A Practical and Modular Construction of C(sp^3)-rich Alkyl Boron Compounds

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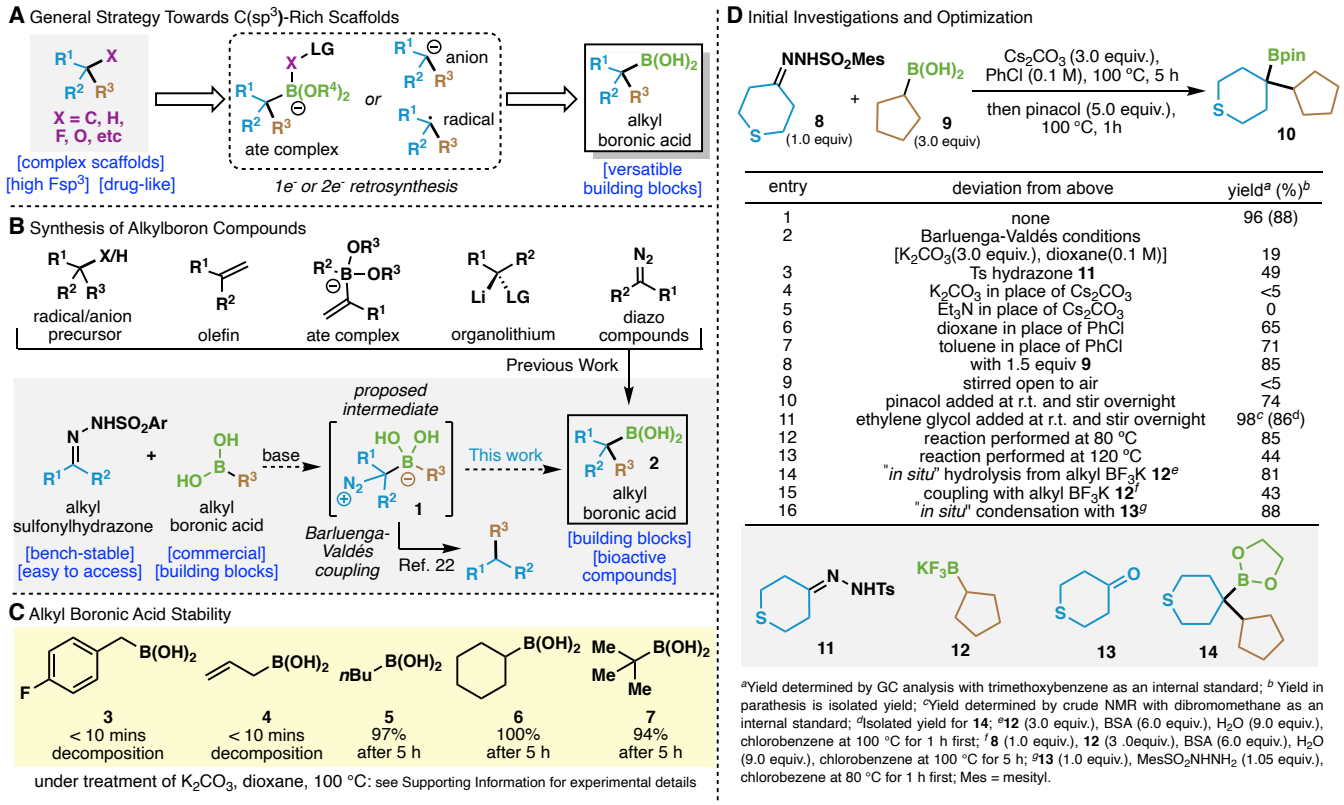
ABSTRACT: Alkyl boronic acids and esters play an important role in the synthesis of C(sp^3) rich medicines, agrochemicals, and other materials. This work describes a new type of transition-metal free mediated transformation to enable the construction of C(sp^3)-rich, and sterically hindered alkyl boron 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 acid as a linchpin, 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 previously 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), has resulted in an increased emphasis on sp^3-rich moieties[1,2]. 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 *et al.*) represents one of the most reliable approaches to construct C(sp^3)–C(sp^3) bonds[3]. Additionally, transition metal-mediated cross-coupling, a "go-to" approach to access diverse chemical space[4], 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[5] owing to the propensity of intermediary metal-alkyl complexes to undergo β-hydride elimination[6,7]. As such, complex hydrocarbons are often assembled in "roundabout" ways, leading to non-modular, 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 to stitch a variety of C(sp^3) scaffolds and heteroatoms together (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-metallate rearrangements[8-10]. To this end, radical precursors (such as halides, pseudo-halides, redox-active esters)[11,12], olefins, ate complexes[13], organolithium reagents[14], and stable diazo compounds[15,16] have been demonstrated as powerful precursors to such alkyl boron species (Figure 1B). However, these approaches towards alkyl boron compounds are either non-modular and/or require air- and moisture sensitive organometallic reagents or potentially explosive diazo compounds. 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 strong 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 present the invention of a general, operationally friendly, modular and scalable synthesis of C(sp^3)-rich alkyl boronic esters. The transformation is exemplified through the synthesis of >110 alkyl boronic esters, including late-stage derivatization of bioactive molecules and synthetic applications to rapidly access pharmaceutically relevant targets.



