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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 diffunctionalization 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.

5One method to activate C–C σ-bonds is to use strain energy.6For example, the central C–C bond in [1.1.1]propellane is7highly strained (98 kcal/mol of strain energy),² which enables it8to react with many radicals and nucleophiles.³ In several cases,9of a C–C single bond, wherein the C–C bond is cleaved and0replaced by a new substituent (≠ H) on each carbon atom.⁴1Bicyclo[1.1.0]butanes⁵ are another class of highly strained2carbocycles (63.9 (experimental)/66.3 (calculated)² kcal/mol of3strain energy) which have been used in C–C bond activation4reactions;⁶ however, in contrast to [1.1.1]propellane, there are5limited examples of bicyclo[1.1.0]butanes being used in C–C6bond difunctionalization reactions.⁷ In a notable report, Fox7showed 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

A Fox's difunctionalization of bicyclo[1.1.0]butyl esters:8



 ${\boldsymbol{\mathsf{B}}}$ Reactions of alkenyl boronate complexes with electrophiles:

$$\overset{\oplus}{\underset{\substack{\mathsf{B} \\ \mathsf{P} \\ \mathsf{R}^{1}}}} \overset{\alpha}{\underset{\substack{\mathsf{B} \\ \mathsf{P} \\ \mathsf{R}^{1}}}} \overset{\Theta}{\underbrace{electrophile}} \overset{\mathsf{B} \\ \mathsf{E} \\ \mathsf{R}^{1}} \overset{\mathsf{B} \\ \mathsf{E} \\ \mathsf{R}^{1}}$$

C Reactions of bicyclo[1.1.0]butyl boronate complexes with electrophiles (this work):



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.

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 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.

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Alkenyl boronate complexes react with electrophiles,⁹ as well as electrophilic radicals¹⁰ 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, R¹, 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, R¹, 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.

28 The products of this reaction would be 1,1,3-trisubstituted 29 cyclobutanes bearing two easily varied substituents 30 (electrophile and migrating group) as well as a boronic ester, 31 which itself can be readily converted into a range of functional 32 groups.¹⁶ Current methods to prepare 1,1,3-trisubstitued 33 cvclobutanes are limited.17 especially with high 34 diastereoselectivity, so this method could provide a unique 35 entry point to this particular class of substituted cyclobutanes. 36 Furthermore, cyclobutanes are of increasing value in medicinal 37 chemistry because they can function as rigid, C(sp³)-rich bioisosteres of phenyl rings¹⁸ to help chemists 'escape 38 *flatland*',¹⁹ so this method could find application in the modular 39 preparation of diverse cyclobutane-containing building blocks 40 for use in medicinal chemistry discovery programs. 41

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 ¹¹B 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), Et₂O, -78 to -50 °C, 1.5 h. ^b BuLi (1.2 equiv), -78 °C, 20 min. ^ci) −78 °C, MgBr₂ (2.4 equiv), 2 h. ii) methyl 4methylbenzenesulfinate (1.0 equiv). ^d 5 (1.3 equiv), ^tBuLi (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. ^gDBDMH (1.2 equiv), -78 °C, 1 min.

To increase the vield 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 bromide²³ followed by methyl 4-methylbenzene sulfinate. This sulfoxide was found to be a crystalline compound which was stable at ambient temperature under N₂. Its structure was confirmed by single crystal X-ray crystallography. Treatment of sulfoxide 5 at -78 °C with tertbutyl lithium in the presence of cyclohexylpinacol boronic ester quantitatively formed the corresponding boronate complex **3** as determined by ¹¹B 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 complexes²⁴ 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 1,2migration 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 ¹H NMR spectroscopy before purification. ^aTFE added before addition of the electrophile. ^b/BuOH 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*-benzylidenebenezenesulfonamide (**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. ^AConditions A were used.

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^BConditions B were used. ^CProducts 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 ¹H 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 15 benzaldehyde as a model electrophile (Figure 4). As with the 16 formation of bicyclo[1.1.0]butyl boronate complex 3 (Figure 2), 17 each boronic ester tested was mixed with sulfoxide 5 at -78 °C 18 and then treated with tert-butyl lithium to form the 19 corresponding bicyclo[1.1.0]butyl boronate complex 20 intermediate. These boronate complexes were treated with 21 benzaldehyde without any additional additives (conditions A), 22 or with TFE followed by benzaldehyde (conditions B) if 23 vield conditions Α resulted in modest and/or 24 diastereoselectivity, or an unclean reaction profile (Figure 4A). 25 A range of secondary boronic esters was first investigated and the scope was found to be very broad (Figure 4B). With respect 26 to cyclic substrates, use of indanyl (29), 4-N-Boc-piperidinyl 27 (30), 4-tetrahydropyranyl (31), 1,1-difluoro-4-cyclohexyl (32), 28 а derivative of pinene (33). cyclopropyl (34), 29 tetramethylcyclopropyl (35) and cyclododecyl (36) boronic 30 esters all delivered the corresponding functionalized 31 borylcyclobutane products in good to excellent yields and very 32 high diastereoselectivity. Acyclic boronic esters worked 33 equally well, with 1,1-phenylpropyl (37), isopropyl (38), and an 34 α -alkoxy (39) boronic ester giving the corresponding products 35 in good yields and very high diastereoselectivity. Tertiary 36 boronic esters could also be employed, with *tert*-butyl (40), 37 adamantyl (41), 1,1-phenylcyclopropyl (42), substituted cyclobutane (43)^{20a} and bicyclo[2.2.2]octane (44) all giving the 38 functionalized borylcyclobutane products in excellent yield and 39 selectivity. Compound 43 was formed with complete 40 diastereospecificity. A small number of natural product and 41 drug-derived boronic esters were also successfully reacted, 42 including those derived from gemfibrozil (45) and cholesterol 43 (46), the latter being formed with complete enantio- and 44 diastereospecificity. In both cases, the cyclobutane products 45 were obtained with excellent diastereoselectivity.

