$B(C_6F_5)_3$-Catalyzed Formal (n+3) (n = 5,6) Cycloaddition of Bicyclo[1.1.0]butanes to Medium Bicyclo[n.1.1]alkanes

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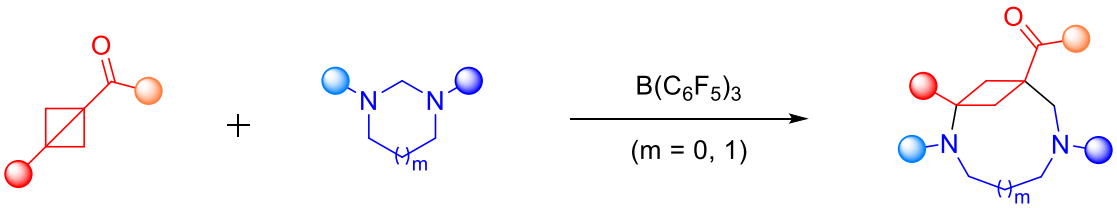
Abstract Graphic



■ First high order cycloaddition of BCBs ■ $B(C_6F_5)_3$ catalysis ■ Novel bicyclo[n.1.1]alkanes (n = 5,6)

Abstract

Herein, a $B(C_6F_5)_3$-catalyzed formal (n+3) (n = 5,6) cycloaddition of bicyclo[1.1.0]butanes (BCBs) with imidazolidines/hexahydropyrimidines is described. The reaction provides a modular, atom-economical and efficient strategy to two libraries of synthetically challenging medium-bridged rings, 2,5-diazabicyclo[5.1.1]nonanes and 2,6-diazabicyclo[6.1.1]decanes, in moderate to excellent yields. This reaction also features simple operation, mild reaction conditions and broad substrate scope. A scale-up experiment and various synthetic transformations of products further highlight the synthetic utility. Control experiments support that the reaction mechanism involves a nucleophilic addition of imidazolidines/hexahydropyrimidines to $B(C_6F_5)_3$-activated BCBs, succeeded by an intramolecular

cyclization. As we know, this methodology represents the first high order (n+3) (n > 3) cycloaddition of BCBs to saturated bicyclo[n.1.1]alkanes. We anticipate that this report will promote the exploration of BCB-based high order cycloaddition chemistry to access diverse challenging medium-bridged rings.