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 parathesis 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**) The state-of-art for synthesis of alkyl boron compounds and our modular approach towards 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.

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[17] and Eschenmoser-Tanabe fragmentation[18], to both transition metal-mediated[19,20] and transition-metal free cross-couplings[21]. In the latter regard, the breakthrough report by Barluenga, Valdés and co-workers[22] 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 intermediate, which is spontaneously eliminated via protodeboronation[22-25]. While the lability of benzylic and allylic boronic acids likely leads to the observed protodeboronation, we presumed other unactivated alkyl boronic acids would be more stable under these conditions. 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 heat conditions. Based on these 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-metallate rearrangement of the 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 the tertiary boronic ester **10** was observed in only 19% yield, with majority of the mass balance resulting in decomposition of **8** to an uncharacterized complex mixture. We hypothesized that the sulfonylhydrazone with steric hindered or electro-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, full table in supplementary information) resulted in the identification of optimal conditions, which employ mesitylsulfonyl hydrazone, cesium carbonate and chlorobenzene to afford the coupling product **10** in 88% isolated yield (96% GC yield) (Entry 1). Any deviation from these optimized conditions, such as using an alternative sulfonylhydrazone (Entry 3), base (Entries 4 and 5), or solvent (Entries 6 and 7) led to reduced yields or starting material remained. Employing 1.5 equivalents of boronic acid **9** (Entry 8) or using different temperatures also afforded the 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 for pinacol alcohol (Entry 1) or using ethylene glycol as a condensation reagent (Entry 11)[26] 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 14–15) that employ the more stable potassium alkyltrifluoroborate **12** as a cross-coupling partner were also developed[27]. Under these conditions, the less Lewis acidic alkyl boronic ester were not competent as coupling partners.

