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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c00813 • Publication Date (Web): 07 Mar 2020

Ring Expansion Induced 1,2-Metallate Rearrangements: Highly Diastereoselective Synthesis of Cyclobutyl Boronic Esters

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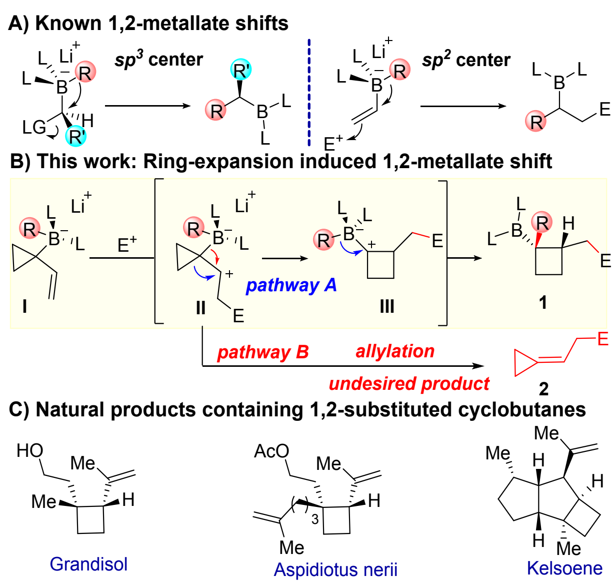
Supporting Information Placeholder

ABSTRACT: The broad synthetic utility of organoboron compounds stems from their ready ability to undergo 1,2-migrations. Normally, such shifts are induced by α-leaving groups or by reactions of alkenyl boronates with electrophiles. Herein, we present a new strategy to induce 1,2-metallate rearrangement, via ring expansion of vinylcyclopropyl boronate complexes activated by electrophiles. This leads to a cyclopropane-stabilized carbocation which triggers ring expansion and concomitant 1,2-metallate rearrangement. This novel process delivers medicinally relevant 1,2-substituted cyclobutyl boronic esters with high levels of diastereoselectivity. A wide range of organolithiums and Grignard reagents, electrophiles, and vinylcyclopropyl boronic esters could be used. The methodology was applied to a short, stereoselective synthesis of (±)-grandisol. Computational studies indicate that the reaction proceeds via a non-classical carbocation followed by anti 1,2-migration.

Organoboronic esters are highly versatile synthetic intermediates as they can be converted into a broad range of functional groups, often with complete stereospecificity.[1] These transformations are typically initiated by addition of a nucleophile to boron which subsequently rearranges by a 1,2-shift to an adjacent electrophilic center, expelling a leaving group (Scheme 1A).[1] From the classic Matteson homologation[1b] to our own lithiation-borylation reaction, this reaction has found broad applications in synthesis.[2] 1,2-Metallate rearrangements to *sp*[2] carbons can also be triggered by reaction with a suitable electrophile,[3] as in the Zweifel olefination reaction,[4] or more recently in Morken's conjunctive coupling reaction where the rearrangement is induced by reaction with an electrophilic palladium(II) species.[5] Recently, we and the Studer group independently reported that the 1,2-metallate rearrangement could be induced without recourse to a leaving group, through oxidation of an α-boryl radical.[6]

