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Communication

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Strain-Release-Driven Homologation of Boronic Esters: Application to the Modular Synthesis of Azetidines

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Supporting Information Placeholder

ABSTRACT: Azetidines are important motifs in medicinal chemistry, but there are a limited number of methods for their synthesis. Herein, we present a new method for their modular construction by exploiting the high ring strain associated with azabicyclo[1.1.0]butane. Generation of azabicyclo[1.1.0]butyl lithium followed by its trapping with a boronic ester gives an intermediate boronate complex which, upon *N*-protonation with acetic acid, undergoes 1,2-migration with cleavage of the central C–N bond to relieve ring strain. The methodology is applicable to primary, secondary, tertiary, aryl and alkenyl boronic esters, and occurs with complete stereospecificity. The homologated azetidinyl boronic esters can be further functionalized through reaction of the N–H azetidine, and through transformation of the boronic ester. The methodology was applied to a short, stereoselective synthesis of the azetidine-containing pharmaceutical, cobimetinib.

Nitrogen-containing heterocycles are the most prevalent and important heterocycles in medicinal chemistry, as evidenced by their presence in approximately 60% of U.S. FDA approved small-molecule drugs.[1] Among this class of compounds, the saturated heterocycles piperidine and pyrrolidine are some of the most commonly encountered. However, their four-membered ring analogue, azetidine,[2] is much less prevalent, despite possessing a range of desirable characteristics; its small, strained ring structure confers structural rigidity and fewer rotatable bonds, which has been shown to correlate with increased bioavailability,[3] and they have been demonstrated to exhibit greater metabolic stability and improved physicochemical properties relative to their larger ring analogues.[4] Indeed, the azetidine moiety is featured in several pharmaceuticals, including cobimetinib (**1**),[5] azelnipidine (**2**)[6] and baricitinib (**3**)[7] (Figure 1A), as well as in biologically-active natural products.[8] However, despite these attractive features, there is a dearth of methods available to prepare azetidines.[2,9] Some current methods include inter- and intramolecular alkylation of amine nucleophiles, reduction of β-lactams,[2] and the aza Paternò-Büchi reaction.[10] Therefore, the development of new methodologies that facilitate the modular synthesis of azetidines from common building blocks would be highly attractive, particularly in advancing medicinal chemistry programs.[11] Herein, we describe a method to homologate readily available boronic esters with azabicyclo[1.1.0]butyl lithium (a novel species) to form versatile borylated azetidines, which can then be diversified through transformation of the amine and boronic ester functional groups.[12]

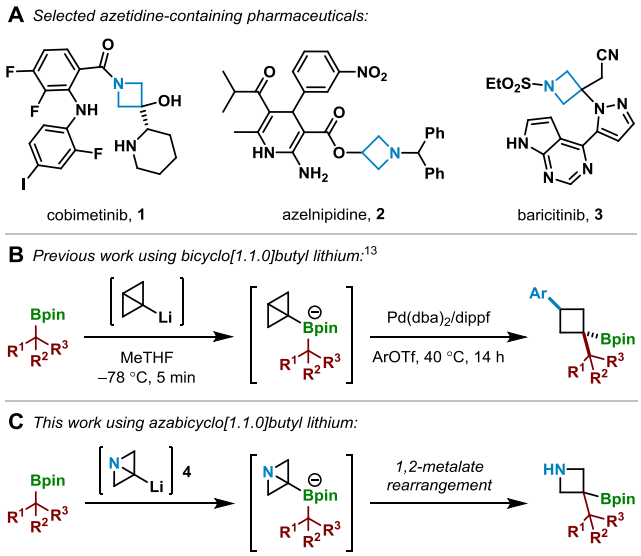
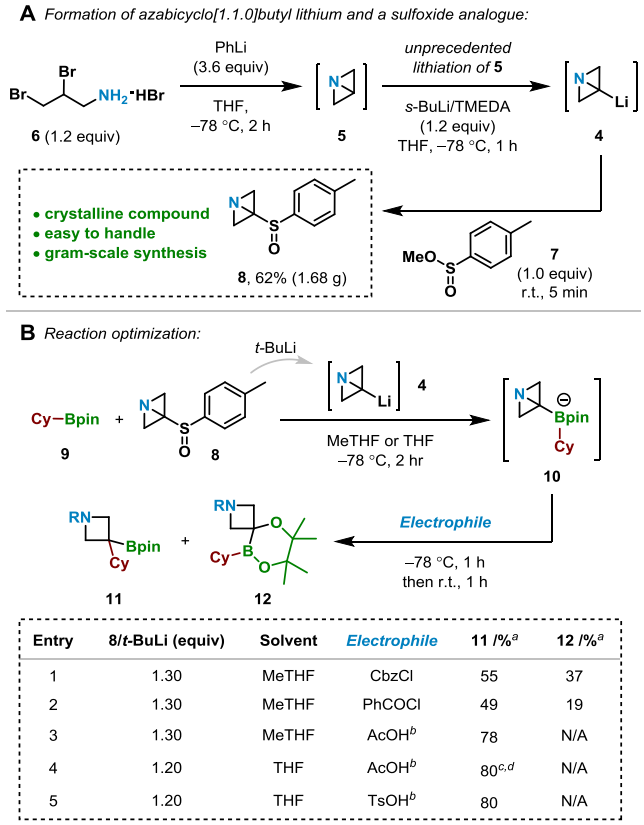


