Difunctionalization of C–C σ-Bonds Enabled by the Reaction of Bicyclo[1.1.0]butyl Boronate Complexes with Electrophiles: Reaction Development, Scope, and Stereochemical Origins

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ABSTRACT: Difunctionalization reactions of C–C σ-bonds have the potential to streamline access to molecules that would otherwise be difficult to prepare. However, the development of such reactions is challenging because C–C σ-bonds are typically unreactive. Exploiting the high ring-strain energy of polycyclic carbocycles is a common strategy to weaken and facilitate the reaction of C–C σ-bonds, but there are limited examples of highly strained C–C σ-bonds being used in difunctionalization reactions. We demonstrate that highly strained bicyclo[1.1.0]butyl boronate complexes (strain energy: *ca.* 65 kcal/mol), which were prepared by reacting boronic esters with bicyclo[1.1.0]butyl lithium, react with electrophiles to achieve the diastereoselective difunctionalization of the strained central C–C σ-bond of the bicyclo[1.1.0]butyl unit. The reaction shows broad substrate scope, with a range of different electrophiles and boronic esters being successfully employed to form a diverse set of 1,1,3-trisubstituted cyclobutanes (>50 examples) with high diastereoselectivity. The high diastereoselectivity observed has been rationalized based on a combination of experimental data and DFT calculations, which suggests that separate concerted and stepwise reaction mechanisms are operating depending upon the migrating substituent and electrophile used.

Introduction

Methods for cleaving C–C σ-bonds have recently risen to prominence because they have the potential to streamline chemical synthesis by enabling access to new chemical transformations and molecules that would otherwise be difficult to prepare.[1] However, the development of such methods is challenging because C–C σ-bonds are typically strong, inert, and geometrically inaccessible. Furthermore, overlap of the high energy C–C σ* orbital (which is usually not the LUMO of the molecule) with the HOMO of the reagent/catalyst is difficult to achieve. Thus, features that modulate the electronic structure of C–C σ-bonds are usually required to enable them to engage in chemical reactions.

One method to activate C–C σ-bonds is to use strain energy. For example, the central C–C bond in [1.1.1]propellane is highly strained (98 kcal/mol of strain energy),[2] which enables it to react with many radicals and nucleophiles.[3] In several cases, these reactions provide rare examples of the difunctionalization of a C–C single bond, wherein the C–C bond is cleaved and replaced by a new substituent (≠ H) on each carbon atom.[4] Bicyclo[1.1.0]butanes[5] are another class of highly strained carbocycles (63.9 (experimental)/66.3 (calculated)[2] kcal/mol of strain energy) which have been used in C–C bond activation reactions;[6] however, in contrast to [1.1.1]propellane, there are limited examples of bicyclo[1.1.0]butanes being used in C–C bond difunctionalization reactions.[7] In a notable report, Fox showed that the central strained σ-bond of a bicyclo[1.1.0]butane bearing a bridgehead *tert*-butyl ester could be cleaved by the homo-conjugate addition of an organocuprate. The enolate was then trapped by an electrophile, resulting in the formal difunctionalization of the central C–C σ-bond of the bicyclo[1.1.0]butane (Figure 1A).[8] Whilst this chemistry demonstrated a groundbreaking use of bicyclo[1.1.0]butanes, the cyclobutane

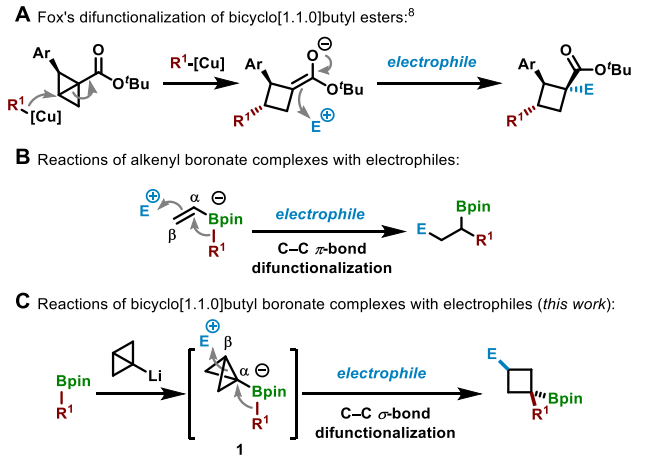

Figure 1. (A) Fox's homo-conjugate addition of organocuprates followed by electrophilic trapping for the difunctionalization of bicyclo[1.1.0]butyl esters.[8] (B) The reaction of alkenyl boronate complexes with electrophiles. (C) Proposed reaction of bicyclo[1.1.0]butyl boronate complexes with electrophiles.

products were often obtained with modest diastereoselectivity. Considering these limited precedents, we were interested in developing alternative methods to achieve the difunctionalization of C–C σ-bonds by exploiting highly strained intermediates.

