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Bis-boronic Esters

Intramolecular Lithiation-Borylation for the Stereoselective Synthesis of Cyclopentyl and Cyclobutyl Bis-Boronic Esters

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Abstract: Saturated carbocycles are common motifs in natural products and pharmaceuticals, and so methods for their construction, particularly with high diastereo- and enantiocontrol, are of high importance. Lithiation-borylation has emerged as powerful methodology for the stereocontrolled construction of acyclic carbon chains but has not previously been used for the stereocontrolled synthesis of carbocycles. Herein, we report that benzylic diethylcarbamates with a tethered vicinal bis-boronic ester moiety can be deprotonated with lithium amide bases, resulting in cyclization and 1,2-metallate rearrangement to give carbocycles. This intramolecular lithiation-borylation reaction is completely regioselective and, rather than being stereospecific like the acyclic variants, it is diastereoconvergent. Stereochemistry of the boronic ester is retained but the benzylic stereocenter undergoes epimerization, furnishing carbocycles with high diastereo- and enantiocontrol from easily accessible precursors. Site-selective transformations of the bis-boronic ester products are also demonstrated.

Introduction

Saturated carbocycles constitute the core motif in a vast array of natural products,[1] and in addition, are increasingly prominent in medicinal chemistry, providing rigidity, three-dimensionality and metabolic stability compared with sp^2-rich ring systems.[2] However, examples of FDA-approved drugs containing cyclobutanes are all achiral, and the majority of cyclopentanes appear as a constituent of steroid or prostaglandin cores.[3] This lack of diversity can be attributed to the challenging synthesis of these scaffolds, particularly with high control of stereochemistry and substitution pattern.[4] We considered that a general, stereospecific method to cycloalkyl boronic esters could provide access to a library of useful building blocks following derivatization of the C–B bond.[5]

Homologation of boronic esters with enantioenriched lithium carbenoids, termed lithiation-borylation, is a highly enabling methodology for the construction of acyclic carbon chains bearing multiple stereogenic centers (Scheme 1a).[6–8] However, intramolecular lithiation-borylation has not been applied to the stereocontrolled synthesis of carbocycles.

This is because the strong base (*s*-BuLi) required for deprotonation of the carbenoid precursor is incompatible with the presence of a boronic ester. Nevertheless, cyclic alkenyl boronate complexes prepared by rapid lithium-halogen exchange of alkenyl halide-tethered boronic esters underwent a ring-contracting 1,2-metallate rearrangement to afford carbocyclic boronic esters upon treatment with electrophiles[9–12] or electrophilic radicals[13] (Scheme 1b).

We reasoned that intramolecular lithiation-borylation methodology could be employed for the stereocontrolled construction of carbocycles if weaker bases were used to generate the lithium carbenoid, which would avoid competitive direct reaction of the base with the boronic ester. In this context, Matteson[14] (and most recently Dong[15]) demonstrated that LDA was a suitable base for the generation of cyclic boronate complexes from nitrile-containing substrates bearing a chloroboronic ester (Scheme 1c). However, even when using $MgBr_2$ as an activator, slow 1,2-migration ensued to give the cyclobutyl boronic ester products in "erratic yields" and variable diastereoselectivity. Nonetheless, inspired by this work, we considered an intramolecular lithiation-borylation using benzylic carbamates as carbenoid-precursors because we and Fandrick had shown that the weakly acidic benzylic positions can be deprotonated with LDA-type bases in the presence of boronic esters.[16–18] Given that intermolecular lithiation-borylations of benzylic carbamates are stereospecific, we anticipated an intramolecular variant would allow carbocycle formation with high stereoselectivity, since this should be controlled by the stereochemistry of the carbamate and the boronic ester. Herein, we report intramolecular lithiation-borylations of benzylic carbamates tethered to vicinal bis-boronic esters, which proceed via ring contractive

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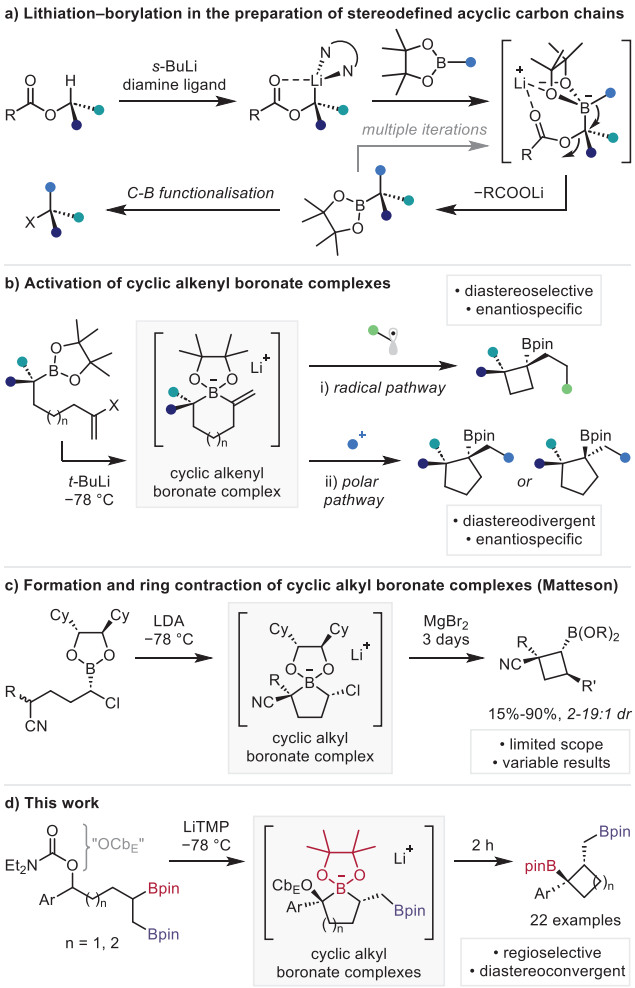


