Fawcett, A., Murtaza, A., Gregson, C. H. U., & Aggarwal, V. K. (2019). Strain-Release-Driven Homologation of Boronic Esters: Application to the Modular Synthesis of Azetidines. *Journal of the American Chemical Society*, 141(11), 4573–4578.
<https://doi.org/10.1021/jacs.9b01513>

Peer reviewed version

License (if available):
Other

Link to published version (if available):
[10.1021/jacs.9b01513](https://doi.org/10.1021/jacs.9b01513)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the accepted author manuscript (AAM). The final published version (version of record) is available online via ACS at <https://doi.org/10.1021/jacs.9b01513> . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

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

Alexander Fawcett, Amna Murtaza,[†] Charlotte H. U. Gregson, and Varinder K. Aggarwal*

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, United Kingdom

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 azetidinyll 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

A Selected azetidine-containing pharmaceuticals:

B Previous work using bicyclo[1.1.0]butyl lithium:¹³

C This work using azabicyclo[1.1.0]butyl lithium:

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.

^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 azabicyclo[1.1.0]butane, generated *in situ* from ammonium salt **6** by treatment with phenyl lithium at $-78\text{ }^{\circ}\text{C}$,^{15l} could be lithiated using *s*-butyl lithium/TMEDA at $-78\text{ }^{\circ}\text{C}$ 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-methylbenzenesulfonate (**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 $-78\text{ }^{\circ}\text{C}$ with 1.3 equivalents of *tert*-butyl lithium¹³ 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 ¹¹B 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 group¹⁸ 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 group²⁰ 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] $\times$ 100%. d.s. (diastereospecificity) = [d.e. of product/d.e. of starting material] $\times$ 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-coupling³⁰ 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, azetidyl 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 fluoride⁵ delivered boronic ester **55** in 62% yield and with complete enantioselectivity. 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

A Alternative nitrogen reactions:

B Transformations of the boronic ester:

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, Et₃N; ^b benzyl chloroformate, Et₃N; ^c PhCOOH, *N,N*-diisopropylethylamine, HATU; ^d Tosic acid salt used, Pd₂(dba)₃, Xantphos, 4-bromobenzonitrile, NaOtBu; ^e Ar-X (X = F or Cl), Et₃N. (B) Boronic ester transformations using **11** as the substrate. Abbreviated reaction conditions: ^f H₂O₂/NaOH; ^g vinyl lithium, then I₂, then NaOMe; ^h ArLi, then 2,2,2-trichloroethyl chloroformate, then H₂O₂/NaOH; ⁱ KHF₂; ^j trifluoroacetic acid, AgNO₃, Selectfluor®, then Boc₂O, Et₃N. 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).

AUTHOR INFORMATION

Corresponding Author

*v.aggarwal@bristol.ac.uk

ORCID

Alexander Fawcett: 0000-0003-1880-3269

Varinder K. Aggarwal: 0000-0003-0344-6430

Present Addresses

[†]Department of Chemistry, Quaid-i-Azam University, Islamabad-45320, Pakistan.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENTS

We thank EPSRC (EP/I038071/1) and H2020 ERC (670668) for financial support. A.M. thanks the Commonwealth Scholarship Commission UK for a PhD Split Site Scholarship 2017–2018. We thank Steven H. Bennett for technical support and Dr A. Noble for proofreading.

REFERENCES

- Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.
- For reviews on the preparation and use of azetidines in organic synthesis, see: (a) Antermite, D.; Degennaro, L.; Luisi, R. Recent Advances in the Chemistry of the Metallated Azetidines. *Org. Biomol. Chem.* **2017**, *15*, 34–50; (b) Brandi, A.; Cicchi, S.; Cordero, F. M. Novel Syntheses of Azetidines and Azetidinones. *Chem. Rev.* **2008**, *108*, 3988–4035; (c) Cromwell, N. H.; Phillips, B. The Azetidines. Recent Synthetic Developments. *Chem. Rev.* **1979**, *79*, 331–358.

