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Strain-release driven spirocyclization of bicyclo [1.1.0]butanes: access to 6,7-diazaspiro[3.4]octanes†

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The use of ring strain in bicyclo[1.1.0]butanes (BCBs) to facilitate organic transformations is a powerful strategy in organic synthesis. However, their application to the synthesis of spirocyclic scaffolds has remained challenging. Spirocyclobutanes have attracted considerable interest in medicinal chemistry due to their diverse biological activities and potential clinical applications. In this work, we present a method for scandium-catalyzed spirocyclization of simple BCBs with azomethine imines, creating a new platform for the synthesis of previously inaccessible 6,7-diazaspiro[3.4]octanes. We demonstrate the utility of this approach by performing scaled-up reactions and transforming the products, highlighting its synthetic potential.

Introduction

Strain energy in organic molecules serves as a powerful driving force that enhances reactivity by facilitating the release of ring strain. This energy release enables a wide range of valuable transformations with broad applications across various research fields, including total synthesis, bioisosterism, and polymer science.¹ Bicyclo[1.1.0]butanes (BCBs), strained carbocycles consisting of two fused cyclopropane rings, have become well-established building blocks in organic synthesis, medicinal chemistry, and chemical biology.² This is primarily due to the unique reactivity of their inter-bridgehead C1–C3 bond (Scheme 1A), which exhibits almost entirely p-character.³ The ring-opening chemistry of this high-energy bond (with a ring strain of 64 kcal mol⁻¹) has been successfully harnessed using a variety of reagents, including nucleophiles,⁴ radicals,⁵ electrophiles,⁶ and transition metal catalysts.⁷ Beyond ring-opening, the ring expansion of BCBs to bicyclo[*n*.1.1]alkanes through formal one-,⁸ two-,⁹ three-,¹⁰ or four-atom¹¹ stepwise insertion processes has emerged as a particularly valuable method, owing to the relevance of these scaffolds in drug discovery. Additionally, metalation of the acidic C–H bonds of BCBs provides further opportunities for scaffold diversification.¹² Despite this rich chemistry, the exploration of BCBs in spirocyclization reactions remains limited, likely due to the ease

with which the aforementioned reactions proceed.¹³ However, developing novel spirocyclization strategies would offer rapid access to functionalized spirocyclobutane derivatives, which are increasingly valuable in pharmaceutical applications.

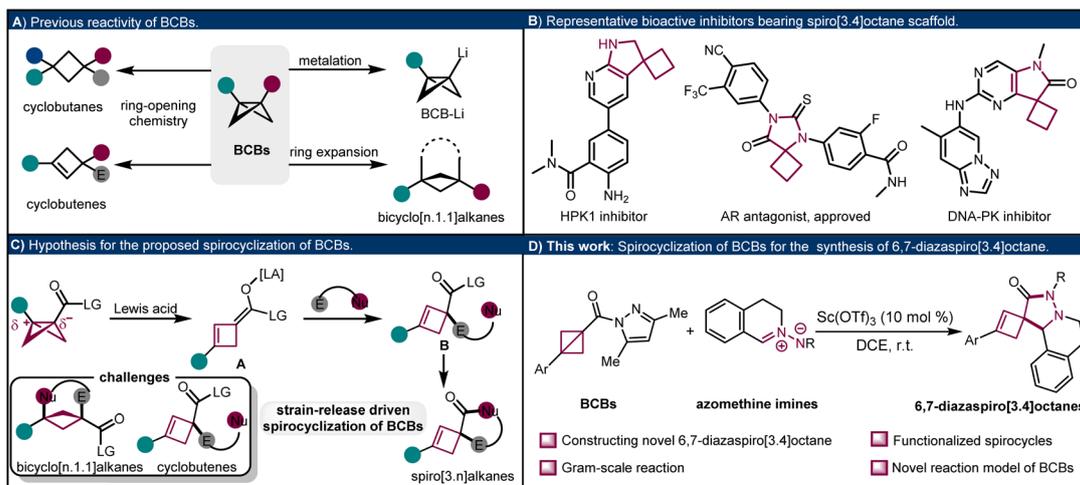
Over the past few decades, spirocyclic scaffolds have emerged as privileged pharmacophores in medicinal chemistry, with the discovery of numerous spirocyclic compounds exhibiting significant biological activities.¹⁴ These scaffolds are now successfully incorporated into various approved drugs and drug candidates used to treat a wide range of diseases, including infections, neurological and metabolic disorders, and cancer.¹⁵ Notably, spiro[3.4]octane-containing compounds stand out for their remarkable anticancer activity (Scheme 1B).¹⁶ Despite their promising potential, the exploration of spirocyclic chemical space remains in its early stages, largely due to the limited variety of synthetic methodologies available for their construction. Research in this area typically focuses on the development of molecules with specific targets, underscoring the increasing demand for general, modular methods for the synthesis of highly functionalized spirocycle-based structures.¹⁷