Figure 1. (A) Selected azetidine-containing pharmaceuticals. (B) Strain-release 1,2-metalate rearrangement of bicyclo[1.1.0]butyl boronate complexes. (C) This work: strain-release 1,2-metalate rearrangement of azabicyclo[1.1.0]butyl boronate complexes.

We recently reported the homologation of boronic esters by a cyclobutane unit by using bicyclo[1.1.0]butyl lithium (Figure 1B).[13] It was shown that bicyclo[1.1.0]butyl lithium could react with boronic esters to form highly strained bicyclo[1.1.0]butyl boronate complexes, which then underwent 1,2-metalate rearrangement upon treatment with electrophilic palladium(II)-aryl complexes to ultimately form a range of diastereomerically pure borylated cyclobutanes. The 1,2-metalate rearrangement is driven by relief of the high ring strain of the bi-cycle. We reasoned that the power inherent in the relief of ring strain could be harnessed to drive 1,2-metalate rearrangements in other related ring systems.[14] In particular, we were interested in the use of nitrogen-containing analogues of bicyclo[1.1.0]butyl lithium, such as azabicyclo[1.1.0]butyl lithium (**4**), since this would potentially enable the homologation of boronic esters to give synthetically- and pharmaceutically-important azetidines bearing a versatile boronic ester moiety (Figure 1C). However, such a nucleophilic species (azabicyclo[1.1.0]butyl lithium, **4**) has not been previously reported. Reactions involving the parent azabicyclo[1.1.0]butane (**5**) are dominated by nucleophilic ring opening, which break the strained central C–N bond.[15]

Scheme 1. (A) Lithiation of azabicyclo[1.1.0]butane and its trapping to form a sulfoxide. (B) Reaction optimization.



Entry	8/*t*-BuLi (equiv)	Solvent	*Electrophile*	11 /%[a]	12 /%[a]
1	1.30	MeTHF	CbzCl	55	37
2	1.30	MeTHF	PhCOCl	49	19
3	1.30	MeTHF	AcOH[b]	78	N/A
4	1.20	THF	AcOH[b]	80[c,d]	N/A
5	1.20	THF	TsOH[b]	80	N/A