46 The reaction of boronate complexes derived from primary 47 boronic esters were more challenging as they initially reacted 48 with benzaldehyde to give the corresponding borylcyclobutane 49 with low d.r. For example, when the boronate complex derived from *n*-hexylpinacol boronic ester was allowed to react with 50 benzaldehyde, borylcyclobutane 47 was formed with 79:21 d.r. 51 In order to address this issue, we explored the use of additives, 52 particularly hydrogen bonding donors/acceptors, because these 53 had previously been successful in improving the d.r. with 54 several electrophiles (vide supra). From a range of additives, we 55 discovered that by adding 2,2,2-trifluoroethanol (TFE) (10% by 56 volume) after formation of the boronate complex, the 57 diastereoselectivity was increased to >95:5 d.r. when using n-58

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 acid²⁹ 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



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.

group and the electrophile was observed.

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Our model for the origin of stereocontrol is shown in Figure 5. For bicyclo[1.1.0]butyl boronate complex 1, the migrating group, R¹, and the central C–C σ -bond have to align antiperiplanar for 1,2-migration to occur. This orientation provides orbital overlap between the HOMO $\sigma(B-R^1)$ and the LUMO $\sigma^*(C-C)$ 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 R¹ 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 proposal mechanistic 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 R¹ 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 R¹ 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 R¹ 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 R¹ substituent on **1** showed a 1:2.4 ratio of conformers in favor of conformer B; the larger R¹ 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 R¹ substituents.

45 Based on these computational results, we can now rationalize 46 the diastereoselectivity experimentally observed. To account 47 for the lower diastereoselectivity observed experimentally 48 when smaller migrating R^1 substituents or more reactive 49 electrophiles were used, we propose that a stepwise reaction 50 pathway that proceeds via an intermediate carbocation is also operative. When small R¹ substituents were used, such as 51 methyl which gave 48 with an 80:20 d.r., a concerted reaction 52 pathway via the more reactive, but sparsely populated, 53 conformer B dominates to give *cis*-61 (Figure 5A). Reaction via 54 the more highly populated but less reactive conformer A at the 55 exo face of the β -carbon leads to the carbocationic intermediate 56 62 which undergoes 1,2-migration of R^1 giving *trans*-61. The 57

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 R¹/electrophile combination. By contrast, when larger R¹ 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 R1 groups,20a always react through the concerted pathway via the more reactive conformer B, leading to high diastereoselectivity for all sizes of R¹ groups.

It is also possible to rationalize the formation of the minor *trans* product by either the syn-periplanar 1,2-migration of the R¹ 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 R¹ 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



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Figure 6. Derivation of the borylcyclobutane products. Abbreviated reaction conditions: ${}^{a}H_{2}O_{2}/NaOH$; ${}^{b}H_{2}NOMe$, KO/Bu, then Boc₂O; ${}^{c}vinyl$ lithium, then I₂, then NaOMe; ${}^{d}KHF_{2}$; ${}^{e}ArLi$, then NBS; ${}^{f}ArLi$, then 2,2,2-trichloroethyl chloroformate, then H₂O₂/NaOH; ${}^{e}Et_{3}SiH$, 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 10 O-methyl protected analog 64, the tertiary boronic ester was 11 transformed into the corresponding alcohol 65, amine 66,34 12 alkene 67,³⁵ and the trifluoroborate salt 68.³⁶ Furthermore, the 13 boronic ester was arylated to give both the furan 6937 and 14 pyridine 70^{48} using transition metal-free cross-coupling 15 chemistry. In all cases, good to excellent yields of the 16 functionalized products were obtained with complete 17 diastereospecificity (d.s.).28 The alcohol functional group of 4 could also be removed using a mixture of trifluoroacetic acid 18 and triethylsilane, to give alkane 71 in 49% yield. Since 19 cyclobutanes can be bioisosteres of aromatic rings, this 20 arylcyclobutylmethane structure could potentially be 21 considered a bioisostere of the highly pharmaceutically 22 prevalent diarylmethane moiety. Finally, the treatment of 23 boronic ester 52 with TBAF effected protodeboronation³⁹ to 24 give 72 in 87% yield. 25

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.

