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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Article

# Practical and Modular Construction of C(sp$^3$)-Rich Alkyl Boron Compounds

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Cite This: https://dx.doi.org/10.1021/jacs.0c11964
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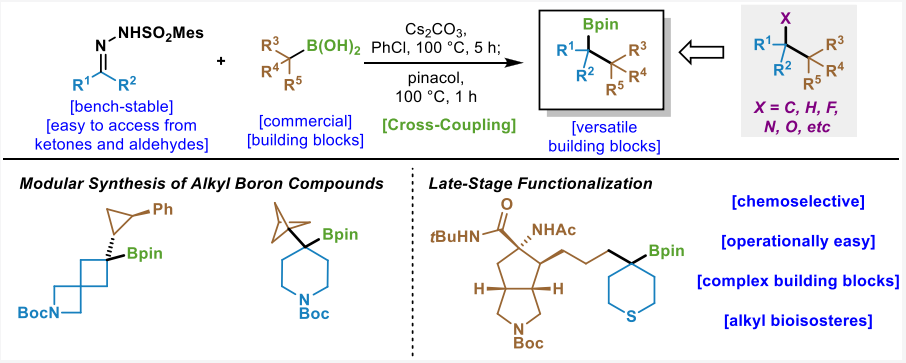


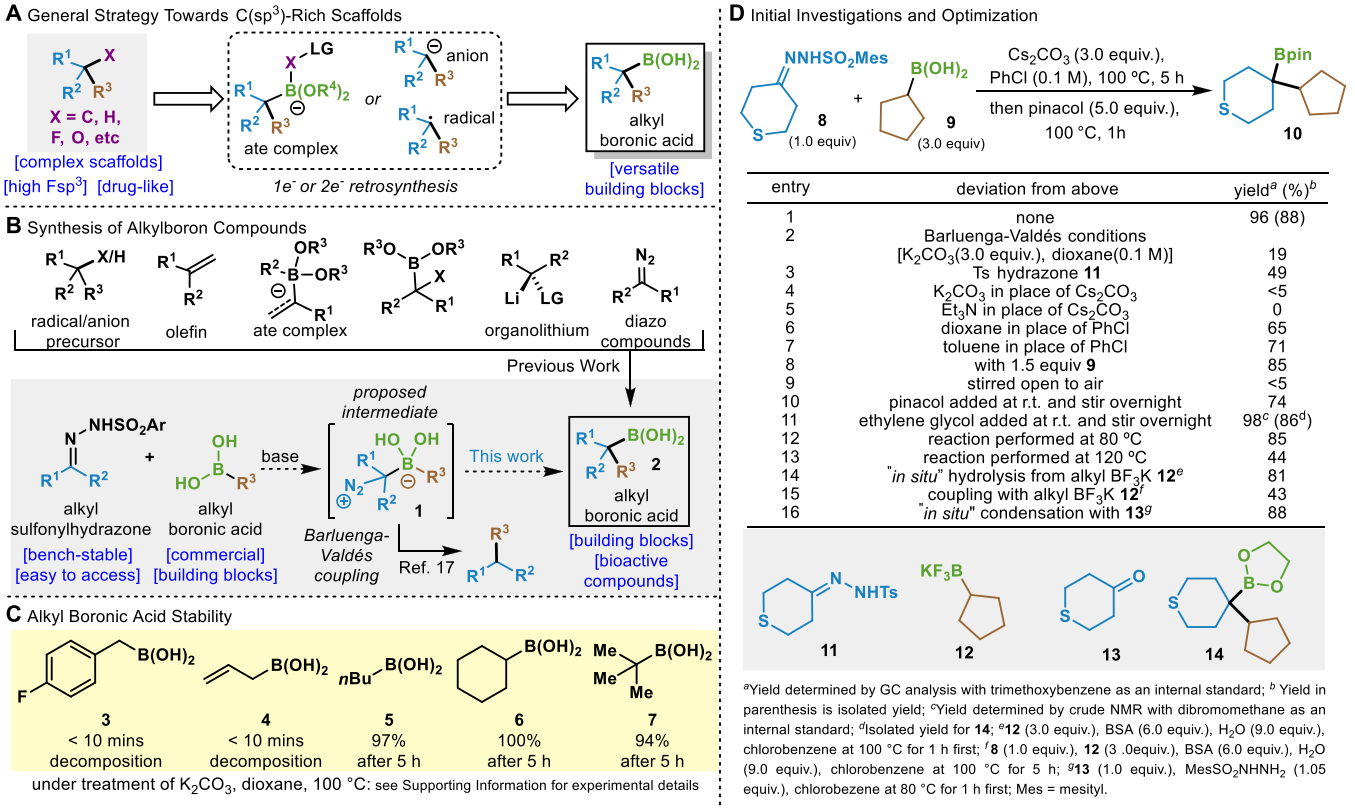

**ABSTRACT:** Alkyl boronic acids and esters play an important role in the synthesis of C(sp$^3$)-rich medicines, agrochemicals, and material chemistry. This work describes a new type of transition-metal-free mediated transformation to enable the construction of C(sp$^3$)-rich and sterically hindered alkyl boron reagents in a practical and modular manner. The broad generality and functional group tolerance of this method is extensively examined through a variety of substrates, including synthesis and late-stage functionalization of scaffolds relevant to medicinal chemistry. The strategic significance of this approach, with alkyl boronic acids as linchpins, is demonstrated through various downstream functionalizations of the alkyl boron compounds. This two-step concurrent cross-coupling approach, resembling formal and flexible alkyl−alkyl couplings, provides a general entry to synthetically challenging high Fsp$^3$-containing drug-like scaffolds.

