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# Direct Alkylation of 1-Azabicyclo[1.1.0]butanes

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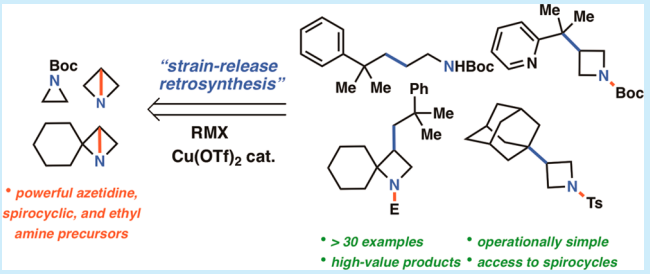
Supporting Information

**ABSTRACT:** The facile synthesis of functionalized azetidines has been an ongoing challenge. Here, we report a general method to directly alkylate 1-azabicyclo[1.1.0]butane (ABB) with organometal reagents in the presence of $Cu(OTf)_2$ to rapidly prepare *bis*-functionalized azetidines. This method allows for the preparation of azetidines bearing alkyl, allyl, vinyl, and benzyl groups. This catalyst system was extended to aziridines and spirocycles. Several building blocks and drug-like compounds were prepared in rapid fashion and in good yield.



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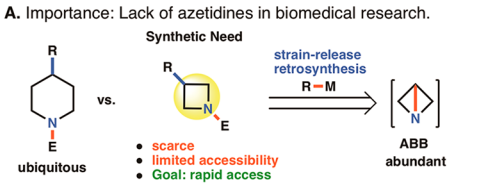
In comparison to common rings such as piperidines which are prevalent in marketed drugs, the presence of azetidines as a core scaffold is scarce.[1,2] It can be reasoned that the absence of azetidines as a privileged motif is due to low synthetic tractability.[2] An in-depth search of chemical literature revealed a lack of methods to install carbon atoms at the 3-position of azetidines (Figure 1A). Methodologies to prepare azetidines are in high demand due to their potential application in the pharmaceutical and agrochemical fields.[2] It was envisaged that the invention of a rapid and robust synthesis of azetidines could lead to an increase in their use in biomedical research. It has been shown that 1-azabicyclo[1.1.0]butanes can serve as powerful intermediates to prepare *bis*-functionalized azetidines in short order.[3] Nagao and others have shown that ABB can be intercepted with various nucleophiles to prepare functionalized azetidines.[4,5] Recently, Baran has shown that ABB can be aminated with "turbo amides" in a one-pot fashion.[6] The aforementioned studies inspired us to ponder whether ABB could be functionalized with carbon nucleophiles. A method to rapidly prepare libraries of alkylated azetidines would allow medicinal chemists to quickly investigate structure−activity relationships (SARs). Thus, we sought to develop a method to functionalize ABB with alkyl nucleophiles. Due to the ability of nucleophiles to break the C−N bond and functionalize the C-3 position, we sought to find a suitable carbon species that could attack ABB to afford 3-substituted azetidines. Initial experiments were conducted with different *tert*-butyl nucleophiles. Tosyl chloride (1 M in THF) was used to trap the resulting functionalized azetidine for ease of isolation and characterization to provide compound **3**. Attempts to functionalize ABB with *t*-BuLi, *t*-BuZnBr, and *t*-BuMgCl led to either no reaction or trace observable product (Figure 1B, entries 1−3). Also, it should be noted that attempts to functionalize ABB with phenylmagnesium bromide (and other aryl-metal reagents) led to isolation of complex mixtures that contained the desired product.[7] Seeking a method to increase the reactivity of the metal species, a Gilman-type cuprate was reacted with ABB