42 This process proceeds through a unique C-C σ -bond 43 carbofunctionalization mechanism, where a migrating carbonbased boronic ester substituent and an electrophile are added 44 across a C–C σ -bond. The high diastereoselectivity observed 45 has been rationalized by separate concerted and stepwise 46 reaction mechanisms operating, depending upon the migrating 47 substituent and electrophile used. Larger migrating substituents 48 and less reactive electrophiles react via a concerted mechanism 49 to give the cis product with high diastereoselectivity, whereas 50 smaller migrating substituents and more reactive electrophiles 51 react via both concerted and stepwise pathways which leads to 52 lower diastereoselectivity. 53

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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REFERENCES

 For reviews on C–C σ-bond activation, see: (a) Murakami, M.; Chatani, N. (eds) Cleavage of Carbon– Carbon Single Bonds by Transition Metals (Wiley, New York, 2015). (b) Souillart, L.; Cramer, N. Catalytic C–C Bond Activations via Oxidative Addition to Transition Metals, *Chem. Rev.* 2015, *115*, 9410–9464. (c) Murakami, M.; Ishida, N. Potential of Metal-Catalyzed C–C Single Bond Cleavage for Organic Synthesis, *J. Am. Chem. Soc.* **2016**, *138*, 13759–13769. (d) Morcillo, S. P. Radical-Promoted C–C Bond Cleavage: A Deconstructive Approach for Selective Functionalization, *Angew. Chem. Int. Ed.* **2019**, *58*, 14044–14054. (e) Wang, B.; Perea, M. A.; Sarpong, R. Transition Metal-Mediated C–C Single Bond Cleavage: Making the Cut in Total Synthesis, *Angew. Chem. Int. Ed.* **2020**, doi: 10.1002/anie.201915657.

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52

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54

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58 59

60

- (2) (a) Khoury, P. R.; Goddard, J. D.; Tam, W. Ring Strain Energies: Substituted Rings, Norbornanes, Norbornenes and Norbornadienes. *Tetrahedron* 2004, *60*, 8103–8112.
 (b) Wiberg, K. B. The Concept of Strain in Organic Chemistry, *Angew. Chem. Int. Ed. Engl.* 1986, *25*, 312–322.
- (3) (a) Kanazawa, J.; Uchiyama, M. Recent Advances in the Synthetic Chemistry of Biyclo[1.1.1]pentane, *Synlett* 2019, 30, 1–11. (b) Dilmaç, A. M.; Spuling, E.; de Meijere, A.; Bräse, S. Propellanes–From a Chemical Curiosity to "Explosive" Materials and Natural Products, *Angew. Chem. Int. Ed.* 2017, 56, 5684–5718.
- (4) For some recent examples of the difunctionalization of the central C–C bond of [1.1.1]propellane, please see: (a) Zhang, X.; Smith, R. T.; Le, C.; McCarver, S. J.; Shireman, B. T.; Carruthers, N. I.; MacMillan, D. W. C. Copper-Mediated Synthesis of Drug-like Bicyclopentanes, Nature 2020, 580, 220-226. (b) Kim, J. H.; Ruffoni, A.; Al-Faiyz, Y. S. S.; Sheikh, N. S.; Leonori, D. Divergent Strain-Release Amino-Functionalization [1.1.1]Propellane of with Electrophilic Nitrogen-Radicals, Angew. Chem. Int. Ed. 2020, 59, 8225-8231. (c) Yu, S.; Jing, C.; Noble, A.; Aggarwal. V. K. 1,3-Difunctionalization of [1.1.1]Propellane via 1,2-Metallate Rearrangements of Boronate Complexes, Angew. Chem. Int. Ed. 2020, 59, 3917-3921. (d) Kanazawa, J.; Maeda, K.; Uchiyama, M. Radical Multicomponent Carboamination of [1.1.1]Propellane, J. Am. Chem. Soc. 2017, 139, 17791-17794. (e) Makarov, I. S.; Brocklehurst, C. E.; Karaghiosoff, K.; Koch, G.; Knochel, P. Synthesis of Bicyclo[1.1.1]pentane Bioisosteres of Internal Alkynes and para-Disubstituted Benzenes from [1.1.1]Propellane, Angew. Chem. Int. Ed. 2017, 56, 12774-12777. (f) Nugent, J.; Arroniz, C.; Shire, B. R.; Sterling, A. J.; Pickford, H. D.; Wong, M. L. J.; Mansfield, S. J.; Caputo, D. F. J.; Owen, B.; Mousseau J. J.; Duarte, F.; Anderson, E. A. A General Route to Bicyclo[1.1.1]pentanes through Photoredox Catalysis, ACS Catal. 2019, 9, 9568-9574. (g) Kondo, M.; Т.; Kanazawa, J.; Ichikawa, T.; Shimokawa, Nagashima, Y.; Miyamoto, K.; Uchiyama, M. Silaboration of [1.1.1]Propellane: A Storable Feedstock for Bicyclo[1.1.1]pentane Derivatives, Angew. Chem. Int. Ed. 2020, 59, 1970-1974. (h) Hughes, J. M. E.; Scarlata, D. A.; Chen, A. C.-Y.; Burch, J. D.; Gleason, J. L. Aminoalkylation of [1.1.1]Propellane Enables Direct Access to High-Value 3-Alkylbicyclo[1.1.1]pentan-1-amines, Org. Lett. 2019, 21, 6800-6804. (i) Rout, S. K.; Marghem, G.; Lan, J.; Leyssens, T.; Riant, O. A Radical Exchange Process:

Synthesis of Bicyclo[1.1.1]pentane Derivatives of Xanthates, *Chem. Commun.* **2019**, *55*, 14976–14979. (j) Caputo, D. F. J.; Arroniz, C.; Dürr, A. B.; Mousseau, J. J.; Stephan, A. F.; Mansfield, S. J.; Anderson, E. A. Synthesis and Applications of Highly Functionalized 1-Halo-3-substituted Bicyclo[1.1.1]pentanes, *Chem. Sci.* **2018**, *9*, 5295–5300.