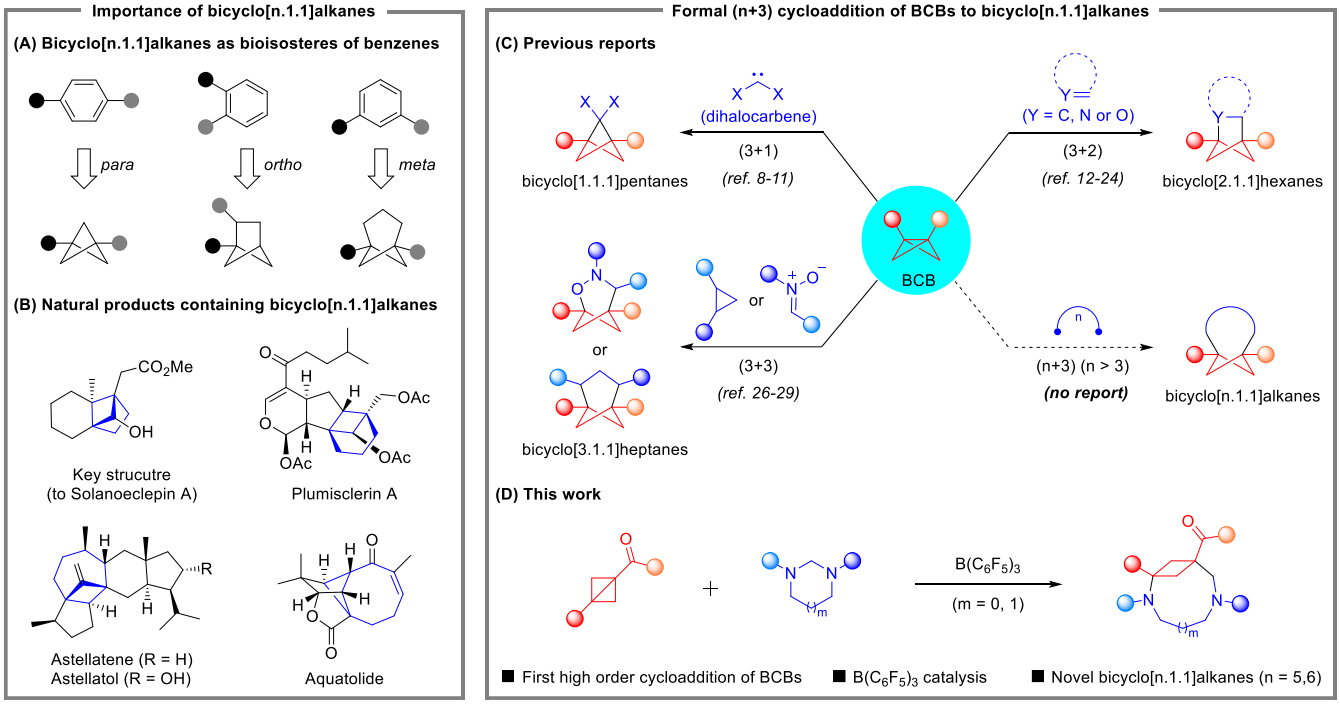
Introduction

Bridged ring systems represent long-standing targets for organic chemists because they are versatile skeletons of natural products and pharmaceuticals.[1–4] Among them, saturated bicyclo[n.1.1]alkanes have emerged as attractive synthetic targets because they are becoming ever more important in the design and development of new pharmaceuticals.[5–10] For example, bicyclo[1.1.1]pentanes,[11] bicyclo[2.1.1]hexanes[12] and bicyclo[3.1.1]heptanes[13,14] are emerging benzene bioisosteres (Scheme 1A). Replacing planar benzene rings with such three-dimensional bicyclic molecules could potentially ameliorate physicochemical and pharmacokinetic properties, thereby increasing the odds of drug development success. In addition, bicyclo[n.1.1]alkanes are widely present in natural products[15–18] or as key intermediates to complex molecules[19] (Scheme 1B). Therefore, the development of novel strategies for the synthesis of bicyclo[n.1.1]alkanes would not only enrich the toolkit of synthetic chemists but also greatly enlarge the compound library accessible for drug discovery.

Cycloaddition reactions are among the most important tools in organic chemistry. In particular, the formal (n+3) cycloaddition of bicyclo[1.1.0]butanes (BCBs)[20–28] has recently become a particularly valuable strategy for the rapid construction of saturated bicyclo[n.1.1]alkanes (Scheme 1C). The formal (3+1) cycloaddition of BCBs with dihalocarbenes was first reported by Applequist in 1977[29] and further developed by Mykhailiuk,[30] Ma[31] and Anderson,[32] respectively, providing a route to various halogenated bicyclo[1.1.1]pentanes. In the past two years, the formal (3+2) cycloaddition of BCBs with 2π-components for making (aza-/oxa-)bicyclo[2.1.1]hexanes has been extensively reported through different novel strategies, including photocycloaddition

protocols enabled by triplet energy transfer (Glorius,[33–37] Brown[38] and Bach[39]), Procter's SmI_2-catalysed redox reaction,[40] pyridine-boryl radical catalysis (Li[41] and Wang[42]) and Shi's photoexcited Hantzsch ester promoted cycloaddition.[43] In addition, Lewis acid catalyzed (3+2) cycloaddition of BCBs with 2π-components including imines (Leitch[44]), ketenes (Studer[45]), indoles (Deng[46] and Feng[47]), aldehydes (Glorius[48]) and 2-azadienes (Zheng[49]) has also proved to be feasible, wherein the Lewis acid activated BCBs act as formal 1,3-dipoles in analogy to the established donor-acceptor cyclopropane (DAC) reactivity.[50] Meanwhile, the formal (3+3) cycloaddition for the synthesis of (aza-/oxa-)bicyclo[3.1.1]heptanes was also realized successively by treating BCBs with three-atom components including cyclopropanes and nitrones through photochemical process (Molander[51] and Waser[52]), pyridine-boryl radical strategy (Li[53]) and Lewis acid catalysis (Deng[54]).[55] Albeit with these impressive progress, the formal (n+3) cycloaddition of BCBs still remains in its infancy as compared to DAC chemistry, and high order (n+3) (n > 3) cycloaddition of BCBs to saturated bicyclo[n.1.1]alkanes has not yet been reported in the literature. As we know, only one formal (5+3) example of BCBs with thiophenes to unsaturated bicyclic rings exists via a photoredox-induced radical pathway.[56]

Recently, our group demonstrated that the readily available and bench-stable imidazolidines/hexahydropyrimidines could act as potent 1,5-/1,6-dipole precursors,[50,57–59] and developed a copper-catalyzed (5+3)/(6+3) cycloaddition of DACs with imidazolidines/hexahydropyrimidines.[59] In the course of our studies, we became interested in that whether BCBs in place of DACs could undergo similar (5+3)/(6+3) cycloaddition with imidazolidines/hexahydropyrimidines, while the high strain of the target medium-bridged products poses a big challenge. Inspired by this idea, we herein reported the first high order (n+3) (n = 5,6) cycloaddition of BCBs with imidazolidines/hexahydropyrimidines under $B(C_6F_5)_3$ catalysis, providing a modular and efficient strategy to two libraries of structurally intriguing medium-bridged rings, 2,5-diazabicyclo[5.1.1]nonanes and 2,6-diazabicyclo[6.1.1]decanes (Scheme 1D).



