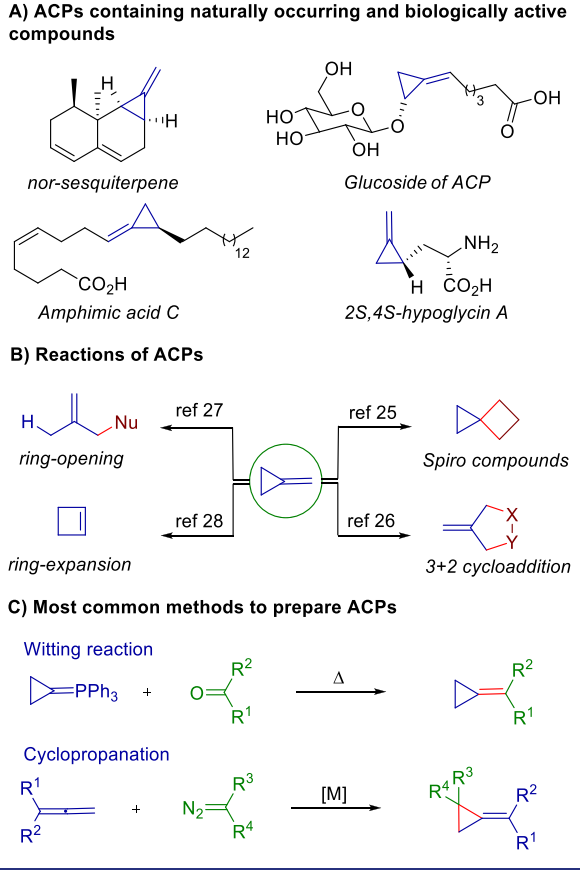
Scheme 1. (A) General Allylboration Reactions and (B) Strain-Increase Allylboration



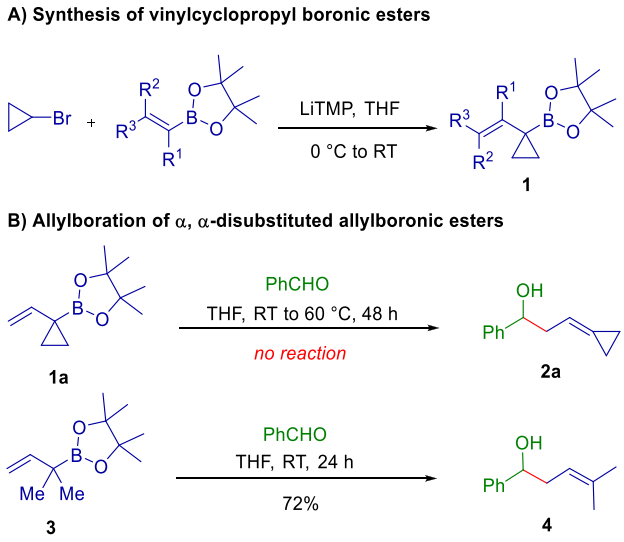
addition of carbenes to allenes mediated by transition metals.[33−35]

Scheme 2. (A) ACPs Containing Naturally Occurring and Biologically Active Compounds, (B) Reactions of ACPs, and (C) Most Common Methods to Prepare ACPs



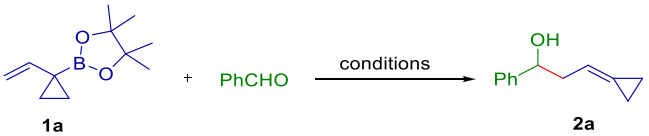
As part of our ongoing interest in allylboration chemistry,[36−39] we were interested in developing an allylboration method to rapidly access functionalized ACPs

Scheme 3. (A) Synthesis of Vinylcyclopropyl Boronic Esters and (B) Allylboration of α,α-Disubstituted Allylboronic Esters

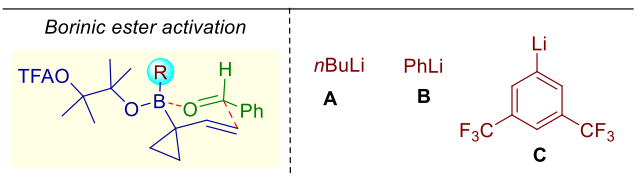


starting from stable, easily accessible vinylcyclopropyl boronic esters (Scheme 1B).[40] However, this is highly challenging due to the unfavorable ring-strain developing during the allylboration.[20] To overcome the unfavorable ring-strain developed during the allylboration, we considered the possibility of activating the boronic ester by converting it into the more reactive borinic ester.[36] We envisaged that the boron atom of a borinic ester, being more electrophilic, would create a stronger boron−carbonyl-oxygen interaction which would lower the activation energy of the reaction. Furthermore, the steric and electronic environment around