- (5) Wiberg, K. B.; Lampman, G. M.; Ciula, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J. Bicyclo[1.1.0]butane, *Tetrahedron* 1965, *21*, 2749–2769.
- (6) For recent reviews, see: (a) Fawcett, A. Recent Advances in the Chemistry of Bicyclo- and 1-Azabicyclo[1.1.0]butanes. Pure Appl. Chem. 2020, 92, 751-765. (b) Trukowska, J.; Durka, J.; Gryko, D. Strain Release - An Old Tool for New Transformations, Chem. *Commun.* **2020**. *56*. 5718–5734. For recent synthetic applications of bicyclo[1.1.0]butanes, see: (c) Ociepa, M.; Wierzba, A. J.; Turkowska, J.; Gryko, D. Polarity-Reversal Strategy for the Functionalization of Electrophilic Strained Molecules via Light-Driven Cobalt Catalysis, J. Am. Chem. Soc. 2020, 142, 5355-5361. (d) Milligan, J. A.; Busacca, C. A.; Senanayake, C. H.; Wipf, P. Hydrophosphination of Bicyclo[1.1.0]butane-1-carbonitriles, Org. Lett. 2016, 18, 4300-4303. (e) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Amination, Science 2016, 351, 241-246. (f) Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C.-M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J. Baran, P. S. Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity, J. Am. Chem. Soc. 2017, 139, 3209-3226. (g) Pratt, C. J.; Aycock, R. A.; King, M. D.; Jui, N. T. Radical α -C-H Cyclobutylation of Aniline Derivatives, Svnlett 2020, 31, 51-54. (h) Ernouf, G.; Chirkin, E.; Rhyman, L.; Ramasami, P.; Cintrat, J.-C. Photochemical Strain-Release-Driven Cyclobutylation of C(sp³)-H Centered Radicals, Angew. Chem. Int. Ed. 2020, 132, 2640-2644. (i) Walczak, M. A. A.; Krainz, T.; Wipf, P. Ring-Strain-Enabled Reaction Discovery: New Heterocycles from Bicyclo[1.1.0]butanes, Acc. Chem. Res. 2015, 48, 1149-1158.
- (7) For the insertion of carbenes into the central C-C bond of bicyclo[1.1.0]butanes, see: (a) Ma, X.; Sloman, D. L.; Han, Y.; Bennett, D. J. A Selective Synthesis of 2,2-Difluorobicyclo[1.1.1]pentane Analogues: "BCP-F₂", Org. Lett. 2019, 21, 7199–7203. (b) Bychek, R. M.; Hutskalova, V.; Bas, Y. P.; Zaporozhets, O. A.; Zozulya, S.; Levterov, V. V.; Mykhailiuk, P. K. Difluoro-Substituted Bicyclo[1.1.1]pentanes for Medicinal Chemistry: Design, Synthesis, and Characterization, J. Org. Chem. 2019, 84, 15106–15117. (c) Wiberg, K. B.; Dailey, W. P.; Walker, F. H.; Waddell, S. T.; Crocker, L. S.; Newton, M. Vibrational Spectrum, Structure, and Energy of [1.1.1]Propellane, J. Am. Chem. Soc. 1985,