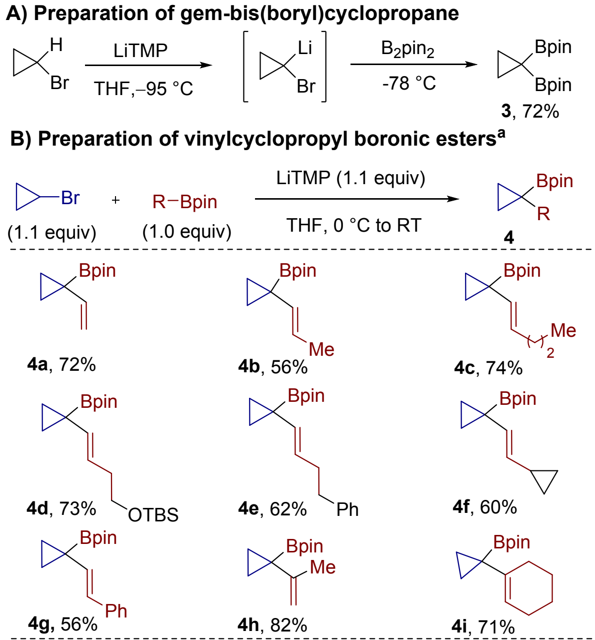
Fundamentally new triggers for 1,2-metallate rearrangement are rare but they have the potential to open up substantial chemical space and can lead to new opportunities in synthesis. We considered the possibility of a novel method to induce 1,2-metallate rearrangements via ring-expansion of vinylcyclopropyl boronate complexes. We envisaged that reaction of a vinylcyclopropyl boronate complex **I** with an electrophile would generate a carbocation α to the cyclopropyl ring **II**, which should trigger ring expansion with concomitant 1,2-metallate rearrangement to give cyclobutyl boron product **1** (Scheme 1B, pathway A). Although allylboronate complexes related to **I** are known to react with electrophiles with loss of the boronate group,[7] we believed that this undesired pathway (B) would be retarded by the increase in ring strain of the corresponding alkylidenecyclopropane product **2**.[8] The cyclopropyl group is therefore not only integral to the ring-expansion 1,2-metallate rearrangement, but its presence should also favor the desired pathway A by stabilising the carbocation and disfavor the undesired pathway B by the increase in ring strain. Additional attractive features of the methodology include the generation of three new bonds, two stereogenic centers and a four membered ring and the potential for synthetic diversity. Furthermore, it provides ready access to 1,2-substituted cyclobutanes **1**,[9] which are not only common in natural products[10] (Scheme 1C) but are finding increasing application in pharmaceuticals[11, 12] In this paper we report our success in developing a novel ring-expansion triggered 1,2-metallate rearrangement and demonstrate its utility in a short stereoselective synthesis of (±)-grandisol.

Scheme 1: (A) Known 1,2-metallate shifts. (B) Proposed 1,2-metallate shift. (C) Natural products containing 1,2-substituted cyclobutanes.



Scheme 2: A) Reported method for the preparation of gem-

bis(boryl)cyclopropane. B) Preparation of vinylcyclopropyl boronic esters.

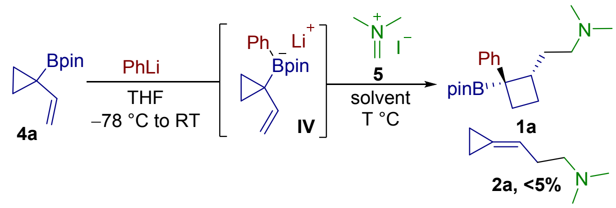


[a]All reactions were run on 5 mmol scale and yields are of isolated products.

Our initial investigations focused on designing a route to vinylcyclopropyl boronic esters **4**. Recently, Harris reported the synthesis of gem-bis(boryl)cyclopropane **3** (Scheme 2A).[13] Following deprotonation, reaction with B_2pin_2 gave an intermediate boronate complex which underwent 1,2-metallate rearrangement to give **3**. Subsequent cross-coupling with an aryl halide gave an arylcyclopropyl boronic ester. We wondered whether we could employ vinyl boronic esters in place of B_2pin_2 to access vinylcyclopropyl boronic esters **4** directly from cyclopropyl bromide. After optimization,[14] this reaction successfully provided the desired products in high yield, with **4a** formed in 72% yield on 5 mmol scale and 66% yield on gram scale (Scheme 2B). A variety of β-substituted vinyl boronic esters were homologated to give the products **4b**-**4g** in good yields. α-Substituted vinyl boronic ester could also be used in the reaction (product **4h**). Furthermore, cyclohexenyl boronic esters was also shown to be viable substrate (product **4i**).

With a selection of vinylcyclopropyl boronic esters **4** in hand, we began our studies of the ring-expansion induced 1,2-metallate rearrangement. For the optimization studies, boronate complex **IV** was generated in situ by the addition of phenyllithium to a solution of vinylcyclopropyl boronic ester **4a** in THF. Addition of Eschenmoser's salt (**5**)[7] to boronate complex **IV** gave the desired cyclobutyl boronic ester **1a** in a promising 47% yield as a single diastereomer (Table 1, entry 1) together with trace amount of allylation product **2a**.[14] The stereochemistry of **1a** was unambiguously determined by X-ray analysis. Increasing the loading of Eschenmoser's salt (**5**) improved the yield of **1a** to 75% (Table 1, entry 2). Among the solvents tested (Table 1, entries 2–6),[15] DMF emerged as the optimum. Finally, adding DMF to the THF solution of **IV** without solvent exchange also gave **1a** in similar yield which simplified the reaction procedure (Table 1, entry 7). The reaction was found to be robust on multigram scale, giving product **1a** in 91% yield as a single diastereomer on >6 g scale.