Table 1. Optimization studies[a]



entry	conditions	yield[b]
1	$Sc(OTf)_3$ (0.2 equiv), toluene	nd
2	$AlCl_3$ (0.2 equiv), toluene	nd
3	$SnCl_4$ (0.2 equiv), toluene	nd
4	$BF_3{\cdot}OEt_2$ (0.2 equiv), DCM	nd
5	**A**, TFAA (1.4 equiv), THF	33%
6	**B**, TFAA (1.4 equiv), THF	54%
7	**C**, TFAA (1.4 equiv), THF	86%
8	**C**, no TFAA, THF	nd



[a]Reaction conditions. For entries 1−4, 0.15 mmol of **1a**, 1.5 equiv of PhCHO, 0.2 equiv of Lewis acid and solvent (0.075 M) at RT; whereas for entries 5−8, 0.15 mmol of **1a**, 1.5 equiv of PhCHO, 1.3 equiv of organolithium, 1.4 equiv of TFAA and THF (0.075 M) from −78 °C to RT. [b]NMR yields using dibromomethane as the internal standard. nd = not detected.

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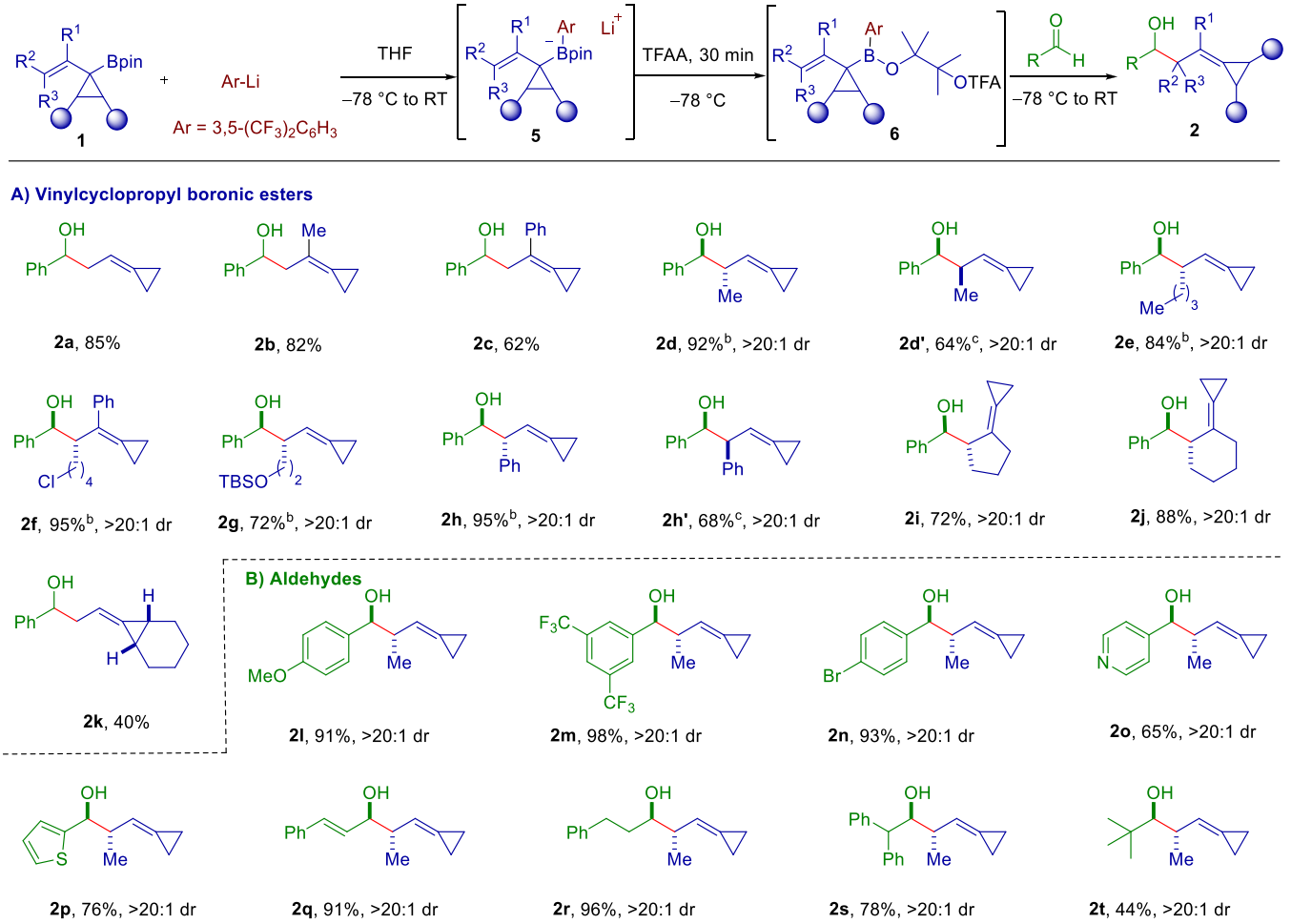
Scheme 4. Scope of Reactions of Vinylcyclopropyl Boronic Esters and Aldehydes[a]



