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# A General C(sp$^3$)−C(sp$^3$) Cross-Coupling of Benzyl Sulfonylhydrazones with Alkyl Boronic Acids

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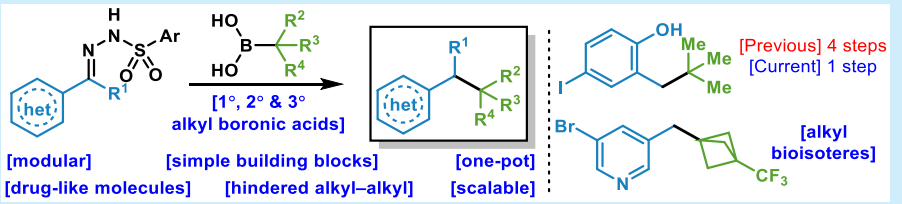


**ABSTRACT:** A general transition-metal-free cross-coupling between benzylic sulfonylhydrazones and 1°, 2°, or 3° alkyl boronic acids is reported. The base-promoted reaction is operationally simple and exhibits a broad substrate scope to forge a variety of alkyl−alkyl bonds, including between sterically encumbered secondary and tertiary sp$^3$-carbons. The ability of this method to simplify retrosynthetic analysis is exemplified by the improved synthesis of multiple medicinally relevant scaffolds.



There has been growing interest in the pharmaceutical industry to increase the sp$^3$-character of small molecules.[1] Alkyl bioisosteres (e.g., bicyclo[1.1.1]pentane) have been shown to possess improved physiochemical properties compared to their aromatic counterparts,[2] resulting in a need to access both aromatic and alkyl analogs during a medicinal chemistry campaign. Therefore, new retrosynthetic strategies that forge C(sp$^3$)−C(sp$^2$) and C(sp$^3$)−C(sp$^3$) bonds in a divergent and efficient manner are required. For example, the hypothetical medicinal chemistry building blocks **1** and **2** (Figure 1A) contain the same heterocyclic core with aryl or alkyl substituents appended. An ideal medicinal chemistry strategy would involve a robust late-stage cross-coupling, allowing for diversification of a bench-stable common intermediate (e.g., tosylhydrazone **3**) with a wide range of commercially available alkyl and aryl building blocks (e.g., boronic acids **4**).[3] A synthetic approach that could enable this type of strategy would notably expedite structure−activity relationship (SAR) studies in medicinal chemistry.

In recent years, there have been significant advances in the area of alkyl−alkyl transition-metal catalyzed cross-coupling reactions.[4,5] However, due to substantial challenges (such as $\beta$-hydride elimination, protonation of electrophile, or need for unstable organometallic nucleophile) new approaches to access these alkyl−alkyl bonds are still desired.[5] In 2009, Barluenga and Valdés reported a transition-metal-free, reductive cross-coupling between alkyl tosylhydrazones **5** and boronic acids (Figure 1B) to forge C−C bonds without the need for precious metal catalysts or ligands.[6] The transformation utilizes boronic acids, a widely available building block, and alkyl sulfonylhydrazones, bench-stable solids that are readily prepared from aldehydes or ketones.[7] Since the original report, the method has been widely adopted by industry chemists, demonstrating its practicality.[8,9] However, to the best of our knowledge, these reports have focused on cross-coupling of benzylic sulfonylhydrazones with *aryl* and *heteroaryl* boronic acids **6**[10,11] and a general protocol for coupling *alkyl* boronic acids **7** to construct sp$^3$−sp$^3$ C−C bonds remains elusive.

In this communication, we report a general and operationally facile method for the cross-coupling between benzylic sulfonylhydrazones and widely available alkyl boronic acids. Starting from 1°, 2°, or 3° alkyl boronic acids, this method provides a straightforward solution for generating a variety of C(sp$^3$)−C(sp$^3$) bonds.