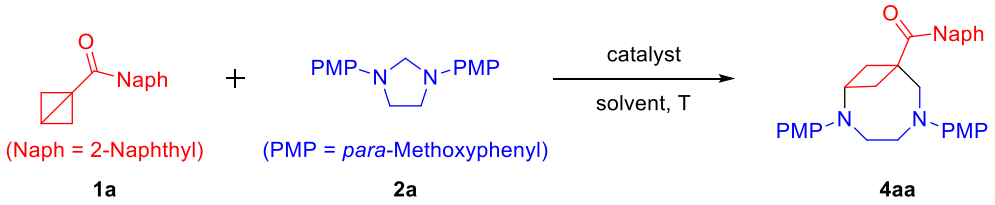
Scheme 1. Bicyclo[n.1.1]alkanes: importance and synthesis via formal (n+3) cycloaddition of BCBs

Results and discussion

At the beginning of our study, we selected two known compounds, 2-naphthyl BCB ketone **1a** and N-PMP substituted imidazolidine **2a**, as model substrates because both are relatively stable, easy to handle and store (Table 1). We were pleased to find that by using $Cu(OTf)_2$ as catalyst in CH_2Cl_2 at room temperature for 2 h,[59] the desired 2,5-diazabicyclo[5.1.1]nonane product **4aa** was obtained in 59% isolated yield (Table 1, entry 1). A control experiment in the absence of catalyst led to no product formation (Table 1, entry 2). Then, various Lewis acids were evaluated. To our delight, $Ga(OTf)_3$,[44] $Yb(OTf)_3$,[46] AgOTf,[47] TMSOTf[45] and $B(C_6F_5)_3$ all successfully promoted this (5+3) cycloaddition, with $Yb(OTf)_3$ and $B(C_6F_5)_3$ giving the same better results (Table 1, entries 3–7). Notably, Glorius reported that BF_3•OEt_2 could serve as an effective Lewis acid catalyst to trigger a (3+2) cycloaddition of BCBs with aldehydes,[48] but it was not suitable for this (5+3) reaction, resulting in almost complete decomposition of both substrates and no formation of any product (Table 1, entry 8). Besides Lewis acids, Brönsted acid TfOH was also tested, providing product **4aa** in reasonable yield (Table 1, entry 9). The non-metallic $B(C_6F_5)_3$ rather than

metallic $Yb(OTf)_3$ was chosen as the optimal catalyst, since the removal of undesired metal contamination is often nontrivial and costly in the pharmaceutical industry, to examine other solvents including toluene, tetrahydrofuran (THF) and N,N-dimethylformamide (DMF), while no improvement over CH_2Cl_2 was seen (Table 1, entries 10–12). A number of other reaction parameters including temperature, concentration and catalyst loading were then varied, but the key advance was an increased temperature (Table 1, entries 14–16). Finally, the optimal reaction conditions for this (5+3) cycloaddition were established as 20 mol% of $B(C_6F_5)_3$ catalyst in CH_2Cl_2 at 40 °C, offering the target product **4aa** in 81% yield (Table 1, entry 13)

Table 1. Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Yield[b]
1	$Cu(OTf)_2$	CH_2Cl_2	59
2	-	CH_2Cl_2	-
3	$Ga(OTf)_3$	CH_2Cl_2	53
4	$Yb(OTf)_3$	CH_2Cl_2	75
5	AgOTf	CH_2Cl_2	46
6	TMSOTf	CH_2Cl_2	40
7	$B(C_6F_5)_3$	CH_2Cl_2	75
8	$BF_3•OEt_2$	CH_2Cl_2	-
9	TfOH	CH_2Cl_2	62
10	$B(C_6F_5)_3$	toluene	15
11	$B(C_6F_5)_3$	THF	28
12	$B(C_6F_5)_3$	DMF	-