Scheme 1. a) Lithiation-borylation methodology in the synthesis of acyclic stereodefined carbon chains. b) Formation and reactivity of cyclic alkenyl boronate complexes through polar or radical pathways. c) Cyclic alkyl boronate complexes from alkyl cyanides or d) benzylic carbamates.

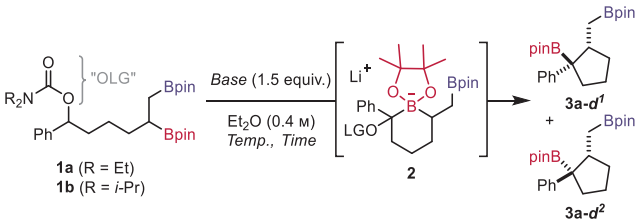
1,2-metallate rearrangements to generate cyclopentyl and cyclobutyl boronic esters (Scheme 1d). However, we were surprised to discover that for many substrates the reactions were not diastereospecific, as expected, but were in fact diastereoconvergent due to epimerization of the benzylic carbamate stereocenter. This has a major advantage since it enables the stereochemistry of the boronic ester, which is easily installed through catalytic alkene diboration, to control the overall diastereoselectivity of the reaction.

Results and Discussion

Reaction Development

Our study began with model substrate **1b**, a benzylic carbamate with a tethered vicinal bis-boronic ester (Table 1). 1,2-Bis-boronic esters represent a privileged motif of high synthetic value since they can be readily prepared from feedstock alkenes and with exceptionally high enantioselectivity.[19–29] Furthermore, we anticipated the cyclic products to be

Table 1: Optimization of the ring contractive 1,2-metallate rearrangement.[a]



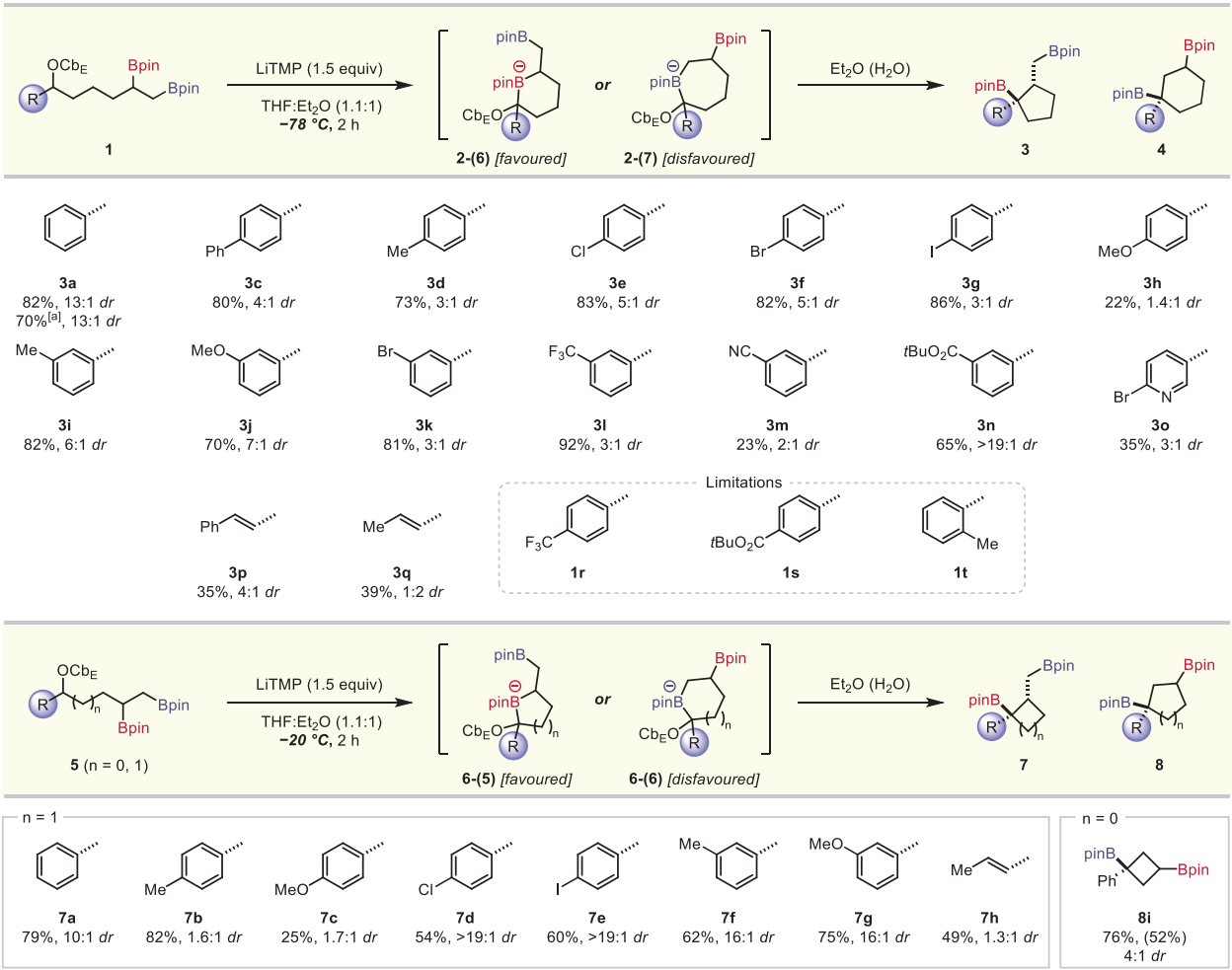
	R	Base	Temp [°C]	Time [min]	Yield[b] [%]	dr[c]
1	iPr	LDA	0	120	<5	–
2	Et	LDA	0	120	10	–
3	Et	LiTMP	0	120	51	3:1
4	Et	LiTMP	−40	120	78	5:1
5	Et	LiTMP	–78	120	91	13:1
6	Et	LiTMP[d]	–78	120	38	2:1
7	Et	LiTMP[e]	–78	120	54	6:1
8[f]	Et	LiTMP	–78	120	92	13:1