- (3) Veber, D. F.; Johnson, S. R.; Cheng, Y.-Y.; Smooth, B. R.; Ward, K. W.; Kopple, K. D. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* **2002**, *45*, 2615–2623.
- (4) (a) St. Jean, Jr., D. J.; Fotsch, C.; Mitigating Heterocycle Metabolism in Drug Discovery. *J. Med. Chem.* **2012**, *55*, 6002–6020. (b) Fish, P. V.; Brown, A. D.; Evrard, E.; Roberts, L. R. 7-Sulfonamido-3-benzazepines as Potent and Selective 5-HT_{2c} Receptor Agonists: Hit-to-Lead Optimization. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1871–1875. (c) Yan, Q.; Wang, Y.; Zhang, W.; Li, Y. Novel Azetidine-Containing TZZ-1027 Analogues as Antitumor Agents. *Mar. Drugs* **2016**, *14*, 85.
- (5) Rice, K. D.; Aay, N.; Anand, N. K.; Blazey, C. M.; Bowles, O. J.; Bussenius, J.; Costanzo, S.; Curtis, J. K.; Defina, S. C.; Dubenko, L.; Engst, S.; Joshi, A. A.; Kennedy, A. R.; Kim, A. I.; Koltun, E. S.; Lougheed, J. C.; Manalo, J.-C. L.; Martini, J.-F.; Nuss, J. M.; Peto, C. J.; Tsang, T. H.; Yu, P.; Johnston, S. Novel Carboxamide-Based Allosteric MEK Inhibitors: Discovery and Optimization Efforts Toward XL518 (GDC-0973). *ACS Med. Chem. Lett.* **2012**, *3*, 416–421.
- (6) Oizumi, K.; Nishino, H.; Koike, H.; Sada, T.; Miyamoto, M.; Kimura, T. Antihypertensive Effects of CS-905, a Novel Dihydropyridine Ca²⁺ Channel Blocker. *Japan J. Pharmacol.* **1989**, *51*, 57–64.
- (7) Keystone, E. C.; Taylor, P. C.; Drescher, E.; Schlichting, D. E.; Beattie, S. D.; Berclaz, P.-Y.; Lee, C. H.; Fidelus-Gort, R. K.; Luchi, M. E.; Rooney, T. P.; Macias, W. L.; Genovese, M. C. Safety and Efficacy of Baricitinib at 24 Weeks in Patients with Rheumatoid Arthritis who have had an Inadequate Response to Methotrexate. *Ann. Rheum. Dis.* **2015**, *74*, 333–340.
- (8) Yoda, H.; Takahashi, H. Sengoku, T. Chapter 2, Azetidine and Its Derivates, in *Heterocycles in Natural Product Synthesis*, First Edition, Eds. Majumdar, K.; Chattopadhyay, S. K. Wiley-WCH, 2011.
- (9) For recent articles on the preparation of piperidines, see: (a) Nebe, M. M.; Opatz, T. In *Advances in Heterocyclic Chemistry*; Scriven, E. F. V., Ramsden, C. A., Eds.; Academic Press: Cambridge, MA, **2017**, Vol. 122, 191–244; (b) Liu, G.-Q.; Opatz, T. In *Advances in Heterocyclic Chemistry*; Scriven, E. F. V., Ramsden, C. A., Eds.; Academic Press: Cambridge, MA, **2018**, Vol. 125, 201–234.
- (10) For recent examples, see: (a) Sakamoto, R.; Inada, T.; Sakurai, S.; Maruoka, K. [2+2] Photocycloadditions Between the Carbon–Nitrogen Double Bonds of Imines and Carbon–Carbon Double Bonds. *Org. Lett.* **2016**, *18*, 6252–6255; (b) Kumarasamy, E.; Kandappa, S. K.; Raghunathan, R.; Jockusch, S.; Sivaguru, J. Realizing an Aza Paternò-Büchi Reaction. *Angew. Chem. Int. Ed.* **2017**, *56*, 7056–7061; (c) Becker, M. R.; Richardson, A. D.; Schlindler, C. S. Visible Light-Mediated [2+2] Cycloaddition for the Synthesis of Azetidines via Energy Transfer. *ChemRxiv*, doi: 10.26434/chemrxiv.7218272.v1.
- (11) (a) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **2018**, *10*, 383–394. (b) See <https://www.europeanleadfactory.eu/> for a recent collaborative initiative toward discovering novel treatments for a variety of diseases using small molecular structures built in a modular fashion.
- (12) Sandford, C.; Aggarwal, V. K. Stereospecific Functionalizations and Transformations of Secondary and Tertiary Boronic Esters. *Chem. Commun.* **2017**, *53*, 5481–5494.
- (13) Fawcett, A.; Biberger, T.; Aggarwal, V. K. Carbopalladation of C–C σ -Bonds Enabled by Strained Boronate Complexes. *Nat. Chem.* **2019**, *11*, 117–122.