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43

44

45

46

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57

58 59

60

107, 7247-7257. (d) Measom, N. D.; Down, K. D.; Hirst, D. J.; Jamieson, C.; Manas, E. S.; Patel, V. K.; Somers, D. O. ACS Med. Chem. Lett. 2017, 8, 43-48. (e) Applequist, D. E.; Renen, T. L.; Wheeler, J. W. Polar Substituent Effects in 1.3-Disubstituted Bicyclo[1.1.1]pentanes, J. Org. Chem. 1982, 47, 4985-4995. (f) Applequist, D. E.; Wheeler, J. W. Synthesis of 1,3-Disubstituted Bicyclo[1.1.1]pentanes, Tetrahedron Lett. 1977, 18, 3411-3412. (g) Wiberg, K. B.; Williams, V. Z. Bicyclo[1.1.1]pentane Derivatives, J. Org. Chem. 1970, 35, 369-373. (h) Hall Jr., H. K.; Smith, C. D.; Blanchard Jr., E. P.; Cherkofsky, S. C.; Sieja, J. B. Synthesis and Polymerization of Bridgehead-Substituted Bicyclobutanes, J. Am. Chem. Soc. 1971, 93, 121-130. For formal [2+2] reactions involving the central C-C bond of bicyclo[1.1.0]butanes, see: (i) Wipf, P.; Walczak, M. A. A. Pericyclic Cascade (Bicyclo[1.1.0]butylmethyl)amines, Reactions of Angew. Chem. Int. Ed. 2006, 45, 4172-4175. (j) Walczak, M. A. A.; Shin, B.-k.; Wipf, P.; Saxena, S. An ESR Analysis of the Mechanism of Pericyclic Reactions of Bicyclobutane, Org. Biomol. Chem. 2009, 7, 2363-2366. (k) Cairneross, A.; Blanchard Jr., E. P. Bicyclo[1.1.0]butane Chemistry. II. Cycloddition Reactions of 3-Methylbicyclo[1.1.0]butanecarbonitriles. The Formation of Bicyclo[2.1.1]hexanes, J. Am. Chem. Soc. 1966, 88, 496-504. (1) De Meijere, A.; Wenck, H.; Seyed-Mahdavi, F.; Viehe, H. G.; Gallez, V.; Erden, I. Cycloadditions of Methylenecyclopropanes and Strained Bicyclo[n.1.0]alkanes to Radicophilic Olefins, Tetrahedron 1986, 42, 1291–1297. For the dihalogenation of the central C-C bond of bicyclo[1.1.0]butanes, see: (m) Wiberg, K. B.: Lampman, G. M. Conformational Equilibration among 1,3-Dihalocyclobutanes, J. Am. Chem. Soc. 1966, 88, 4429-4433. (n) Mazal, C.; Škarka, O.; Kaleta, J.; Michl, J. cis-endo-Bicyclo[1.1.1]pentane-1.2,3,4tetracarboxylic Acid and Its Derivatives, Org. Lett. 2006, 8, 749-752. (o) Vasin, V. A.; Semenov, A. V.; Razin, V. V. Iodination of Tricyclo [4.1.0.0^{2,7}] heptane in the Presence of External Nucleophiles, Russ. J. Org. Chem. 2002, 38, 803-809. (p) Roth, R. J.; Katz, T. J. Uses of Benzvalene in Synthesis. Synthesis of Tricyclo[2.2.0.0^{2,6}]hexane, J. Am. Chem. Soc. 1972, 94, 4770-4771. (g) Vasin, V. A.; Petrov, P. S.; Kalyazin, V. A.; Razin, V. V. Products and Mechanism of Some Halogenation Reactions of 1-Sulfonyl-Substituted Tricyclo[4.1.0.0^{2,7}]heptanes, Russ. J. Org. Chem. 2012, 48, 358-367. For miscellaneous addition reactions across the central C-C bond of bicyclo[1.1.0]butanes, see: (r) Vasin, V. A.; Korovin, D. Y.; Petrov, P. S.; Razin, V. V.; Somov, N. V. Synthesis of 7-Sulfonyl-Substituted Norpinan-6-ones and -thiones from 1-Bromotricyclo4.1.0.0^{2,7}]heptane, Russ. J. Org. Chem. 2015, 51, 1697-1702. (s) Vasin, V. A.; Korovin, D. Y.; Kildeev, I. N.; Razin, V. V. Radical Reactions of Tricyclo[4.1.0.0^{2,7}]heptane and 1-Phenyltricyclo[4.1.0.0^{2,7}]heptane with Trifluoromethyl (Phenylethynyl) Sulfone, Russ. J. Org. Chem. 2016, 52, 1711-1714. (t) Vasin, V. A.; Korovin, D. Y.; Razin, V.

V.; Petrov, P. S. Synthesis of Tricyclo[4.4.0.0^{2,7}]decane Derivatives from Tricyclo[4.1.0.0^{2,7}]heptane Precursors, *Russ. J. Org. Chem.* **2019**, *55*, 415–425.

- (8) Panish, R.; Chintala, S. R.; Boruta, D. T.; Fang, Y.; Taylor, M. T.; Fox, J. M. Enantioselective Synthesis of Cyclobutanes via Sequential Rh-catalyzed Bicyclobutanation/Cu-catalyzed Homoconjugate Addition, J. Am. Chem. Soc. 2013, 135, 9283–9286.
- (9) Armstrong, R. J.; Aggarwal, V. K. 50 Years of Zweifel Olefination: A Transition-Metal-Free Coupling. Synthesis 2017, 49, 3323–3336.
- (10) (a) Silvi, M.; Sandford, C.; Aggarwal, V. K. Merging Photoredox with 1,2-Metallate Rearrangements: The Photochemical Alkylation of Vinyl Boronate Complexes. J. Am. Chem. Soc. 2017, 139, 5736–5739.
 (b) Kischkewitz, M.; Okamoto, K.; Mück-Lichtenfeld, C.; Studer, A. Radical-Polar Corssover Reactions of Vinylboron Ate Complexes. Science 2017, 355, 936–938.
- (11) (a) For a review, see: Namirembe, S.; Morken, J. P. Reactions of Organoboron Compounds Enabled by Catalyst-Promoted Metalate Shifts. Chem. Soc. Rev. 2019, 48, 3464-3474. (b) Koo, S. M.; Vendola, A. J.; Momm, S. N.; Morken, J. P. Alkyl Group Migration in Ni-Catalyzed Conjunctive Coupling with $C(sp^3)$ Electrophiles: Reaction Development and Application to Targets of Interest. Org. Lett. 2020, 22, 666-669. (c) Aparece, M. D.; Hu, W.; Morken, J. P. Catalytic Enantioselective Synthesis of β-Allenyl Boronic Esters by Conjunctive Cross-Coupling with Propargylic Carbonates. ACS Catal. 2019, 9, 11381-11385. (d) Law, C.; Meng, Y.; Koo, S. M.; Morken, J. P. Catalytic Conjunctive Coupling of Carboxylic Acid Derivatives with 9 BBN Derived Ate Complexes. Angew. Chem. Int. Ed. 2019, 131, 6726-6730. (e) Aparece, M. D.; Gao, C.; Lovinger, G. J.; Morken, J. P. Vinylidenation of Organoboronic Esters Enabled by a Pd Catalyzed Metallate Shift. Angew. Chem. Int. Ed. 2019, 58, 592-595. (f) Myhill, J. A.; Wilhelmsen, C. A.; Zhang, Р. L.; Morken, J. Diastereoselective and Enantioselective Conjunctive Cross-Coupling Enabled by Boron Ligand Design. J. Am. Chem. Soc. 2018, 140, 15181-15185. (g) Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. Enantioselective Construction of Tertiary Boronic Esters by Conjunctive Cross Coupling. Angew. Chem. Int. Ed. 2018, 57, 12799-12803. (h) Lovinger, G. J.; Morken, J. P. Ni-Catalyzed Enantioselective Conjunctive Coupling with $C(sp^3)$ Electrophiles: A Radical-Ionic Mechanistic Dichotomy. J. Am. Chem. Soc. 2017, 139, 17293-17296. (i) Chierchia, M.; Law, C.; Morken, J. P. Nickel Catalyzed Enantioselective Conjunctive Cross Coupling of 9 BBN Borates, Angew. Chem. Int. Ed. 2017, 56, 11870-11874. (j) Edelstein, E. K.; Namirembe, S.; Morken, J. P. Enantioselective Conjunctive Cross-Coupling of Bis(alkenyl)borates: A General Synthesis of Chiral Allylboron Reagents. J. Am. Chem. Soc. 2017, 139, 5027-5030. (k) Zhang, L.; Lovinger, G. J.; Edelstain, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. Catalytic Conjunctive Cross-Coupling Enabled by Metal-Induced Metallate Rearrangement. Science 2016,