## INTRODUCTION

Convergence and modularity are the key driving forces in the development of modern organic chemistry methodologies for the synthesis of complex molecules in both industry and academia. Recent developments in medicinal chemistry, showcasing the improved physiochemical and pharmacokinetic profiles of compounds with higher Fsp$^3$ (fraction of sp$^3$ carbon atoms), have resulted in an increased emphasis on sp$^3$-rich moieties.[1] This trend toward "increasing saturation" calls for a modular and versatile platform to form these C(sp$^3$)−C(sp$^3$) bonds. Over the past century, addition of alkyl organometallics, such as Grignard reagents, to electrophiles (carbonyls, imides, Michael acceptors, etc.) represents one of the most reliable approaches to construct C(sp$^3$)−C(sp$^3$) bonds.[2] Additionally, transition-metal-mediated cross-coupling, a "go-to" approach to access a diverse chemical space,[3] has more recently enabled the construction of a variety of C(sp$^3$)−C(sp$^3$) bonds. However, this process remains a very challenging undertaking[4] owing to the propensity of intermediary metal−alkyl complexes to undergo $\beta$-hydride elimination.[5] As such, complex hydrocarbons are often assembled in "roundabout" ways, leading to nonmodular, linear processes and detracting from overall efficiency.

With the increasing demand for the construction of C(sp$^3$)−C(sp$^3$) bonds in mind, we envisioned an alternate approach to access C(sp$^3$)-rich scaffolds via the preparation of an alkyl boronic acid intermediate that can be subsequently employed in further transformations. The alkyl boronic acid would function as a linchpin, allowing for stitching together of a variety of C(sp$^3$) scaffolds and heteroatoms (Figure 1A). The ability to access such an alkyl boron reagent would provide a powerful functional handle, allowing for a myriad of downstream functionalizations, including single- and two-electron transfer pathways, and 1,2-metalate rearrangements.[6] To this end, radical precursors (such as halides, pseudohalides, redox-

Received: November 15, 2020




| entry | deviation from above | yield[a] (%)[b] |
|---|---|---|
| 1 | none | 96 (88) |
| 2 | Barluenga-Valdés conditions [$K_2CO_3$(3.0 equiv.), dioxane(0.1 M)] | 19 |
| 3 | Ts hydrazone **11** | 49 |
| 4 | $K_2CO_3$ in place of $Cs_2CO_3$ | <5 |
| 5 | $Et_3N$ in place of $Cs_2CO_3$ | 0 |
| 6 | dioxane in place of PhCl | 65 |
| 7 | toluene in place of PhCl | 71 |
| 8 | with 1.5 equiv **9** | 85 |
| 9 | stirred open to air | <5 |
| 10 | pinacol added at r.t. and stir overnight | 74 |
| 11 | ethylene glycol added at r.t. and stir overnight | 98[c] (86[d]) |
| 12 | reaction performed at 80 °C | 85 |
| 13 | reaction performed at 120 °C | 44 |
| 14 | "*in situ*" hydrolysis from alkyl $BF_3K$ **12**[e] | 81 |
| 15 | coupling with alkyl $BF_3K$ **12**[f] | 43 |
| 16 | "*in situ*" condensation with **13**[g] | 88 |

[a]Yield determined by GC analysis with trimethoxybenzene as an internal standard; [b] Yield in parenthesis is isolated yield; [c]Yield determined by crude NMR with dibromomethane as an internal standard; [d]Isolated yield for **14**; [e]**12** (3.0 equiv.), BSA (6.0 equiv.), $H_2O$ (9.0 equiv.), chlorobenzene at 100 °C for 1 h first; [f]**8** (1.0 equiv.), **12** (3 .0equiv.), BSA (6.0 equiv.), $H_2O$ (9.0 equiv.), chlorobenzene at 100 °C for 5 h; [g]**13** (1.0 equiv.), $MesSO_2NHNH_2$ (1.05 equiv.), chlorobezene at 80 °C for 1 h first; Mes = mesityl.

**Figure 1.** Alkylboron synthesis enabled by transition-metal-free mediated alkyl−alkyl coupling. (A) Alkyl boronic acids as useful intermediates for synthesis of C($sp^3$)-rich scaffolds. (B) State-of-art synthesis of alkyl boron compounds and our modular approach toward alkylboron synthesis. (C) Alkyl boronic acid represents a more stable boronic acid in comparison with benzyl and allylic boronic acid. (D) Identification of a viable sulfonylhydrazone and reaction conditions to achieve the cross-coupling to access tertiary boronic ester.

active esters, and pyridinium salts),[7] olefins,[8] ate complexes,[9] organolithium reagents,[10] α-boryl carbanion/radical,[11] and diazo compounds[12] have been demonstrated to be powerful precursors to such alkyl boron species (Figure 1B). Given the advantages of boron intermediates in chemical synthesis, development of new practical and efficient methodologies to construct boron compounds are highly sought after. By leveraging the unique reactivity of the sulfone (VI) → sulfinate(IV) reduction, herein we showcase that readily available alkyl sulfonylhydrazones (from aldehydes or ketones) and alkyl boronic acids can be directly utilized to access sterically congested alkyl boron compounds in the absence of air-sensitive base or explosive reagents. This strategy would thus allow for modular and convergent construction of sterically hindered C($sp^3$)−C($sp^3$) bonds.