Alkenyl boronate complexes react with electrophiles,[9] as well as electrophilic radicals[10] and palladium/nickel complexes (Figure 1B).[11] The electrophile (E^+) reacts at the β-carbon of the alkene group and induces a concomitant 1,2-metalate rearrangement, where the carbon substituent, R^1, migrates to the α-carbon of the alkene group. This results in the formal carbofunctionalization of the C–C π-bond. Relief of ring strain in small heterocycles, including epoxides,[12] aziridines,[13] azetidinium ions,[14] and 1-azabicyclo[1.1.0]butanes,[15] has also been used to trigger 1,2-metalate rearrangements. In a merger of these two concepts, we questioned whether a boronate complex bearing the highly strained carbocycle bicyclo[1.1.0]butane (**1**) would provide sufficient strain energy to facilitate reaction with an electrophile to trigger 1,2-metalate rearrangement with concomitant cleavage of its strained central bond (Figure 1C). By analogy to the alkenyl boronate complexes, the migrating group, R^1, would migrate to the α-carbon with simultaneous cleavage of the central C–C σ-bond of the bicyclo[1.1.0]butyl unit and formation of a C–E bond at the β-carbon. This step would represent a formal carbofunctionalization of a C–C σ-bond, albeit a highly strained one, wherein the carbon-based migrating group and the electrophile are added across the central bond of the bicyclo[1.1.0]butyl unit.

The products of this reaction would be 1,1,3-trisubstituted cyclobutanes bearing two easily varied substituents (electrophile and migrating group) as well as a boronic ester, which itself can be readily converted into a range of functional groups.[16] Current methods to prepare 1,1,3-trisubstitued cyclobutanes are limited,[17] especially with high diastereoselectivity, so this method could provide a unique entry point to this particular class of substituted cyclobutanes. Furthermore, cyclobutanes are of increasing value in medicinal chemistry because they can function as rigid, C(sp^3)-rich bioisosteres of phenyl rings[18] to help chemists '*escape flatland*',[19] so this method could find application in the modular preparation of diverse cyclobutane-containing building blocks for use in medicinal chemistry discovery programs.

In this article, we present our success in realizing this concept, providing full details of the design and development of bicyclo[1.1.0]butyl boronate complexes and the exploration of their reactivity with a broad array of electrophiles, resulting in the diastereoselective difunctionalization of the central C–C σ-bond of the bicyclo[1.1.0]butyl unit.[20] Using a combination of experimental results and DFT calculations, the origins of stereocontrol in these reactions has been rationalized.

Results and Discussion

Formation and Initial Reactions of Bicyclo[1.1.0]butyl Boronate Complexes

To prepare bicyclo[1.1.0]butyl boronate complexes, we required access to bicyclo[1.1.0]butyl lithium,[21] a reactive intermediate that had previously been prepared from dibromocyclopropane **2** (Figure 2A). Employing this method, bicyclo[1.1.0]butyl lithium was generated and treated with cyclohexylpinacol boronic ester (Figure 2B). However, analysis of the reaction mixture with ^{11}B NMR spectroscopy revealed that only 75% of the cyclohexylpinacol boronic ester had been converted to the corresponding bicyclo[1.1.0]butyl boronate complex **3**. The subsequent reaction between **3** and a model electrophile, benzaldehyde,[22] proceeded smoothly within 1 h at –78 °C to give borylcyclobutane **4** in 45% yield with >95:5 d.r.

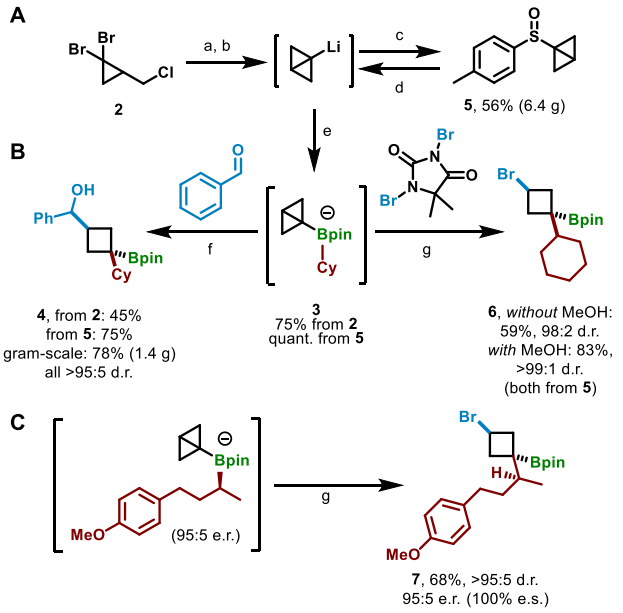

Figure 2. (A) Preparation of bicyclo[1.1.0]butyl lithium from dibromocyclopropane **2** and sulfoxide **5**. (B) The reaction of bicyclo[1.1.0]butyl lithium with cyclohexylpinacol boronic ester to form bicyclo[1.1.0]butyl boronate complex **3**, and the subsequent reaction of **3** with benzaldehyde and DBDMH to give borylcyclobutane products **4** and **6**. (C) Enantiospecific reaction of a bicyclo[1.1.0]butyl boronate complex with DBDMH. Abbreviated reaction conditions: [a] **2** (1.2 equiv), MeLi (1.2 equiv), Et_2O, –78 to –50 °C, 1.5 h. [b] ^{t}BuLi (1.2 equiv), –78 °C, 20 min. [c] i) $MgBr_2$ (2.4 equiv), –78 °C, 2 h. ii) methyl 4-methylbenzenesulfinate (1.0 equiv). [d] **5** (1.3 equiv), ^{t}BuLi (1.3 or 2.6 equiv), –78 °C, 2-methyltetrahydrofuran. [e] –78 °C, 5 min, then r.t., 15 min. [f] benzaldehyde (1.3 equiv), –78 °C, 1 h. [g] DBDMH (1.2 equiv), –78 °C, 1 min.