Table 1: Optimization studies[a]

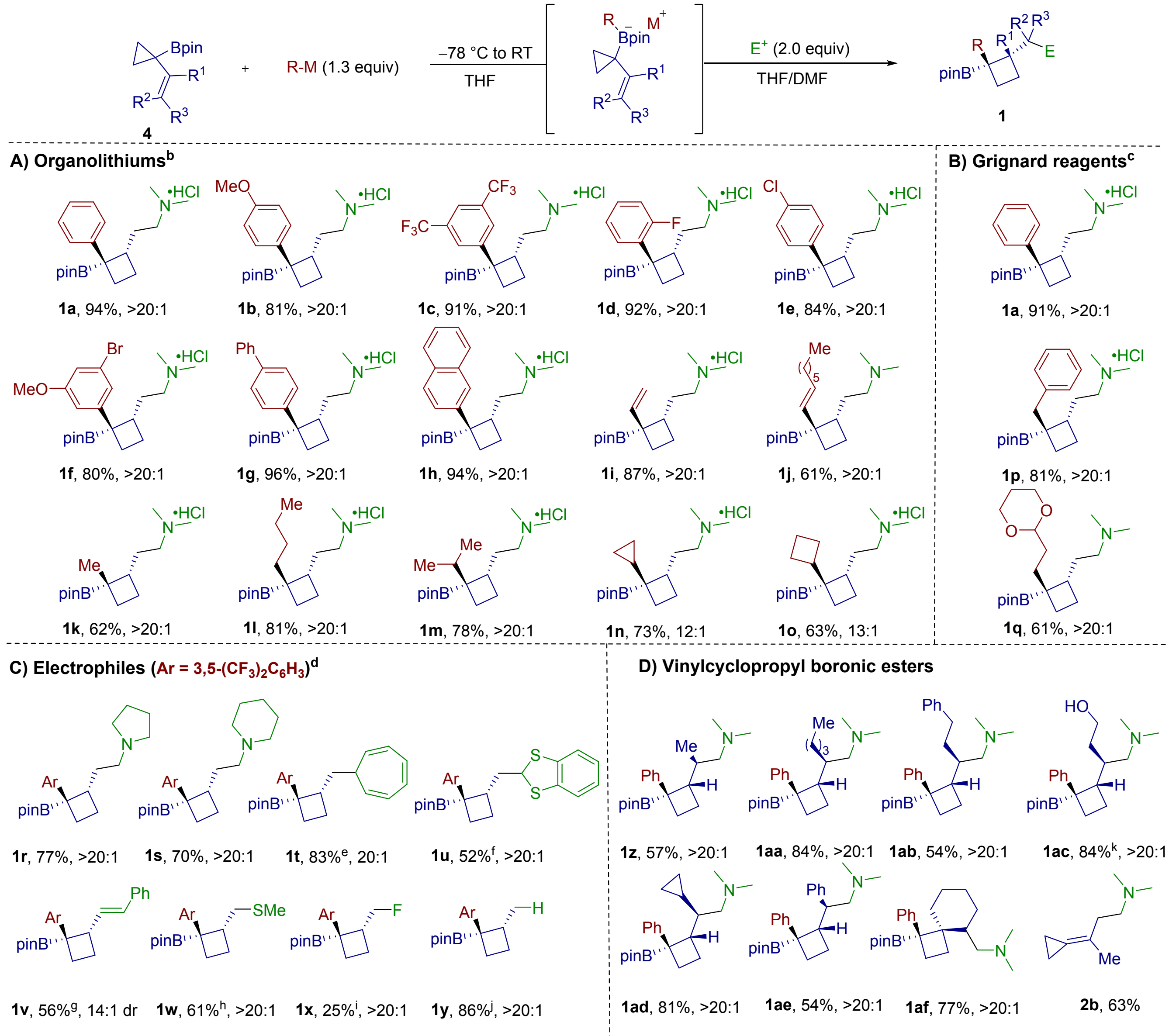


Entry	5 (x equiv)	Solvent	T (°C)	Yield (%)[b]	d.r.[c]
1	1.1	THF	–78	47	>20:1
2	2	THF	–78	75	>20:1
3	2	2-MeTHF	–78	61	>20:1
4	2	MeOH	–78	46	16:1
5	2	CH_3CN	–40	51	12:1
6	2	DMF	–40	95	>20:1
7[d]	2	DMF/THF	–40	94	>20:1

[a]Reaction conditions: 0.15 mmol of **4a**, 1.3 equiv of PhLi and THF (0.15 M) followed by removal of THF and addition of solvent (0.075 M) and **5** at temperature T. The reactions were stirred for 2 h at –78 °C (entries 1-4) or –40 °C (entries 5-7) before slowly warming to RT overnight. [b]Yields determined by ^{1}H NMR using trimethoxybenzene as internal standard. [c]Determined by GC-MS. [d]DMF was added to the reaction in THF.