Here we describe a general, operationally friendly, modular, and scalable method for synthesis of C($sp^3$)-rich alkyl boronic esters. The transformation is exemplified through the synthesis of >110 alkyl boronic esters, including the late-stage derivatization of bioactive molecules and synthetic applications to rapidly access pharmaceutically relevant targets.

## RESULTS AND DISSCUSSION

**Identification of Sulfonylhydrazone for Boron-Preserved Coupling.** The literature is replete with examples of sulfonylhydrazones serving a variety of different roles in synthesis, from the venerable Bamford−Stevens reduction[13] and Eschenmoser−Tanabe fragmentation,[14] to both transition-metal-mediated[15] and transition-metal-free cross-couplings.[16] In the latter regard, the breakthrough report by Barluenga, Valdés, and co-workers[17] previously demonstrated the coupling of alkyl tosyl hydrazones with aryl/vinyl boronic acids in the presence of mild base to forge the C($sp^3$)−C($sp^2$) linkage (Figure 1B). In this seminal transformation, they propose formation of an alkyl boronic acid intermediate, which is spontaneously eliminated via protodeboronation[17] or intramolecular trapping by a cyano- or azide in a classic five- or six-membered ring transition state.[18,19] The isolation of the intermediate alkyl boronic acid was not reported in any of these communications. While the lability of benzylic and allylic boronic acids likely leads to the observed protodeboronation, we presumed nonbenzylic alkyl boronic acids would be more stable under these conditions ($K_2CO_3$, dioxane at 100 °C). To that end, the stability of a series of alkyl boronic acids were evaluated under Barluenga−Valdés conditions (Figure 1C). Gratifyingly, although the benzylic (**3**) and allylic (**4**) boronic acids decomposed rapidly (<10 min) under these conditions, simple primary, secondary, and tertiary alkyl boronic acids (**5**−**7**) demonstrated remarkable stability (>5 h) to the basic and high temperature conditions. On the basis of our results, we surmised that direct access to complex alkylboronic acids **2** could be achieved in a simple and modular fashion from the readily available sulfonylhydrazone and alkylboronic acid building blocks via 1,2-metalate rearrangement of zwitterion intermediate **1**. With this hypothesis in mind, we subjected alkyl tosylhydrazone **8** and cyclopentyl boronic acid **9** to the Barluenga−Valdés conditions (Figure 1D, entry 2) and observed that tertiary boronic ester **10** was observed in only 19% yield, with the majority of the mass balance resulting in decomposition of **8** to an uncharacterized complex mixture.


https://dx.doi.org/10.1021/jacs.0c11964
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