Figure 1C presents an abbreviated picture of the optimization conducted on bromopyridine tosylhydrazone **8** and cyclopentyl boronic acid **9**, culminating in an 82% isolated yield. To establish the optimal conditions, a broad evaluation of sulfonylhydrazones (entries 1−3), bases (entries 4−6), solvents (entries 7−8), and temperatures (entry 9) was undertaken, with the optimal conditions requiring tosylhydrazone **8** (1 equiv), boronic acid **9** (1.5 equiv), and $Cs_2CO_3$ (1.5 equiv) in 1,4-dioxane (0.25 M) at 110 °C (see Supporting Information (SI) for full optimization table). Here, we benefited from the pioneering studies preceding ours,[6,8] which had showcased the importance of modulating the electron density of the sulfonylhydrazone moiety, and the identity of the base on the efficiency of reductive cross-

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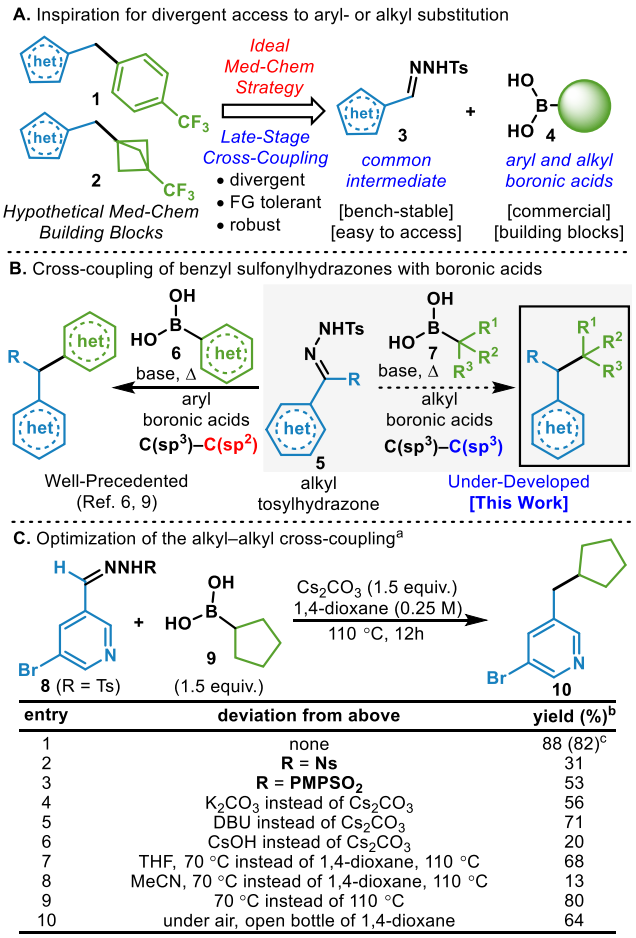


| entry | deviation from above | yield (%)[b] |
|---|---|---|
| 1 | none | 88 (82)[c] |
| 2 | **R = Ns** | 31 |
| 3 | **R = PMPSO$_2$** | 53 |
| 4 | $K_2CO_3$ instead of $Cs_2CO_3$ | 56 |
| 5 | DBU instead of $Cs_2CO_3$ | 71 |
| 6 | CsOH instead of $Cs_2CO_3$ | 20 |
| 7 | THF, 70 °C instead of 1,4-dioxane, 110 °C | 68 |
| 8 | MeCN, 70 °C instead of 1,4-dioxane, 110 °C | 13 |
| 9 | 70 °C instead of 110 °C | 80 |
| 10 | under air, open bottle of 1,4-dioxane | 64 |

**Figure 1.** (A and B) Inspiration for developing alkyl–alkyl cross-coupling between alkyl sulfonylhydrazones and alkyl boronic acids and (C) optimization of alkyl–alkyl cross-coupling. [a]0.1 mmol. [b]Yield determined by $^1$H NMR with 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield.

coupling between alkyl sulfonylhydrazones and aryl boronic acids. Gratifyingly, when the reaction was performed without any precautions, under air and with an open bottle of 1,4-dioxane (dump and stir), the desired coupling product was still obtained in 64% yield, thus demonstrating the robustness of the method (entry 10).