[a]All reactions were run on a 0.3 mmol scale. Yields are of isolated products. dr determined by ^{1}H NMR. [b]*trans*-γ-Substituted vinylcyclopropyl boronic esters were used. [c]*cis*-γ-Substituted vinylcyclopropyl boronic esters were used.

boron would be very different from the pinacol boronic ester, and both reactivity and selectivity could be easily tuned by the nature of the organometallic reagent (R) added (Scheme 1B).

In this paper, we report our success in developing a novel strain-increase allylboration reaction, which leads to a wide range of functionalized ACPs in high yields with excellent stereocontrol using a borinic ester activation and using nonhazardous reagents.[32,41] This methodology was further extended to access alkylidenecyclobutanes (ACBs), another important class of compounds in organic synthesis. Boronic and borinic esters are electrophilic reagents and as such are unreactive toward a range of other electrophiles. Using more nucleophilic boronate complexes, this reaction was further extended to a wide range of ionic and radical-based electrophiles. With a combination of ^{11}B NMR and density functional theory (DFT) calculations, the origins of reactivity in these reactions have been rationalized.

RESULTS AND DISCUSSION

Our investigations began by studying the allylboration of benzaldehyde using vinylcyclopropyl boronic ester **1a** (Scheme 3B), easily obtained by the reaction of commercially available cyclopropyl bromide with vinylboronic esters (Scheme 3A).[40] However, under standard conditions[42] or even elevated temperature (60 °C) no desired product **2a** was obtained; the SMs were simply reisolated (Scheme 3B). A successful control experiment using dimethyl substituted boronic ester **3**[43] under standard conditions showed that the lack of reactivity with vinylcyclopropyl boronic ester **1a** was not due to steric hindrance in the α-position but must be due to increased ring-strain developing in the product **2a** (Scheme 3B).

Attempts to promote the reaction using Lewis acids were carried out. Hall and others reported that Lewis acids could accelerate the allylboration reaction by coordinating to the boronate oxygen, which is thought to increase the electrophilicity of the boron atom.[44−46] Evaluation of a range of Lewis acids such as $Sc(OTf)_3$, $AlCl_3$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ however did not provide the desired product **2a** (Table 1, entries 1−4). Next, we considered the possibility of activating the boronic ester **1a** by converting it into the more reactive borinic ester. In our previous studies of borinic ester activation,[37] we had observed high reactivity and selectivity in allylboration using allyl/crotyl boronic esters which allowed ketones and imines to be employed and enabled the construction of contiguous quaternary centers, and so this was examined here too. Vinylcyclopropyl boronic ester **1a** was treated sequentially with *n*BuLi and TFAA (trifluoroacetic anhydride) to generate the corresponding borinic ester