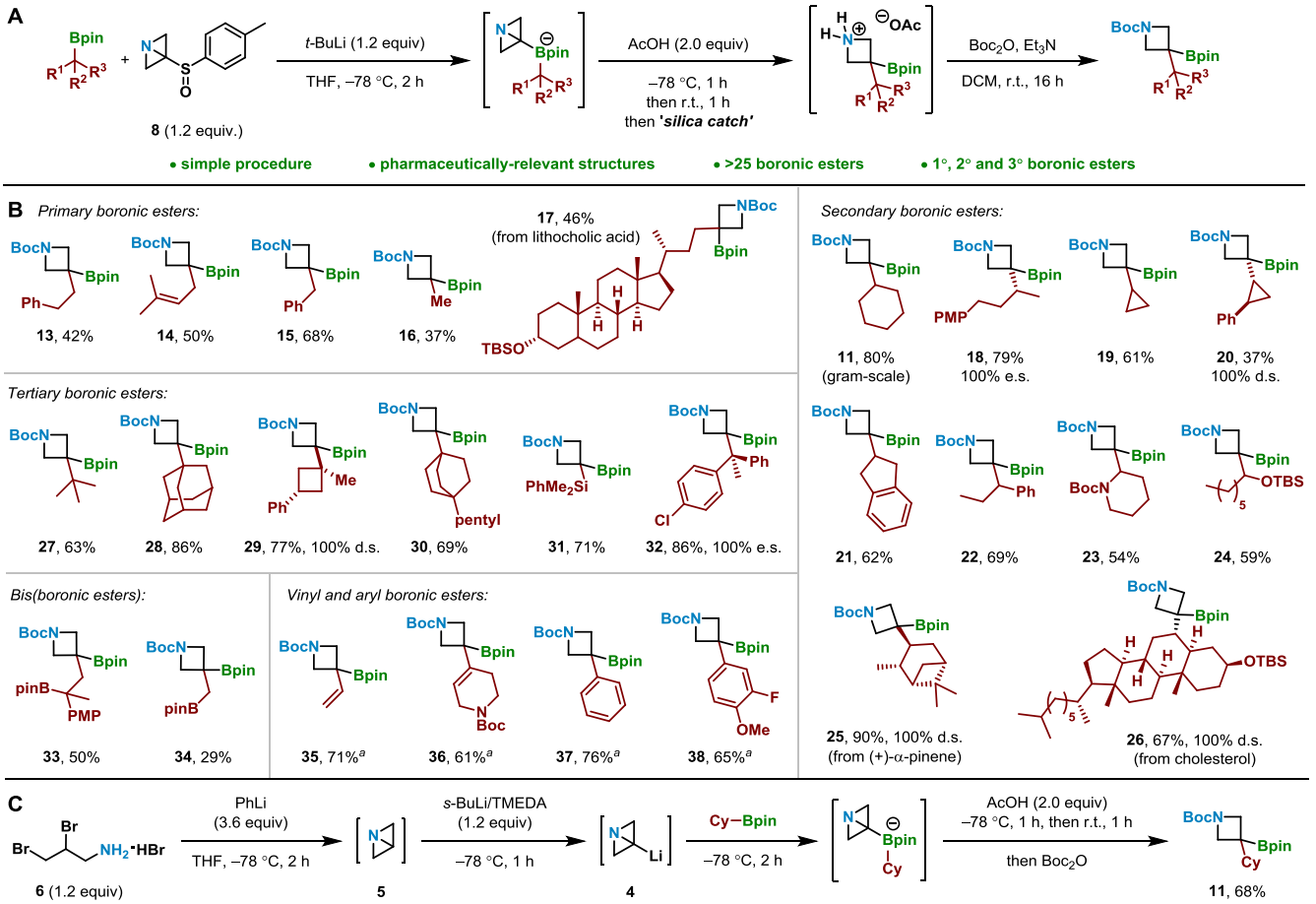
[a] NMR yield. [b] Followed by Boc protection. [c] Isolated yield. [d] Gram-scale (4.76 mmol).