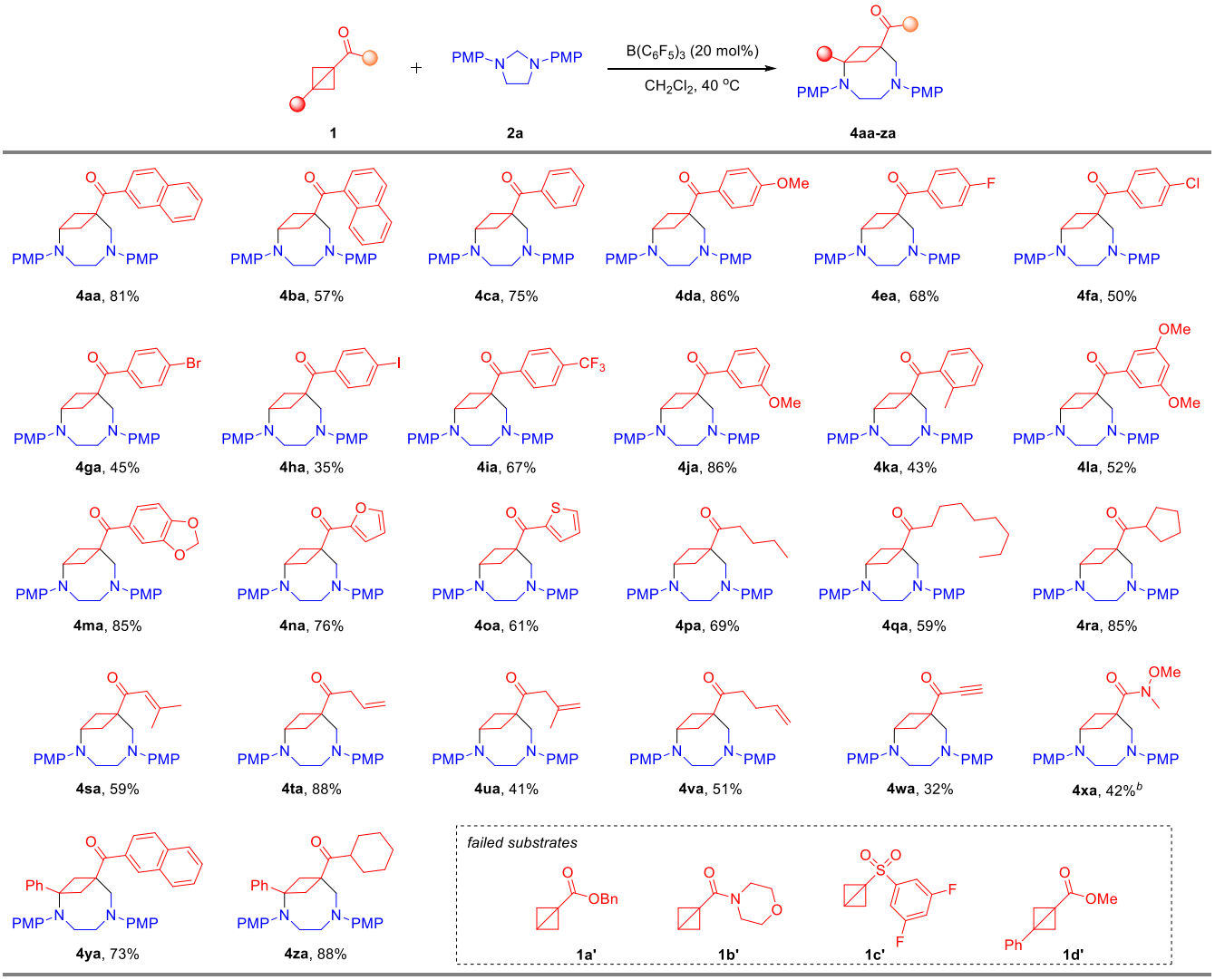
13[c]	$B(C_6F_5)_3$	CH_2Cl_2	81
14[d]	$B(C_6F_5)_3$	CH_2Cl_2	43
15[e]	$B(C_6F_5)_3$	CH_2Cl_2	62
16[f]	$B(C_6F_5)_3$	CH_2Cl_2	48

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), catalyst (20 mol%), solvent (1.0 mL), rt, 2 h. [b]Isolated yields. [c]At 40 °C. [d]At 0 °C for 12 h. [e]Solvent (2.0 mL). [f]Catalyst (10 mol%) for 6 h.