To increase the yield of the reaction we needed to increase the conversion of the boronic ester to the boronate complex. We therefore sought to synthesize and isolate a latent bicyclo[1.1.0]butyl nucleophile from which we could generate bicyclo[1.1.0]butyl lithium cleanly and quantitatively. Bicyclo[1.1.0]butyl sulfoxide **5** was prepared on multi-gram scale in 56% yield by the treatment of bicyclo[1.1.0]butyl lithium with magnesium bromide[23] followed by methyl 4-methylbenzene sulfinate. This sulfoxide was found to be a crystalline compound which was stable at ambient temperature under N_2. Its structure was confirmed by single crystal X-ray crystallography. Treatment of sulfoxide **5** at –78 °C with *tert*-butyl lithium in the presence of cyclohexylpinacol boronic ester quantitatively formed the corresponding boronate complex **3** as determined by ^{11}B NMR spectroscopy. Subsequent treatment of **3** with benzaldehyde gave borylcyclobutane **4** in 75% yield with >95:5 d.r. This reaction was found to be scalable: when using 1.0 g (4.76 mmol) of cyclohexylpinacol boronic ester, borylcyclobutane **4** was obtained in 78% yield (1.38 g, 3.71 mmol) with >95:5 d.r. Finally, to get an appreciation of the reactivity of boronate complex **3**, its reaction with benzaldehyde was

followed by ReactIR at −78 °C (see Supporting Information). This revealed that the reaction was completed within just 5 min, showing the extraordinarily high reactivity of these strained boronate complexes[24] and gave us confidence that they would react with a range of other electrophiles.

We next investigated the reaction of bicyclo[1.1.0]butyl boronate complex **3** with electrophilic brominating reagents (Figure 2B), but the results were initially disappointing. The reaction of **3** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) yielded 59% of **6** with 98:2 d.r. alongside significant quantities of unidentified side-products. In related chemistry, where alkenyl boronate complexes were reacted with a range of electrophiles, it was discovered that diastereoselectivity could be increased by the addition of hydrogen bond donors such as methanol or trifluoroethanol.[25] Thus, we added a small amount of methanol (10% by volume) after boronate complex formation, before addition of DBDMH, which led to a significant increase in yield and selectivity to give **6** in 83% yield and >99:1 d.r. and without any contaminating side-products. Although the origin for the increase in yield and selectivity is unclear, it is possible that hydrogen bonding between methanol and the Lewis basic oxygen atoms of the pinacol unit stabilizes the intermediate boronate complex **3**, tempering its reactivity, thereby resulting in increased selectivity. This strategy of adding a hydrogen bond donor to the reaction mixture before addition of the electrophile was found to be a general strategy for improving both the yield and diastereoselectivity of reactions between certain bicyclo[1.1.0]butyl boronate complexes and electrophiles. We also found that, in some instances, addition of a hydrogen bonding donor also led to considerably cleaner reactions (*vide infra*). Finally, we treated the bicyclo[1.1.0]butyl boronate complex derived from an enantioenriched secondary boronic ester (95:5 e.r.) with DBDMH in the presence of methanol and it gave the corresponding bromocyclobutane **7** in 68% yield, >95:5 d.r. and 95:5 e.r., which demonstrated that the 1,2-migration step of this reaction proceeds with complete enantiospecificity (e.s.) (Figure 2C).

Reaction of Bicyclo[1.1.0]butyl Boronate Complexes with Electrophiles: Electrophile and Boronic Ester Scope