Having established optimal reaction conditions, we initially investigated the scope of the reaction with respect to the organolithium (Scheme 3A). A range of aryllithiums of different steric and electronic properties worked well (**1a**-**1h**). Notably, the bromo-substituted product **1f**, bearing a useful handle for further transformations could be isolated in 80% yield. Simple vinyllithium and substituted alkenyllithiums could also be employed (products **1i** and **1j**), showing that the allyl boronate is more reactive than the vinyl boronate towards Eschenmoser's salt (**5**).[14] Primary and secondary alkyllithiums all performed well in the reaction (products **1k**-**1m**). Notably, methyl, which is generally poor migrating group[16] and has even been used as a non-migrating group, gave the cyclobutane **1k** in very good yield and selectivity, demonstrating how strongly pathway A is favoured over pathway B (Scheme 1B). Cycloalkyllithiums, including cyclopropyl and cyclobutyl, were also found to be viable substrates (products **1n** and **1o**). Attempts to use the more readily available Grignard reagents e.g. phenylmagnesium bromide were unsuccessful. Morken reported that boronate complex formation using Grignard reagents was facilitated by the addition of LiCl[17] which is known to increase the reactivity of Grignard reagents. To our delight, addition of LiCl to phenylmagnesium bromide prior to boronic ester **4a** followed by addition of Eschenmoser's salt (**5**) resulted in the formation of cyclobutane **1a** in excellent yield (91%) and essentially complete selectivity. Other commercially Grignard reagents were also applicable, with benzyl and alkyl Grignard reagents providing **1p** and **1q** in good yields and selectivities (Scheme 3B). In all cases, chromatographic purification was avoided by isolating the products as HCl salts.

Scheme 3: Reaction scope[a]

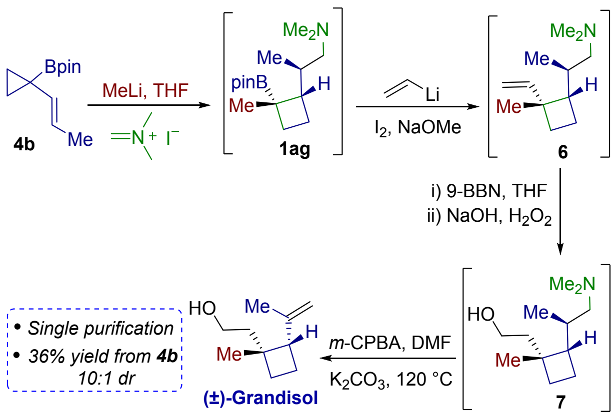


[a]All reactions were run on 0.3 mmol scale; yields are of isolated products; dr determined by GC-MS, ^{1}H NMR or ^{19}F NMR. [b]Eschenmoser's salt added at –40 °C to a mixture of THF/DMF solvents. [c]LiCl (1.5 equiv) was added to Grignard reagent in THF at RT. [d]Electrophiles were added at −78 °C in THF, unless otherwise noted. [e]Tropylium tetrafluoroborate was used. [f]1,3-Benzodithiolylium tetrafluoroborate was used. [g]Benzaldehyde dimethyl acetal and TESOTf (2.0 equiv) were used. [h]Dimethyl(methylthio)sulfonium tetrafluoroborate was used. [i]Solution of boronate complex in MeCN was added to a solution of Selectfluor in MeCN at –40 °C. [j]HBF_4 was used. [k]TBS group was cleaved during the purification.