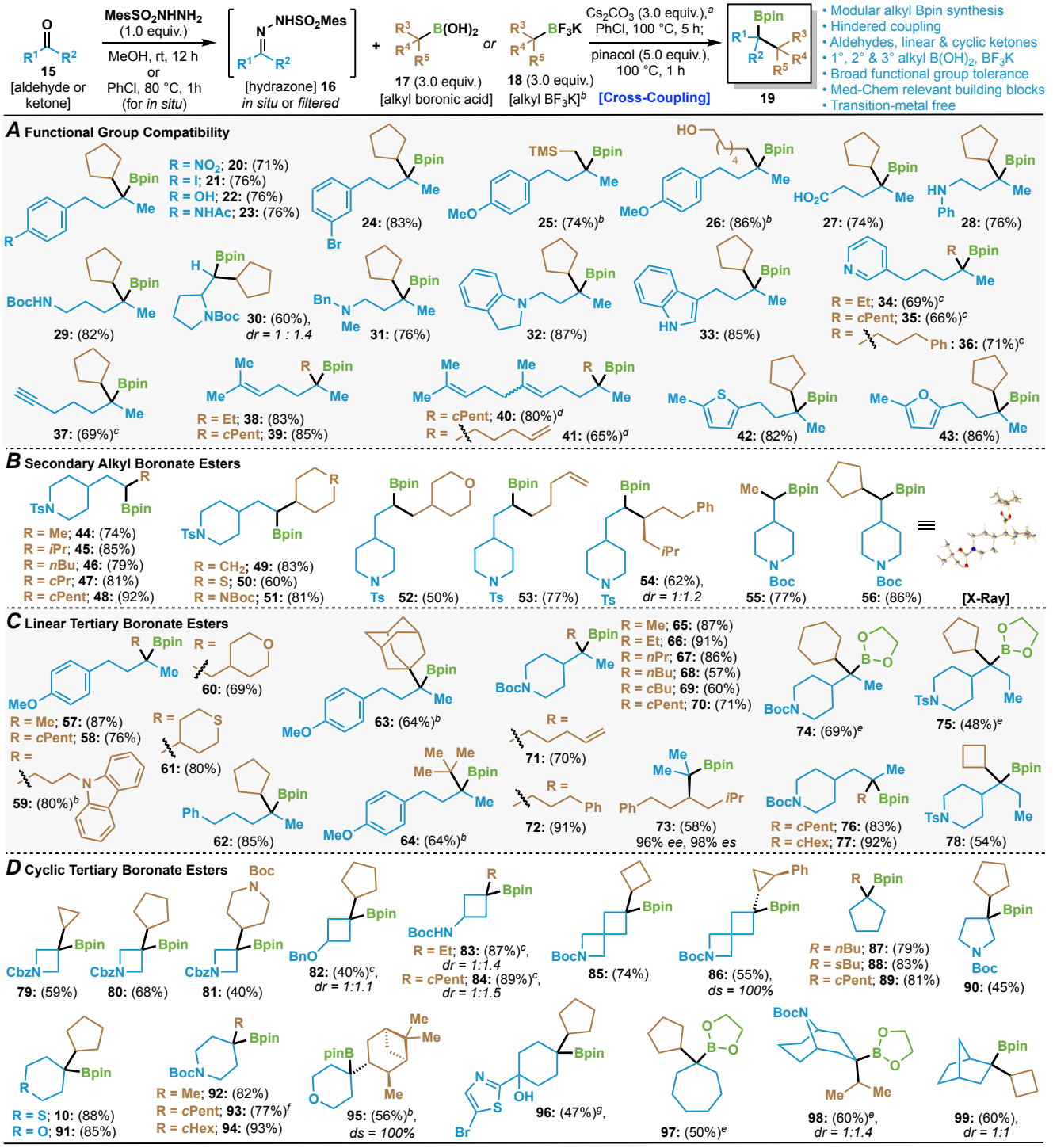


Figure 2. Scope of the Cross-Coupling between Alkyl Sulfonylhydrazones and Alkyl Boronic acids or Alkyl Trifluoroborate Salts. Reaction conditions: [a] Sulfonylhydrazone **16** (1.0 equiv.), $RB(OH)_2$ **17** (3.0 equiv.), Cs_2CO_3 (3.0 equiv.) in chlorobenzene (0.1-0.2 M) heated at 100 ºC for 5 h; then 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 ºC for 1h; [c] *In situ* formation of sulfonylhydrazone. **15** (1.0 equiv.), $MesSO_2NHNH_2$ (1.0 equiv.), chlorobenzene at 80 ºC for 1 h; [d] starting material is an E/Z mixture; [e] add glycol (5.0 equiv.) instead of pinacol; [f] 5 mmol scale; [g] diastereomeric ratio is undetermined; See the Supplementary information for experimental details.

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 2, Panels A-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 2, Panel A). Of note, the nitro group (**20**), iodide (**21**), bromide (**24**), silyl (**25**), tertiary amines (**31**, **32**), alkyne (**37**), olefins (**38**–**41**), electron-rich heterocycles (**33**, **42**, **43**), and electron-deficient heterocycles (**34**–**36**) are all compatible with this transformation. Additionally, despite alcohols, acids, and amines, are known coupling partners with sulfonylhydrazones[28,29], this transformation was competent for a range of acidic proton-containing substrates, such as phenol (**22**), anilines (**23**, **28**), unprotected indole (**33**), alkyl alcohol (**26**), carboxylic acid (**27**) and alkyl amines (**29**). Therefore, the relatively mild conditions and excellent chemoselectivity of this transformation enables access to products that would be either difficult or impossible to prepare via other known methodologies, including organolithium-promoted 1,2-metallate rearrangement and transition-metal catalysis (one- or two-electron)[30].