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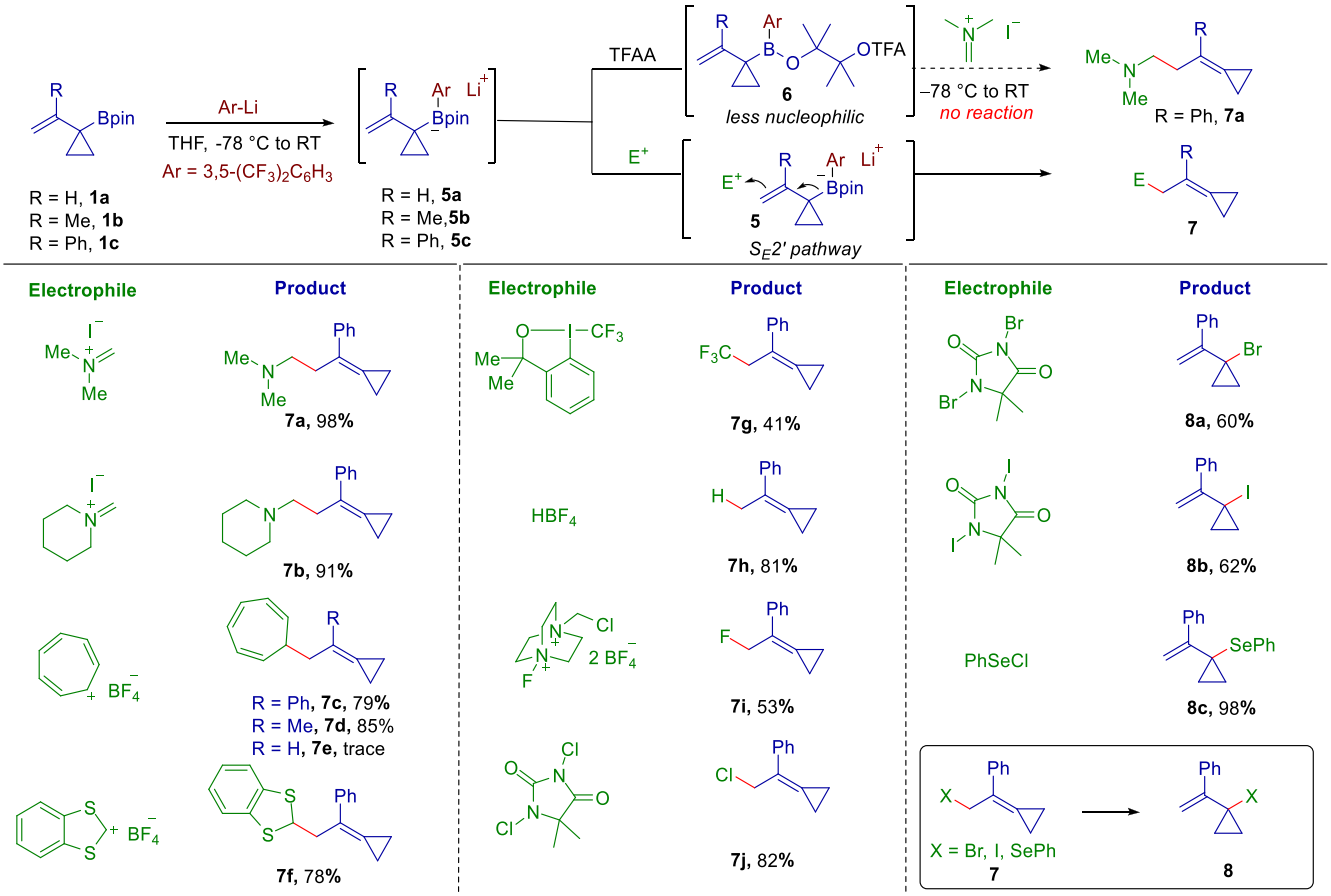
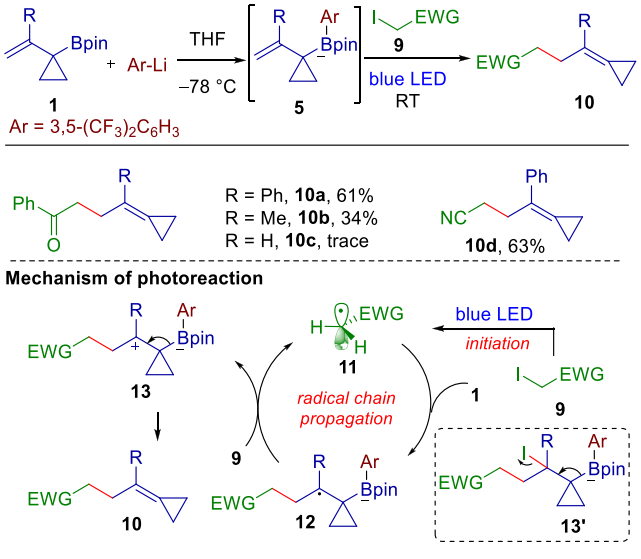
Scheme 5. Scope of Reactions of Vinylcyclopropyl Boronic Esters with Non-Carbonyl-Based Electrophiles[a]



[a]All reactions were run on a 0.3 mmol scale, and yields are of isolated products.

Scheme 6. Reactions of Vinylcyclopropyl Boronic Esters with Radicals



in situ. Benzaldehyde was subsequently added at −78 °C, and the mixture was slowly warmed up to room temperature (RT) overnight. Pleasingly, ACP **2a** was obtained in 33% yield (Table 1, entry 5). Hoping to improve the reactivity by increasing the boron atom's electrophilicity, we turned to aryllithiums (Table 1, entries 6 and 7). To our delight, this approach proved successful: using more electron-deficient aryllithium **C**, the desired product **2a** was obtained in 86% yield. Finally, control experiments highlighted the importance of TFAA activation; no product formation was observed without TFAA (Table 1, entry 8). The reaction was found to be robust on a large scale, giving the product **2a** in 83% yield on a 10 mmol scale.