The scope of the electrophile was investigated using the

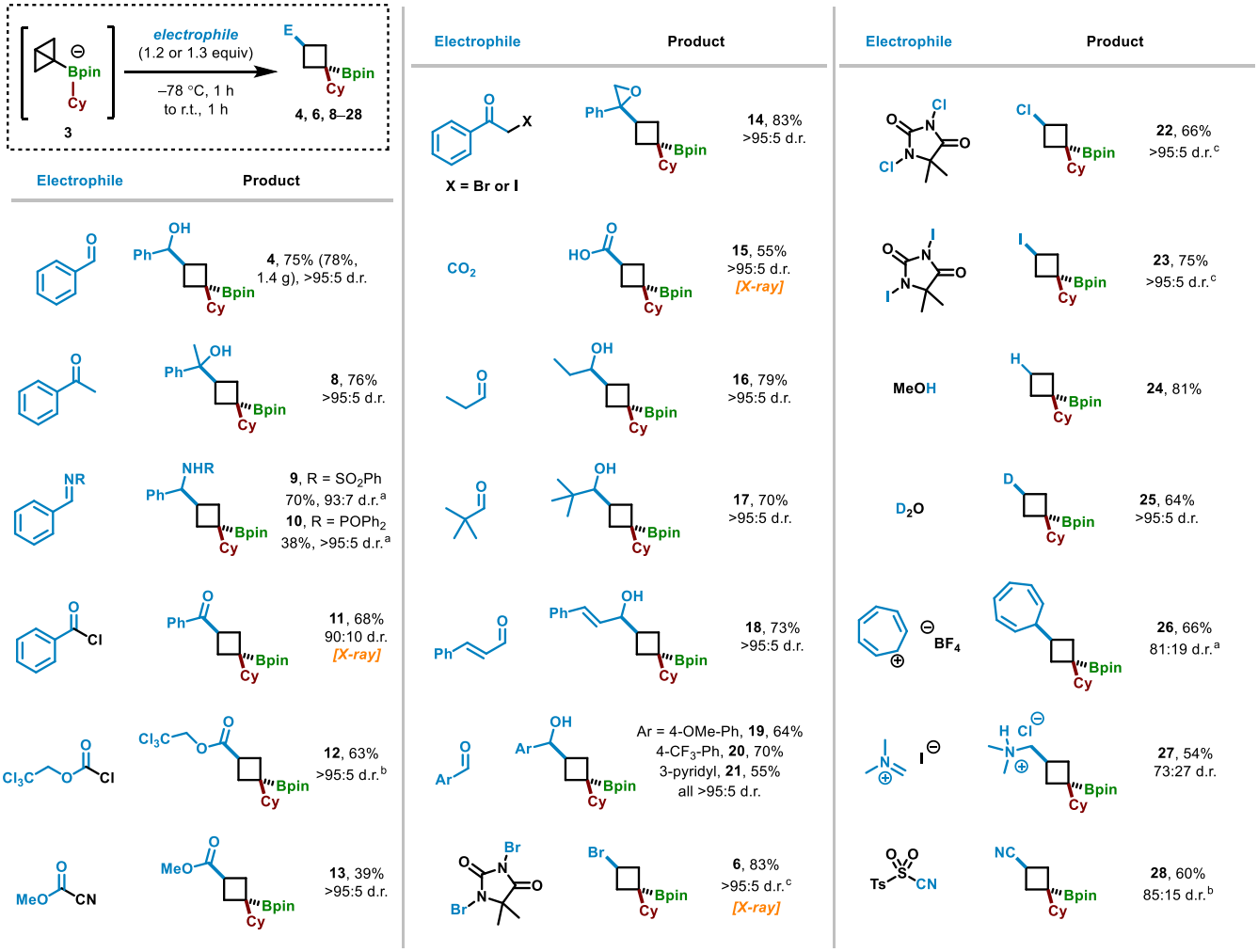

Figure 3. Electrophile scope of the reaction of bicyclo[1.1.0]butyl boronate complex **3** with electrophiles. All reactions were conducted using 0.24 mmol of **3** formed as described in Figure 2 via sulfoxide **5**. All yields refer to isolated yield of pure material. All d.r.s were measured using ^{1}H NMR spectroscopy before purification. [a]TFE added before addition of the electrophile. [b] ^{t}BuOH added before addition of the electrophile. [c]Methanol added before addition of the electrophile.

bicyclo[1.1.0]butyl boronate complex of cyclohexylpinacol boronic ester (**3**) as the model intermediate (Figure 3). Firstly, in addition to benzaldehyde (**4**), the reaction proceeded well using a range of carbonyl-containing functional groups and imines, including, acetophenone (**8**),[26] *N*-benzylidenebenezene-sulfonamide (**9**),[27] *N*-benzylidene-diphenylphosphinic amide (**10**), benzoyl chloride (**11**), Troc-Cl (**12**), methyl cyanoformate (Mander's reagent) (**13**) and α-iodo/bromo acetophenone. The last of which underwent chemoselective 1,2-addition of **3** to the ketone followed by a 3-*exo*-tet cyclization to deliver the corresponding epoxide **14**. Carbon dioxide could also be used as an electrophile, reacting with boronate complex **3** to give carboxylic acid **15** in good yield and d.r. A range of different aldehydes could also be used, including primary and tertiary alkyl (**16** and **17**, respectively), α,β-unsaturated (which exclusively gave the 1,2-addition product **18**), and (hetero)aromatic aldehydes (**19–21**). In all cases, excellent yields and diastereomeric ratios were achieved. Next, much like with DBDMH, the use of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and 1,3-diiodo-5,5-dimethylhydantoin (DIDMH) both delivered the corresponding halogenated borylcyclobutanes **22** and **23**, respectively, in excellent yields and with >95:5 d.r. The boronate complex **3** could also be protonated using methanol, to give the unfunctionalized borylcyclobutane **24** in excellent yield, and deuterated using deuterium oxide to give the deuterated