In order to form azabicyclo[1.1.0]butyl lithium, we reasoned that the C–H bond at the bridgehead of **5** would be the most acidic, since it has the greatest s-character, and so could be selectively lithiated.[16] However, this route raised significant concerns since the strongly nucleophilic species, azabicyclo[1.1.0]butyl lithium, could potentially react with **5** to trigger a polymerization reaction.[15a,n] To this end, it was discovered that azabicylo[1.1.0]butane, generated *in situ* from ammonium salt **6** by treatment with phenyl lithium at –78 °C,[15l] could be lithiated using *s*-butyl lithium/TMEDA at –78 °C[17] to form azabicyclo[1.1.0]butyl lithium (**4**). We elected to trap **4** as a sulfoxide, since this would potentially offer a stable, solid reagent from which **4** could be conveniently regenerated.[13] Therefore, **4** was trapped with methyl 4-methylbenzenesulfinate (**7**) to give azabicyclo[1.1.0]butyl sulfoxide **8** in 62% yield (Scheme 1A). Sulfoxide **8** was formed as a single regioisomer, showing that selective deprotonation had indeed occurred, and problems relating to polymerization did not materialize, presumably due to a fast, low temperature lithiation step. The reaction was scalable and, as anticipated, **8** was a stable, easy-to-handle crystalline compound.

With the azabicyclo[1.1.0]butyl sulfoxide **8** in hand, its conversion to azabicyclo[1.1.0]butyl lithium and subsequent reaction with cyclohexyl pinacol boronic ester **9** was investigated. Treatment of a mixture of **9** and 1.3 equivalents of **8** in 2-methyl tetrahydrofuran at –78 °C with 1.3 equivalents of *tert*-butyl lithium[13] and then allowing the reaction mixture to stir for two hours resulted in complete boronate complex formation, as evidenced by a single peak at ca. 6 ppm in the ^{11}B NMR spectrum of the reaction mixture. Surprisingly, the boronate complex **10** did not undergo spontaneous 1,2-metalate rearrangement, despite the high strain energy that would be released upon ring opening. We therefore needed to make the amine into a better leaving group[18] and so explored different activating reagents. Addition of benzyl chloroformate at low temperature followed by warming did result in complete conversion of the boronate complex but gave an inseparable mixture of boronic and borinic esters **11** and **12**, resulting from *C*-and *O*-migration respectively, in a 1.5:1.0 ratio and a combined 92% NMR yield (Scheme 1B, entry 1). Benzoyl chloride behaved similarly (entry 2). By contrast, we were pleased to find that simple protonation of the boronate complex with acetic acid resulted in exclusive *C*-migration and, following protection with a Boc group, azetidine **11** was obtained in 78% NMR yield (Scheme 1B, entry 3). The added benefit of this approach is that it generates an unprotected N–H azetidine intermediate, which can then be reacted in any desired manner. Further improvements were achieved by switching the solvent to THF and modifying the stoichiometry of the reagents (1.2 equivalents of **8** and *tert*-butyl lithium). The N–H azetidine products were easily separated from the sulfoxide by-product by filtering through a plug of silica gel: the azetidine acetic acid salt was retained on the silica and all other compounds eluted ('silica catch' method). The top layer of the silica gel plug was then collected and subjected to Boc protection, giving pure **11** in 80% isolated yield (1.39 g, 3.81 mmol, Scheme 1B, entry 4). It was also discovered that the reaction could be triggered using TsOH which enabled purification of the azetidine by precipitation of the tosylate salt without using the 'silica catch' purification (entry 5, see Supporting Information for details).

The robustness of these optimized conditions is illustrated by the preparation of over 25 unique azetidines (Scheme 2B). The scope of the boronic ester component was first explored and was found to encompass a broad range of primary, secondary and tertiary boronic esters. The range of primary boronic esters included *n*-alkyl (**13**), allylic (**14**), benzylic (**15**) and methyl (**16**), the latter being an important substituent in medicinal chemistry.[19] The methyl group is normally a poor migrating group[20] and so we were concerned that competing *O*-migration might occur, as had been observed when using benzyl chloroformate as an activating reagent. However, exclusive *C*-migration was observed when using acetic acid as the activator with this challenging substrate to give **16** in modest yield. Notable secondary boronic esters included an α-amino boronic ester,[21] giving azetidine **23** featuring a piperidine substituent in 54% yield, and α-alkoxy boronic ester, giving 3-oxypropylamine **24** in 59% yield, both of which are motifs present in previously reported azetidine-containing pharmaceuticals.[5,22] The tertiary boronic esters included *tert*-butyl (**27**), adamantyl (**28**), substituted cyclobutyl (**29**),[13] bicyclo[2.2.2]octyl (**30**),[23] dimethyl phenyl silyl (**31**), and a doubly benzylic (**32**)[24] boronic ester, giving the azetidine products in good to excellent yields. It was also possible to regioselectively homologate the primary boronic ester of a 1,2-bis(boronic ester),[25] giving 1,3-bis(boronic ester) **33**, and perform a mono-homologation of a 1,1-bis(boronic ester),[26] giving 1,2-bis(boronic ester) **34**, in moderate yields. The enantiospecificity (e.s.)[27] of the transformation was demonstrated using two enantioenriched boronic esters, which gave products **18** and **32** with complete retention of stereochemistry (100% e.s.). Furthermore, four diastereomerically pure boronic esters were homologated to give the corresponding azetidine products, **20**, **25**, **26** and **29**, with complete diastereospecificity (100% d.s.)[28] Aryl and vinyl boronic esters could also be employed, giving the desired azetidines **35**–**38** in good yields.[29]