As part of our ongoing efforts to develop new chemistry for BCBs,¹⁸ we reasoned that a strain-release-driven spirocyclization strategy could provide a straightforward route to spiro[3.4]octanes (Scheme 1C). We hypothesized that activation of BCBs by a Lewis acid would generate the carbanionic intermediate **A**. This intermediate could then react with electrophilic moiety of dipole to form intermediate **B**. Finally, intramolecular nucleophilic substitution of **B** would yield the spirocyclobutane. We identified two key challenges for the successful realization of this spirocyclization: (1) the intramolecular nucleophilic substitution of **B** must occur rapidly to prevent the formation of the bicyclo[*n*.1.1]alkane cycloaddition product, and (2) the

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Scheme 1 General reactivity of BCBs. (A) Previous reactivity of BCBs. (B) Representative bioactive inhibitors bearing spiro[3.4]octane scaffold. (C) Hypothesis for the proposed spirocyclization of BCBs. (D) This work: spirocyclization of BCBs for the synthesis of 6,7-diazaspiro[3.4]octane.

leaving group must be sufficiently labile to facilitate nucleophilic substitution, avoiding the formation of cyclobutene products. Guided by this hypothesis, we turned to *C,N*-cyclic azomethine imines, which are known for their high reactivity as 1,3-dipoles in annulation reactions.¹⁹ However, research on azomethine imines has largely focused on their role in constructing various nitrogen heterocycles *via* [3 + 2],²⁰ [3 + 3]²¹ and [3 + 4]²² cycloaddition reactions. To date, spirocyclization reactions involving these compounds to form spirocyclic nitrogen heterocycles have not been explored. In light of this, we investigated the potential for strain-release-driven spirocyclization between BCBs and azomethine imines as a means to efficiently access 6,7-diazaspiro[3.4]octanes. Herein, we report the first examples of scandium-catalyzed spirocyclization between simple BCBs and azomethine imines, establishing a new platform for the synthesis of previously inaccessible 6,7-diazaspiro[3.4]octane (Scheme 1D).

