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Strain Release of Donor-Acceptor Cyclopropyl Boronate Complexes

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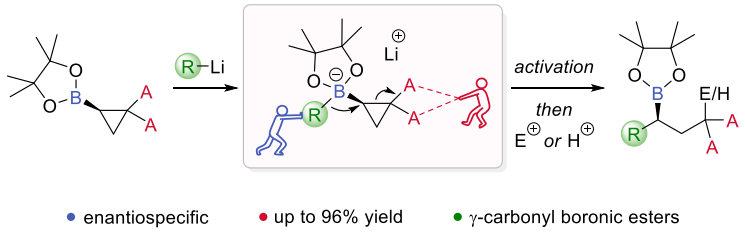
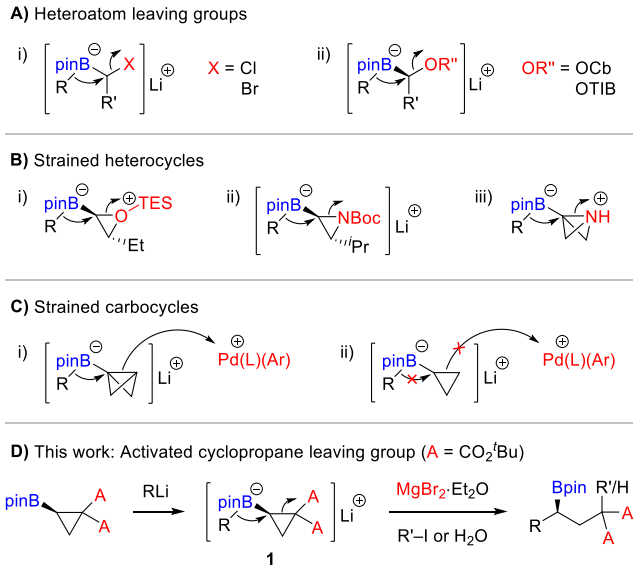
Supporting Information Placeholder



ABSTRACT: The reactivity of boronate complexes which resemble donor-acceptor cyclopropanes is described. The enantioenriched cyclopropyl boronate complexes were shown to undergo concerted 1,2-metallate rearrangement/ring opening upon activation with a Lewis acid. This method provides atom-efficient access to optically active γ-carbonyl boronic esters in moderate to excellent yields with complete enantiospecificity. Furthermore, a three-component variant of the reaction was established through *in-situ* alkylation, and the synthetic utility of the products as chiral building blocks was demonstrated.

The enantiospecific rearrangement of boronate complexes is an invaluable tool in modern synthetic chemistry as it enables the formation of new C–C and C–X bonds with high levels of stereocontrol.[1,2] Furthermore, the boronic ester is often retained in the product allowing additional transformations to be conducted, including iterative homologations.[2,3]

Scheme 1. Examples of leaving group employed in the 1,2-metallate rearrangements of boronate complexes



Cb = *N*,*N*-diisopropylcarbamoyl, TIB = 2,4,6-triisopropylbenzoyl

The classic Matteson homologation involves a 1,2-metallate rearrangement with a halide leaving group in the α position,[4,5] but carbamates or benzoate esters can also be employed (Scheme 1A).[2,6,7] Related reactions have been developed with a heteroatom-incorporated small ring as the leaving group.[8,9] For example, the cleavage of both oxygen- and nitrogen-containing small rings have been employed in 1,2-metallate rearrangements of boronate complexes (Scheme 1B).[10] In these strategies, both strain release and stabilization of the resulting anion contribute to the driving force for the 1,2-metallate rearrangement. However, whilst heteroatoms have been extensively employed in 1,2-metallate rearrangements, examples of the use of a carbon leaving group are much rarer.