With optimum conditions in hand, we screened a broad range of vinylcyclopropyl boronic esters with benzaldehyde (Scheme 4A). *β*-Substituted boronic esters gave highly substituted ACPs **2b** and **2c** in good yields. We were delighted to find that *trans*-*γ*-methyl substituted boronic ester gave the corresponding product **2d** in 92% yield as a single diastereomer.[47] The high selectivity observed implies the involvement of a six-membered closed boracyclic transition state. Encouraged by these results, we further screened various *γ*-substituted boronic esters. We were pleased to find that boronic esters bearing simple alkyl, chloro and OTBS bearing alkyl groups, and phenyl substituents worked very efficiently, providing the corresponding products (**2e**−**2h**) in excellent yields as single diastereomers. Notably, by using *cis*-*γ*-methyl/phenyl substituted boronic esters, the opposite diastereomers of **2d** and **2h** were obtained in good yields. Furthermore, cyclopropylidenecycloalkanes **2i** and **2j** could also be efficiently synthesized in good yields with high selectivities from cycloalkenyl boronic esters. Finally, the procedure was applied to the more complex bicyclo[4.1.0]-

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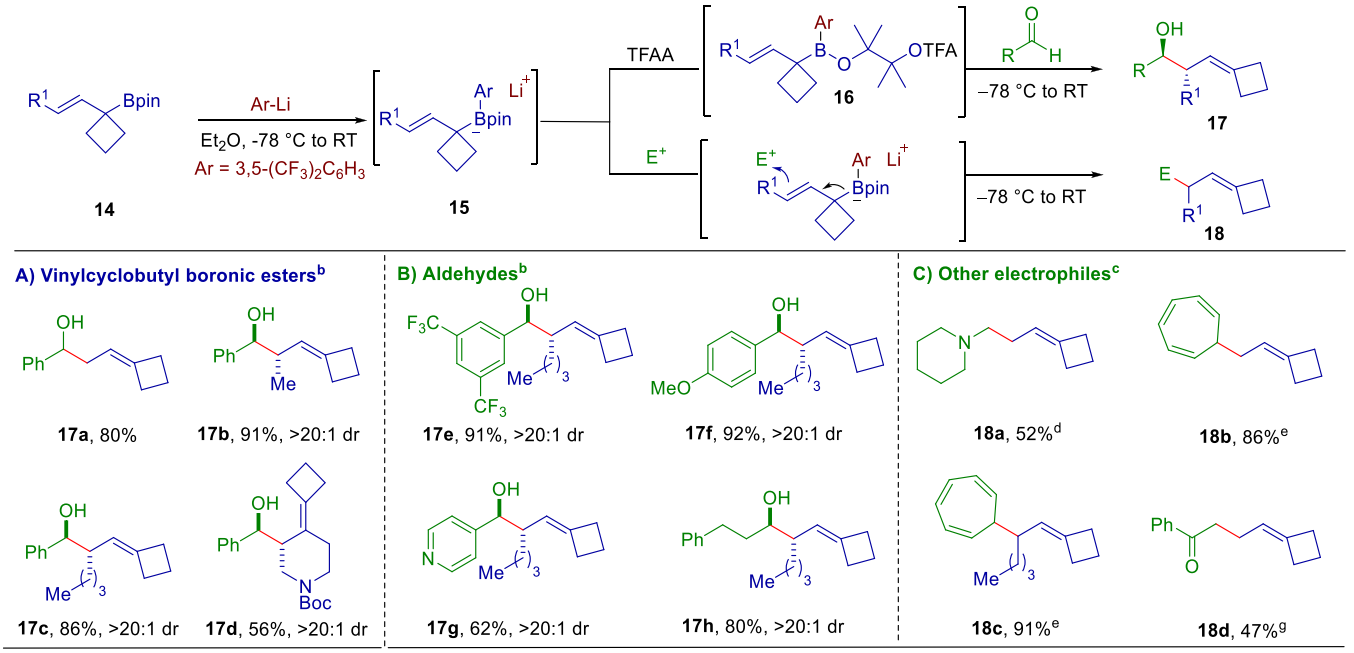
Scheme 7. Scope of Reactions of Vinylcyclobutyl Boronic Esters with Aldehydes and Other Electrophiles[a]



[a]All reactions were run on a 0.3 mmol scale. Yields are of isolated products. dr determined by ^{1}H NMR. [b]TFAA was added after the formation of boronate complexes. [c]Boronate complexes were reacted directly with electrophiles. [d]Piperidine-derived iminium salt was used. [e]Tropylium tetrafluoroborate was used. [f]Phenacyl iodide was used under blue light irradiation.

heptane ring system bearing boronic ester to afford the corresponding product **2k** in 40% yield.