351, 70–74. (l) Law, C.; Kativhu, E.; Wang, J.; Morken, J. P. Diastero- and Enantioselective 1,4-Difunctionalization of Borylenynes by Catalytic Conjunctive Cross-Coupling, *Angew. Chem. Int. Ed.*2020, 59, 10311–10315. (m) Meng, Y.; Kong, Z.; Morken, J. P. Catalytic Enantioselective Synthesis of *anti*-Vicinal Silylboronates by Conjunctive Cross-Coupling, *Angew. Chem. Int. Ed.* 2020, 59, 8456–8459.

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42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58 59

60

- (12) (a) Nandakumar, M.; Rubial, B.; Noble, A.; Myers, E.; Aggarwal, V. K. Ring-Opening Lithiation-Borvlation of 2-Trifluoromethyl Oxirane: A Route to Versatile Tertiary Trifluoromethyl Boronic Esters. Angew. Chem. Int. Ed. 2020, 59, 1187-1191. (b) Fordham, J. M.; Grayson, M. N.; Aggarwal, V. K. Vinylidene Homologation of Boronic Esters and its Application to the Synthesis of the Proposed Structure of Machillene. Angew. Chem. Int. Ed. 2019, 58, 15268-15272. (c) Armstrong, R. J.; Aggarwal, V. K. Homologation of Boronic Esters with Lithiated Epoxides. Org. Synth. 2017, 94, 234-251. (d) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. Homologation of Boronic Esters with Lithiated Epoxides for the Stereocontrolled Synthesis of 1,2 and 1,3-Diols, and 1,2,4-Triols. Org. Lett. 2009, 11, 165-168.
- (13) Schmidt, F.; Keller, F.; Vedrenne, E.; Aggarwal, V. K. Stereocontrolled Synthesis of β-Amino Alcohols from Lithiated Aziridines and Boronic Esters. *Angew. Chem. Int. Ed.* **2009**, *48*, 1149–1152.
- (14) Casoni, G.; Myers, E. L.; Aggarwal, V. K. Synthesis of 3-Aryl-1-aminopropane Derivatives: Lithiation– Borylation–Ring-Opening of Azetidinium Ions. Synthesis 2016, 48, 3241–3253.
- (15) Fawcett, A.; Murtaza, A.; Gregson, C. H. U.; Aggarwal, V. K. Strain-Release-Driven Homologation of Boronic Esters: Application to the Modular Synthesis of Azetidines. J. Am. Chem. Soc. 2019, 141, 4573–4578.
- (16) Sandford, C.; Aggarwal, V. K. Stereospecific Functionalizations and Transformations of Secondary and Tertiary Boronic Esters. *Chem. Commun.* **2017**, *53*, 5481–5494.
- (17) (a) Conner, M. L.; Brown, M. K. Synthesis of 1,3-Substituted Cyclobutanes by Allenoate-Alkene [2+2] Cycloaddition, *J. Org. Chem.* 2016, *81*, 8050–8060. (b) Namyslo, J. C.; Kaufmann, D. E. The Application of Cyclobutane Derivatives in Organic Synthesis. *Chem. Rev.* 2003, *103*, 1485–1538. (c) Xu, Y.; Conner, M. L.; Brown, M. K. Cyclobutane and Cyclobutene Synthesis: Catalytic Enantioselective [2+2] Cycloadditions, *Angew. Chem. Int. Ed.* 2015, *54*, 11918–11928.
- (18) (a) Wrobleski, M. L.; Reichard, G. A.; Paliwal, S.; Shah, S.; Tsui, H.-C.; Duffy, R. A.; Lachowicz, J. E.; Morgan, C. A.; Varty, G. B.; Shih, N.-Y. Cyclobutane Derivatives as Potent NK₁ Selective Antagonists. *Bioorg. Med. Chem. Lett.* 2006, *16*, 3859–3863. (b) Stepan, A. F.; Subramanyam, C; Efremov, I. V.; Dutra, J. K.; O'Sullivan, T. J.; DiRico, K. J.; McDonald, W. S.; Won, A.; Dorff, P. H.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. P.; Riddell, D. R.; Kauffman, G. W.; Kormos, B. L.; Zhang, L.; Lu, Y.; Capetta, S. H.; Green, M. E.; Karki, K.; Sibley, E.; Atchison, K. P.; Hallgren, A. J.; Oborski, C. E.; Robshaw, A. E.; Sneed, B.;