With the optimal reaction conditions established, the substrate scope of BCBs was first investigated (Scheme 2). A diverse range of aryl BCB ketones successfully underwent this transformation (**4aa**–**oa**). In these cases, variation of the 2-naphthyl BCB ketone to more bulky 1-naphthyl one was permissible, forming the corresponding 2,5-diazabicyclo[5.1.1]nonane product **4ba** in 57% yield. The phenyl BCB ketone was suitable for this reaction, and the target product **4ca** was isolated in 75% yield. With the electron-rich *p*-methoxyphenyl BCB ketone, the desired product **4da** was obtained in excellent yield (86%). Halides in the *para*-position of the BCB phenyl group were well tolerated, which could serve as a useful handle for diversification by cross-coupling reactions, and the expected 2,5-diazabicyclo[5.1.1]nonanes were formed in moderate to good yields: 68% (*p*-fluoro, **4ea**), 50% (*p*-chloro, **4fa**), 45% (*p*-bromo, **4ga**) and 35% (*p*-iodo, **4ha**). The even more electron-deficient and unstable *p*-trifluoromethylphenyl BCB ketone was also compatible with this transformation, affording product **4ia** in 67% yield. Both *m*-methoxy and *o*-methyl phenyl BCB ketones were viable substrates, resulting in the aimed products **4ja** and **4ka** in 86% and 43% yields, respectively. Moreover, BCB ketones bearing a multi-substituted phenyl or heteroaromatic (furan and thiophene) group all participated well in the reaction to furnish the corresponding products **4la**–**oa** in 52–85% yields. Along with aryl BCB ketones, alkyl ones were suitable reaction partners as well (**4pa**–**ra**). Thus, the *n*-butyl-, sterically more hindered *n*-octyl- and cyclopentyl-substituted BCB ketones reacted efficiently to afford the aimed products: 69% (*n*-butyl, **4pa**), 59% (*n*-octyl, **4qa**) and 85% (cyclopentyl, **4ra**). Besides aryl and alkyl BCB ketones, various alkenyl and alkynyl ones were also proved to be viable reaction partners, giving rise to 2,5-

diazabicyclo[5.1.1]nonanes **4sa–wa** with high degrees of molecular complexity in moderate to excellent yields (32–88%). Of note, with the less electrophilic BCB Weinreb amide **1x** in place of BCB ketones, the reaction proceeded very slowly under standard reaction conditions (**4xa**, < 10%), while after a brief optimization, $Sc(OTf)_3$ instead of $B(C_6F_5)_3$ as the catalyst improved the yield significantly to 42%. When an additional phenyl group is attached to the bridgehead bond of BCB, the expected products **4ya** and **4za** were formed in good yields (73% and 88%). Unfortunately, BCB esters (**1a'** and **1d'**), amide (**1b'**) and sulfone (**1c'**) led to no (5+3) cycloadducts under the optimal or varied reaction conditions.

Scheme 2. BCB scope of (5+3) cycloaddition[a]