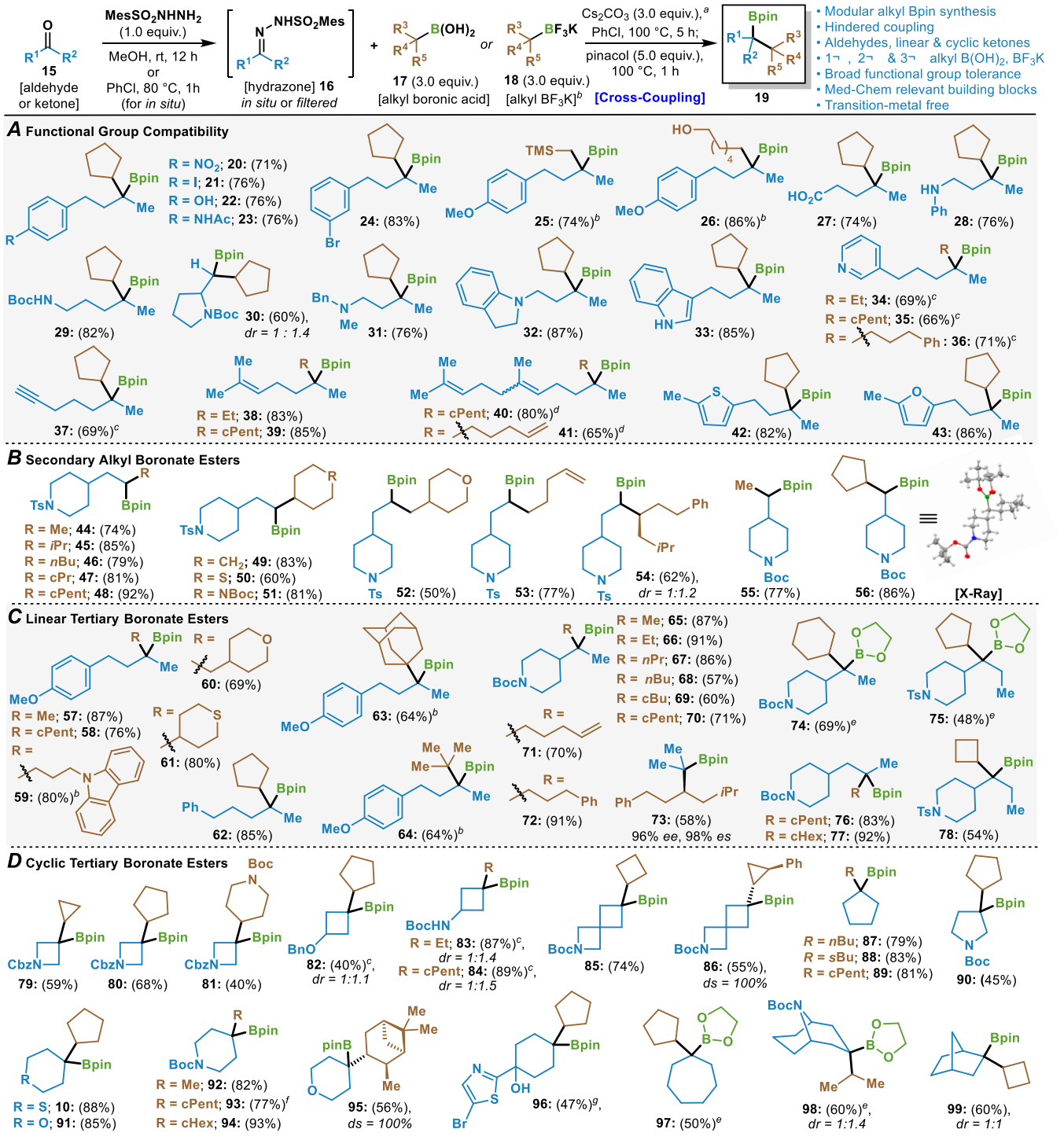



**Figure 2.** Scope of the cross-coupling between alkyl sulfonylhydrazones and alkyl boronic acids or alkyl trifluoroborate salts. Reaction conditions (denoted by superscript labels): (a) Sulfonylhydrazone **16** (1.0 equiv), $RB(OH)_2$ **17** (3.0 equiv), $Cs_2CO_3$ (3.0 equiv) in chlorobenzene (0.1−0.2 M) heated at 100 °C for 5 h; then pinacol (5.0 equiv) was added and stirred at 100 °C for another 1 h. (b) *In situ* hydrolysis of potassium alkyltrifluoroborates: $RBF_3K$ **18** (3.0 equiv), BSA (6.0 equiv), and $H_2O$ (9.0 equiv) in chlorobenzene (0.1−0.2 M) heated at 100 °C for 1 h. (c) *In situ* formation of sulfonylhydrazone. **15** (1.0 equiv), $MesSO_2NHNH_2$ (1.0 equiv), chlorobenzene at 80 °C for 1 h. (d) Starting material is an *E*/*Z* mixture. (e) Add glycol (5.0 equiv) instead of pinacol. (f) At 5 mmol scale. (g) Diastereomeric ratio is undetermined. See the Supporting Information for experimental details. BSA = bis(trimethylsilyl)acetamide.

We hypothesized that the sulfonylhydrazone with sterically hindered or electron-withdrawing substitutions could provide a mild approach to access the proposed intermediate **1**. Subsequent optimization of sulfonylhydrazone, base, solvent, and temperature (summarized in Figure 1D; see the Supporting Information for additional details) resulted in the identification of optimal conditions, which employ mesitylsulfonyl hydrazone, cesium carbonate, and chlorobenzene to afford coupling product **10** in 88% isolated yield (96% GC yield, entry 1). The combination of using mesitylsulfonyl hydrazone with cesium carbonate as the base was found to be the key, with any deviation from these optimized conditions,


https://dx.doi.org/10.1021/jacs.0c11964
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