We then tested a more diverse range of aldehydes (Scheme 4B). Electron-rich and electron-poor aromatic aldehydes underwent the desired transformation successfully, giving the products **2l** and **2m** in high yields as single diastereomers. *p*-Bromobenzaldehyde, bearing a useful handle for further synthetic elaboration, gave **2n** in 93% yield. Electron-deficient and electron-rich heteroaromatic aldehydes were also viable substrates in this reaction giving products **2o** and **2p**. Using cinnamaldehyde, the allylic alcohol **2q** was obtained in 91% yield. Pleasingly, aliphatic linear, branched, and neopentylic aldehydes reacted well and afforded the desired products (**2r**–**2t**) in good yields and selectivities. Unfortunately, ketones and imines did not undergo the desired transformation. We then proceeded to explore other non-carbonyl-based electrophiles in this reaction. In allylboration reactions, dual activation of both the nucleophile and the electrophile occurs upon complexation of the carbonyl group to boron. In the absence of a carbonyl group, this dual mode of activation is not available, but it is still possible to activate the nucleophile by converting the boronic ester into the boronate complex, which now "switches on" the nucleophilic S_E2' reactivity of these species.[48] Pleasingly, the boronate complex **5c**, which was obtained by the addition of aryllithium (3,5-$(CF_3)_2C_6H_3Li$) to boronic ester **1c**, reacted readily with Eschenmoser's salt to afford the desired product **7a** in 98% yield (Scheme 5). In a control experiment, treatment of the boronic ester to Eschenmoser's salt did not lead to any reaction demonstrating the low reactivity of the allylic boronic ester. Piperidine-derived iminium salt and tropylium tetrafluoroborate also reacted well in this reaction giving products **7b** and **7c**, respectively. Benzodithiolylium tetrafluoroborate also participated in this reaction providing the desired product **7f** in 78% yield. By using Togni's reagent, CF_3 substituted product **7g** was accessed in 41% yield. Pleasingly, a simple proton (addition of HBF_4) gave the corresponding ACP **7h** in good yield. Electrophiles that create new carbon–heteroatom bonds could also be utilized in the reaction, enabling the formation of C–F and C–Cl bonds (products **7i** and **7j**). Interestingly, the reaction of the boronate complex **5c** with 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione did not deliver the γ-addition product. Instead, α-addition product **8a** was isolated in 60% yield, probably resulting from a rearrangement of the initially formed γ-addition product to release the ring-strain. Similar reactivity was also observed with 1,3-diiodo-5,5-dimethylimidazolidine-2,4-dione and phenylselenyl chloride (products **8b** and **8c**).

We also investigated the reaction of vinylcyclopropyl boronic esters bearing different β-substituents (Me/H) with tropylium tetrafluoroborate. We found that β-methyl substituted vinylcyclopropyl boronic ester **1b** underwent the desired transformation successfully to give the corresponding product **7d** in 85% yield, but the simple vinylcyclopropyl boronic ester **1a** did not furnish the desired ACP **7e**. This indicates that electron-rich vinylcyclopropyl boronate complexes are required for reactivity.

Finally, we sought to explore radical electrophiles in our reaction (Scheme 6).[49,50] To our delight, phenacyl iodide underwent a productive reaction under blue light irradiation, giving the products **10a** and **10b** in 61% and 34% yields, respectively. Iodoacetonitrile provided the corresponding nitrile bearing ACP **10d** in 63% yield. A control experiment highlighted the importance of light; no product was observed in the absence of blue LED irradiation. The mechanism of this photochemical radical allylation reaction is depicted in Scheme 6. Blue-light-induced homolytic cleavage of the carbon–iodine bond in alkyl iodide **9** leads to electrophilic radical **11**, which readily adds to the double bond giving