| Entry | MX | additive | Eq. (Metal) | Temp. | Time | Yield(%) |
|---|---|---|---|---|---|---|
| 1 | Li | none | 2 | rt | 16 h | 0 |
| 2 | ZnBr | none | 2 | rt | 16 h | <1 |
| 3 | MgCl | none | 2 | rt | 16 h | 15* |
| 4 | MgCl | CuCN (100%) | 2 | rt | 16 h | 56 |
| 5 | MgCl | CuCN (10%) | 2 | rt | 16 h | 21 |
| 6 | MgCl | Cu powder (10%) | 2 | rt | 16 h | 11 |
| 7 | MgCl | $Cu(OAc)_2$ (10%) | 2 | rt | 16 h | 22 |
| 8 | MgCl | CuOAc (100%) | 2 | rt | 16 h | 20 |
| 9 | MgCl | CuOAc (10%) | 2 | rt | 16 h | 32 |
| 10 | MgCl | $Cu(OTf)_2$ (10%) | 2 | rt | 16 h | 36 |
| 11 | MgCl | $Cu(OTf)_2$ (5%) | 2 | rt | 16 h | 51 |
| 12 | MgCl | $Cu(OTf)_2$ (3%) | 2 | rt | 16 h | 49** |
| 13 | MgCl | $Cu(OTf)_2$ (3%) | 1 | rt | 16 h | 7 |
| 14 | MgCl | $Cu(OTf)_2$ (3%) | 2 | rt | 1 h | 52 |
| 15 | MgCl | $Cu(OTf)_2$ (3%) | 2 | 40 °C | 16 h | 57 |
| **16** | **MgCl** | **$Cu(OTf)_2$ (3%)** | **2** | **rt** | **16 h** | **85** |

*Estimated by NMR (Isolated as a inseparable mixture of products).**TsCl (1 eq)

**Figure 1.** (A) Azetidines as a scaffold in medicinal chemistry. (B) Invention of a copper catalyzed synthesis of azetidines (catalysts shown as mol %).

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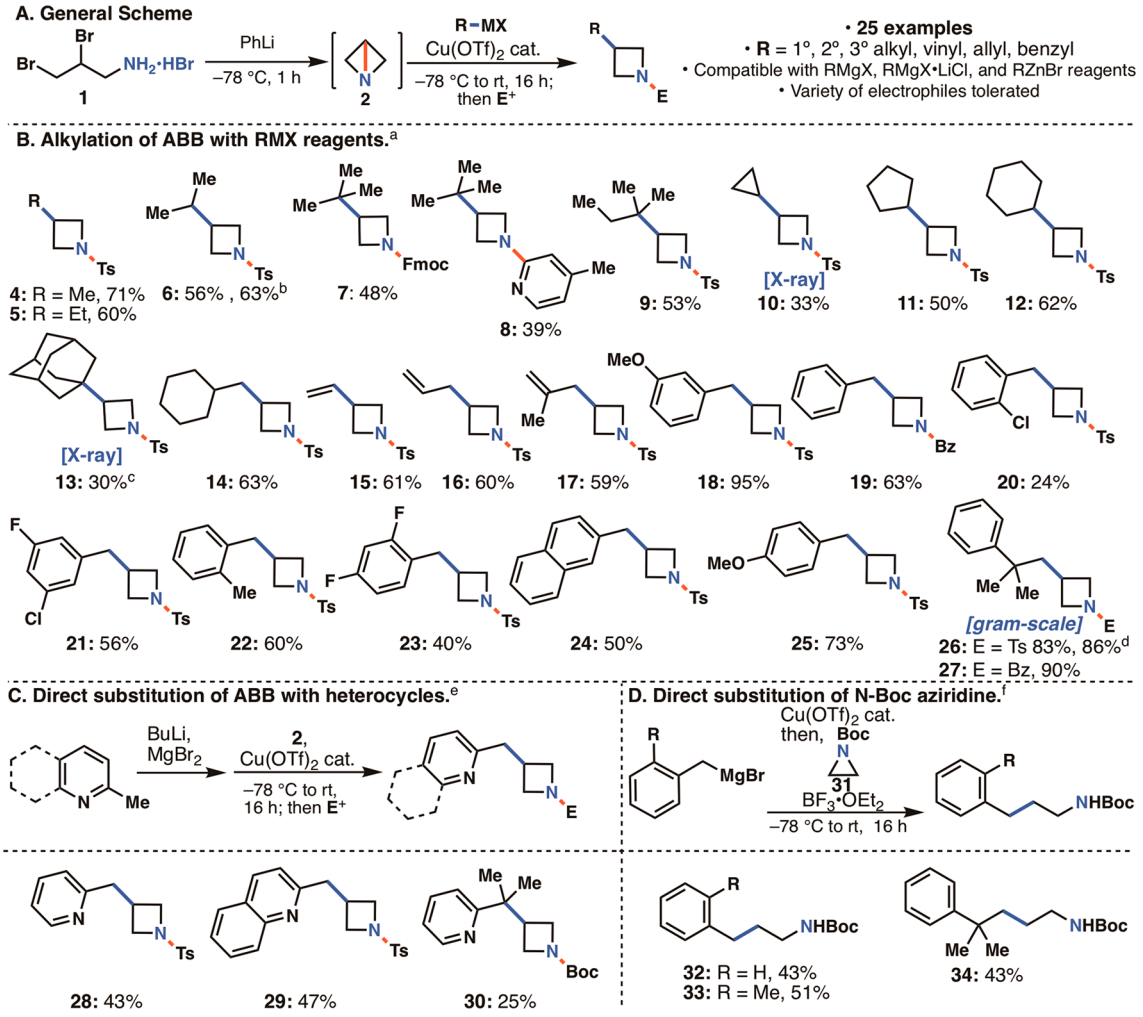