- (14) For the opening of epoxides, aziridines and azetidinium ions with concurrent 1,2-metalate rearrangement of a boronate complex, see: (a) Schmidt, F.; Keller, F.; Vedrenne, E.; Aggarwal, V. K. Sterecontrolled Synthesis of β -Amino Alcohols from Lithiated Aziridines and Boronic Esters *Angew. Chem. Int. Ed.* **2009**, *48*, 1149–1152. (b) 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. (c) 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) (a) Bartnik, R.; Marchand, A. P. Synthesis and Chemistry of Substituted 1-Azabicyclo[1.1.0]butanes. *Synlett* **1997**, 1029–1039. (b) Hayashi, K.; Sato, C.; Hiki, S.; Kumagai, T. Tamai, S.; Abe, T.; Nagao, Y. *Tetrahedron Lett.* **1999**, *40*, 3761–3764. (c) Hayashi, K.; Hiki, S.; Kumagai, T.; Nagao, Y. Synthesis of Azetidine Derivatives Using 1-Azabicyclo[1.1.0]butane. *Heterocycles* **2002**, *56*, 433–442. (d) Ikee, Y.; Hashimoto, K.; Kamino, M.; Nakashima, M.; Hayashi, K.; Sano, S.; Shiro, M.; Magao, Y. Synthesis of New Quinolone Antibiotics Utilizing Azetidine Derivatives Obtained from 1-Azabicyclo[1.1.0]butane. *Chem. Pharm. Bull.* **2008**, *56*, 246–356. (e) Woznicka, M.; Urbaniak, K.; Mloston, G.; Heimgartner, H. Strained 1-Azabicyclo[1.1.0]butanes in the Synthesis of Azetidinethiocarboxylate Derivatives. *Heterocycles* **2006**, *69*, 351–364. (f) Ikee, Y.; Hashimoto, K.; Nakashima, M.; Hayashi, K.; Sano, S.; Shiro, M.; Nagao, Y. Synthesis and Antibacterial Activities of New Quinolone Derivatives using 1-Azabicyclo[1.1.0]butane. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 942–945. (g) Dave, P. R. Acylative Dealkylation of *N*-tert-Butyl-3-substituted Azetidines: Facile Access to [1.1.0]Azabicyclobutane, 3-Hydroxyazetidinium Hydrochloride, and 3-Azetidinones. *J. Org. Chem.* **1996**, *61*, 5453–5455. (h) Bartnik, R.; Cal, D. New Method for the Generation and Trapping of 1-Azabicyclo[1.1.0]butane. Application to the Synthesis of 1,3-Dinitroazetidine. *Synth. Commun.* **1998**, *28*, 3949–3954. (i) Hayashi, K.; Sato, C.; Hiki, S.; Kumagai, T.; Tamai, S.; Abe, T.; Nagao, Y. Novel Efficient Synthesis of 1-Azabicyclo[1.1.0]butane and its Application to the Synthesis of 1-(1,3-Thiazolin-2-yl)azetidines-3-thiol Useful for the Pendant Moiety of an Oral β -Methylcarbapenem Antibiotic L-084. *Tetrahedron Lett.* **1999**, *40*, 3761–3764. (j) Marchand, A. P.; Rajagopal, D.; Bott, S. G. Reaction of 1-Aza-3-ethylbicyclo[1.1.0]butane with Electrophiles. A Facile Entry into New, N-Substituted 3-Ethylideneazetidines and 2-Azetines. *J. Org. Chem.* **1994**, *59*, 1608–1612. (k) Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C.-M.; Gianattasio, 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, J.; Baran, P. S. Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity. *J. Am. Chem. Soc.* **2017**, *139*, 3209–3226. (l) Gianattasio, 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. (m) Ji, Y.; Wojitas, L.; Lopchuk, J. M. An Improved, Gram-scale Synthesis of Protected 3-Haloazetidines: Rapid Diversified Synthesis of Azetidine-3-carboxylic Acids. *Arkivoc* **2018**, *4*, 195–214. (n) Marchand, A. P.; Alihodžić, S.; Bartnik, R.; Mloston, G. Reactions of 3-Ethyl- and 3-Phenyl-1-azabicyclo[1.1.0]butanes with Tosyl Chloride and Tosyl Azide. *Heterocycles* **1999**, *50*, 131–146.
- (16) For a review on the lithiation of aziridines, see: Florio, S.; Luisi, R. Aziridinyl Anions: Generation Reactivity, and Use in Modern Synthetic Chemistry. *Chem. Rev.* **2010**, *110*, 5128–5157.
- (17) Dammacco, M.; Degennaro, L.; Florio, S.; Luisi, R.; Musio, B.; Altomare, A. Lithiation of *N*-Alkyl-(*o*-tolyl)aziridine: Stereoselective Synthesis of Isochromans. *J. Org. Chem.* **2009**, *74*, 6319–6322.
- (18) Aichhorn, S.; Bigler, R.; Myers, E. L.; Aggarwal, V. K. Enantiospecific Synthesis of *ortho*-Substituted Benzylic Boronic Esters by a 1,2-Metalate Rearrangement/1,3-Borotropic Shift Sequence. *J. Am. Chem. Soc.* **2017**, *139*, 9519–9522.
- (19) (a) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215–5246. (b) Schönherr, H.; Cernak, T. Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation Reactions. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256–12276.