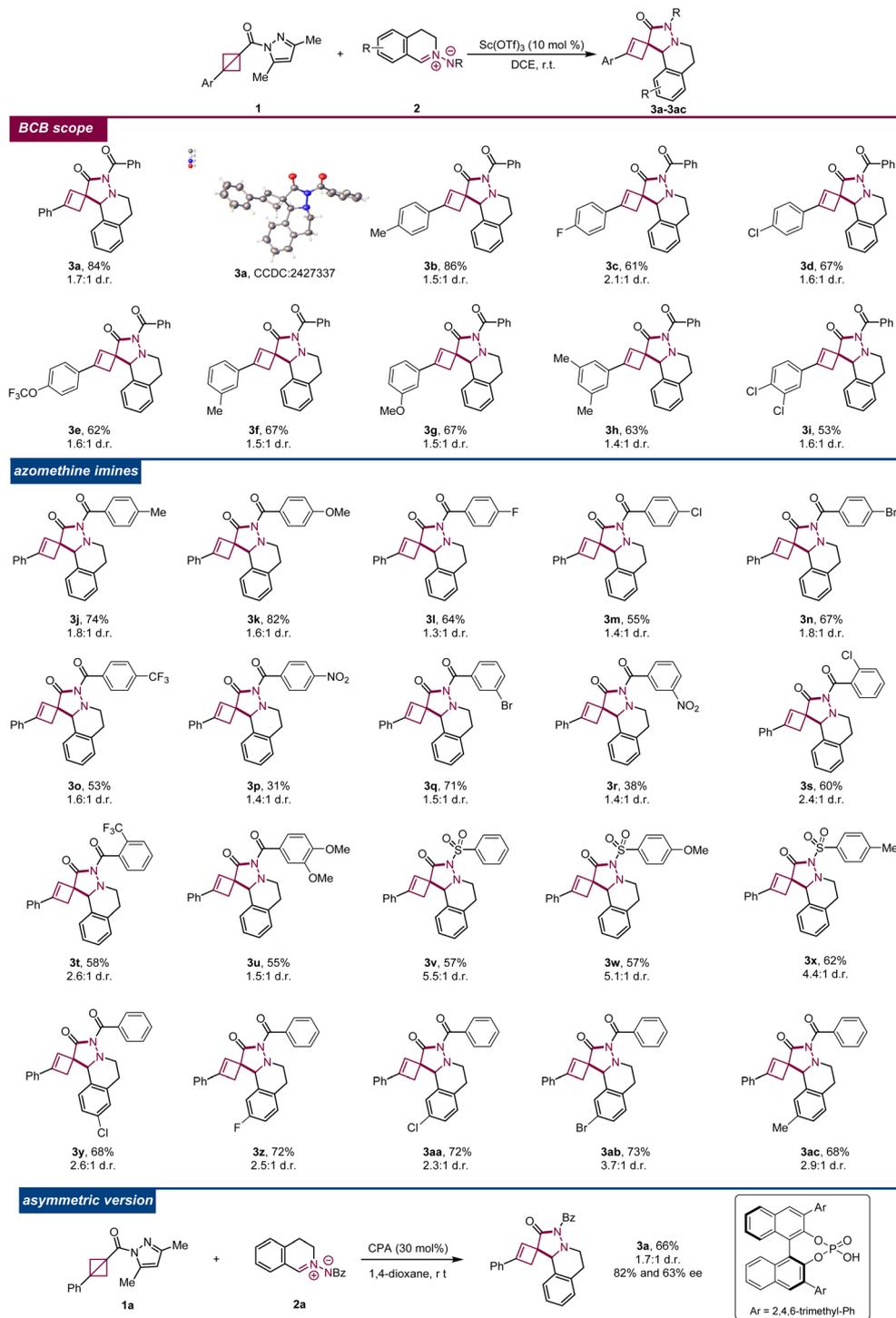
Results and discussion

To assess the feasibility of the spirocyclization reaction and optimize the conditions, we used pyrazole amide-substituted BCB (**1a**) and *C,N*-cyclic azomethine imine (**2a**) as standard substrates. Initial screening of various metal Lewis acids in THF at room temperature under argon for 12 hours (entries 1–6) revealed that the desired 6,7-diazaspiro[3.4]octane **3a** was obtained in good yield and with low diastereoselectivity (78% yield, 1.7 : 1 d.r. as determined by ¹H NMR spectroscopy) when Sc(OTf)₃ or Zn(OTf)₂ was used as the Lewis acid (entries 1 and 5). Other Lewis acids provided lower yields, and no cycloaddition products were detected. Subsequent solvent screening, using Sc(OTf)₃ as the catalyst, showed that dichloroethane was the optimal solvent, yielding **3a** in 87% yield and 1.7 : 1 d.r. (entries 7–12). Lowering the reaction temperature to 0 °C resulted in a reduced yield but improved diastereoselectivity (entry 13). Increasing the temperature to 60 °C did not affect the yield, but it led to poorer diastereoselectivity (entry 14). Control

experiments demonstrated that no reaction occurred in the absence of Sc(OTf)₃ (entry 15). Ultimately, the optimal conditions were determined to be: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), and Sc(OTf)₃ (10 mol%) in dichloroethane (2 mL) at room temperature under argon for 12 hours (entry 12). The structure of **3a** was confirmed by X-ray diffraction analysis of a single crystal (Scheme 2 and Table 1).