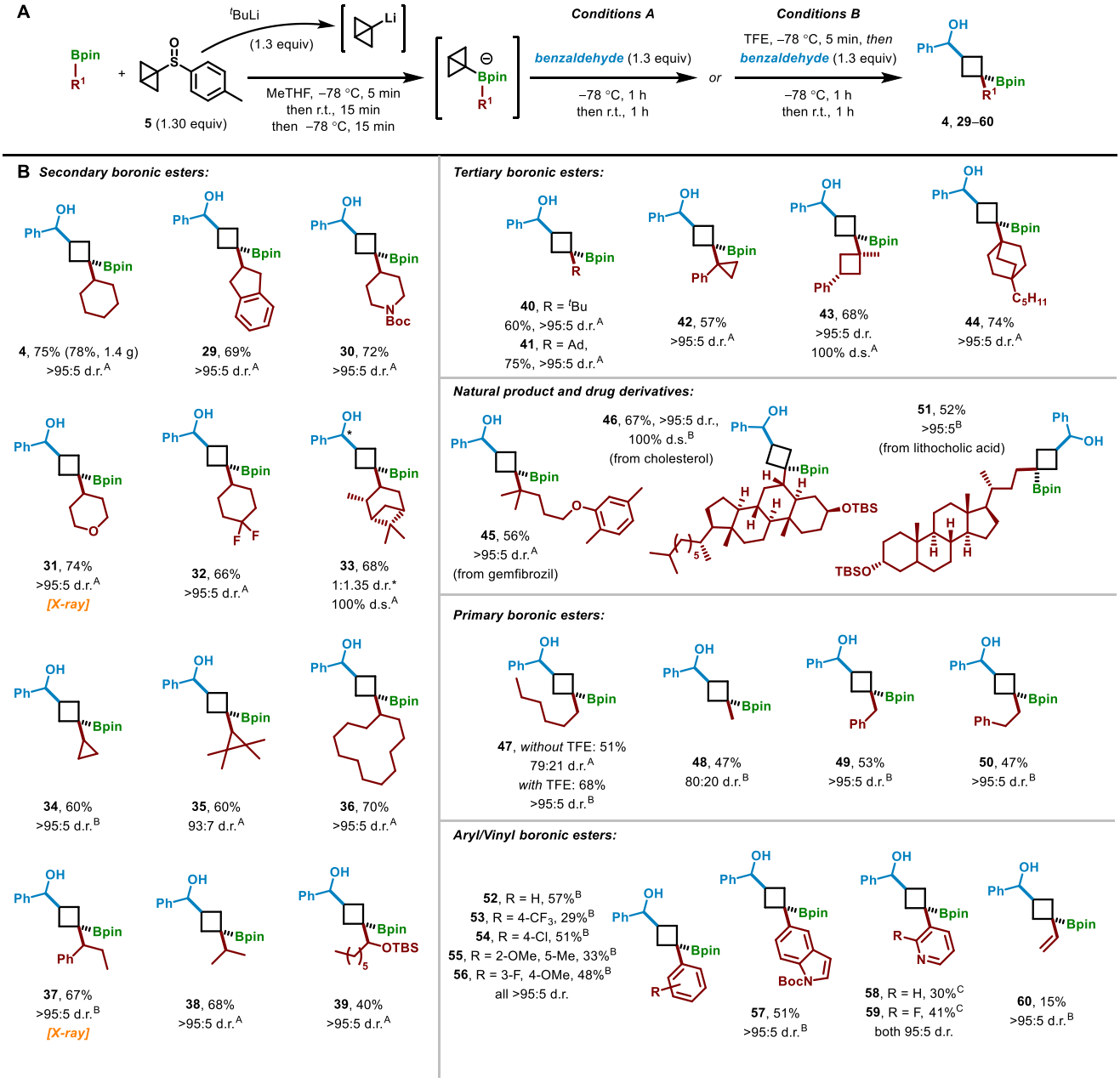

Figure 4. (A) General reaction conditions for the (B) boronic ester scope of the reaction of bicyclo[1.1.0]butyl boronate complexes with benzaldehyde. All reactions were conducted using 0.24 mmol of the boronic ester unless otherwise specified. [A]Conditions A were used. [B]Conditions B were used. [C]Products isolated as the corresponding alcohols following oxidation of the boronic ester with a mixture of NaOH and H_2O_2. All yields refer to isolated yield of pure material. All d.r.s were measured using ^{1}H NMR spectroscopy before purification. d.s. = diastereospecificity.[28]

borylcyclobutane **25** in good yield and as a single diastereomer. Finally, highly reactive electrophiles such as tropylium tetrafluoroborate (**26**), Eschenmoser's salt (**27**), and tosyl cyanide (**28**) were also successful electrophiles but gave lower diastereoselectivity with or without addition of a hydrogen bond donor.

It is noteworthy that many of the electrophiles that have reacted successfully here, such as methanol, carbon dioxide and alkyl aldehydes, have never previously been reacted with boronate complexes of any type, highlighting the unique reactivity of bicyclo[1.1.0]butyl boronate complexes.