Panel B demonstrates the construction of $C(sp^3)$–$C(sp^3)$ bond as a means to synthesize a broad range of secondary alkyl boronate esters. Primary (**44**, **46**, **52**, **53**, **55**), branched (**45**, **54**) and cyclic (**47**, **48**–**51**, **56**) secondary boronic acids were successfully coupled with an aldehyde derived sulfonylhydrazone to afford the desired alkyl boronate 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 boronate esters, 22 compounds with diverse substitution patterns were prepared and are delineated in Panel C (**57**–**78**). Anisylacetone-derived sulfonylhydrazone was reacted with seven different alkyl boronic acids and alkyltrifluoroborate salts to access a series of tertiary alkyl boronate esters (**57**–**61**, **63**, **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 the 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 α-substitutions on the ketone (**75**, **78**). In the case of transition-metal mediated stereospecific coupling[31], 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-metallate rearrangement on boron, enables the coupling of a chiral alkyl boronic acid (**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**, **75**) in lieu of pinacol.

In Panel D, 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**, **86**), cyclopentane (**87**–**89**), pyrrolidine (**90**), thiane (**10**), tetrahydropyran (**91**, **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**, **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**; **118**, *vide infra*).

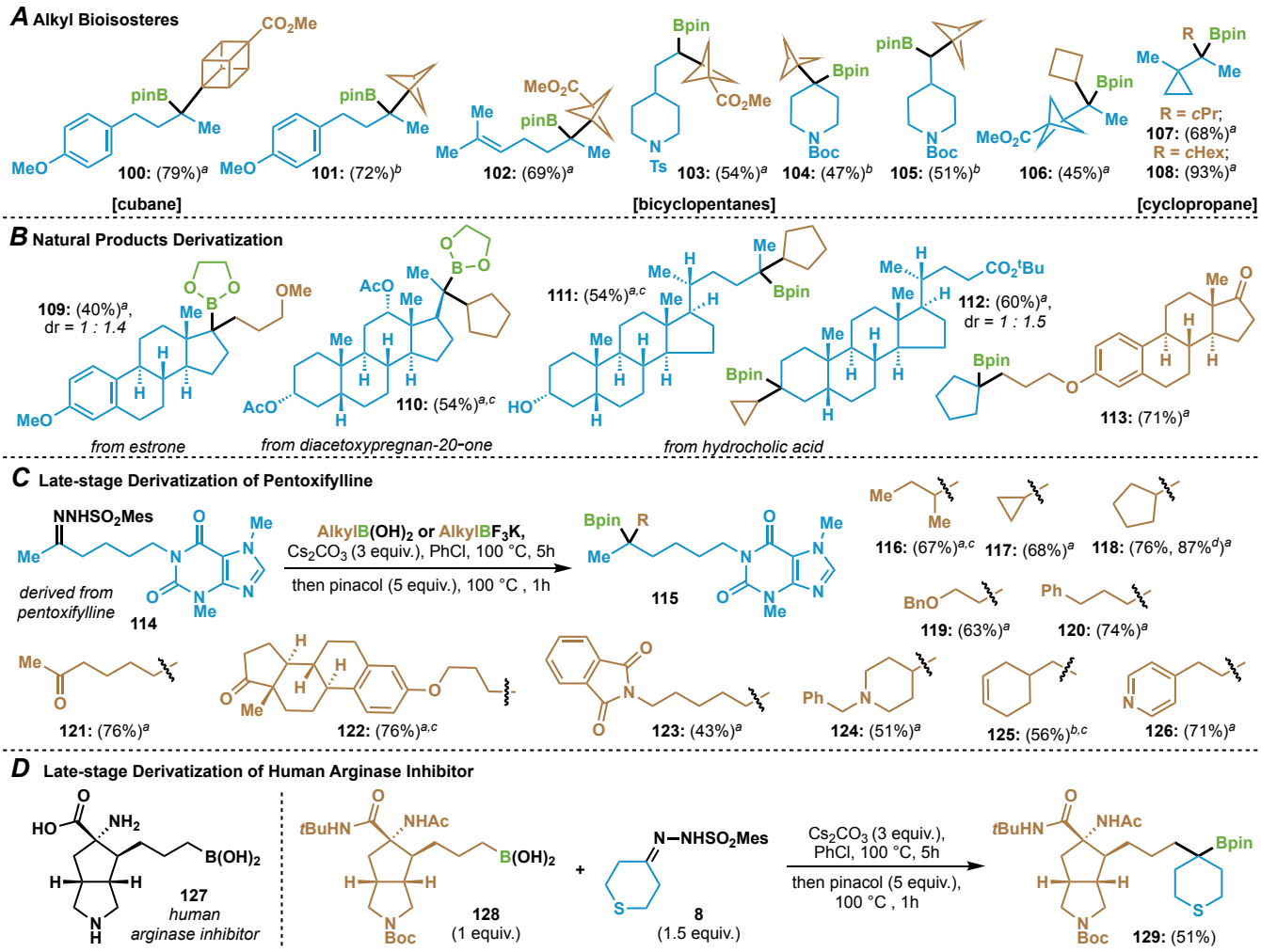