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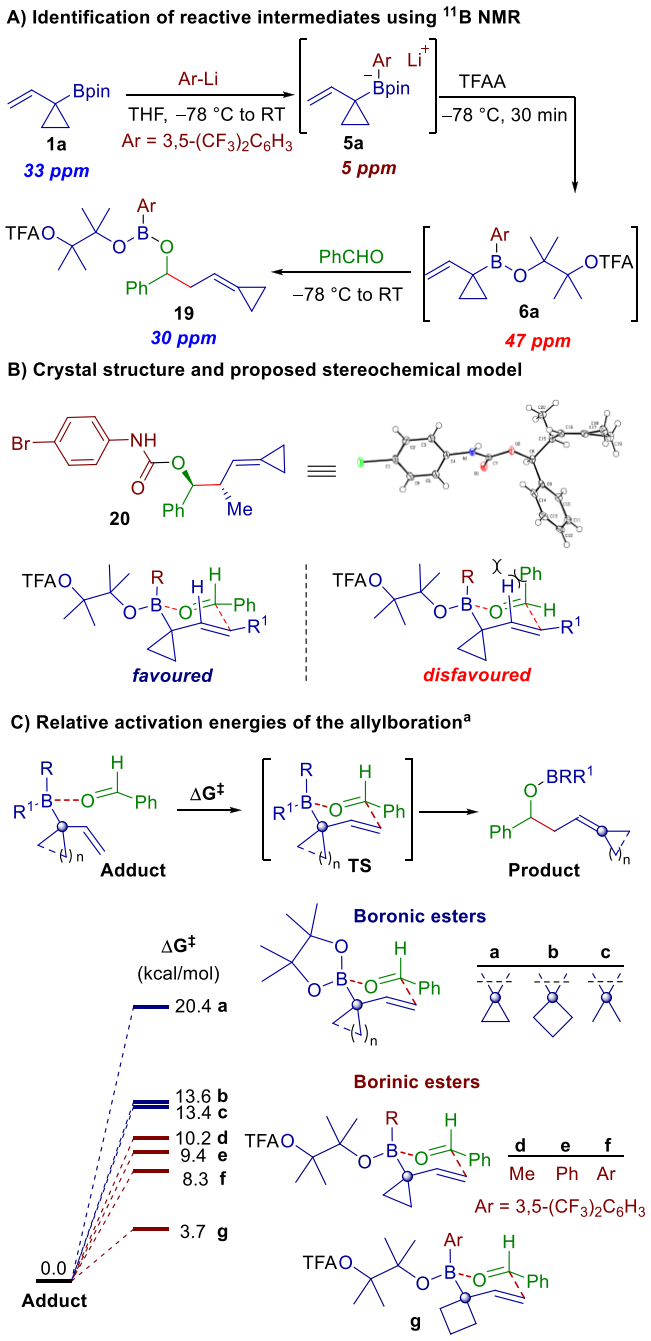
Scheme 8. (A) Identification of Reactive Intermediates Using ^{11}B NMR, (B) Crystal Structure and Proposed Stereochemical Model, and (C) Relative Activation Energies of the Allylboration



[a]DFT at the M06-2X/6-311G(d,p) level, with a polarizable continuum model of solvation (PCM, THF). See the SI for the transition states with R placed in the equatorial position.[55]

tertiary alkyl radical **12** that could further react via two potential pathways. Single-electron transfer (SET) from the electron-rich radical **12** to the electron-deficient alkyl iodide **9** regenerates radical **11** to propagate the radical chain while also forming carbocation **13**.[49,50] Subsequent loss of the boronic ester (ArBpin) leads to the allylation product **10**.[51] Alternatively, radical **11** could abstract the iodine atom of alkyl iodide **9** to give the atom transfer product **13′**, which could further lose the boronic ester (ArBpin) to provide product **10**. Interestingly, this reaction only worked in the cases of **1b** and **1c**, which lead to tertiary radical intermediates; it did not work for **1a** which leads to a secondary radical intermediate. In the latter case, the less stabilized radical underwent fast ring opening of the cyclopropane[52−54] instead of single-electron transfer (SET) to generate the carbocation and ultimately decomposition products.