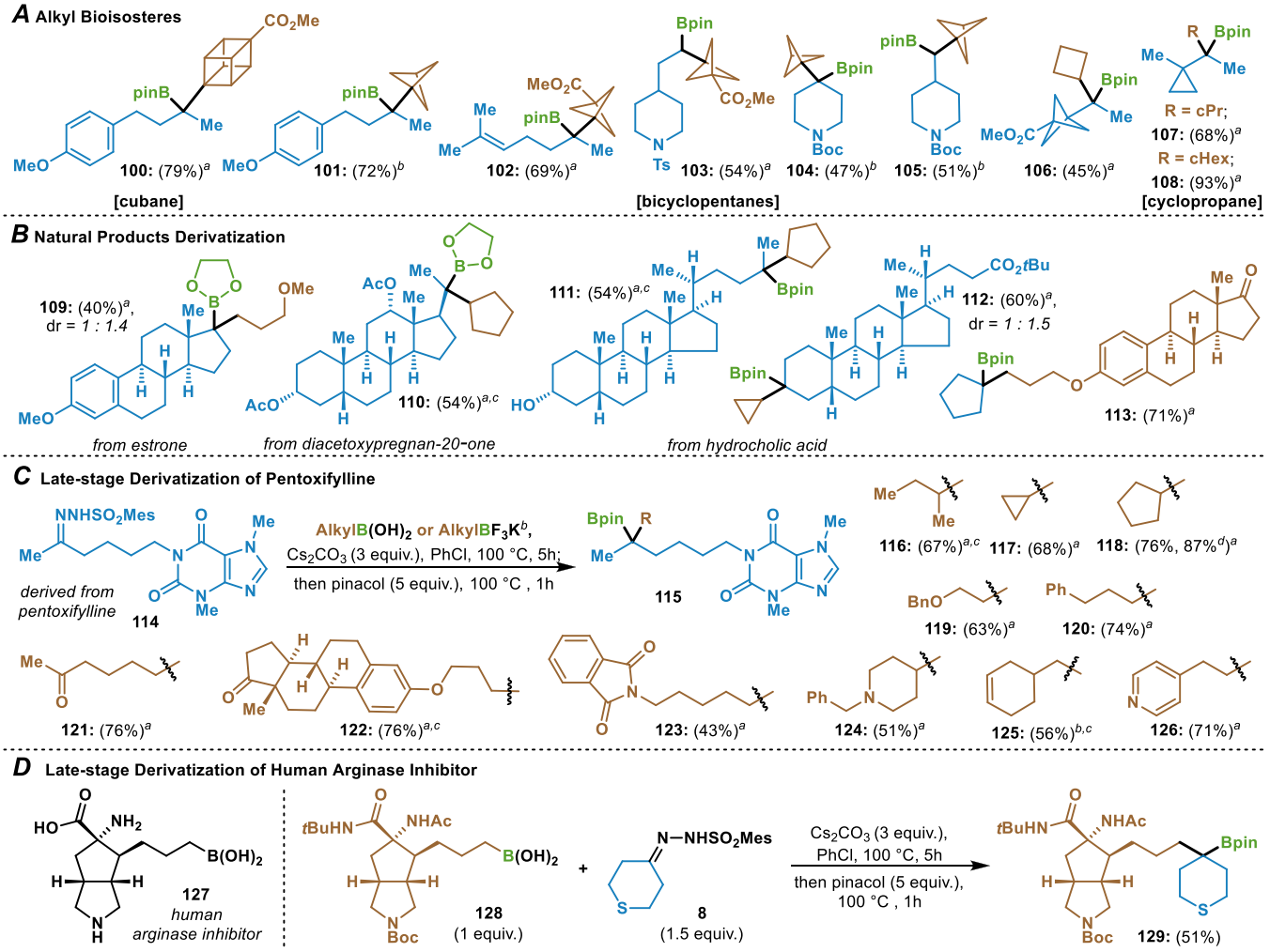



**Figure 3.** Late-stage derivatization to access alkyl boronic ester building blocks for enabling structure−activity relationship efforts. Superscripts denote reaction conditions: (a) Sulfonylhydrazone **16** (1.0 equiv), $RB(OH)_2$ **17** (3.0 equiv), $Cs_2CO_3$ (3.0 equiv) in chlorobenzene (0.1−0.2 M) heated at 100 °C for 5 h; then pinacol (5.0 equiv) was added and stirred at 100 °C for another 1 h. (b) *In situ* hydrolysis of potassium alkyltrifluoroborates: $RBF_3K$ **18** (3.0 equiv), BSA (6.0 equiv), and $H_2O$ (9.0 equiv) in chlorobenzene (0.1−0.2 M) heated at 100 °C for 1 h. (c) Diastereomeric ratio is undetermined. (d) At 5 mmol scale. See the Supporting Information for experimental details.

such as using an alternative sulfonylhydrazone (entry 3), base (entries 4 and 5), or solvent (entries 6 and 7) led to reduced yields or unreacted starting material. Employing 1.5 equiv of boronic acid **9** (entry 8) or using different temperatures also afforded product **10** (entries 12 and 13), albeit in lower yields. It is noteworthy that converting the initially generated alkylboronic acid to the corresponding pinacol ester was unexpectedly challenging (e.g., 0% yield for compound **74**, *vide infra*), presumably due to the steric hindrance of the generated tertiary boronic acid (entry 10). However, after further optimization, it was found that heating at 100 °C with pinacol (entry 1) or using ethylene glycol as a condensation reagent (entry 11)[20] enabled efficient boronic ester formation. Notably, despite sulfonylhydrazone **8** being easy to prepare and bench-stable (usually isolated as a crystalline solid by filtration), an *in situ* protocol was developed to enable functionalization of the starting ketone **13** in one pot (entry 16), resulting in comparable results to the optimized procedure. Additionally, procedures (entries 14 and 15) that employ the more stable (and commercial) potassium alkyltrifluoroborate **12** as a cross-coupling partner were also developed.[21] As a current limitation, pinacol boronic esters are not competent as coupling partners in this transformation (see the Supporting Information for detailed substrate limitations).

**Scope of the Alkyl Boronic Esters.** With the optimal conditions in hand, the robustness of this cross-coupling reaction was demonstrated through the preparation of over 80 substrates (Figure 2A−D). The substrate scope of this methodology was initially evaluated with a variety of functional groups on both sulfonylhydrazone and boronic acid coupling partners (Figure 2A). Of note, the nitro group (**20**), iodide (**21**), bromide (**24**), silyl (**25**), tertiary amines (**31** and **32**), alkyne (**37**), olefins (**38**−**41**), electron-rich heterocycles (**33**, **42**, and **43**), and electron-deficient heterocycles (**34**−**36**) are all compatible with this transformation. Additionally, this transformation was competent for a range of acidic proton-containing substrates, such as phenols (**22**), anilines (**23** and **28**), unprotected indoles (**33**), alkyl alcohols (**26**), carboxylic acids (**27**), and alkyl amines (**29**).[22] Therefore, the relatively mild conditions and excellent chemoselectivity of this transformation enables access to products that would be either be difficult or impossible to prepare via other known methodologies, including organolithium-promoted 1,2-metal-


https://dx.doi.org/10.1021/jacs.0c11964
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