[a] All reactions carried out on racemic **1** (0.2 mmol), which was used as a 1:1 mixture of diastereomers. The base was prepared by addition of *n*-BuLi in hexanes to the corresponding amine in THF. Freshly prepared LDA/LiTMP was added dropwise to a solution of **1** in Et_2O at the indicated temperature and the mixture was stirred for the allotted time, followed by dilution with non-anhydrous Et_2O. [b] Yields were determined by ^1H NMR analysis using CH_2Br_2 as an internal standard. [c] The diastereomeric ratios (*dr*, **3a-*d*^{1}/3a-*d*^{2}**) were determined by ^1H NMR analysis. [d] LiTMP was prepared in Et_2O. [e] LiTMP was added to a solution of **1** in THF. [f] $MgBr_2$ in MeOH (1 M, 1.5 equiv.) added at –78 °C after 2 h. See Supporting Information for full experimental details

amenable to regioselective functionalization, providing useful building blocks towards carbocyclic targets.[30] Using conditions previously employed for acyclic systems,[18] we investigated the reaction of diisopropylcarbamate **1b** with LDA, however, only traces of product was observed and the majority of **1b** was recovered (entry 1). Cognizant of the severe congestion around the carbamate and boronic ester, which could inhibit both the formation and rearrangement of the boronate complex, we considered using the less bulky diethylcarbamate **1a**.

Following the same procedure, cyclopentane **3a** was now obtained as the sole product, albeit in low yield (entry 2).[31] Using lithium 2,2,6,6-tetramethylpiperidide (LiTMP, prepared as a solution in THF) instead of LDA significantly improved the yield to 51% (entry 3), with a 3:1 *dr* favouring diastereomer **3a-*d*^{1}** where the primary boronic ester and the aryl group have a *cis*-relationship. Decreasing the temperature led to improved yields and diastereoselectivity (entries 4,5), leading to optimum conditions at −78 °C (entry 5, 13:1 *dr*). When the reaction of **1a** was performed in pure Et_2O or THF, **3a** was formed in poor yield and selectivity (entries 6,7). Finally, addition of Lewis acidic $MgBr_2$ in MeOH after 2 h (entry 8) gave the same result as addition of non-anhydrous Et_2O and warming.

Two further noteworthy observations were made in this study. Firstly, the lithiated carbamate can react with the more hindered secondary boronic ester, giving a six-membered ring



Scheme 2. Substrate scope. All reactions were carried out on 0.2 mmol scale. LiTMP was prepared by addition of *n*-BuLi to 2,2,6,6-tetramethylpiperidine in THF. Freshly prepared LiTMP (0.4 M in THF) was added dropwise to a solution of **1** or **8** in Et_2O (0.4 M) and the mixture was stirred for 2 h, followed by dilution with non-anhydrous Et_2O. Yields were determined by ^1H NMR analysis using CH_2Br_2 as an internal standard, isolated yields in parentheses as a mixture of diastereomers; *dr* determined by ^1H NMR analysis of the crude reaction mixture. [a] Reaction carried out on 2.0 mmol scale, isolated yield.

boronate complex (Scheme 2, **2-(6)**), or the less hindered primary boronic ester, giving seven-membered ring boronate complex **2-(7)**. Following 1,2-metallate rearrangement and concomitant ring contraction, these complexes would afford cyclopentane **3** or cyclohexane **4**, respectively. Since only cyclopentane **3** was obtained, there is clearly very high preference for formation of the six-membered ring boronate complex, indicating that the higher rates of ring closure (6 over 7) dominate over steric effects. Secondly, starting from a 1:1 mixture of diastereoisomers we obtained high diastereocontrol, showing that the reaction was diastereoconvergent, not diastereospecific as we had expected based on acyclic systems.