- (20) (a) Bottoni, A.; Lombardo, M.; Neri, A.; Trombini, C. Migratory Aptitudes of Simple Alkyl Groups in the Anionotropic Rearrangement of Quaternary Chloromethyl Borate Species: A Combined Experimental and Theoretical Investigation. *J. Org. Chem.* **2003**, *68*, 3397–3405. (b) Aggarwal, V. K.; Fang, G. Y.; Ginesta, X.; Howells, D. M.; Zaja, M. Towards an Understanding of the Factors Responsible for the 1,2-Migration of Alkyl Groups in Borate Complexes. *Pure Appl. Chem.* **2006**, *78*, 215–229.
- (21) Varela, A.; Garve, L. K. B.; Leonori, D.; Aggarwal, V. K. Stereoccontrolled Total Synthesis of (–)-Stemaphylline. *Angew. Chem. Int. Ed.* **2017**, *56*, 2127–2131.
- (22) Han, Y.; Han, M.; Shin, D.; Song, C.; Hahn, H.-G. Exploration of Novel 3-Substituted Azetidine Derivatives as Triple Reuptake Inhibitors. *J. Med. Chem.* **2012**, *55*, 8188–8192.
- (23) 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.
- (24) 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.
- (25) Fawcett, A.; Nitsch, D.; Ali, M.; Bateman, J. M.; Myers, E. L.; Aggarwal, V. K. Regio- and Stereoselective Homologation of 1,2-Bis(Boronic Esters): Stereoccontrolled Synthesis of 1,3-Diols and Sch 725674. *Angew. Chem. Int. Ed.* **2016**, *55*, 14663–14667.
- (26) Blair, D. J.; Tanini, D.; Bateman, J. M.; Scott, H. K.; Myers, E. L.; Aggarwal, V. K. Selective Uni- and Bidirectional Homologation of Diborylmethane. *Chem. Sci.* **2017**, *8*, 2898–2903.
- (27) Enantiospecificity (e.s.) = [e.e. of product/e.e. of starting material] × 100%.
- (28) Diastereospecificity (d.s.) = [d.e. of product/d.e. of starting material] × 100%.
- (29) Compounds **35–38** decompose on silica gel and were therefore quantified by analysis of the crude reaction mixtures by ¹H NMR spectroscopy against an internal standard. See the Supporting Information for details.
- (30) Bernhard, W. Palladium-Catalyzed N-Arylation Reactions with Aziridine and Azetidine. *Synthesis* **2007**, 243–250.
- (31) (a) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451–3479. (b) Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443–4458.
- (32) 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.
- (33) Llaveria, J.; Leonori, D.; Aggarwal, V. K. Stereospecific Coupling of Boronic Esters with N-Heteroaromatic Compounds. *J. Am. Chem. Soc.* **2015**, *137*, 10958–10961.
- (34) Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. Silver-Catalyzed Radical Fluorination of Alkylboronates in Aqueous Solution. *J. Am. Chem. Soc.* **2014**, *136*, 16439–16443.
- (35) (a) Hu, X.-G.; Hunter, L. Stereoselectively Fluorinated N-heterocycles: A Brief Survey. *Beilstein J. Org. Chem.* **2013**, *9*, 2696–2708. (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359.
- (36) Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. Asymmetric Deprotonation of N-Boc Piperidine: React IR Monitoring and Mechanistic Aspects. *J. Am. Chem. Soc.* **2010**, *132*, 7260–7261.
- (37) Hughes, D. L. Patent Review of Manufacturing Routes to Recently Approved Oncology Drugs: Ibrutinib, Cobimetinib, and Alectinib. *Org. Process Res. Dev.* **2016**, *20*, 1855–1869.

For Table of Contents (TOC) only.