**Figure 2.** Scope of the reaction between nucleophiles, ABB, and N-Boc aziridine. [a] Reaction conditions (all reactions conducted on 1 mmol scale unless otherwise noted): **1** (1 equiv), PhLi (1.9 M in dibutyl ether, 3 equiv), RMgCl (2 equiv), $Cu(OTf)_2$ (3 mol %), −78 °C to rt, then $E^+$ (2 equiv) 5−24 h. [b] With *i*PrMgCl·LiCl. [c] With adamantylzinc bromide. [d] At 3.36 mmol scale. [e] Reaction conditions: Heterocycle (2 equiv), BuLi (2.05 M in hexanes, 2 equiv), $Cu(OTf)_2$ (3 mol %), **2** (1 equiv) −78 °C to rt, then $E^+$ (2 equiv) 5−24 h. [f] Reaction conditions: Grignard (2 equiv), **31** (1 equiv), $BF_3{\cdot}OEt_2$ (1 equiv), $Cu(OTf)_2$ (3 mol %), −78 °C to rt, 16 h.

which drastically increased the yield to 56% (Figure 1B, entry 4). While this result was encouraging, the reaction required 100 mol % CuCN copper. The main challenges in the development of this reaction were to render the reaction catalytic, increase the yields, and expand the scope. Several reactions were conducted in an effort to optimize this reaction including a scan of additives and catalysts. A sampling of our efforts is shown in Figure 1B (see Supporting Information for more details). In the end, $Cu(OTf)_2$ (3 mol %) was found to be the optimal catalyst for this transformation (Figure 1B, entry 16). With these optimal conditions in hand, we sought to explore the scope of the reaction with different Grignard reagents. To our delight, the scope consisted of primary (**3**−**5**, **14**, **26**−**27**), secondary (**6**, **10**−**12**), and tertiary alkyl groups (**3**, **7**−**9**, **13**). Also, other metal species such as the *i*-PrMgCl·LiCl complex (**6**) and 1-adamantylZnBr (**13**) were tolerated. In addition, products from vinyl and allyl Grignard reagents performed in good yield (**15**−**17**). Additionally, a variety of benzylic Grignard reagents were reactive and most products were isolated in good yield (**18**−**25**). It is important to note that this reaction can be conducted on gram-scale (**26**) and tolerates a variety of electrophiles such as tosyl (**3**−**6**, **9**−**18**, **20**−**26**, **28**−**29**), Fmoc (**7**), benzoyl (**19**, **27**), and Boc (**30**). Also, this reaction can be paired with an $S_NAr$ reaction to rapidly build molecular complexity in one pot (**8**). It should be noted that Boc can be used as an electrophile, but tosyl was chosen in many cases due to ease of visualization and purification. In addition, a method was developed for the direct coupling of heterocycles, such as pyridine and quinoline, to ABB (Figure 2C, entries **28**−**30**).