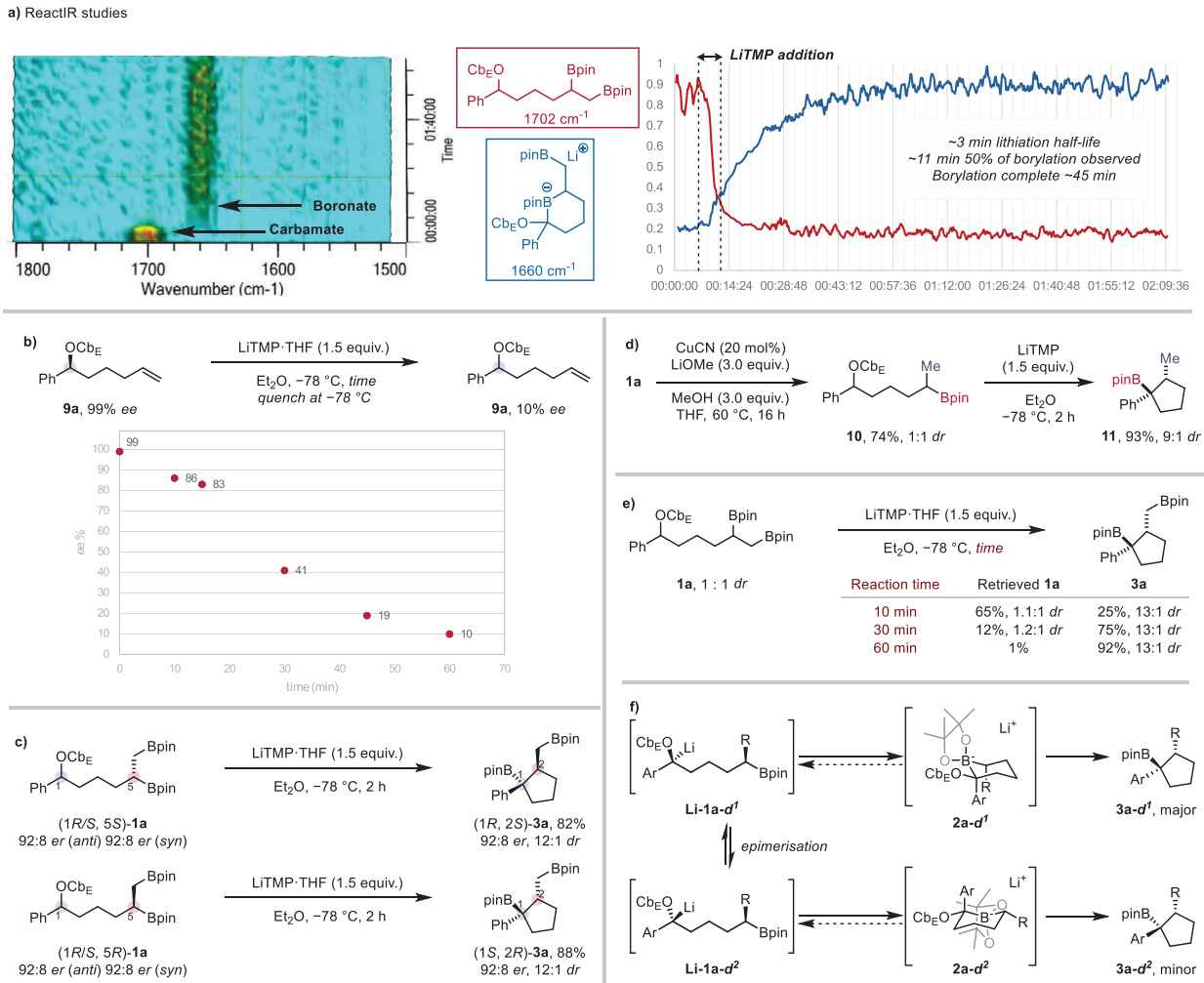
Substrate Scope

With optimized conditions established, we explored the substrate scope (Scheme 2, top). Arenes bearing mildly electron-donating or -withdrawing groups in the *para* position (Ph, Me, Cl, Br, I) gave boronic esters (**3c**-**3g**) in high yield and moderate diastereoselectivity (3–5:1). On gram scale, **3a** was prepared with the same diastereoselectivity and in good yield. Strong electron-donating groups, for example *p*-methoxy (**3h**), gave low yield and poor diastereoselectivity.