Figure 3. Late-Stage Derivatization to Access Alkyl Boronic Ester Building Blocks and Enable Structure-Activity Relationship Efforts. [a] Reaction conditions: Sulfonylhydrazone **16** (1.0 equiv.), $RB(OH)_2$ **17** (3.0 equiv.), Cs_2CO_3 (3.0 equiv.) in chlorobenzene (0.1-0.2 M) heated at 100 ºC for 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 ºC for 1h; [c] diastereomeric ratio is undetermined; [d] 5 mmol scale. See the Supplementary Materials for experimental details.

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 bioisosteres-containing boronic ester building blocks (Figure 3, Panel A). Alkyl bioisosteres such as cubanes, bicyclo[1.1.1]pentanes (BCPs) and cyclopropanes, have been shown to improve drug candidates' physiochemical and pharmacokinetics properties[32] and as such, new methods for their installation and functionalization are highly sought after[33]. To this end, boronic acids derived from BCP and cubane trifluoroborate salts[34,35], 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**, **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, 108**)[36]. 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)[37], 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 encumberedboronic 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 panel C (Figure 3), 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[38]. One such example is the bicyclic alkyl boronic acid **128** which was reported by Merck and Co., Inc as a human arginase inhibitor to enhance cancer immunotherapy[39]. 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 of derivatization of an advanced boronic acid intermediate, such as **128**, in a single step.