With an optimized set of conditions in hand, the scope of this reaction was systematically evaluated, as shown in Figure 2. First, a range of alkyl tosylhydrazones (Figure 2A) were coupled with cyclopentyl boronic acid **9**. Tosylhydrazones derived from the corresponding aldehydes of electron-rich (**11**, **12**) and electron-poor (**13**) aromatics, and that of various heterocycles relevant to medicinal chemistry—such as pyridines (**10**, **17**, **19**), unprotected indazole (**16**), thiazole (**15**), and quinoline (**18**)—were well tolerated. Notably, sulfonylhydrazones derived from both cyclic (**19**) and linear (**20**) ketones underwent facile cross-coupling to generate a C(sp$^3$)–C(sp$^3$) bond between two sterically hindered secondary carbon centers. Historically, under transition-metal catalysis, such hindered alkyl–alkyl bonds are difficult to generate due to the ease of $\beta$-hydride elimination.[5] Under the reaction conditions, aryl bromides (**10**, **15**, **16**, **17**, and **20**) and chlorides (**17**, **19**) go untouched, allowing for subsequent functionalization using transition-metal catalysis in an orthogonal manner. In addition, examples **17** and **19** demonstrate that the conditions to install the sulfonylhydrazone and the cross-coupling are mild enough to tolerate activated 2-chloropyridines, which could then be further functionalized via $S_NAr$. It is worth noting that each aldehyde and ketone was commercially available and the corresponding sulfonylhydrazones were prepared as bench-stable solids and purified by filtration without column chromatography. In contrast, substantially fewer benzylic halides are available and, in some cases, such as electron-rich benzylic halides, they are unstable (e.g., for substrate **11**, **12**). This points again to the operational convenience of this reaction.

Figure 2B outlines the cross-coupling with various 1° and 2° alkyl boronic acids. The reaction was compatible with both primary and secondary acyclic (**21**–**24**), cyclic (**25**–**27**), heterocyclic (**28**, **30**), benzylic (**29**), and $\alpha$-heterocyclic (**31**) alkyl boronic acids. A variety of functional groups including terminal olefin (**22**), alkyl bromide (**23**), protected amines (*N*-Boc **31** and *N*-Bn **28**), and cyclic ethers (**30**) were tolerated under the reaction conditions. Substrates **25** and **26** are striking, as cyclopropanes are privileged scaffolds in medicinal chemistry[12] and this method provides an alternative approach for their installation. The reaction could also be run easily on a gram scale without modification of the optimized conditions to provide **26** without any erosion of relative stereochemistry. This result also highlights the stereoretentive nature of this reaction, wherein the stereochemistry of the alkyl group is transferred with complete fidelity from the corresponding alkyl boronic acid.

Tertiary alkyl boronic acids (Figure 2C, **32**–**37**) also smoothly participated in the cross-coupling, generating all alkyl quaternary centers. It is noteworthy that even extremely sterically hindered C–C bonds between secondary and tertiary sp$^3$-carbons (substrate **37**) can be forged with ease under this reaction scaffold. Tertiary alkyl substituents continue to remain one of the most challenging groups to install via transition-metal catalysis (e.g., *t*Bu has 9 $\beta$-Hs), and this method provides for a simple and practical route for their installation. Bicyclo[1.1.1]pentane boronic acids could also be cross-coupled in a straightforward manner to access substrates **35** and **36**. Bicyclo[1.1.1]pentanes are emerging as a powerful saturated mimic of *para*-substituted benzene,[13] making this a useful method for their installation on a variety of medicinal chemistry projects. Although several alkyl boronic acids are commercial, there were some instances where the alkyl Bpin was easier to access (commercial or synthesized using decarboxylative cross-coupling methodologies[14]). In such scenarios, alkyl BPins were subjected to deprotection and the crude alkyl boronic acid utilized in the cross-coupling to furnish the desired alkyl–alkyl coupling products (**30** and **33**–**36**; see SI for experimental details).