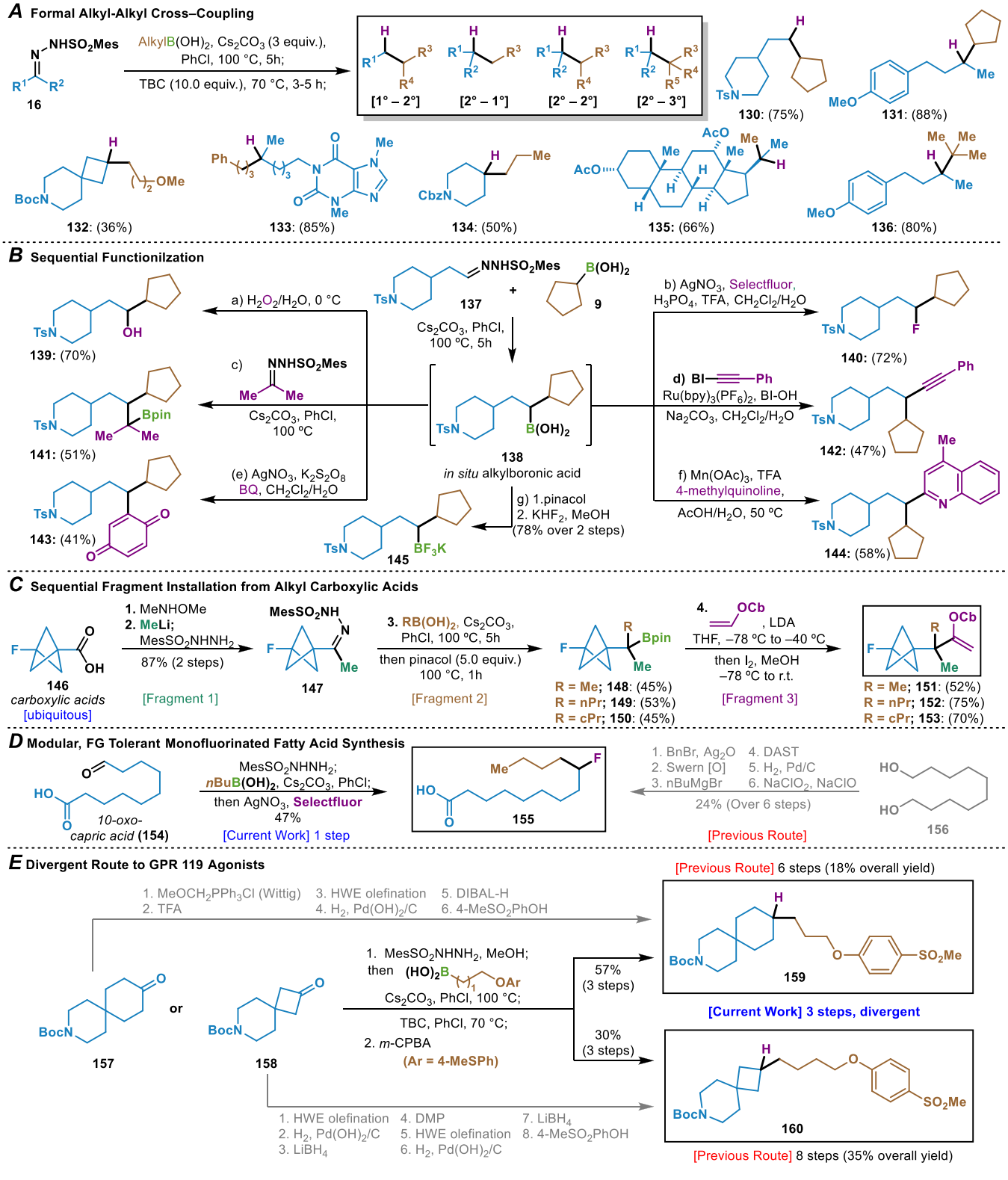



**Figure 4.** Strategic synthetic application. See the Supporting Information for experimental details. TBC = 4-*tert*-butylcatechol.

ate rearrangement and transition metal catalysis (one- or two-electron).[23]

Figure 2B demonstrates the construction of the C($sp^3$)–C($sp^3$) bond as a means to synthesize a broad range of secondary alkyl boronic esters. Primary (**44**, **46**, **52**, **53**, and **55**), branched (**45** and **54**), and cyclic (**47**, **48**–**51**, and **56**) secondary boronic acids were successfully coupled with an aldehyde-derived sulfonylhydrazone to afford the desired alkyl boronic esters in good yields. The structure of compound **56** was unambiguously confirmed by single crystal X-ray analysis.

As a testament to the efficiency of this transformation at enabling access to sterically hindered linear, tertiary alkyl boronic esters, 22 compounds with diverse substitution patterns were prepared and are delineated in Figure 2C


https://dx.doi.org/10.1021/jacs.0c11964
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

(**57**−**78**). Anisylacetone-derived sulfonylhydrazone was reacted with seven different alkyl boronic acids and alkyltrifluoroborate salts to access a series of tertiary alkyl boronic esters (**57**−**61**, **63**, and **64**). Of particular note are the tertiary 1-adamantyl- (**63**) and *tert*-butyl- (**64**) trifluoroborate salts, which served as viable coupling substrates for the formation of very hindered $C(sp^3)-C(sp^3)$ bonds. The sulfonylhydrazone derived from a more hindered piperidyl ketone also coupled smoothly with a variety of alkylboronic acids to deliver boronic ester products **65**−**72** and **74**−**78**. This transformation was not limited to methyl ketone-derived sulfonylhydrazones, and was also compatible with additional $\alpha$-substitutions on the ketone (**75** and **78**). In the case of transition-metal-mediated stereospecific coupling,[24] the stereocenter on a chiral nucleophile readily racemizes via one-electron or metal hydride pathways, thereby leading to erosion in stereochemical fidelity. In contrast, the mechanistic details of this transformation, which involve a direct transition-metal-free 1,2-metalate rearrangement on boron, enables the coupling of a chiral alkyl boronic acid[25] (**73**) with complete stereochemical fidelity. Due to the highly sterically encumbered nature of some of the alkyl boronic acid substrates, ethylene glycol was selected as a more efficient trapping reagent (**74** and **75**) in lieu of pinacol.