Substrates having electron-withdrawing groups in the *para* position were unsuccessful. *p*-CF_3 (**1r**) underwent 1,6-fluoride elimination upon lithiation, while *p*-CO_2tBu (**1s**) just returned starting material (see mechanistic analysis section for further details on **1s**).

Interestingly, *m*-CF_3 in substrate **1l,** which can't undergo the same decomposition pathway of **1r,** gave product **3l** in excellent yield and selectivity.

Also, other aromatic rings bearing both electron-donating and -withdrawing groups (MeO, Br, CF_3, CN, CO_2tBu) in the *meta* position all worked well, giving moderate to high selectivity (2:1→19:1). It should be noted that some of these functional groups would not be compatible with *s*-BuLi (e.g., Br, CN) but are compatible with lithium amide bases. Furthermore, the reaction could be extended to the



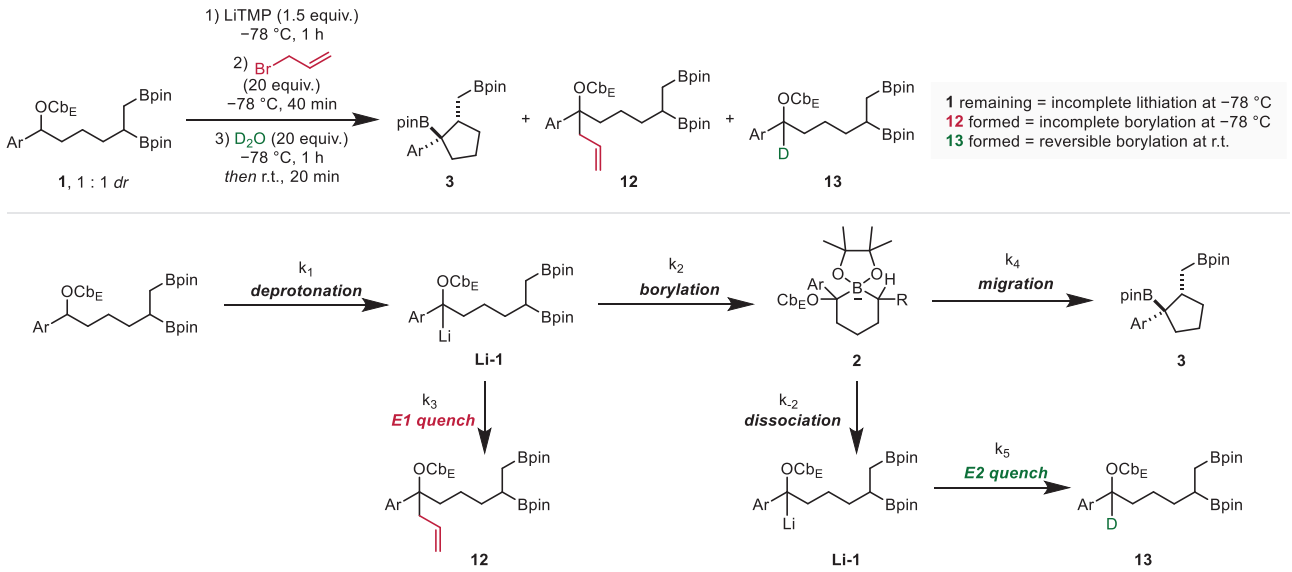
Scheme 3. Mechanistic studies. a) ReactIR studies; b) Racemization of the benzylic stereocenter. c) Retention of the boronic ester stereocenter. d) Protodeboronation/cyclization sequence suggests minimal influence of the primary boronic ester on the diastereoselectivity. e) Time-dependence of the diastereomeric ratio of the starting material and product. f) Proposed stereochemical model.

pyridyl derivative, giving **3o** in moderate yield and selectivity. In addition to benzylic carbamates, the reaction conditions could also be applied to allylic carbamates, affording alkenyl cyclopentanes **3p** and **3q** in moderate yield and selectivity.

Having shown that ring contraction of the six-membered boronate complex was successful, we next investigated the more challenging five- to four-membered ring contraction (Scheme 3, bottom). These systems should preferentially form the five-membered ring boronate complexes over the six-membered ring boronates due to faster rate of cyclization, but would suffer considerably higher barriers to 1,2-metallate rearrangement, if it occurred at all, due to the substantial increase in strain upon ring contraction. Unfortunately, when substrate **5a** (R = Ph, n = 1) was subject to the optimized reaction conditions, only 10% of the desired product was formed. However, upon increasing the temperature to −20 °C, **7a** was obtained in high yield, perfect regioselectivity and good diastereoselectivity. The diastereoselectivity followed a similar pattern as before. Electron-neutral and mildly electron-withdrawing *para* substituents and *meta* substituted aromatics (**7d**-**7 g**) gave high diastereoselectivity, whilst electron-donating *para* substituents (**7b** and **7c**) gave poor selectivity. Once again, allylic carbamates could also be employed, giving alkenylcyclobutane **7h** in good yield and moderate selectivity. Finally, carbamate **5i** (R = Ph, n = 0) was tested. In this case the lithiated carbamate has a choice of reacting with the hindered secondary boronic ester, forming a four-membered ring boronate complex, or the primary boronic ester, forming a five-membered ring boronate complex. For this substrate, both the rate of cyclization and sterics favour formation of the five-membered ring boronate complex, which led to the exclusive formation of cyclobutane **8i** in moderate yield and diastereoselectivity (Scheme 2).