The feasibility of directly employing the carbonyl substrate using an *in situ* protocol was demonstrated with substrate **38** (Figure 2D). Tosylhydrazone **8** was generated *in situ* and subjected to the cross-coupling without any purification or solvent removal to obtain the desired product **10** in comparable yield (85% one pot vs 90% from tosylhydrazone). Owing to the ubiquity and commercial availability of the benzylic aldehydes and ketones, the one-pot procedure can expedite and assist medicinal chemistry efforts by rapid diversification of benzylic heterocycles.

We believe the mechanism for this reaction is analogous to the cross-coupling with aryl boronic acids.[6] The base ($Cs_2CO_3$) promotes the formation of diazo compound *in situ*


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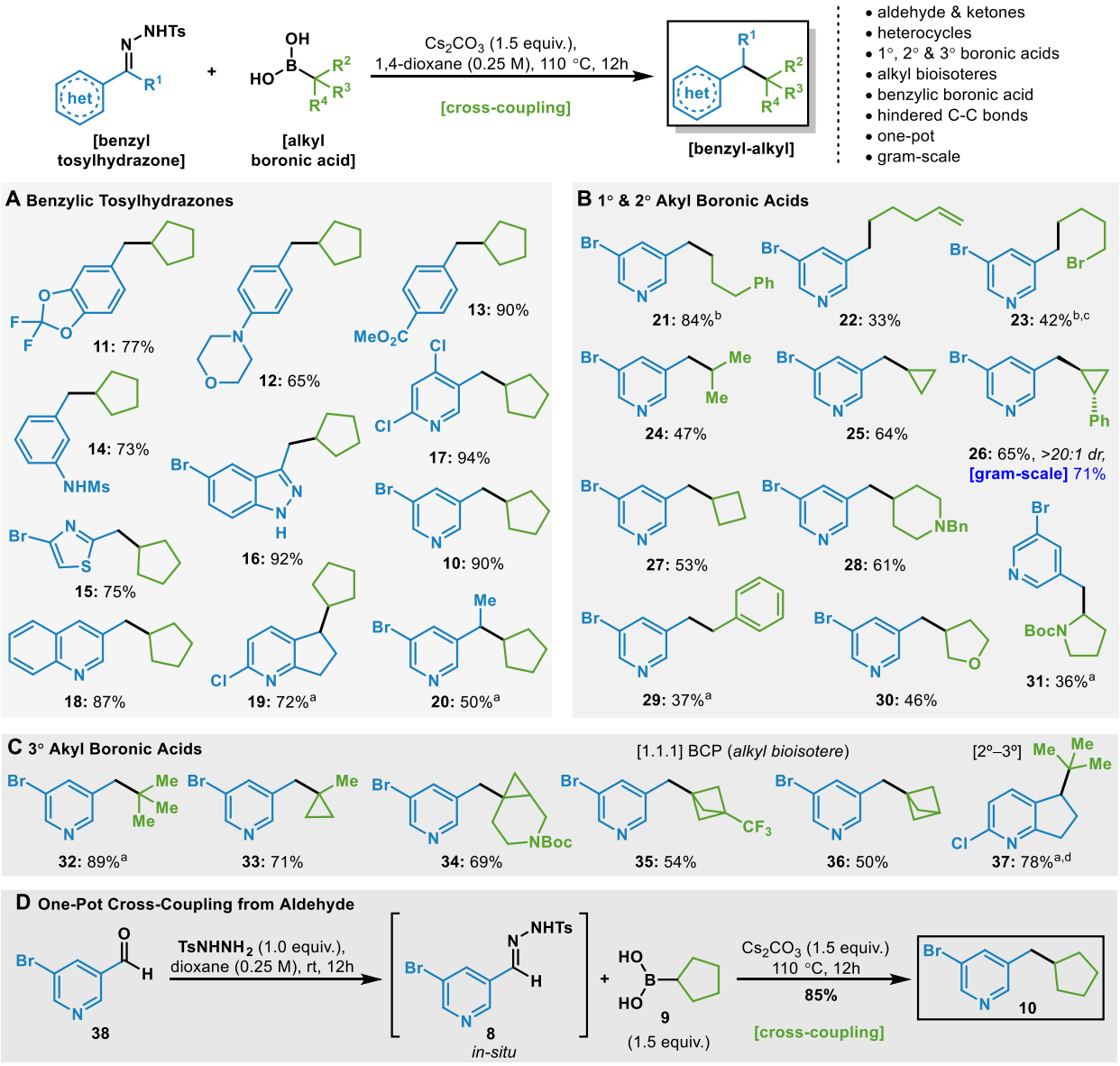