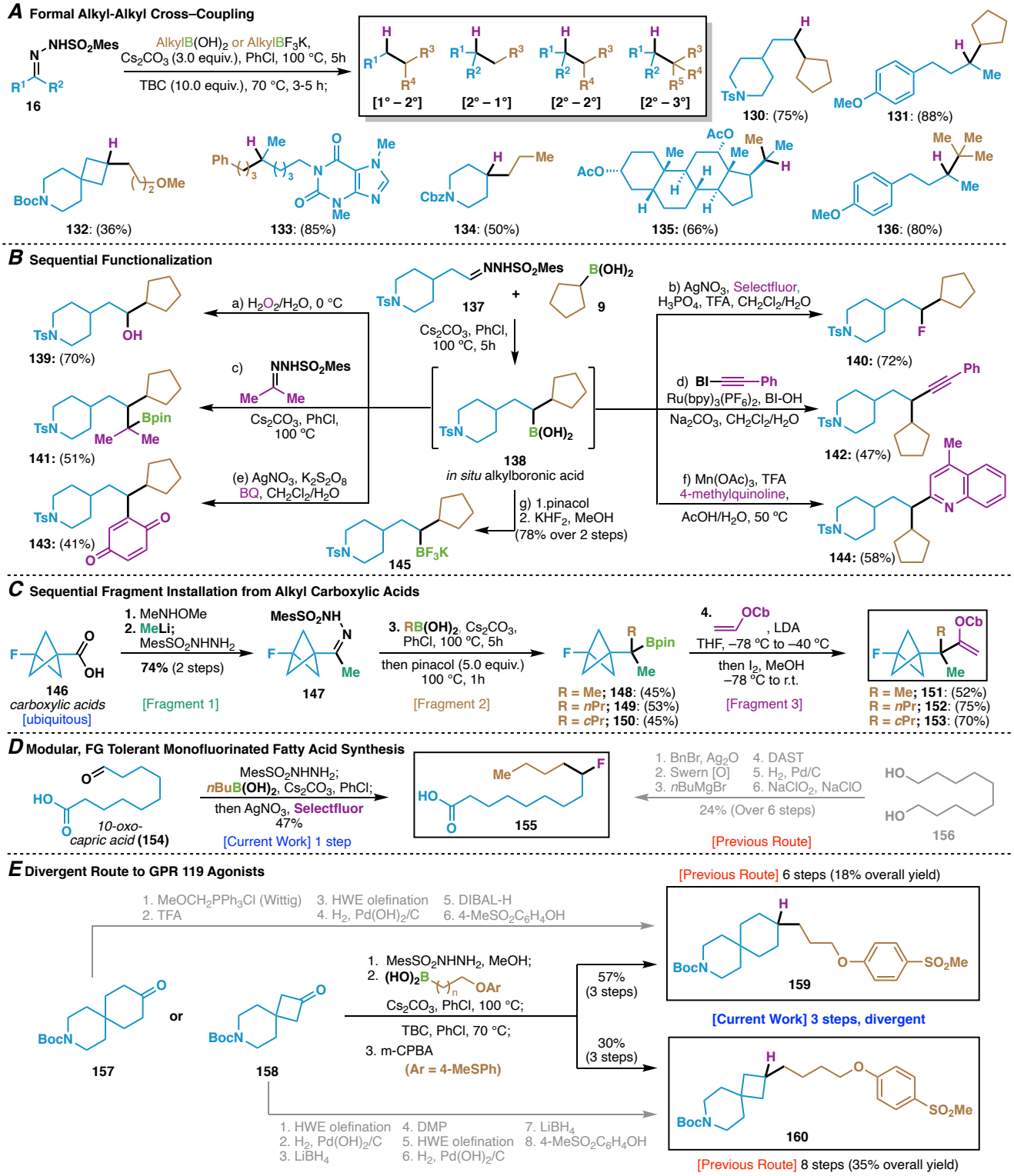


Figure 4. Strategic Synthetic Application. See the Supplementary Materials for experimental details.

Strategic Applications via Alkyl Boronic Acids and Esters Functionalizations. As illustrated in Figure 4, the strategic impact of this methodology shines in the 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 drug-like scaffolds[40,41]. First, as shown in Figure 4 Panel A, 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[42-45]. This formal alkyl-alkyl cross-coupling provides a modular approach to access a variety of unfuctionalized $C(sp^3)$–$C(sp^3)$ 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 mild radical protodeboronation conditions. This modular and highly functional group tolerant protocol proceeds in one-pot from alkyl sulfonylhydrazones **16** and alkyl boronic acids, allowing direct access to a range of $C(sp^3)$–$C(sp^3)$ bonds, with varied substitution patterns and functional groups (**130**–**136**). Therefore, the approach represents a formal cross-coupling between primary- (**130**) or secondary (**131**–**136**) alkyl electrophiles with either primary (**132**–**135**), secondary (**130**, **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 4, Panel B). 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 obviates the requirement of a strong organometallic reagent. One intriguing feature of this methodology is that the products are also viable coupling partners as well. Therefore, iterative coupling to build complex sp^3 rich scaffolds can be realized through sequential addition of different sulfonylhydrozones. As illustrated in Panel B(c), the *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**)[46], photo-mediated alkynylation (**142**)[47] and Minisci-type radical addition (**143, 144**)[48,49] from the *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 photo-induced electron transfer[50,51].

The synthesis of F-BCP analogs (**151**–**153**) in Panel C 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[52] 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 high sensitivity of ^{19}F NMR[53]. The previous approach to **155** required a 6-step linear synthetic sequence starting from 1,2-decanediol **155** (Figure 4 Panel D), 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 the 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 4, Panel E) is drawn from the patent literature wherein medicinal chemists at Taisho Pharmaceutical were interested in the azaspiroalkanes **159** and **160** as intermediates towards GPR119 agonists[54]. 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**, **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 $C(sp^3)$–$C(sp^3)$ that were previously inaccessible.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.

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

Crystallographic information for **56** (CIF)

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Notes

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