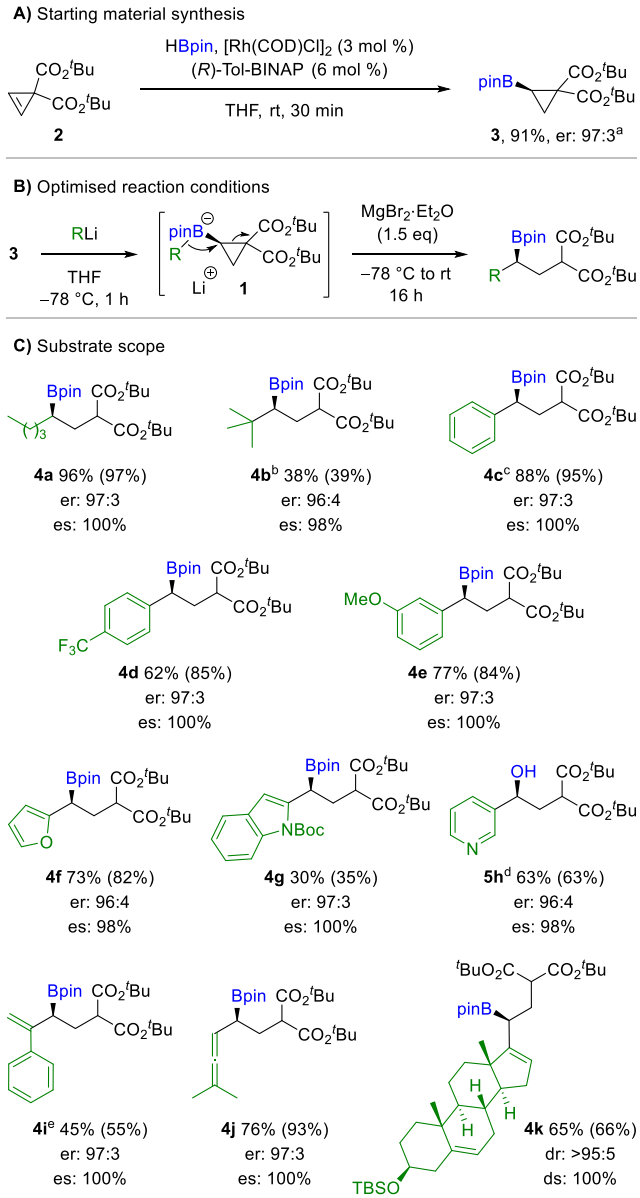
We recently reported the palladium-mediated 1,2-metallate rearrangement of bicyclobutyl boronate complexes which involves a carbon leaving group (Scheme 1Ci).[11] Critical to the success of this chemistry is the very high ring strain of the bicyclobutyl motif. Notably, the equivalent cyclopropyl boronate complex does not undergo a 1,2-metallate rearrangement under the same reaction conditions (Scheme 1Cii).[11] We wondered whether such metallate rearrangements could be promoted by enhancing the stability of the carbon leaving group by introducing a better acceptor (Scheme 1D). This would create an unusual donor-acceptor (D-A) cyclopropane,[12] in which the donor is a boronate complex. In such a scenario, subsequent stereospecific 1,2-metallate rearrangement of boronate **1**, with cleavage of a cyclopropyl C–C bond,[13] would provide access to enantioenriched γ-carbonyl boronic esters (Scheme 1D), a class of substrates with rich functionality but few reports.[14]

Our investigation began with the asymmetric hydroboration of cyclopropene **2** to prepare di-activated cyclopropyl boronic ester **3** with 97:3 enantiomeric ratio (er) (Scheme 2A).[15,16] Upon addition of *n*-butyllithium, full conversion to the boronate complex was observed by ^{11}B NMR spectroscopy. Despite employing a malonate to stabilize the resulting anion, the boronate complex converted very slowly at room temperature to the ring opened boronic ester. On heating to 60 °C, full conversion of the boronate complex was observed by ^{11}B NMR but the desired ring opened boronic ester was obtained in only 45% yield. We therefore screened a number of Lewis acids and solvents and found that the addition of magnesium bromide etherate was the

most effective method to induce a 1,2-metallate rearrangement-ring opening sequence (Scheme 2B). This gave boronic ester **4a** in quantitative yield and 100% es (97:3 er) indicating a concerted ring opening/1,2-metallate rearrangement.

The scope of migrating groups for the 1,2-metallate rearrangement was then explored (Scheme 2C). With *t*-butyllithium, competing *O*-migration was observed resulting in low yields. However, this side-reaction was minimized by performing a solvent switch to toluene before the addition of the Lewis acid which afforded **4b** in 38% yield with 98% es. Phenyl and other aromatic migrating groups bearing -OMe, -CF_3 all worked well with good yields (88-62%) and 100% es (**4c-4e**). On 1 mmol scale, the reaction employing phenyl lithium gave desired product **4c** in similar yield. A related reaction employing the diethyl ester analogue of **3** was also explored but was found to give a reduced yield.[17]

Scheme 2. Synthesis of cyclopropyl boronic ester and scope of organolithium reagents for enantiospecific ring-opening/1,2-metallate rearrangement