The scope of the boronic ester was next explored, using benzaldehyde as a model electrophile (Figure 4). As with the formation of bicyclo[1.1.0]butyl boronate complex **3** (Figure 2), each boronic ester tested was mixed with sulfoxide **5** at –78 °C and then treated with *tert*-butyl lithium to form the corresponding bicyclo[1.1.0]butyl boronate complex intermediate. These boronate complexes were treated with benzaldehyde without any additional additives (conditions A), or with TFE followed by benzaldehyde (conditions B) if conditions A resulted in modest yield and/or diastereoselectivity, or an unclean reaction profile (Figure 4A). A range of secondary boronic esters was first investigated and the scope was found to be very broad (Figure 4B). With respect to cyclic substrates, use of indanyl (**29**), 4-*N*-Boc-piperidinyl (**30**), 4-tetrahydropyranyl (**31**), 1,1-difluoro-4-cyclohexyl (**32**), a derivative of pinene (**33**), cyclopropyl (**34**), tetramethylcyclopropyl (**35**) and cyclododecyl (**36**) boronic esters all delivered the corresponding functionalized borylcyclobutane products in good to excellent yields and very high diastereoselectivity. Acyclic boronic esters worked equally well, with 1,1-phenylpropyl (**37**), isopropyl (**38**), and an α-alkoxy (**39**) boronic ester giving the corresponding products in good yields and very high diastereoselectivity. Tertiary boronic esters could also be employed, with *tert*-butyl (**40**), adamantyl (**41**), 1,1-phenylcyclopropyl (**42**), substituted cyclobutane (**43**)[20a] and bicyclo[2.2.2]octane (**44**) all giving the functionalized borylcyclobutane products in excellent yield and selectivity. Compound **43** was formed with complete diastereospecificity. A small number of natural product and drug-derived boronic esters were also successfully reacted, including those derived from gemfibrozil (**45**) and cholesterol (**46**), the latter being formed with complete enantio- and diastereospecificity. In both cases, the cyclobutane products were obtained with excellent diastereoselectivity.

The reaction of boronate complexes derived from primary boronic esters were more challenging as they initially reacted with benzaldehyde to give the corresponding borylcyclobutane with low d.r. For example, when the boronate complex derived from *n*-hexylpinacol boronic ester was allowed to react with benzaldehyde, borylcyclobutane **47** was formed with 79:21 d.r. In order to address this issue, we explored the use of additives, particularly hydrogen bonding donors/acceptors, because these had previously been successful in improving the d.r. with several electrophiles (*vide supra*). From a range of additives, we discovered that by adding 2,2,2-trifluoroethanol (TFE) (10% by volume) after formation of the boronate complex, the diastereoselectivity was increased to >95:5 d.r. when using *n*-hexylpinacol boronic ester and benzaldehyde as the electrophile (see Supporting Information for further details). These modified conditions were applied to a number of other primary substrates, including methyl (**48**), benzyl (**49**), and phenethyl (**50**) boronic esters, delivering the borylcyclobutane products with mostly >95:5 d.r. and in modest to good yields. A derivative of lithocholic acid[29] was also successful, giving borylcyclobutane **51** in 52% yield and >95:5 d.r.

These modified conditions turned out to be beneficial for aryl boronic esters too, which otherwise returned borylcyclobutane products contaminated with minor side products. Using these conditions, a number of aryl boronic esters featuring a range of substitution patterns and functional groups were employed, giving the borylcyclobutane products (**52**–**57**) with high purity. Whilst the d.r.s were consistently high, only moderate yields were obtained due to the instability of the products to flash column chromatography. Medicinally relevant pyridines were also successfully employed but the borylcyclobutane products **58** and **59** proved unstable on silica, readily undergoing protodeboronation. As such, in situ oxidation was performed and the corresponding alcohols were isolated in moderate yield with 95:5 d.r. Finally, vinylpinacol boronic ester was also used, delivering allylic boronic ester **60** in 15% yield with >95:5 d.r.

Rationale for the Stereochemical Outcome and Reaction Mechanism

The relative stereochemistry of borylcyclobutane products **6**, **11**, **15**, **31**, and an oxidized derivative of **37** were confirmed by X-ray crystallography. In all cases, regardless of the boronic ester or electrophile used, a *cis* relationship between the migrating group and the electrophile was observed.

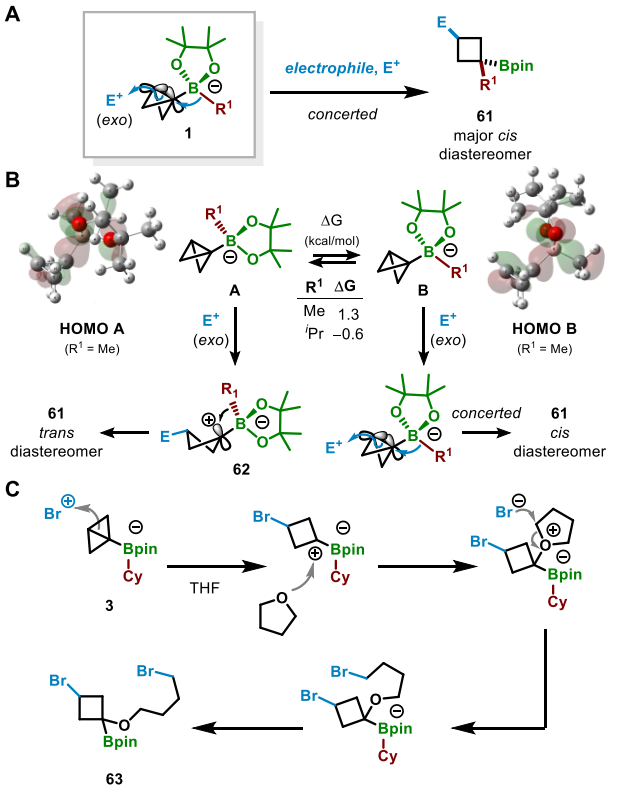

Figure 5. (A) Concerted reaction pathway leading to the major *cis* diastereomer of **61**. (B) Calculated conformations and HOMO energies of bicyclo[1.1.0]butyl boronate complexes and how these factors influence the stereocontrol in reactions with electrophiles. (C) Proposed mechanism for the formation of side-product **63** by the reaction of **3** with DBDMH and THF.