Scheme 2. Substrate scope of the azetidine homologation of boronic esters. (A) Optimized reaction conditions. (B) Boronic ester substrate scope. (C) Reaction performed without use of sulfoxide.



All reactions were performed using 0.24 mmol of the boronic ester and all yields refer to isolated material. [a] NMR yield. PMP = *para*-methoxyphenyl. e.s. (enantiospecificity) = [e.e. of product/e.e. of starting material] × 100%. d.s. (diastereospecificity) = [d.e. of product/d.e. of starting material] × 100%.

Finally, we explored whether the reaction could be achieved directly from the ammonium salt **6**, thereby by-passing the sulfoxide intermediate **8**, which could be more convenient when a single azetidine product is required. Thus, treatment of the ammonium salt **6** with phenyl lithium, followed by *sec*-butyl lithium/TMEDA, cyclohexyl pinacol boronic ester, acetic acid and finally Boc protection, gave the homologated azetidine boronic ester product **11** in 68% yield (Scheme 2C).

We next demonstrated that a range of different transformations of the nitrogen atom of the intermediate N–H azetidine is possible (Figure 2A). In addition to the Boc protecting group, the nitrogen atom could also be protected with the tosyl (**39**) and Cbz (**40**) protecting groups in good yields. An amide coupling reaction with benzoic acid, using HATU as the coupling reagent, gave **41** also in good yield. A representative Buchwald–Hartwig cross-coupling[30] using 4-bromobenzonitrile gave aniline **42** in 71% yield. The intermediate could also be engaged in S_NAr reactions with a range of (hetero)aryl halides to give **44**–**49** in good yields. These reaction classes are among the most commonly used reactions within the field of medicinal chemistry.[31]

To demonstrate the synthetic utility of the borylated azetidine products, azetidinyl boronic ester **11** was subjected to a range of representative boronic ester transformations, including oxidation to the corresponding alcohol (**48**), vinylation (**49**),[32] arylation to incorporate a pyridine (**50**)[33] and formation of trifluoroborate salt **51** (Figure 2B).[24] In all cases, good to excellent yields of the functionalized azetidines were achieved. Finally, a deboronative fluorination was performed,[34] yielding fluorinated azetidine **52** in moderate yield. Fluorinated amines are important motifs since the fluorine atom can lead to beneficial modulation of the molecules' physical and chemical properties, including the pK_a of the amine.[35]

Finally, to showcase the application of this new method we targeted the preparation of cobimetinib (**1**), an MEK inhibitor used in the treatment of melanoma.[5] Starting from ammonium salt **6**, azabicyclo[1.1.]butyl lithium **4** was prepared by deprotonation (see Scheme 2C) and reacted with (*R*)-*N*-Boc piperidyl 2-pinacol boronic ester **53**[21,36] to give the N–H azetidine intermediate **54**. Subsequent *in situ* acylation of **54** with the required acid fluoride[5] delivered boronic ester **55** in 62% yield and with complete enantiospecificity. Finally, oxidation with basic peroxide gave alcohol **56** in 89% yield, and subsequent Boc deprotection gave cobimetinib (Scheme 3).[5] This asymmetric synthesis of cobimetinib is shorter than previously reported routes,[37] and provides a modularity that potentially enables facile preparation of analogues through use of different boronic esters, acid halides, and/or boronic ester transformations.