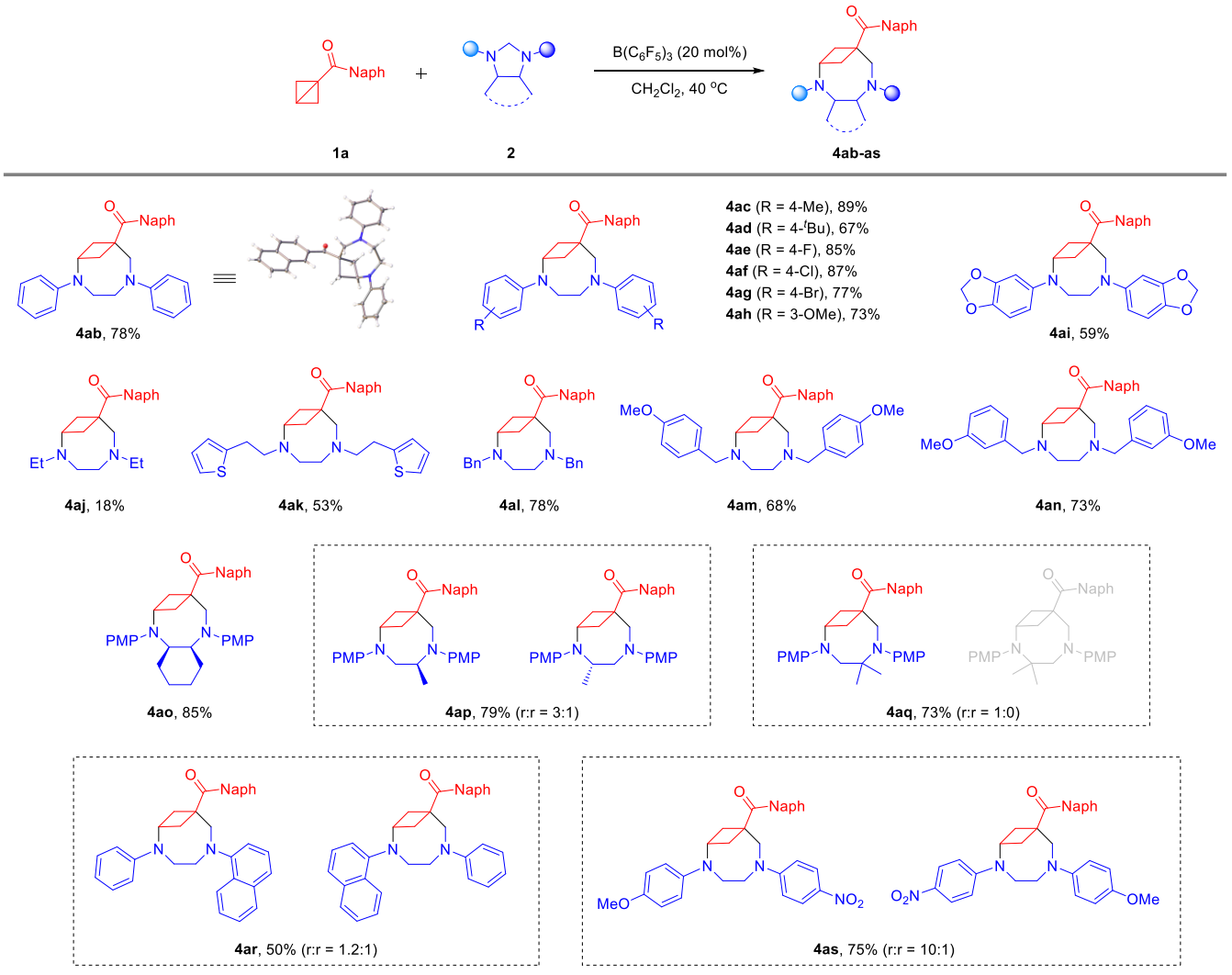


[a]Reaction conditions: **1** (0.15 mmol), **2a** (0.1 mmol), $B(C_6F_5)_3$ (20 mol%), CH_2Cl_2 (1.0 mL), 40 °C, 2 h. Isolated yields. [b]$Sc(OTf)_3$ (20 mol%) as catalyst for 24 h.

We then continued our studies by using 2-naphthyl BCB ketone **1a** as reaction partner to examine the imidazolidine scope (Scheme 3). Various symmetrical imidazolidines were first tested (**4ab–ap**). Symmetrical N-aryl imidazolidines bearing substituents at *para*- and/or *meta*-positions of the phenyl ring all reacted smoothly to afford the corresponding products **4ab–ai** in good to excellent yields (59–89%). Moreover, both symmetrical N-alkyl and N-benzyl congeners turned out to be suitable substrates, leading to the target products in 18% (**4aj**), 53% (**4ak**), 78% (**4al**), 68% (**4am**) and 73% (**4an**) yields, respectively. Notably, deprotection of the benzyl group allows for further N-modification of the obtained products. Besides, this method is also amenable to symmetrical C-substituted cyclohexane-fused imidazolidine **2o**, providing the structurally interesting tricyclic product **4ao** in 85% yield. Next, several unsymmetrical imidazolidines were explored (**4ap–as**). When 4-methylimidazolidine **2p** was employed, only moderate regioselectivity was observed (**4ap**). With the increase of steric hindrance, excellent regioselectivity was achieved by using 4,4-dimethylimidazolidine **2q** as substrate, and only one regioisomer was formed (**4aq**). When unsymmetrical imidazolidine **2r** possessing significant N-steric effect was used, unfortunately, there was almost no regioselectivity (**4ar**). Gratifyingly, imidazolidine **2s** with obvious N-electronic difference resulted in good regioselectivity (**4as**). The structure of **4ab** was unambiguously assigned by X-ray structure analysis (CCDC 2327804).[60]

Encouraged by the above success, we speculate that a Lewis acid catalyzed (6+3) cycloaddition of BCBs with hexahydropyrimidines should be feasible, because it has been well demonstrated by our group that hexahydropyrimidines exhibit similar reactivity to imidazolidines and can be considered as 1,6-dipole precursors.[57–59] This would be a straightforward method for the construction of synthetically challenging bicyclo[6.1.1]decane scaffolds. We then focused on the Lewis acid catalyzed (6+3) cycloaddition of BCBs with hexahydropyrimidines (Scheme 4). Gratifyingly, the expected 2,6-diazabicyclo[6.1.1]decane

Scheme 3. Imidazolidine scope of (5+3) cycloaddition[a]