Using the optimized conditions, we evaluated the substrate scope with respect to the BCB (Scheme 2, top panel). Pyrazole amide-substituted BCBs, featuring electron-neutral, electron-donating, or electron-withdrawing substituents on the aryl ring at the bridgehead position, proved reactive, delivering the desired products (**3a–3i**) in yields ranging from 53% to 86%. Specifically, phenyl BCBs with a methyl group, halogen atom, or trifluoromethoxy group at the *para* position gave the corresponding products **3b–3e** in 61–86% yields. Additionally, phenyl BCBs with *meta*-methyl or -methoxy substituents were also suitable, providing **3f** and **3g** in 67% yields. Multi-substituted phenyl BCBs afforded 6,7-diazaspiro[3.4]octanes **3h** and **3i** in 63% and 53% yields, respectively. Different leaving groups, such as ester or amide-substituted BCB substrates were also tested, yielding no products, with significant amounts of starting material remaining (see ESI[†]). Next, we explored the substrate scope with respect to various structurally diverse *C,N*-cyclic azomethine imines (Scheme 2, middle panel). *C,N*-Cyclic azomethine imines with electron-neutral, electron-donating, or electron-withdrawing substituents on the phenyl ring of the benzoyl moiety were reactive, yielding products **3j–3u** in 31–82% yields. Specifically, *C,N*-cyclic azomethine imines with methyl, methoxy, halogen, trifluoromethyl, or nitro groups in the *para* position of the benzoyl moiety gave the corresponding products **3j–3p** in yields ranging from 31% to 82%. Additionally, *C,N*-cyclic azomethine imines with *meta*-bromine or -nitro substituents were also effective, producing **3q** and **3r** in 71% and 38% yields, respectively. Notably, *ortho*-chlorine and trifluoromethyl-substituted *C,N*-cyclic azomethine imines afforded the desired 6,7-diazaspiro[3.4]octanes **3s** and **3t** in 60%



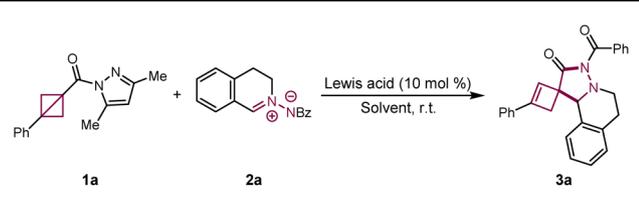


Scheme 2 Exploration of substrate scope. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), Sc(OTf)₃ (0.02 mmol, 10 mol%), DCE (4.0 mL), Ar, r.t., 12 h. For details, see ESI†

and 58% yields, respectively. Furthermore, multi-substituted *C,N*-cyclic azomethine imines gave 6,7-diazaspiro[3.4]octane **3u** in 55% yield. In addition to *C,N*-cyclic azomethine imines with the benzoyl group, *C,N*-cyclic azomethine imines bearing an *N*-sulfonyl group were also suitable, yielding 6,7-diazaspiro [3.4]octanes **3v–3x** in 57–62% yields. Subsequently, various

functional groups including methyl and halogen atoms were successfully introduced into the isoquinoline ring moiety without significantly compromising reaction efficiency, affording the desired products **3y–3ac** in satisfactory yields. After successfully establishing the non-asymmetric spirocyclization of BCBs with azomethine imines, we wish to describe our