In Figure 2D, a wide range of sulfonylhydrazones derived from cyclic ketones were investigated (**79**−**99**). A variety of four- to seven-membered ring systems, including azetidine (**79**−**81**), cyclobutane (**82**−**84**), azaspiro[3.3]-heptane (**85** and **86**), cyclopentane (**87**−**89**), pyrrolidine (**90**), thiane (**10**), tetrahydropyran (**91** and **95**), piperidine (**92**−**94**), cyclohexane (**96**), cycloheptane (**97**), azabicyclo[3.3.1]nonane (**98**), and norbornane (**99**) underwent cross-coupling smoothly with primary and secondary alkyl boronic acids. The transformation exemplifies excellent diastereomeric specificity, with the stereochemistry of the starting alkyl boronic acid transferred to the product with complete fidelity (**86** and **95**).

A number of these substrates in Figure 2 were accessed using the *in situ* protocol from the corresponding aldehyde or ketone or via the *in situ* hydrolysis of the potassium alkyl trifluoroborate salts, highlighting the synthetic practicality of this method. This operationally simple reaction was also scalable and provided comparable yields on 5 mmol scale couplings (**93** and **118**, *vide infra*).

**Synthesis of Alkyl Bioisostere-Containing Boronic Esters and Late-Stage Derivatization.** The synthetic applicability of this modular cross-coupling is showcased by straightforward preparation of a variety of alkyl bioisostere-containing boronic ester building blocks (Figure 3A). Alkyl bioisosteres such as cubanes, bicyclo[1.1.1]pentanes (BCPs) and cyclopropanes, have been shown to improve drug candidates' physiochemical and pharmacokinetics properties[26] and as such, new methods for their installation and functionalization are highly sought after.[27] To this end, boronic acids derived from BCP and cubane trifluoroborate salts,[7c,d] reacted smoothly with linear ketone- (**100**−**102**) and aldehyde- (**103**) derived sulfonylhydrazones to afford the expected coupling products in good yields. Excellent results were also observed for the introduction of BCPs onto the C4-position of the pharmaceutically relevant piperidine scaffold (**104** and **105**). Moreover, a sulfonylhydrazone derived from highly sterically encumbered BCP ketone also coupled readily with cyclobutyl boronic acid (**106**). In a similar vein, the 1-methyl cyclopropyl group, a *tert*-butyl bioisostere, was also compatible in the coupling (**107** and **108**).[28] In contrast to one-electron approaches, where rapid ring opening is observed when a radical is generated adjacent to strained ring systems (such as 1-methyl cyclopropyl and BCPs),[29] this cross-coupling demonstrates remarkable tolerance in preserving these motifs (**106**−**108**).

Given the prevalence of steroids as biologically active scaffolds, functionalization of a variety of steroids was targeted. Both ketone (**109**−**112**) and boronic acid (**113**) derived steroidal coupling partners delivered products in synthetically useful yields. Among which, the resultant highly sterically encumbered boronic acids from estrone (**109**) and pregnane-20-one (**110**) were trapped by ethylene glycol, while pinacol was used in the cases of lithocholic acidic derivatives (**111**−**113**).

The modularity of this approach and ability to rapidly generate a "library" of complex alkyl boronic esters from simple building blocks was exemplified in the late-stage functionalization of nitrogen atom-rich pentoxifylline, a commonly used medication to treat peripheral arterial disease. As shown in Figure 3C, a variety of primary (**119**−**123**) and secondary (**116**−**118**) alkyl motifs, including medicinally relevant heterocycles such as pyridine (**126**) and piperidine (**124**), were introduced with good to excellent yields. Notably, estrone and pentoxifylline, two distinct and structurally complex molecules, could be linked together (**122**) in excellent yield.

Historically, alkyl boronic acids have been primarily regarded as versatile synthetic building blocks. However, more recently, their unique biological activity has attracted medicinal chemists' attention for incorporation into drug candidates.[30] One such example is the bicyclic alkyl boronic acid **127** reported by Merck and Co., Inc., as a human arginase inhibitor to enhance cancer immunotherapy.[31] Notably, any transposition of the boronic acid motif itself would typically require a *de novo* route for each new analog during structure−activity relationship (SAR) exploration. However, this methodology now enables the late-stage derivatization of an advanced boronic acid intermediate, such as **128**, in a single step.

**Strategic Applications via Alkyl Boronic Acid and Ester Functionalizations.** As illustrated in Figure 4, the strategic impact of this methodology shines in its ability to combine the modular synthesis of any alkyl boronic acid with the power of boronic acids to serve as one of the most versatile functional groups. This synergistic application of two highly modular and complexity generating transformations opens up limitless possibilities for rapid synthesis of complex druglike scaffolds.[32] First, as shown in Figure 4A, to address the limitations of transition-metal-catalyzed cross-couplings to access hindered $C(sp^3)-C(sp^3)$ bonds (*vide supra*), a cross-coupling/reductive protodeboronation sequence was developed.[33] This formal alkyl−alkyl cross-coupling provides a modular approach to access a variety of unfunctionalized $C(sp^3)-C(sp^3)$ bonds. Starting from ketones, these targets have traditionally been prepared via olefination followed by hydrogenation (*vide infra*) or Grignard addition followed by deoxygenation. Such multistep routes typically rely on often difficult to access reagents and harsh conditions, while the sequential coupling shown in this context has combined our $2e^-$ coupling with 4-*tert*-butylcatechol (TBC)-mediated mild radical protodeboronation conditions.[33] This modular and highly functional group tolerant protocol proceeds in one pot from alkyl sulfonylhydrazones **16** and alkyl boronic acids,


https://dx.doi.org/10.1021/jacs.0c11964
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allowing direct access to a range of C($sp^3$)−C($sp^3$) bonds, with varied substitution patterns and functional groups (**130**−**136**). Therefore, this approach represents a formal cross-coupling between primary (**130**) or secondary (**131**−**136**) alkyl electrophiles with either primary (**132**−**135**), secondary (**130** and **131**), or tertiary (**136**) nucleophiles (boronic esters) and enables the formation of C($sp^3$)−C($sp^3$) bonds that could not be accessed by the state-of-the-art transition metal catalysis.