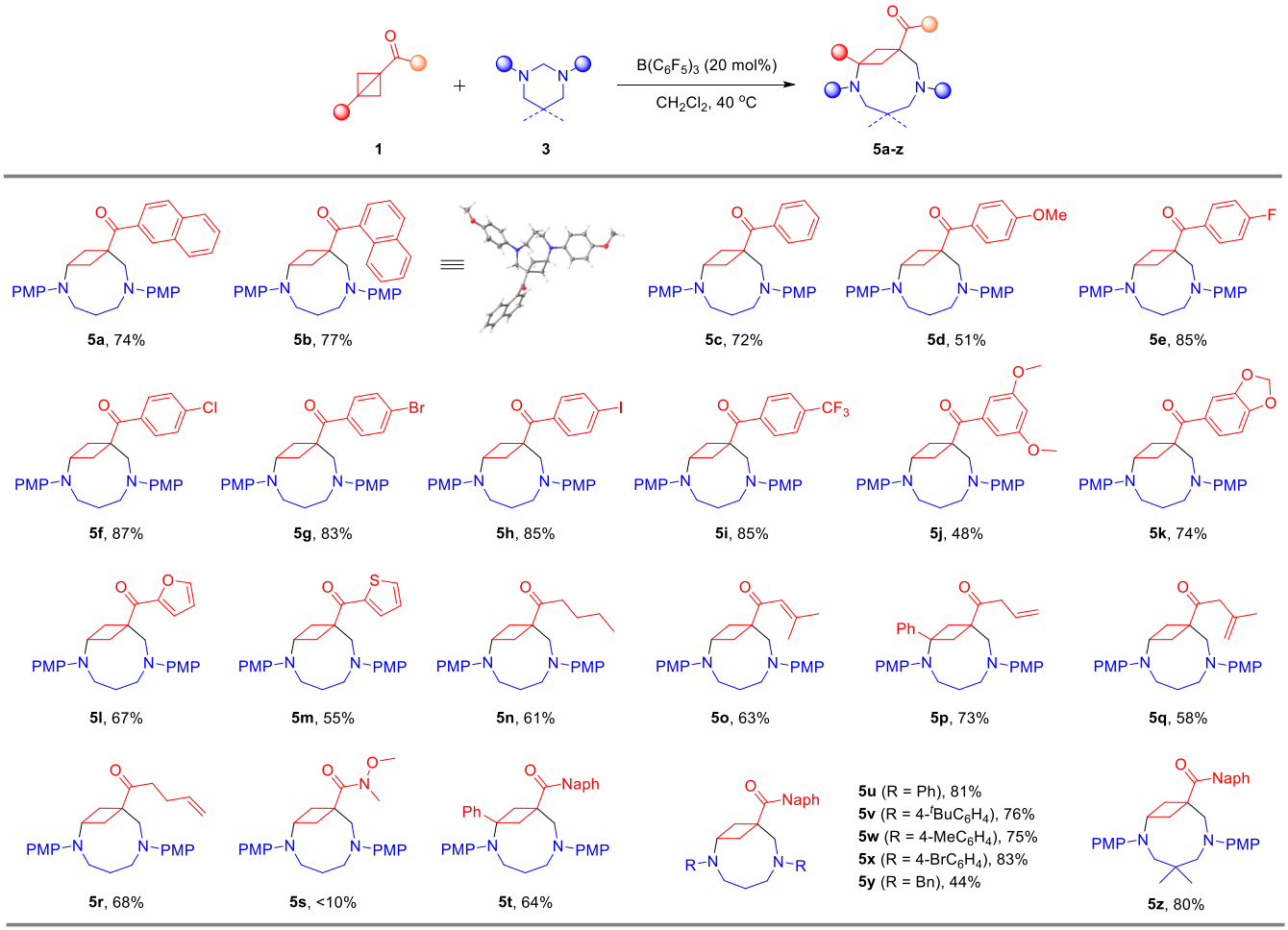


[a]Reaction conditions: **1a** (0.15 mmol), **2** (0.1 mmol), $B(C_6F_5)_3$ (20 mol%), CH_2Cl_2 (1.0 mL), 40 °C, 2 h. Isolated yields. The r:r values were determined by ^1H NMR analysis of the crude reaction mixture.