Mechanistic Analysis

To gain further understanding of the mechanism, the reaction of **1a** was monitored using in situ IR spectroscopy (ReactIR, Scheme 3a) which showed that the starting carbamate at 1698 cm^{-1} was rapidly consumed ($t_{1/2}$ = 3 min). Neither the pre-lithiation complex nor the lithiated carbamate were



Scheme 4. "Two-electrophile tests" carried out on substrates **1a**, **1d**, **1l** and **1s**.

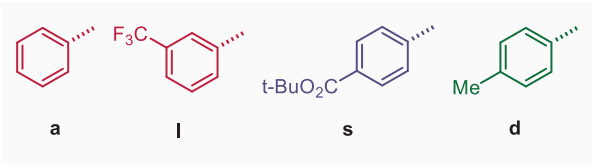
observed, but a second peak at 1666 cm^{-1} rapidly emerged which was identified as the boronate complex **2a**.[18,32] In ~11 min, **2a** reached half of the final concentration, and as expected, the boronate complex accumulated at −78 °C. No migration was observed at this temperature.

As deprotonation was rapid, we wanted to investigate the rate of racemization. We generated **Li-9a** (99% *ee*) at−78 °C in a 1.1:1 mixture of THF-Et_2O and quenched the anion at the same temperature at various time intervals and observed rapid racemization over 60 minutes (99% *ee* to 10% *ee*) (Scheme 3b). We had not expected epimerization of the Li-benzylic carbamate to be so rapid at −78 °C,[33–35] since we had previously employed related carbamates in stereospecific lithiation-borylation reactions without erosion of enantioselectivity.[10,36] However, these reactions were conducted in Et_2O, whereas the current conditions use a Et_2O-THF mixture. Indeed, Hoppe showed that lithiated benzylic carbamates rapidly isomerize in THF, but are configurationally stable in Et_2O.[35] When the reaction of **1a** was performed in pure Et_2O or THF, **3a** was formed in poor yield and selectivity (entries 6 and 7, Table 1).

Next, the origin of diastereoselectivity was probed. Racemic carbamate **9a** was subjected to Morken asymmetric Pt-catalyzed diboration using both chiral ligands to give a 1:1 mixture of diastereoisomers (5*R*)-**1a** and (5*S*)-**1a** with high enantioselectivity (Scheme 3c).[24] Subjecting each mixture of diastereoisomers to the optimized reaction conditions gave boronic esters (1*S*,2*R*)-**3a** and (1*R*,2*S*)-**3a** in high yield, enantiomeric excess and with high diastereoselectivity. This result not only confirmed that epimerization occurred at the benzylic position and that the boronic ester retained its stereochemical integrity, but it also demonstrated that the stereochemistry of the migrating center was translated to cyclic products with perfect selectivity.

To determine whether the primary boronic ester played any role, it was selectively removed by protodeboronation[37] and the 1:1 mixture of diastereomeric products **10** was subjected to the optimized reaction conditions (Scheme 3d). Once again, cyclopentane **11** was obtained in excellent yield and high diastereomeric ratio, showing that the high diastereoselectivity was not a function of the spectator boronic ester, further demonstrating the generality of the process.

Table 2: Two-electrophile test. [a]



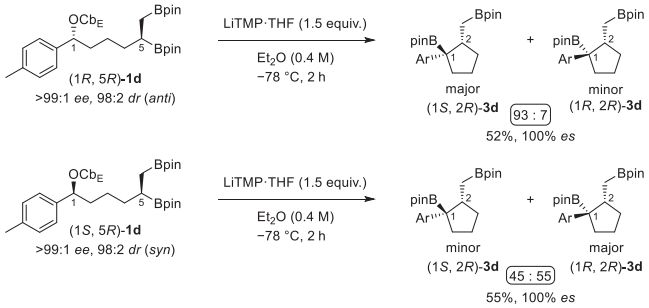
Entry	Substrate	1[b]	12[b]	13[b]	3[c]
1	**1a**	7%	0%	7%	63%, >19:1 *dr*
2	**1l**	0%	0%	11%	55%, 3:1 *dr*
3	**1s**	11%	54%	31%	0%
4	**1d**	40%	0%	0%	44%, 1.5:1 *dr*

[a] All reactions carried out on racemic **1** (0.2 mmol), which was used as a 1:1 mixture of diastereomers. [b] Yields were determined by ^1H NMR analysis using CH_2Br_2 as an internal standard from the carbamate-containing fraction. [c] Isolated yield. See Supporting Information for full experimental details.