In conclusion, we have developed a procedure that enables the modular construction of a diverse family of azetidines by the

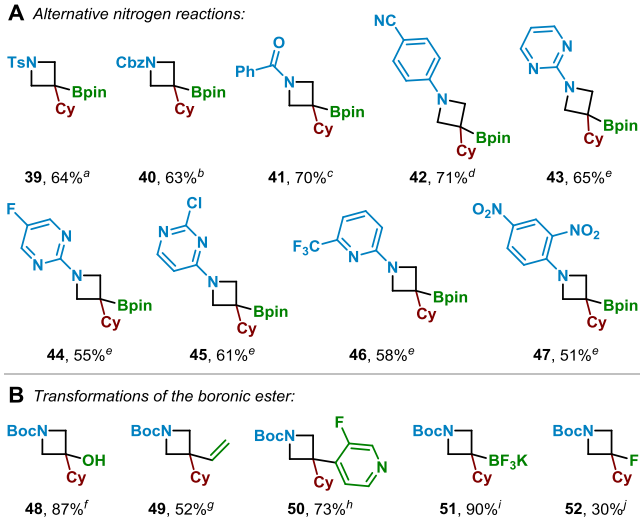
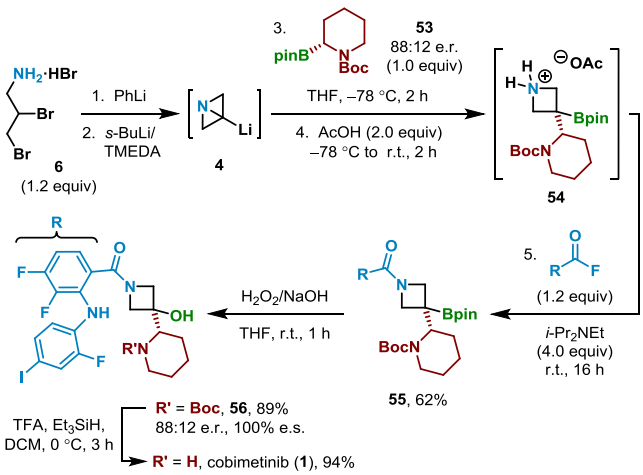


Figure 2. Synthetic transformations of borylated azetidines. (A) Alternative reactions at nitrogen. See Scheme 1A for conditions to form the acetic acid ammonium salt intermediate. Abbreviated reaction conditions: [a] TsCl, Et_3N; [b] benzyl chloroformate, Et_3N; [c] PhCOOH, *N*,*N*-diisopropylethylamine, HATU; [d] Tosic acid salt used, $Pd_2(dba)_3$, Xantphos, 4-bromobenzonitrile, NaO*t*Bu; [e] Ar-X (X = F or Cl), Et_3N. (B) Boronic ester transformations using **11** as the substrate. Abbreviated reaction conditions: [f] H_2O_2/NaOH; [g] vinyl lithium, then I_2, then NaOMe; [h] ArLi, then 2,2,2-trichloroethyl chloroformate, then H_2O_2/NaOH; [i] KHF_2; [j] trifluoroacetic acid, $AgNO_3$, Selectfluor®, then Boc_2O, Et_3N. Cbz = carboxybenzyl. Ts = *para*-toluenesulfonyl.

homologation of boronic esters with an azetidine unit. Key to success was the generation of azabicyclo[1.1.0]butyl lithium either directly from the ammonium salt **6** or via the sulfoxide **4**. This novel nucleophilic source of azabicyclo[1.1.0]butane is an unusual chemical building block that is likely to find broader applications in synthesis.

Scheme 3. Modular synthesis of cobimetinib.



ASSOCIATED CONTENT

Supporting Information

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

Detailed experimental procedures, and characterization data for new compounds (PDF).

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Notes

The authors declare no competing financial interests.

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