Our model for the origin of stereocontrol is shown in Figure 5. For bicyclo[1.1.0]butyl boronate complex **1**, the migrating group, R^1, and the central C–C σ-bond have to align anti-periplanar for 1,2-migration to occur. This orientation provides orbital overlap between the HOMO σ(B–R^1) and the LUMO σ^*(C–C) of the bicyclo[1.1.0]butyl unit.[30–32] In this conformation, the reaction of the electrophile with **1** occurs on the *exo* face of the β-carbon. The HOMO σ(C–C) of the bicyclo[1.1.0]butyl unit, which has significant electron density protruding from the *exo* face, can interact with an electrophile[32,33] to induce 1,2-migration of R^1 to the α-carbon, cleavage of the central C–C bond of the bicyclo[1.1.0]butyl unit, and formation of the C–E bond at the β-carbon. This concerted process leads to the borylcyclobutane product **61** with a *cis* relationship between R^1 and E, as is observed in the products obtained from this reaction (Figure 5A). To test this mechanistic proposal and understand why lower diastereoselectivity was observed for some boronic esters and electrophiles, we conducted DFT calculations to probe the conformational preferences and reactivity of bicyclo[1.1.0]butyl boronate complexes bearing different R^1 substituents (Figure 5B). Using Gaussian with the M06-2X functional and 6-311G(d,p) as the basis set, it was found that **1** bearing a small methyl R^1 substituent strongly favors a conformation with an approximate 60° dihedral angle between the B–R^1 and the central C–C bond of the bicyclo[1.1.0]butyl unit (conformer A), and with the larger pinacol group occupying open space. The other conformer (conformer B) has R^1 aligned anti-periplanar to the central C–C σ-bond of the bicyclo[1.1.0]butyl unit, which is the orientation required for the concerted reaction pathway. Based on the relative energy difference, at the reaction temperature of –78 °C, a 59:1 ratio of conformers A:B was calculated. By contrast, a larger isopropyl R^1 substituent on **1** showed a 1:2.4 ratio of conformers in favor of conformer B; the larger R^1 substituent now preferentially occupies open space. These calculations also showed that conformer B has a higher energy HOMO than conformer A (1.3 and 2.0 kcal/mol higher for methyl and isopropyl, respectively), making conformer B more reactive than conformer A for both R^1 substituents.

Based on these computational results, we can now rationalize the diastereoselectivity experimentally observed. To account for the lower diastereoselectivity observed experimentally when smaller migrating R^1 substituents or more reactive electrophiles were used, we propose that a stepwise reaction pathway that proceeds via an intermediate carbocation is also operative. When small R^1 substituents were used, such as methyl which gave **48** with an 80:20 d.r., a concerted reaction pathway via the more reactive, but sparsely populated, conformer B dominates to give *cis*-**61** (Figure 5A). Reaction via the more highly populated but less reactive conformer A at the *exo* face of the β-carbon leads to the carbocationic intermediate **62** which undergoes 1,2-migration of R^1 giving *trans*-**61**. The combination of these two reaction pathways results in low diastereoselectivity. Supporting evidence for this stepwise pathway comes from the observation of a THF-incorporation product **63** when bicyclo[1.1.0]boronate complex **3** was allowed to react with DBDMH in THF (Figure 5C). We propose that a carbocation intermediate, formed after reaction of **3** with DBDMH, is trapped by THF to give an adduct which is subsequently ring-opened by an adventitious bromide anion to give the side-product **63**. This observation suggests that carbocationic intermediate **62** is a plausible reaction intermediate with this R^1/electrophile combination. By contrast, when larger R^1 substituents were used, such as isopropyl which gave **38** with >95:5 d.r., the more populated conformer B is also the more reactive conformer, resulting in the concerted pathway dominating to give *cis*-**61** with high diastereoselectivity. When more reactive electrophiles are used, such as tropylium tetrafluoroborate which resulted in **26** with 81:19 d.r., both conformers A and B can react rapidly with the electrophile via stepwise and concerted pathways, respectively, resulting in lower diastereoselectivity which reflects the relative populations of conformers A and B. Less reactive electrophiles, such as palladium(II)-aryl complexes which give high diastereoselectivity with all R^1 groups,[20a] always react through the concerted pathway via the more reactive conformer B, leading to high diastereoselectivity for all sizes of R^1 groups.