O'Donnell, C. J. Application of the Bicyclo[1.1.1]pentane Motif as a Nonclassical Phenyl Ring Bioisostere in the Design of a Potent and Orally Active y-Secretase Inhibitor. J. Med. Chem. 2012, 55, 3414-3424. (c) Nicolaou, K. C.; Vourloumis, D.; Totokotsopoulos, S.; Papakyriakou, A.; Karsunky, H.; Fernando, H.; Gavrilyuk, J.; Webb, D.; Stephan, A. F. Synthesis and Biopharmaceutical Evaluation of Imatinib Analogues Featuring Unusual Structural Motifs. ChemMedChem 2016, 11, 31-37, (d) Wager, T. T.: Pettersen, B. A.; Schmidt, A. W.; Spracklin, D. K.; Mente, S.; Butler, T. W.; Howard, Jr, H.; Letteire, D. J.; Rubitski, D. M.; Wong, D. F.; Nedza, F. M.; Nelson, F. R.; Rollema, H.; Raggon, J. W.; Aubrecht, J.; Freeman, J. K.; Marcek, J. M.; Cianfrogna, J.; Cook, K. W.; James, L. C.; Chatman, L. A.; Iredale, P. A.; Banker, M. J.; Homiski, M. L.; Munzner, J. B., Chandrasekaran, R. Y. Discovery of Two Clinical Histamine H₃ Receptor Antagonists: trans-N-Ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidinylmethyl)-phenyl]cyclobutanecarboxamide (PF-03654746) and trans-3-Fluoro-3-[3fluoro(pyrrolidin-1-ylmethyl)phenyl]-N-(2methylpropyl)cyclobutanecarboxamide (PF-03654764), J. Med. Chem. 2011, 54, 7602-7620.

- (19) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. J. Med. Chem. 2009, 52, 6752–6756. (b) Lovering, F. Escape from Flatland 2: Complexity and Promiscuity. Med. Chem. Commun. 2013, 4, 515–519.
- (20) (a) Fawcett, A.; Biberger, T.; Aggarwal, V. K. Carbopalladation of C–C σ-Bonds Enabled by Strained Boronate Complexes. *Nat. Chem.* 2019, *11*, 117–122.
 (b) Silvi, M.; Aggarwal, V. K. Radical Addition to Strained σ-Bonds Enables the Stereocontrolled Synthesis of Cyclobutyl Boronic Esters. *J. Am. Chem. Soc.* 2019, *141*, 9511–9515.
- (21) (a) Walczak, M. A. A.; Wipf, P. Rhodium(I)-Catalyzed Cycloisomerizations of Bicyclobutanes. J. Am. Chem. Soc. 2008, 130, 6924–6925. (b) Weber, J.; Haslinger, U.; Brinker, U. H. 1-Bromobicyclo[1.1.0]butane as an Easily Obtainable C4-Building Block: A Novel Route to Cyclobutanone. J. Org. Chem. 1999, 64, 6085–6086. (c) Schwartz, B. D.; Zhang, M. Y.; Attard, R. H.; Gardiner, M. G.; Malins, L. R. Structurally Diverse Acyl Bicyclobutanes: Valuable Strained Electrophiles. Chem. Eur. J. 2020, 26, 2808–2812.
- (22) Hollerbach, M. R.; Barker, T. J. Chemoselective Benzylation of Aldehydes Using Lewis Base Activated Boronate Nucleophiles. *Organometallics* 2018, 37, 1425–1427.
- (23) (a) Casoni, G.; Kucukdisli, M.; Fordham, J. M.; Burns, M.; Myers, E. L.; Aggarwal, V. K. α-Sulfinyl Benzoates as Precursors to Li and Mg Carbenoids for the Stereoselective Iterative Homologation of Boronic Esters. J. Am. Chem. Soc. 2017, 139, 11877–11886. (b) Abramovitch, A.; Fensterbank, L.; Malacria, M.; Marek, I. Convergent Preparation of Enantiomerically Pure Polyalkylated Cyclopropane Derivatives, Angew. Chem. Int. Ed. 2008, 47, 6865–6868. (c) Alwedi, E.; Zakharov, L. N.; Blakemore, P. R. Chain Extension of Boronic