We then tested a more diverse range of electrophiles (Scheme 3C). We were delighted to find that pyrrolidine and piperidine derived iminium salts worked well, providing a broader range of medicinally-relevant cyclobutanes **1r** and **1s**.[18] The reaction was extended to other classes of electrophiles, including the tetrafluoroborate salts of tropylium and benzodithiolylium giving good yields and high selectivity (products **1t** and **1u**). Benzaldehyde dimethyl acetal in the presence of TESOTf could also be used but in this case subsequent elimination to the styrene **1v** occurred. Electrophiles that create new carbon−heteroatom bonds could also be utilized in the reaction, enabling formation of C–S and C−F bonds, again with very high selectivity (products **1w** and **1x**). Surprisingly, a simple proton (addition of HBF_4) gave the desired ring-expansion product **1y** in good yield and selectivity. No competing protodeboronation[19] was observed in this case highlighting the high chemoselectivity of the process.

We next proceeded to explore the scope of the reaction with respect to the vinylcyclopropyl boronic esters **4** (Scheme 3D). We were delighted to find that γ-substituted vinylcyclopropyl boronic esters bearing alkyl, cycloalkyl and phenyl substituents worked efficiently, providing the highly complex cyclobutanes containing three contiguous stereogenic centers in good yield and excellent selectivity (products **1z**-**1ae**).[20] Remarkably, spiro-[5,3]decane **1af** could also be efficiently synthesized from boronic ester **4i**, creating three contiguous stereogenic centers, two of which are quaternary. Surprisingly, *β*-substituted boronic ester **4h** gave allylation product **2b** instead of the ring-expansion product. Attempts to switch the selectivity by using the electron-poor aryllithium, 3,5-$(CF_3)_2C_6H_3$-Li, was unsuccessful, giving the same allylation product **2b**.

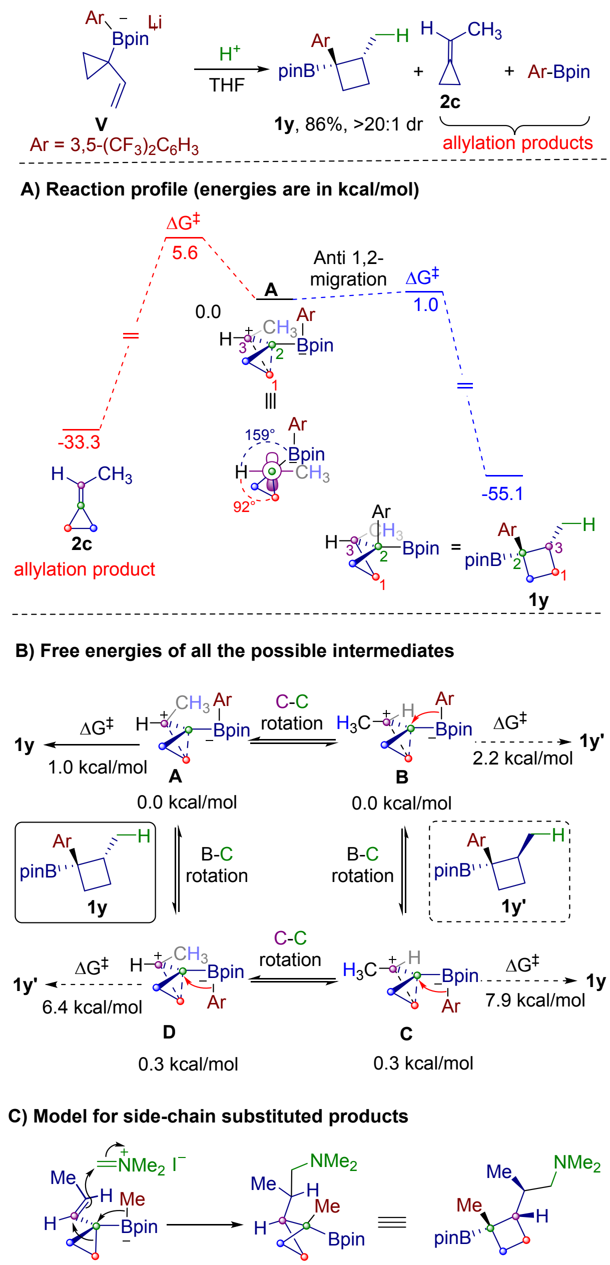
Scheme 4: Stereoselective synthesis of (±)-grandisol



Finally, we have demonstrated the utility of this methodology in the synthesis of (±)-grandisol (Scheme 4), the main component of the sexually attracting pheromone of the cotton boll weevil, which is a serious pest responsible for significant damage to cotton crops.[21] Starting from vinylcyclopropyl boronic ester **4b**, methyllithium was added and the corresponding boronate complex was reacted with Eschenmoser's salt (**5**) to give the cyclobutane **1ag**. The crude material was carried forward to the Zweifel olefination, followed by hydroboration-oxidation of alkene **6** to give alcohol **7**. Again, without purification, treatment with *m*CPBA in DMF at 120 °C resulted in Cope elimination,[22] leading to (±)-grandisol in 36% yield with 10:1 dr. This synthesis is notable for its brevity and high selectivity, and its modularity provides ready access to a range of analogues, if required.