Table 1 Optimization of reaction conditions^a


Entry	Lewis acid	Solvent	d.r.	Yield (%)
1	Sc(OTf) ₃	THF	1.7 : 1	78
2	Cu(OTf) ₂	THF	2.7 : 1	63
3	Yb(OTf) ₃	THF	2.0 : 1	57
4	Mg(OTf) ₂	THF	—	Trace
5	Zn(OTf) ₂	THF	1.7 : 1	78
6	Eu(OTf) ₃	THF	1.5 : 1	72
7	Sc(OTf) ₃	1,4-Dioxane	1.3 : 1	86
8	Sc(OTf) ₃	MeOH	1.3 : 1	58
9	Sc(OTf) ₃	MeCN	1.3 : 1	75
10	Sc(OTf) ₃	EtOAc	1.3 : 1	69
11	Sc(OTf) ₃	DCM	1.4 : 1	84
12	Sc(OTf)₃	DCE	1.7 : 1	87 (84^b)
13 ^c	Sc(OTf) ₃	DCE	2.0 : 1	58
14 ^d	Sc(OTf) ₃	DCE	1.3 : 1	84
15	—	DCE	—	NR

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Lewis acid (10 mol%), solvent (2.0 mL), Ar, room temperature (r.t.), 12 h. Yields were determined by ¹H NMR spectroscopy with CH₂Br₂ as an internal standard. The d.r. values were measured by ¹H NMR. NR, no reaction. ^b Isolated yield. ^c Reaction temperature, 0 °C. ^d Reaction temperature, 60 °C.

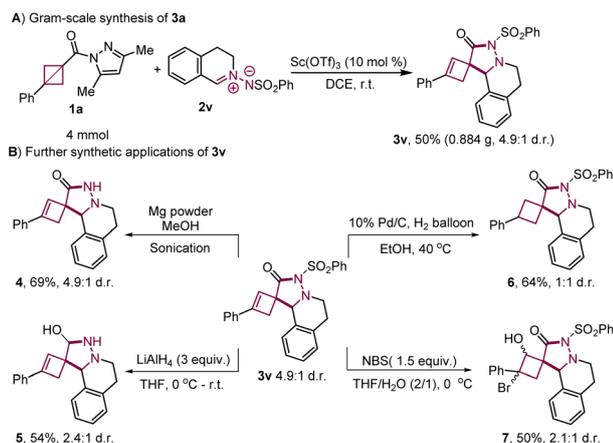
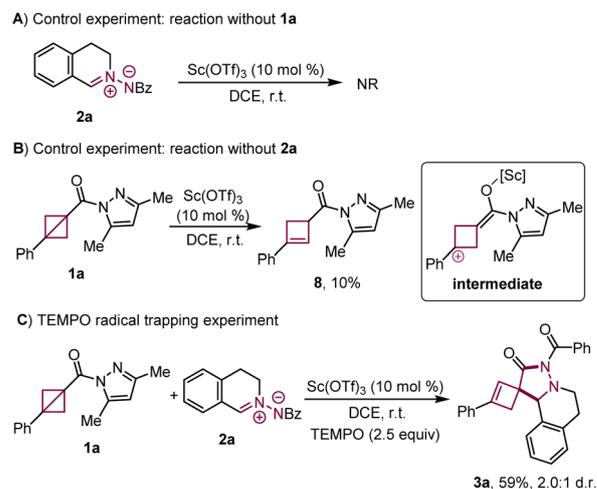
preliminary results on the asymmetric version of the reaction. The desired product **3a** was obtained in 66% yield and the highest enantioselectivity (1.7 : 1 d.r., 82% and 63% ee) when using BINOL-derived CPA as the catalyst and 1,4-dioxane as the solvent (Scheme 2, bottom panel).

To demonstrate the utility of our spirocyclization method, we scaled up the reaction to 4 mmol and successfully generated 6,7-diazaspiro[3.4]octanes **3v**, with only a slight decrease in

yield (Scheme 3A). Additionally, we carried out several transformations of **3v** (Scheme 3B). Specifically, deprotection of **3v** with Mg/MeOH yielded compound **4** in 69% yield. Furthermore, the carbonyl group of **3v** was reduced to the corresponding alcohol, resulting in the formation of **5** in 54% yield. Subsequently, compound **3v** underwent successful hydrogenation under reducing conditions using Pd/C as the catalyst, affording product **6** in 64% yield. Finally, halohydrin **7** was synthesized *via* the reaction of **3v** with *N*-bromosuccinimide (NBS) in the presence of water. These transformation products are valuable heterocyclic structures found in both natural and synthetic bioactive compounds.