56 57

58 59

60

Esters with Lithioxiranes Generated by Sulfoxide-Metal Exchange – Stereocontrolled Access to $2^{\circ}/2^{\circ}$, $2^{\circ}/3^{\circ}$, and $3^{\circ}/3^{\circ}$ Vicinal Diols and Related Compounds, *Chem. Eur. J.* **2014**, 6643–6648. (d) Rayner, P. J.; O'Brien, P.; Horan, R. A. J. Preparation and Reactions of Enantiomerically Pure α -Functionalized Grignard Reagents, *J. Am. Chem. Soc.* **2013**, *135*, 8071–8077. (e) Blakemore, P. R.; Burge, M. S. Iterative Stereospecific Reagent-Controlled Homologation of Pinacol Boronates by Enantioenriched α -Chloroalkyllithium Reagents, *J. Am. Chem. Soc.* **2007**, *129*, 3068–3069.

- (24) Feeney, K.; Berionni, G.; Mayr, H.; Aggarwal, V. K. Structure and Reactivity of Boron-Ate Complexes Derived from Primary and Secondary Boronic Esters, *Org. Lett.* **2015**, *17*, 2614–2617.
- (25) Armstrong, R. J.; Sandford, C.; García-Ruiz, C.; Aggarwal, V. K. Conjunctive Functionalization of Vinyl Boronate Complexes with Electrophiles: A Diastereoselective Three-Component Coupling. *Chem. Commun.* 2017, 53, 4922–4925.
- (26) Hayes, J. C.; Hollerbach, M. R.; Barker, T. J. Nucleophilic addition of benzylboronates to activated ketones. *Tetrahedron Lett.* **2020**, *61*, 151505–151508.
- (27) Hollerbach, M. R.; Hayes, J. C.; Barker, T. J. Benzylation of Imines with Activated Boronate Nucleophiles. *Eur. J. Org. Chem.* **2019**, 1646–1648.
- (28) Diastereospecificity (d.s.) = [d.e. of product/d.e. of starting material] \times 100%.
- (29) Fawcett, A.; Pradeilles, J.; Wang, Y.; Mutsuga, T.; Myers, E. L.; Aggarwal, V. K. Photoinduced Decarboxylative Borylation of Carboxylic Acids. *Science* 2018, 357, 283–286.
- (30) (a) Wiberg, K. B.; Ellison, G. B.; Peters, K. S. Electronic States of Organic Molecules. 4. Ultraviolet Spectrum of Bicyclobutane, *J. Am. Chem. Soc.* 1977, 99, 3941–3946.
 (b) Newton, M. D.; Schulman, J. M. Theoretical Studies of Bicyclobutane, *J. Am. Chem. Soc.* 1972, 94, 767–773.
- (31) Hoz, S. Cyclobutane–Bicyclobutane System–6. An *Ab Initio* Calculation of the Preferred Pathway for Nucleophilic Attack on Bicyclobutane, *Tetrahedron* **1984**, *40*, 5213–5216.

- (32) (a) Fujimoto, H.; Yabuki, T.; Fukui, K. A Study of Orbital Interactions in the Reactions of Bicyclo[1.1.0]butane, J. Mol. Struct. 1989, 198, 267–275. (b) Hoz, S.; Livneh, M.; Cohen, D. Mechanism and Stereochemistry of General Acid Catalyzed Additions to Bicyclobutane, J. Org. Chem. 1986, 51, 4537–4544.
- (33) Lehn, J.-M.; Wipff, G. Theoretical Study of Proton Approach Towards Strained Hydrocarbon Molecules, *J. Chem. Soc., Chem. Commun.* **1973**, 747–748.
- (34) Edelstein, E. K.; Grote, A. C.; Palkowitz, M. D.; Morken, J. P. A Protocol for Direct Stereospecific Amination of Primary, Secondary, and Tertiary Alkylboronic Esters. *Synlett* **2018**, *29*, 1749–1752.
- (35) Armstrong, R. J.; Niwetmarin, W.; Aggarwal, V. K. Synthesis of Functionalized Alkenes by a Transition-Metal-Free Zweifel Coupling. Org. Lett. 2017, 19, 2762–2765.
- (36) Bagutski, V.; Ros, A.; Aggarwal, V. K. Improved Method for the Conversion of Pinacolboronic Esters into Trifluoroborate Salts. Facile Synthesis of Chiral Secondary and Tertiary Trifluoroborates. *Tetrahedron* 2009, 65, 9956–9960.
- (37) (a) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. Enantiospecific sp²-sp³ Coupling of Secondary and Tertiary Boronic Esters. *Nat. Chem.* 2014, *6*, 584–589. (b) Odachowski, M.; Bonet, A.; Essafi, S.; Conti-Ramsden, P.; Harvey, J. N.; Leonori, D.; Aggarwal, V. K. Development of Enantiospecific Coupling of Secondary and Tertiary Boronic Esters with Aromatic Compounds. *J. Am. Chem. Soc.* 2016, *138*, 9521–9532.
- (38) Llaveria, J.; Leonori, D.; Aggarwal, V. K. Stereospecific Coupling of Boronic Esters with N-Heteroaromatic Compounds. J. Am. Chem. Soc. 2015, 137, 10958–10961.
- (39) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. Protodeboronation of Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers. J. Am. Chem. Soc. 2010, 132, 17096–17098.

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