In our efforts to expand the method to provide products of other strained scaffolds, **31** was identified as a suitable precursor to append ethyl amines onto carbon atoms. A literature search revealed that similar reactions have been successful on C-2 functionalized aziridines with various combinations of organometal and copper catalysts.[8] Thus, it was envisioned that our conditions could be utilized to perform a strain−release type reaction on N-Boc aziridines to demonstrate the flexibility of our conditions. In fact, when **31** was allowed to react under our conditions with benzylmagnesium bromide in the presence of $BF_3{\cdot}(OEt)_2$, the desired product was isolated in 43% yield (**32**). Additionally, other Grignard reagents performed well in this reaction (**33**−**34**).


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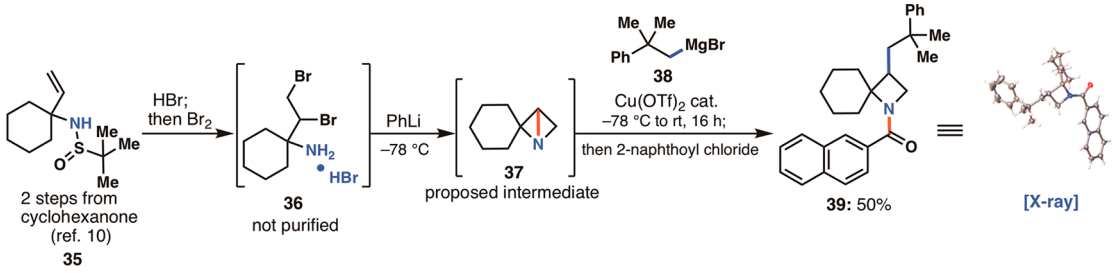
**Scheme 1. Proof of Concept for the Synthesis of an Azaspirocycle**




During the course of our investigation, we became aware that a method to prepare spirocycles would be extremely useful to the medicinal chemistry community. Carreira has extensively reviewed and demonstrated the importance of azaspiro compounds in medicinal chemistry.[9] In particular, spirocycles have shown to impart similar properties to their monocyclic congeners while increasing the number of vectors that can be explored.[9a] Thus, we sought to develop a quick and efficient route to azetidine-containing spirocycles.

Intermediate **35** was synthesized in short order from cyclohexanone using previously reported methods.[10] Treatment of **35** with HBr and bromine afforded **36** which was directly converted to spirocycle **39** in 50% yield using our conditions and trapping with 2-naphthoyl chloride (Scheme 1). The structure of **39** was unambiguously confirmed by X-ray crystallography. We propose that the formation of **39** proceeds through the intermediacy of **37** although **37** was not isolated.

In conclusion, this research describes methods to functionalize azabicyclobutanes and aziridines with carbon nucleophiles in rapid fashion. The methods described herein allow for the preparation of molecules that are difficult to prepare using current methods. It is envisioned that these methods will be widely adopted by medicinal chemists. Lastly, proof of concept for the synthesis and the opening of strained spirocycles was established and the scope of strained rings and nucleophiles are under investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00321.

Characterization data for compounds **3**–**34** and **39** (PDF)

### Accession Codes

CCDC 1883856–1883859 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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(7) (a) A 10% mixture of 3-phenyl azetidine and other products was obtained under the optimized conditions without addition of an electrophile. This was confirmed by comparison of an NMR of an authentic sample of 3-phenyl azetidine which is commercially available through several vendors. (b) Phenyllithium with and without CuCN (100 mol %) and diphenylzinc produced complex mixtures.

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