To determine if any kinetic resolution was occurring, the diastereomeric ratios of starting material **1a** and product **3a** were monitored over time (Scheme 3e). The diastereomeric ratios of both **1a** and **3a** were found to remain constant throughout the course of the reaction, showing that the lithiated carbamates epimerize over the course of the reaction. Based on the above experiments, we propose the mechanism shown in Scheme 3f. Deprotonation of **1a** with LiTMP generates configurationally unstable lithiated carbamates **Li-1a-*d*^{1}** and **Li-1a-*d*^{2}** which cyclise to generate boronate complexes **2a-*d*^{1}** and **2a-*d*^{2}** (a process which is partially reversible), which in turn progress to the products **3a-*d*^{1}** and **3a-*d*^{2}**, respectively.

The final piece of the jigsaw was to establish which substrates underwent reversible boronate formation. Previously, a "two-electrophile test" had been employed to assess the degree of boronate complex dissociation and so this was employed on several representative substrates (Scheme 4, and Table 2).[38] In this test, after deprotonation for 1 h, allyl bromide was added to quench any unreacted lithiated carbamate that had not cyclized to the boronate. After a further 40 min, a second, more reactive electrophile (D_2O) was added and the solution warmed up. Any deuterated carbamate formed must come from dissociation of the boronate. For electron-neutral substrate **1a**, 7% of the starting material remained, showing incomplete deprotonation. No allylation product **12a** was observed, indicating that **Li-1a** rapidly cyclized to give boronate complex **2a**. However, around 7% of deuterated starting material **13a** was obtained, indicating that partial dissociation of the boronate took place. Similar results were observed with the electronically similar *meta*-substituted carbamate **1l**. Using *p*-MeO_2C-aryl carbamate **1s,** no product but significant quantities of both the allylation product **12s** (54%) and deuterated starting material **13s** (31%) were obtained, indicating that boronate dissociation occurred even at −78 °C and that dissociation was faster than 1,2-migration. This explains why electron-poor arenes **1r-t** were poor substrates: they likely formed the boronates but reversed back to the lithiated carbamates instead of undergoing 1,2-migration. *p*-Me-aryl carbamate **1d** was slower at deprotonation, with 40% starting material recovered. Since no other electrophile-trapped products were observed with **1d**, it showed that the lithiated carbamate progressed to the boronate and to 1,2-migration without significant dissociation. We had expected to observe more of the deuterated carbamates **13a**, **13l** and **13d**. However, it is likely that the lithiated carbamates are short-lived, but they can still epimerize before undergoing rapid ring closure to the boronate complexes. Only when the boronate complex does not progress to the cyclized boronic ester and instead reverses back to the lithiated species, as in the case of **3s,** is the deuterated carbamate **13s** formed in high yield. It should be noted that the conditions of the two-electrophile test are different to the optimized procedure which could account for the different selectivity observed.

To further probe the behavior of each diastereoisomer we examined the reaction of the *p*-Me aryl carbamate **1d** which had given only moderate 3:1 *dr* (Scheme 5). Treatment of (1*R*, 5*R*)-**1d** (98:2) to the optimized reaction conditions gave a 93:7 ratio of (1*S*, 2*R*)-**3d**:(1*R*, 2*R*)-**3d** in 52% yield. The high diastereoselectivity observed indicated that the (1*R*, 5*R*)-**1d** diastereomer largely underwent deprotonation, cyclization and 1,2-migration *without* epimerization. In contrast, treatment of (1*S*, 5*S*)-**1d** (98:2) to the same conditions gave a 45:55 ratio (1*S*, 2*R*)-**3d**:(1*R*, 2*R*)-**3d** in 55% yield. This indicated that the other diastereomer *underwent substantial epimerization* prior to irreversible 1,2-migration. This diastereoisomer presumably undergoes deprotonation, and cyclization to form the boronate complex but because 1,2-migration is slow it reverses back to the lithiated carbamate (leading to a partially stabilized anion) prior to epimerization, cyclization and 1,2-migration. Based on the results of the separate



Scheme 5. Treatment of the separate diastereomeric, enantioenriched boronic esters (1*R*, 5*R*)-**1d** and (1*S*, 5*R*)-**1d** to the optimized reaction conditions.

diastereoisomers, a 1:1 mixture of *p*-Me aryl carbamates **1d** would therefore be expected to give a ~3:1 mixture of diastereomeric products **3d**, as observed.

In summary, our mechanistic findings show (Scheme 6):

1. For electron-neutral and mildly electron-withdrawing aromatics (red), boronate formation is partially reversible, the lithiated carbamates can epimerise, and high selectivity is obtained through one diastereomer undergoing faster 1,2-migration than the other. The reactions are diastereoconvergent.