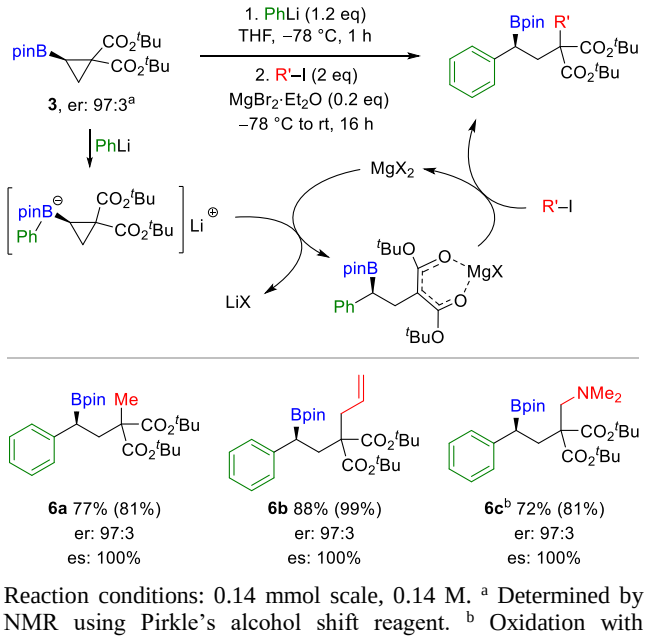


NMR yields given in parentheses. Reaction conditions: 0.14 mmol scale, 0.14 M, 1.1-1.2 equivalents of RLi. [a] Determined by NMR using Pirkle's alcohol shift reagent. [b] Solvent switch to toluene before addition of $MgBr_2{\cdot}Et_2O$. [c] Isolated yield for 1.09 mmol scale. [d] Oxidation with H_2O_2/NaOH performed before work-up. [e] Oxidation with H_2O_2/NaOH performed after crude NMR, before column chromatography.

Heteroaromatic migrating groups were also suitable substrates in this methodology giving the desired products with complete enantiospecificity. With furyllithium, corresponding furyl coupled product **4f** was obtained in 73% yield and 98% es. Employing a lithiated Boc protected indole gave product **4g** in only moderate yield (30%) due to reversible boronate-complex formation. 3-Pyridyl lithium was also successful, however, the boronic ester product underwent rapid protodeboronation during aqueous work-up. Therefore, the crude mixture was subjected to oxidation with H_2O_2/NaOH at 0 ºC to give corresponding alcohol **5h** in 63% and 98% es. Vinyl and allenyl boronate complexes underwent successful ring-opening/1,2-migration to give the corresponding allyl and allenyl products **4i,j** in 45% and 76% yield respectively and with perfect es. A steroid derived organolithium was also a suitable substrate for the transformation. Complete conversion to the boronate complex was possible and, under the influence of magnesium bromide etherate gave boronic ester **4k** in 65% yield and 100% ds.

We were interested to see if the product enolate could be trapped with electrophiles *in situ* in a three-component coupling process as this would provide enhanced efficiency. Furthermore, this could potentially enable sub-stoichiometric quantities of the Lewis acid to be employed.[13b-k] Indeed, our initial attempts showed that the reaction was feasible with 20 mol % $MgBr_2{\cdot}OEt_2$ and 2 equivalents of MeI which gave methylated product **6a** in 77% yield and 100% es (Scheme 3). Allyl iodide and Eschenmoser's salt were also successfully employed as electrophiles giving **6b** and **6c** in 88% and 72% yield respectively and complete enantiospecificity.