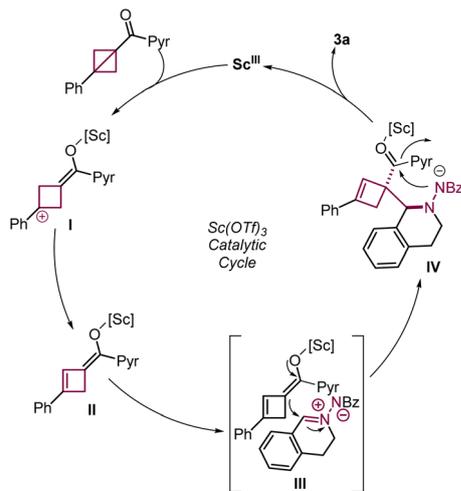
After exploring the reaction's substrate scope and demonstrating the utility of the products in various transformations, we shifted our focus to investigating the reaction mechanism (Scheme 4). First, when **2a** was subjected to the optimized conditions in the absence of pyrazole amide-substituted BCB (**1a**), no product was formed, and a significant amount of starting material remained (Scheme 4A). However, when **1a** was treated under the same conditions in the absence of *C,N*-cyclic azomethine imine (**2a**), cyclobutene **8** was obtained in 10% yield (Scheme 4B), suggesting that **1a** is likely activated directly by Sc(OTf)₃ to form a cationic intermediate. Finally, the addition of the radical-trapping agent TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) to the reaction mixture containing **1a** and **2a** did not significantly affect the yield of **3a** (Scheme 4C), indicating that a radical pathway is not involved in the mechanism.

Based on our mechanistic studies, we propose the mechanism outlined in Scheme 5. Initially, substrate **1a** is activated through coordination of Sc(OTf)₃ to the carbonyl group, forming the cationic intermediate **I**. Elimination of intermediate **I** produces intermediate **II**. Next, nucleophilic addition of **II** to substrate **2a** *via* intermediate **III** results in the formation of intermediate **IV**. This key intermediate undergoes substitution, with the nitrogen atom attacking the pyrazole amide group, yielding the desired 6,7-diazaspiro[3.4]octane product **3a** and regenerating the Sc(OTf)₃ catalyst.

Scheme 3 Gram-scale synthesis of **3v** and synthetic transformations of **3v**.

Scheme 4 Mechanistic experiments.





Scheme 5 Proposed mechanism.

Conclusions

In summary, we have developed a scandium-catalyzed spirocyclization method for simple BCBs, providing a versatile platform for the *de novo* construction of highly sought-after 6,7-diazaspiro[3.4]octanes. This method enables spirocyclizations of a broad range of BCBs with azomethine imines, granting access to 6,7-diazaspiro[3.4]octane frameworks for the first time. The synthetic utility of this approach was demonstrated through gram-scale reactions and subsequent transformations of the products. Notably, this method not only expands the toolbox for BCB spirocyclizations but also holds great potential for accelerating the exploration of novel 6,7-diazaspiro[3.4]octanes in drug discovery. Ongoing research in our laboratory is focused on extending this methodology to other spirocyclic scaffolds and exploring their applications.

Data availability

The data supporting this article have been included as part of the ESL† Crystallographic data for **3a** (CCDC 2427337†) have been deposited at the Cambridge Crystallographic Data Centre.

Author contributions

J. Y. D. and D. X. conceived and directed the project. Q. J. discovered and developed the reaction. Q. J., F. L., D. J. Y., T. L. and H. M. S. performed the experiments and collected the data. All authors discussed and analyzed the data. J. Y. D. and D. X. wrote the manuscript with contribution from other authors.

Conflicts of interest

There are no conflicts to declare.

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