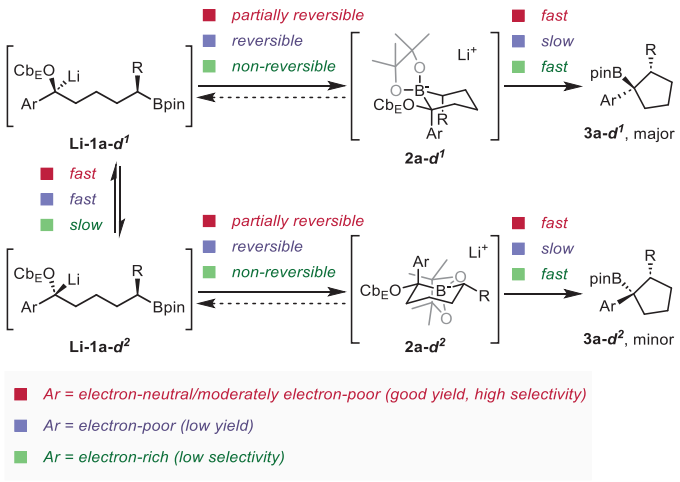
2. For electron-deficient aromatics (purple), boronate formation is reversible, but the higher barrier to 1,2-migration means that low yields result from decomposition/protonation of the lithiated carbamate.

3. For electron-rich aromatics (green), boronate formation is non-reversible, and the reactions are stereospecific. Starting with a mixture of diastereoisomers leads to the same mixture of diastereomeric products.

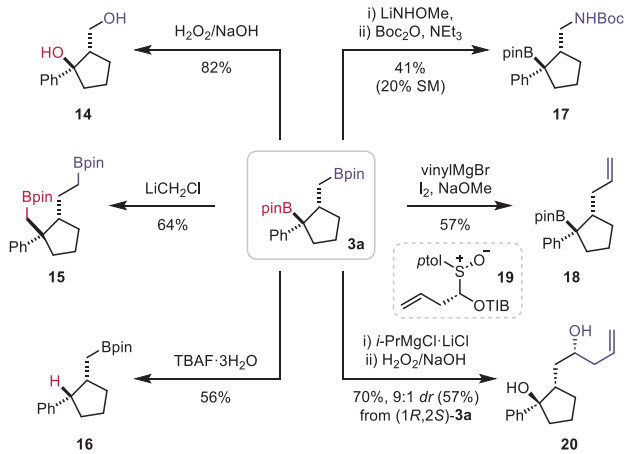
Attempts to model the different steps through DFT calculations lead to ambiguous conclusions, perhaps due to the challenges associated with the large number of species with lithium−solvent interactions and anion−cation ion pairing.[39] The multiple factors affecting stereoselectivity, as revealed by our experimental mechanistic studies, pose an additional challenge for a DFT analysis.

Product Derivatization

The cyclic bis-boronic ester products provide a rich source of independently derivatizable functionality for further stereospecific transformation (Scheme 7). Oxidation with basic peroxide, gave 1,3-diol **14** in high yield as a single diastereomer. Performing a double Matteson-type homologation with excess bromochloromethane and *n*-butyllithium gave access to 1,5-bisboronic ester **15**.[40] The difference in reactivity between the primary aliphatic and tertiary benzylic boronic ester functionality could be manipulated in site-selective functionalization reactions. Protodeboronation with TBAF was carried out at the benzylic site to give **16**, with no reaction at the primary boronic ester.[41] Morken amination selectively transformed the primary boronic ester to an amine, which was then protected as the Boc derivative **17** in moderate yield.[42] Zweifel olefination using vinylmagnesium bromide



Scheme 6. Proposed mechanism depending on the electronic of the aromatic ring.



Scheme 7. Product derivatizations. Reactions were carried out on **1a** (0.1 mmol). Yields are of isolated products; *dr* determined by ^{1}H NMR analysis.

occurred solely at the primary boronic ester to install the terminal alkene **18**.[43,44] Finally, regioselective and stereospecific homologation of the primary boronic ester using the magnesium carbenoid derived from sulfoxide **19** gave 1,4-diol **20** after oxidation.[45] In this case, the enantioenriched boronic ester (1*R*,2*S*)-**3a** was employed, therefore allowing a third stereocenter to be installed with complete control of relative and absolute stereochemistry.

Conclusion

In conclusion, we have developed the first intramolecular lithiation-borylation for the synthesis of cyclopentyl and cyclobutyl 1,3-bis-boronic esters from Hoppe-type benzylic carbamates with tethered vicinal bis-boronic esters. Despite the presence of two reactive boronic ester groups, excellent regioselectivity was observed in all cases The reaction was stereospecific at the migrating center, and stereocontrol at the benzylic position was dependent on the nature of the arene. High selectivity was obtained with electron neutral and mildly electron withdrawing aromatics due to partial reversibility in boronate formation. Detailed mechanistic studies revealed that epimerization of the benzylic center was rapid and that increasing reversibility of boronate formation was observed with increasingly stability of the lithiated carbamate. Since the stereochemistry of the boronic ester is retained and is easy to install with high enantioselectivity, the method enables the asymmetric synthesis of cyclopentanes and cyclobutanes with high enantio- and diastereocontrol in many cases.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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