**Figure 2.** Initial scope for alkyl−alkyl cross-coupling between benzylic sulfonylhydrazones and alkyl boronic acids. Standard reaction conditions: tosylhydrazone (1.0 equiv), boronic acid (1.5 equiv), $Cs_2CO_3$ (1.5 equiv), 1,4-dioxane (0.25 M), 110 °C, 12 h. [a]With sulfonylhydrazone derived from $PMPSO_2NHNH_2$ (1.0 equiv) and alkylB$(OH)_2$ (3.0 equiv). [b]With alkylB$(OH)_2$ (3.0 equiv). [c]Quenched after 4 h. [d]1,4-dioxanes (0.17 M). Ts = tosyl, Ms = mesityl, Ph = phenyl, Bn = benzyl, Boc = *tert*-butyloxycarbonyl, [1.1.1]BCP = bicyclo[1.1.1]pentane, PMP = *para*-methoxyphenyl. See SI for details.

which then reacts with the alkyl boronic acid to form a tetracoordinate boronate. Subsequent 1,2-migration generates the C−C bond with concomitant loss of $N_2$ followed by protodeboration of benzylic boronic acid to give the desired product.[15] Alternatively, the intermediate diazo compound could lose $N_2$ first to form benzylic carbene which could then engage with the boronic acid to form the tetracoordinate boronate. A final sequence involving 1,2-migration and protodeboration then gives the desired product.

The retrosynthetic simplification enabled by this cross-coupling is further demonstrated with application to three reported medicinal chemistry case studies from the patent literature (Figure 3). In one instance (Figure 3A), GSK scientists targeted building blocks differing only in the substituent appended to the triazole core (3-fluorophenyl and cyclopentyl, among others).[16] To access each of these simple structures, a linear *de novo* approach was devised with the point of diversification occurring as the first step in a synthetic sequence that requires condensation at 200 °C to prepare the triazole core. By leveraging the wide commercial availability of boronic acids (aryl and alkyl), in contrast, the tosylhydrazone **39** could instead be directly coupled with 3-fluorophenyl boronic acid, cyclopentyl boronic acid, or $CF_3$-bicyclo[1.1.1]pentane boronic acid to deliver **40** and **41** and a new analog **42** at a later stage and in a much more divergent fashion.