Finally, DFT calculations were performed to gain insight into the ring expansion reaction [M06-2X / 6–311G(d,p) level, with a polarisable continuum model of solvation (PCM,THF)]. Protonation was selected as the model reaction giving cyclobutane **1y** (Scheme 5A).[23] The DFT calculations indicated that the reaction proceeds via the carbocation intermediate **A**, generated upon protonation of the vinyl moiety of boronate complex **V**. The positive charge of the non-classical carbocation is stabilized by hyperconjugation with the σ-electrons of the C1–C2 bond.[24] Indeed, the σ-bond is almost perfectly aligned to stabilise the carbocation (H–C3–C2–C1 = 92°); attempts to align the C-B bond to stabilize the carbocation led to a higher energy species which relaxed back to intermediate **A**. This showed that the bent cyclopropyl bond is better able to stabilize the carbocation than even the C–B(ate) bond. From **A**, a facile *anti*-1,2-migration (ΔG‡ = 1.0 kcal/mol) yields the desired product **1y** which is thermodynamically and kinetically favoured over the allylation product **2c** (ΔG‡ = 5.6 kcal/mol), as observed experimentally. The higher energy for the allylation pathway is partly caused by poor alignment of the C–B bond with the carbocation. To account for the observed diastereoselectivity, different conformations of the intermediate have been considered (**A** - **D**), all of which have similar energies (Scheme 5B). Intermediate **B**, formally obtained upon C2–C3 rotation, would lead to the *cis* isomer **1y'**

Scheme 5: Computational models for selectivity



via a similar *anti*-1,2-migration. However, in this case the corresponding TS is higher in energy (ΔG‡ = 2.2 kcal/mol) than the TS leading to the trans isomer **1y** (relative energy difference ΔΔG‡ = 1.2 kcal/mol) which is sufficient to achieve >90% stereoselectivity at –78 °C.[25] Finally, intermediates **C** and **D** (formally obtained upon C2-B rotation from **B** and **A**) undergo *syn*-migration with significantly higher barriers (ΔG‡ = 7.9 kcal/mol and 6.4 kcal/mol, respectively) and so contribute minimally to the process. This mechanism accounts for the high diastereoselectivity observed for the substituted vinyl boronic esters (Scheme 3d) where addition and migration occur with an anti-arrangement of groups (Scheme 5C).

In conclusion, we have developed a new strategy to induce 1,2-metallate rearrangement via ring expansion of vinylcyclopropyl boronate complexes activated by electrophiles. The methodology enables the modular synthesis of 1,2-substituted cyclobutyl boronic esters in a highly diastereoselective process, including spirocycles with contiguous quaternary centers, and cyclobutanes with three contiguous stereocenters. The reaction shows broad substrate scope and was applied to a short stereoselective synthesis of (±)-grandisol. DFT studies indicated that the reaction proceeds through a non-classical carbocation which readily undergoes *anti*-1,2-migration to give the product.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

DH thanks the EU for a H2020 Marie Skłodowska-Curie Fellowship (840000). JCA thanks the Bristol Chemical Synthesis Centre for Doctoral Training, EPSRC (EP/G036764/1) and UCB for funding. VF thanks the University of Bristol for awarding the EPSRC Doctoral Prize Fellowship Grant Ref: EP/R513179/1. We thank Dr Hazel A. Sparkes for the X-ray studies and Dr. Adam Noble for proofreading this paper.

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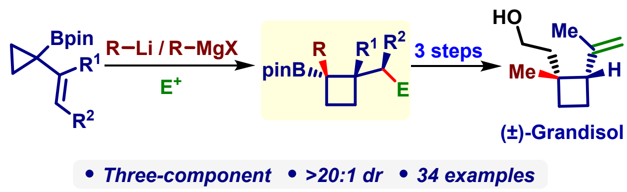
Bpin
R1
R2
R−Li / R−MgX
E+
pinB
R
R1 R2
E
3 steps
HO
Me
Me
H
(±)-Grandisol
• Three-component • >20:1 dr • 34 examples