Scheme 3. Scope of electrophiles for the three-component reaction

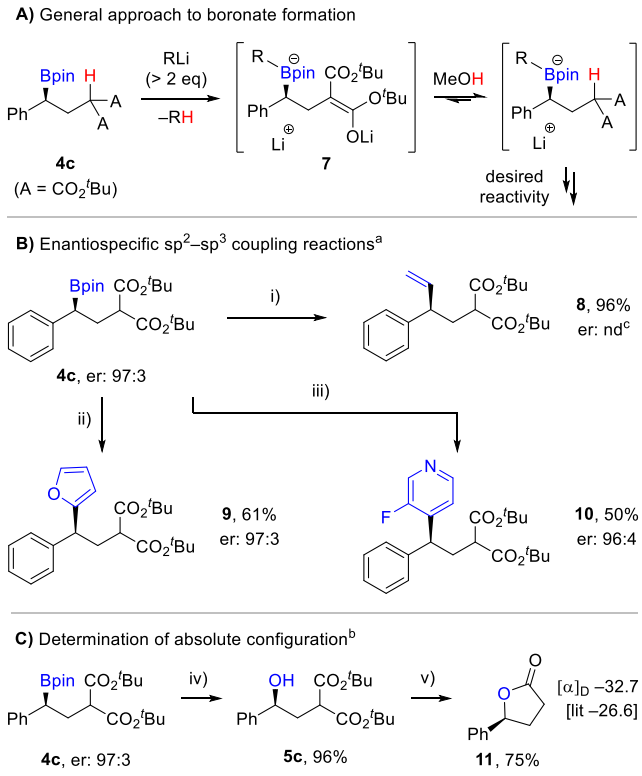


Reaction conditions: 0.14 mmol scale, 0.14 M. [a] Determined by NMR using Pirkle's alcohol shift reagent. [b] Oxidation with

H_2O_2/NaOH was performed after crude NMR, before column chromatography.

Chiral boronic esters are highly useful reagents for organic synthesis due to the multitude of enantiospecific transformations that have been developed.[1,18] We therefore wanted to demonstrate the synthetic utility of the chiral boronic esters reported herein. However, many procedures using chiral boronic esters begin with the addition of an organolithium reagent to access a boronate complex.[1] This is problematic for the boronic esters shown in Scheme 2 as they possess an acidic malonate functional group. It was therefore necessary to modify existing procedures and account for the acidic group by using additional equivalents of organolithium reagent to form di-anionic boronate complexes such as **7** (Scheme 4A). If necessary, the enolate component of the di-anionic boronate complex could then be protonated with a proton source to provide the desired boronate complex for further reactivity.

Scheme 4. Enantiospecific transformations of a γ-carbonyl boronic ester



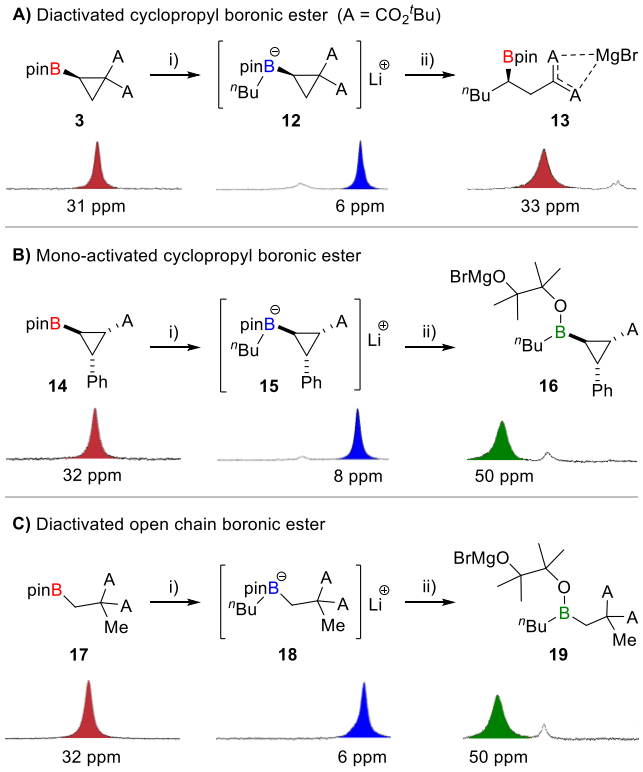
Reaction conditions: [a] 0.11 mmol scale, [b] 0.80 mmol scale. **i) 1.** vinyl lithium (3.2 eq), THF, −78 °C to rt, 30 min, **2.** I_2 (1.2 eq), MeOH, −78 °C, 20 min, **3.** NaOMe (3 eq), MeOH, rt, 1 h. **ii) 1.** furan-2-yllithium (2.4 eq), THF, −78 °C, 1 h, **2.** MeOH/THF, NBS (1.2 eq) in MeCN, −78 °C, 1 h. **iii) 1.** (3-fluoropyridin-4-yl)lithium (2.5 eq), THF, −78 °C, 2 h, **2.** Troc-Cl (2.5 eq), −78 °C, 2 h to rt, 16 h, **3.** NaOH/H_2O_2, THF, rt, 16 h. **iv)** NaOH/H_2O_2, THF, 0 °C to rt, 2 h. **v) 1.** Formic acid, rt, 6 h, **2.** Toluene, 110 °C, 16 h. [c] Enantiomers not separable by chiral HPLC.