The second and third case studies (Figure 3B), drawn respectively from medicinal chemistry campaigns at Yale University and Eli Lilly, highlight the functional group compatibility of this method.[17,18] Previous approaches to the targets, **43** (Yale)[17] and **44** (Eli Lilly),[18] were plagued by the chemoselectivity issues surrounding the Wittig, Grignard, and


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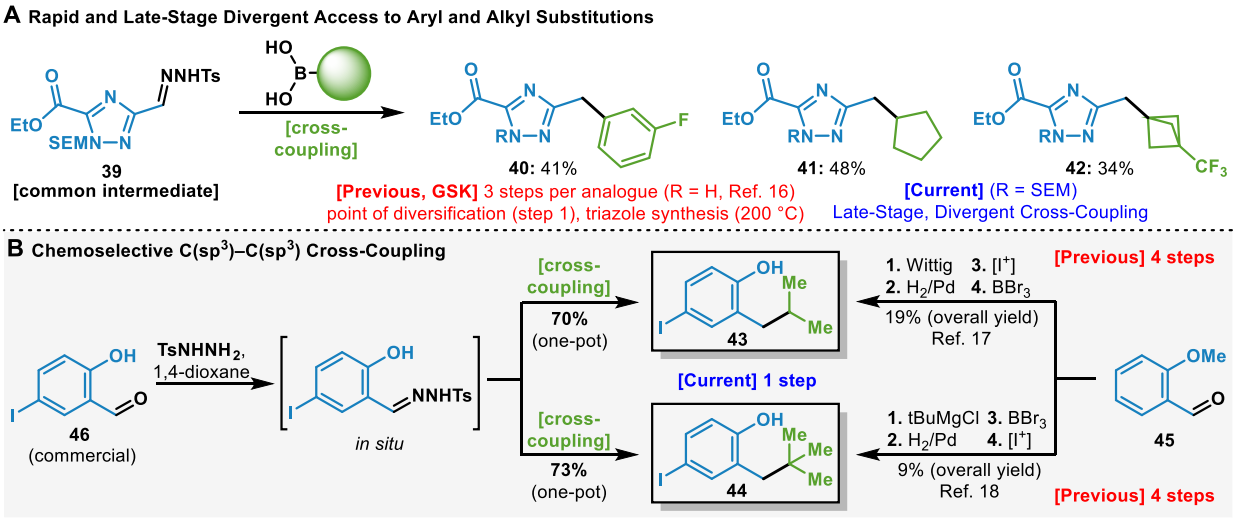


**Figure 3.** (A and B) Applications of alkyl−alkyl cross-coupling between alkyl sulfonylhydrazones and alkyl boronic acids to the synthesis of pharmaceutically relevant building blocks. (B) Cross-couplings were performed with in situ activation of the aldehyde. See SI for details.

hydrogenation reactions. This resulted in both reports starting from the protected phenol **45** for the Wittig or Grignard reaction, followed by hydrogenation prior to late-stage installation of iodine. In contrast, using the method disclosed here, commercial iodophenol aldehyde **46** was subjected to *in situ* coupling with either isopropyl boronic acid or *tert*-butyl boronic acid to obtain **43** and **44**, respectively, in a single step, obviating the need for any protecting group manipulations. Overall, this approach also provides a milder alternative to the traditional Wittig/hydrogenation sequence for appending an alkyl group to an aldehyde or ketone.

In summary, we have reported a general protocol for $C(sp^3)-C(sp^3)$ coupling between benzylic sulfonylhydrazones and 1°, 2°, or 3° alkyl boronic acids. By leveraging the ubiquity of alkyl boronic acids, this operationally simple, scalable, and chemoselective approach extends the ability to diversify sulfonylhydrazones with a diverse range of alkyl substituents. This method has already proven to be invaluable on several internal medicinal chemistry programs, and as such, we anticipate that it will have meaningful impacts within drug discovery and synthetic chemistry.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00471.

Detailed experimental procedures and analytical data (PDF)

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### Notes

The authors declare no competing financial interest.

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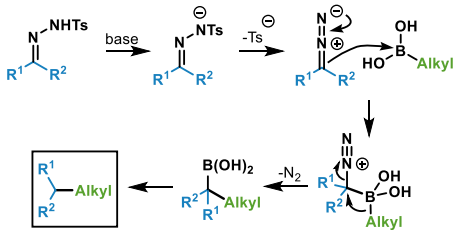


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