It is also possible to rationalize the formation of the minor *trans* product by either the syn-periplanar 1,2-migration of the R^1 group upon the reaction of the electrophile at the *exo* face of the β-carbon of the bicyclo[1.1.0]butyl unit, or by the approach and reaction of the electrophile from the *endo* face of the β-carbon with anti-periplanar 1,2-migration of the R^1 group. However, we consider both of these alternatives to be less plausible than the proposed stepwise pathway because the former does not have the required alignment of molecular orbitals for 1,2-migration and our calculations show that such a conformation of **1** is an energetic maxima (see Supporting Information), and the latter does not have sufficient interaction between the HOMO of the bicyclo[1.1.0]butane and the electrophile for efficient reaction.[30–33]

Derivation of the Borylcyclobutane Products

Molecules featuring boronic esters are highly versatile synthetic building blocks because they can be converted into a broad

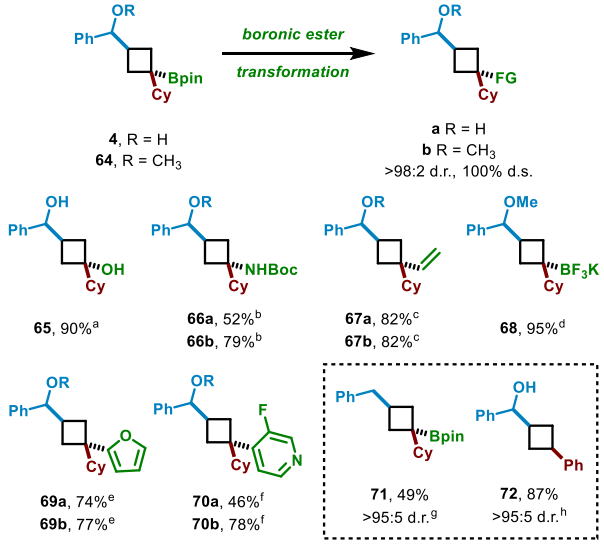

Figure 6. Derivation of the borylcyclobutane products. Abbreviated reaction conditions: [a]H_2O_2/NaOH; [b]H_2NOMe, KO^{t}Bu, then Boc_2O; [c]vinyl lithium, then I_2, then NaOMe; [d]KHF_2; [e]ArLi, then NBS; [f]ArLi, then 2,2,2-trichloroethyl chloroformate, then H_2O_2/NaOH; [g]Et_3SiH, TFA; [h]TBAF. All yields refer to isolated yield of pure material.

range of other valuable functional groups.[16] Because the products feature a unique 1,1,3-trisubstituted borylcyclobutane

emblem, we wanted to demonstrate that they too can be functionalized using these methods (Figure 6). Using **4**, or its *O*-methyl protected analog **64**, the tertiary boronic ester was transformed into the corresponding alcohol **65**, amine **66**,[34] alkene **67**,[35] and the trifluoroborate salt **68**.[36] Furthermore, the boronic ester was arylated to give both the furan **69**[37] and pyridine **70**[48] using transition metal-free cross-coupling chemistry. In all cases, good to excellent yields of the functionalized products were obtained with complete diastereospecificity (d.s.).[28] The alcohol functional group of **4** could also be removed using a mixture of trifluoroacetic acid and triethylsilane, to give alkane **71** in 49% yield. Since cyclobutanes can be bioisosteres of aromatic rings, this arylcyclobutylmethane structure could potentially be considered a bioisostere of the highly pharmaceutically prevalent diarylmethane moiety. Finally, the treatment of boronic ester **52** with TBAF effected protodeboronation[39] to give **72** in 87% yield.

Summary and Conclusions

In summary, we have described the development of bicyclo[1.1.0]butyl boronate complexes and explored how they react with a range of electrophiles. It was found that bicyclo[1.1.0]butyl boronate complexes can be quantitatively formed in situ by reaction of pinacol boronic esters with bicyclo[1.1.0]butyl lithium. These complexes were demonstrated to react with over twenty different electrophiles to give the corresponding functionalized borylcyclobutanes in good to excellent yield and with high diastereoselectivity. The boronic ester scope was also shown to be broad, encompassing a range of primary, secondary, tertiary, vinyl, aryl and heteroaryl boronic esters, including a number derived from natural products and drug molecules. The retention of the boronic ester functional group in the cyclobutane products significantly increases their value because the boronic ester can be transformed into many other functional groups.

This process proceeds through a unique C–C σ-bond carbofunctionalization mechanism, where a migrating carbon-based boronic ester substituent and an electrophile are added across a C–C σ-bond. The high diastereoselectivity observed has been rationalized by separate concerted and stepwise reaction mechanisms operating, depending upon the migrating substituent and electrophile used. Larger migrating substituents and less reactive electrophiles react via a concerted mechanism to give the *cis* product with high diastereoselectivity, whereas smaller migrating substituents and more reactive electrophiles react via both concerted and stepwise pathways which leads to lower diastereoselectivity.

Finally, these reactions enable the modular construction of diastereomerically-enriched 1,1,3-trisubstituted cyclobutane products with three synthetic branchpoints, the boronic ester substituent, the electrophile, and the boronic ester itself. When only considering the building blocks used in this report, >5000 unique cyclobutanes are now readily accessible. For this reason, and because cyclobutanes are of increasing value in medicinal chemistry, we believe that this method will find application in the preparation of cyclobutane-containing building blocks for use in medicinal chemistry discovery programs.

ASSOCIATED CONTENT

Supporting Information.

Detailed experimental procedures, and characterization data for all compounds (PDF).
Crystallographic information for compound **5** (cif)
Crystallographic information for compound **6** (cif)
Crystallographic information for compound **11** (cif)
Crystallographic information for compound **25** (cif)
Crystallographic information for compound **31** (cif)
Crystallographic information for compound **37-[O]** (cif)

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Notes

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