With boronic ester **4c** (Scheme 4B), Zweifel olefination was possible with 3.2 equivalents of vinyllithium and methanol added as a proton source. Upon addition of I_2/methanol, Zweifel olefination product **8** was obtained in 96% yield.[9b] Similarly, sp^2–sp^3 coupling to furan with 2.4 equivalents of furan-2-yllithium followed by a solvent switch to methanol and addition of NBS gave desired product **9** in 61% yield.[19] Furthermore, sp^2–sp^3 coupling to 3-fluoropyridine was also achieved with 2.5 equivalents of (3-fluoropyridin-4-yl)lithium. The 1,2-migration was triggered upon addition of Troc-Cl and oxidation with NaOH/H_2O_2 gave coupled product **10** in 50% yield.[20] Exploring these modifications for boronic ester **4c** has consequently broadened the scope of these existing enantiospecific transformations to tolerate an acidic functional group.

The enantiospecific oxidation of boronic ester **4c** yielded alcohol **5c** (Scheme 4C). This compound was then subjected to hydrolysis and lactonization with formic acid and subsequent decarboxylation to give γ-phenyl-γ-butyrolactone (**11**, Scheme 4C).[21] The optical rotation of **11** corresponded to that reported for the *S* enantiomer which confirmed that the absolute stereochemistry of boronic ester **4c** is *S*.[22,13c] This shows that the 1,2-metallate rearrangement/ring opening sequence of cyclopropyl boronate complexes proceeds through inversion of stereochemistry at the boron attached carbon.

With the knowledge that the cleavage of a strained, di-activated carbon-carbon bond could indeed trigger a 1,2-metallate rearrangement mechanism, we considered whether the reaction could occur if the cyclopropane was substituted with only one electron withdrawing group. A ^{11}B NMR study was undertaken to evaluate this reactivity (Scheme 5).

Scheme 5. Reactivity of different β-carbonyl boronate complexes with $MgBr_2{\cdot}Et_2O$ studied by ^{11}B NMR spectroscopy



Reaction conditions: **i)** ^{n}BuLi (1.1 eq), THF (0.14 M), −78 °C, 1 h, **ii)** $MgBr_2{\cdot}Et_2O$ (1.5 eq), −78 °C to rt, 16 h.

Under the optimised reaction conditions and employing boronic ester **2** (31 ppm), the conversion of boronate **12** (6 ppm) to boronic ester **13** (33 ppm) was followed by ^{11}B NMR spectroscopy (Scheme 5A). Mono-activated cyclopropyl boronic ester **14** (32 ppm) was then subjected to the same reaction conditions (Scheme 5B).[23] While conversion to boronate **15** (8 ppm)

proceeded as before, the addition of magnesium bromide etherate led to the formation of borinic ester **16**, identified by a characteristic ^{11}B NMR chemical shift at 50 ppm. In this case, the cyclopropane was not activated through coordination of the carbonyl oxygen to the Lewis acid. Instead, the Lewis acid interacted with the pinacol group and cleavage of an oxygen-boron bond occurred.[24] We reasoned that the malonate moiety in **12** could act as a bidentate ligand promoting complexation of the Lewis acid and thereby 1,2-metallate rearrangement. We therefore investigated an alternative malonate without the cyclopropyl moiety to see if a related 1,2-metallate rearrangement could occur (Scheme 5C). However, boronic ester **17** (32 ppm), with an open chain structure and two ester groups,[25] also gave a borinic ester (**19**, 50 ppm) as the reaction product (Scheme 5C). These results demonstrate that both strain-release and the presence of two ester groups are necessary to drive the 1,2-metallate rearrangement. Without either structural feature, borinic ester formation dominates completely.[26]

In conclusion, we have developed an enantiospecific coupling reaction between an organolithium reagent and an enantioenriched cyclopropyl boronic ester. The reaction proceeds *via* a boronate complex with an activated cyclopropane in the α position. It was shown that both strain in the cyclopropane and the presence of two ester groups in the β position are essential for 1,2-metallate rearrangement to occur. This method provides efficient access to synthetically useful, enantioenriched γ-carbonyl boronic esters in moderate to excellent yield with complete enantiospecificity.

ASSOCIATED CONTENT

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(17) The transformation was tested with the diethyl ester analogue of boronic ester **3**. With the addition of PhLi (1.1 eq) at −98 °C (methanol/liquid nitrogen) followed by $MgBr_2{\cdot}Et_2O$ (1.5 eq), the desired product was obtained in 35% NMR yield. See SI for further details.
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