We have also explored the potential of this methodology for the construction of functionalized alkylidenecyclobutanes (ACBs), which are attractive motifs that are present in several natural products and have been used as intermediates in the total synthesis of natural products.[22] However, the desired ACB **17a** was obtained only in 27% yield under standard reaction conditions. Switching from THF to Et_2O, this reaction successfully provided the desired product **17a** in a much improved 80% yield (Scheme 7A). Pleasingly, *trans*-γ-methyl and long alkyl chain substituted vinylcyclobutyl boronic esters underwent the desired transformation successfully, giving the products **17b** and **17c** in good yields as a single diastereomers. Notably, dihydropiperidine-derived cyclobutyl boronic ester successfully participated in this reaction, giving the product **17d** in 56% yield. The scope of the reaction was explored with different aldehydes. Electron-rich and electron-deficient aromatic aldehydes and hetero-aromatic aldehyde worked well, giving the products **17e−17g** in high yields as single diastereomers (Scheme 7B). Dihydrocinnamaldehyde also reacted well in this reaction giving the product **17h** in good yield and selectivity. We then proceeded to explore other electrophiles in this reaction by reacting directly with boronate complexes. Pleasingly, Eschenmoser's salt and tropylium tetrafluoroborate underwent the desired transformation giving the products **18a−18c** in moderate to good yields (Scheme 7C). Finally, the radical allylation was also possible using phenacyl iodide, furnishing the product **18d** in 47% yield.

To gain insight into the reactive intermediates involved during allylboration, the reaction was monitored by ^{11}B NMR (Scheme 8A).[36] After addition of vinylcyclopropyl boronic ester **1a** to ArLi (Ar = 3,5-$(CF_3)_2C_6H_3$) in THF at −78 °C, a signal at 5 ppm was observed corresponding to the boronate complex **5a**. Subsequent addition of TFAA at −78 °C resulted in a new signal at 47 ppm, indicative of the formation of borinic ester **6a**. Finally, addition of benzaldehyde to borinic ester **6a** led to a new signal at 30 ppm, indicating the formation of boronic ester **19**. Having identified that the reaction involved the borinic ester intermediate, we propose a model to account for the observed stereochemistry, which was confirmed by X-ray analysis of derivative **2d** (Scheme 8B). In this model, the aldehyde reacts with the allylic borinic ester through a cyclic TS in which the aldehyde substituent occupies the equatorial position.

Finally, DFT calculations were performed to understand how the activation barriers for allylboration are affected by ring-strain substituents (Scheme 8C). For boronic esters, it was found that replacing an α-gem-dimethyl group with a cyclopropyl ring caused a significant increase in activation energy (**c** vs **a**: $\Delta G^{\ddagger}$ = 13.4 and 20.4 kcal/mol, respectively). The strain-increase is almost absent for cyclobutyl boronic esters (**b**: $\Delta G^{\ddagger}$ = 13.6 kcal/mol) evidently because it is easier to incorporate an sp^2-hybridized carbon in a four-membered

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ring.[56,57] This is in agreement with the experimentally[42] observed decrease in reactivity going from the vinyl gem-dimethyl boronic ester to the corresponding cyclobutyl and cyclopropyl analogues (72%, 40%, and 0%, respectively). Conversion of boronic esters into the more reactive borinic esters greatly reduces the activation barrier of the strain-increase allylboration by 10.2−12.1 kcal/mol depending on the R group. Indeed, as observed experimentally, the lowest energy barrier for vinylcyclopropyl borinic esters is obtained using the more electron-deficient organolithium (3,5-$(CF_3)_2C_6H_3Li$). There is a substantial increase in the barrier to allylboration from incorporating a cyclopropyl unit due to strain-increase in the TS (**c** vs **a**, $\Delta\Delta G^{\ddagger}$ = +7.0 kcal/mol), but this is more than compensated for using the borinic ester in place of the boronic ester (**a** vs **f**, $\Delta\Delta G^{\ddagger}$ = −12.1 kcal/mol). Interestingly, the reduction in activation barrier by formation of the borinic ester is similar but more accentuated in the case of the cyclopropyl boronic esters (**a** vs **f**, $\Delta\Delta G^{\ddagger}$ = −12.1 kcal/mol) compared to the cyclobutyl boronic esters (**b** vs **g**, $\Delta\Delta G^{\ddagger}$ = −9.9 kcal/mol).

CONCLUSION

We have developed the first strain-increase allylboration reaction using borinic ester activation. The use of an electron-deficient organolithium was key to the success of the reaction. The reaction is highly diastereoselective and gives rapid access to functionalized ACPs and ACBs. The reaction shows a remarkably broad scope in terms of both the boronic esters and aldehydes that can be employed. Additionally, non-carbonyl-based electrophiles and radicals could be used in this reaction by reacting them directly with the boronate complexes. ^{11}B NMR confirmed the involvement of a borinic ester intermediate, and DFT studies were used to rationalize the reactivities observed: there is a substantial increase in the barrier to allylboration from incorporating a cyclopropyl unit due to strain-increase in the TS, but this is more than compensated for using the borinic ester in place of the boronic ester.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01966.

Experimental procedures and characterization data for new compounds (PDF)

Accession Codes

CCDC 2061386 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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