Additionally, versatile alkyl boronic acid intermediates (e.g., **138**) can be parlayed into diverse structures through distinct modes of reactivity (Figure 4B). For example, the *in situ* oxidation of boronic acid **138** led to the alcohol (**139**) in high yield. This transformation mimics the classical Grignard addition into ketone, but it obviates the requirement of a strong organometallic reagent. One intriguing feature of this methodology is that the products are also viable coupling partners. Therefore, iterative coupling to build complex $sp^3$-rich scaffolds can be realized through sequential addition of different sulfonylhydrozones. As illustrated in Figure 4B(c), *in situ* generated alkyl boronic acid **138** was treated with a second sulfonylhydrazone to generate two new C($sp^3$)−C($sp^3$) bonds. Subsequent trapping with pinacol enables isolation of the iterative coupling product (**141**) in good yield. In addition to $2e^-$ functionalizations of **138**, under treatment with a radical initiator or oxidant, the alkylboronic acid acts as a radical progenitor to generate an alkyl radical, which could then participate in sequential radical cross-couplings. This is showcased by subsequent fluorination (**140**),[34] photomediated alkynylation (**142**),[35] and Minisci-type radical addition (**143** and **144**)[36] from *in situ* alkyl boronic acid **138**. They can also be transformed to the more stable trifluoroborate salt (**145**), which are themselves valuable substrates for radical transformations via photoinduced electron transfer.[37]

The synthesis of F-BCP analogs (**151**−**153**) in Figure 4C provides a template for a general synthetic strategy to enable the programmable construction of fully substituted quaternary carbon centers from ubiquitous alkyl carboxylic acids. Starting from the carboxylic acid oxidation state, sequential installation of three distinct fragments via (1) nucleophilic addition of alkyl lithium to Weinreb-amide, (2) cross-coupling with alkyl boronic acid (**148**−**150**), and (3) Zweifel olefination[38] of boronic esters to vinyl carbamate afforded the desired products (**151**−**152**) with complete control and selectivity.

Monofluorinated myristic acid analogs such as **155** are useful probes in the study of membrane topology due to the high sensitivity of $^{19}F$ NMR.[39] The previous approach to **155** required a 6-step linear synthetic sequence starting from 1,2-decanediol **155** (Figure 4D), with several protecting group and redox manipulations that were dictated by the functional group incompatibility of *n*-butyl Grignard reagents with alcohols or carboxylic acids. In contrast, a much simpler retrosynthetic template emerges using this cross-coupling strategy, wherein all three partners could be stitched together in one step without redox or protecting group manipulations. Starting from 10-oxocapric acid (**154**), cross-coupling with *n*-butyl boronic acid, followed by *in situ* deborylative fluorination of the intermediate alkyl boronic acid provides monofluorinated fatty acid **155** in 47% yield. This demonstrates a real-life example where the power of a successive cross-coupling strategy with broad functional group tolerance allows for rapid and modular generation of C($sp^3$)-rich scaffolds.

The final case study (Figure 4E) is drawn from the patent literature, wherein medicinal chemists at Taisho Pharmaceutical were interested in the azaspiroalkanes **159** and **160** as intermediates toward GPR119 agonists.[40] Although both analogs have a similar alkyl chain spacer with the only difference being the identity of the azaspiro fragment, step-intensive *de novo* approaches (6−8 steps) were required to access each target from the its corresponding azaspiro ketones (**157** and **158**). Using the cross-coupling/radical protodeboronation protocol, late-stage and modular installation of either of the azaspiro fragments could be achieved from a common intermediate, allowing for a streamlined and divergent route to both targets **159** and **160**.

As showcased in Figures 2−4, starting from readily available and bench-stable starting materials, this operationally simple method allows for the rapid and modular preparation of a variety of complex, C($sp^3$)-rich alkyl boronic esters. In addition to providing access to pharmaceutically relevant building blocks, this transformation harnesses the versatility of alkyl boron compounds to delineate a novel template that simplifies retrosynthetic planning and enables structure−activity relationships (SAR) of lead candidates. As such, numerous applications of this methodology can be anticipated in both academia and industry for rapidly accessing boronic acid derivatives and forging C($sp^3$)−C($sp^3$) bonds that were previously inaccessible.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11964.

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

Crystallographic information for **56** (CIF)

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https://dx.doi.org/10.1021/jacs.0c11964
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

### Author Contributions

[‖]Y.Y. and J.T. contributed equally to this work.

### Funding

Financial support for this work was provided by the Robert A. Welch Foundation (Grant I-2010−20190330) and the Eugene McDermott Scholar Endowed Scholarship. Green Fellow supported an undergraduate fellowship to A.B.D.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Feng Lin (UTSW) for assistance with NMR spectroscopy; Hamid Baniasadi (UTSW) for HRMS; Vincent Lynch (UT-Austin) and Delphine Gout (UT-Arlington) for X-ray crystallographic analysis; Prof. Uttam Tambar (UTSW) for chiral HPLC instrument access. We are grateful to Professors Joseph Ready (UTSW), Uttam Tambar (UTSW), Patrick Fier (Merck), Cedric Hugelshofer (Merck), James Roane (Merck) for feedback on this manuscript.

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