product **5a** was obtained in 74% yield when 2-naphthyl BCB ketone **1a** and N-PMP substituted hexahydropyrimidine **3a** were used as model substrates under the same reaction conditions. Subsequently, a series of BCB ketones were examined (**5a–t**). In these cases, 1-naphthyl, (hetero)aryl, alkyl and alkenyl BCB ketones all reacted smoothly to afford the target products **5b–r** in moderate to excellent yields (48–87%). The structure of **5b** was confirmed unambiguously by X-ray structure analysis (CCDC 2327802).[60] For the less electrophilic BCB Weinreb amide **1x**, the (6+3) cycloadduct **5s** was detected by ^1H NMR analysis in traces only under $B(C_6F_5)_3$ or $Sc(OTf)_3$ catalysis. The sterically more demanding phenyl-substituted BCB ketone **1y** was suitable for this (6+3) cycloaddition, giving rise to the desired product **5t**

in 64% yield. Next, several hexahydropyrimidines, including N-aryl, N-benzyl and C-substituted ones, were tested, all of which led to their corresponding products in acceptable yields (**5u–z**).

Scheme 4. Substrate scope of (6+3) cycloaddition[a]

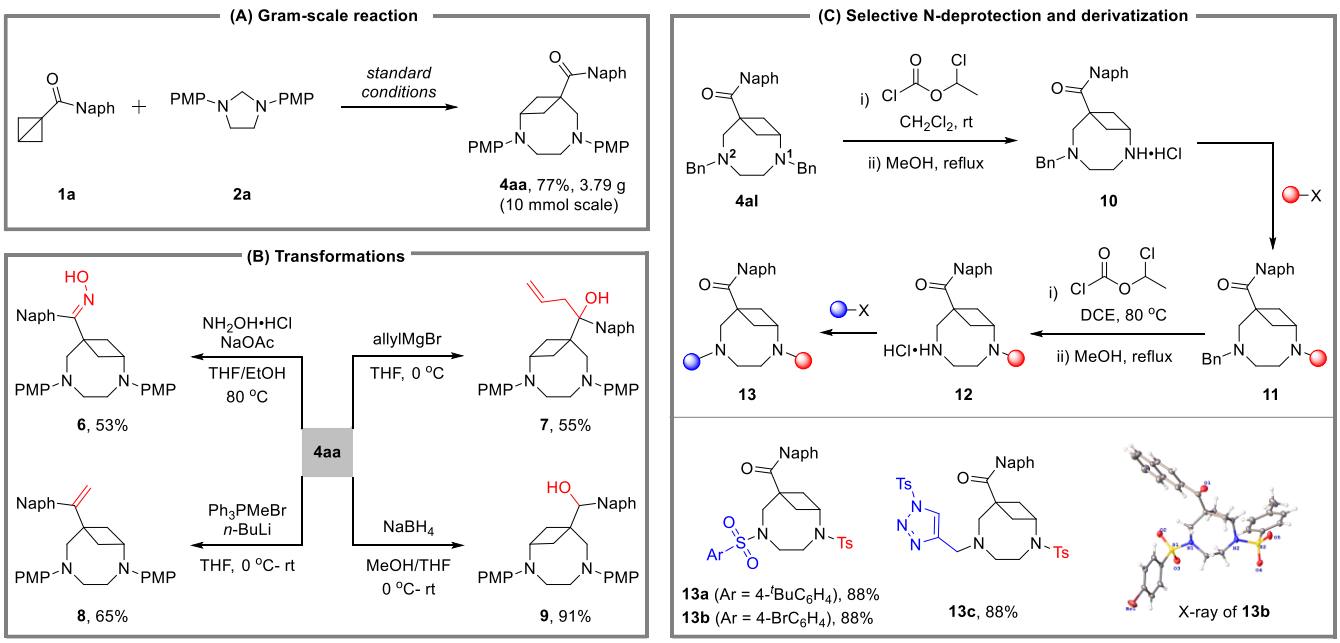


[a]Reaction conditions: **1** (0.15 mmol), **3** (0.1 mmol), $B(C_6F_5)_3$ (20 mol%), CH_2Cl_2 (1.0 mL), 40 °C, 2 h. Isolated yields.

As shown in Scheme 5A, the robustness of the protocol was further demonstrated by a gram-scale reaction of BCB ketone **1a** with imidazolidine **2a**, and the outcome was almost maintained, paving a practical and economical way for large-scale production. Moreover, the obtained product **4aa** could be employed as a handle for diverse downstream transformations to access a variety of medium-bridged ring systems by condensation (**6**), allylation (**7**), Wittig olefination (**8**) and reduction (**9**), as shown in Scheme

5B. In addition, the N-PMP cleavage of **4aa** under oxidative conditions was also explored,[61–63] but **4aa** totally decomposed and no major product was detected. Gratifyingly, selective N-debenzylation of **4al** could be easily achieved (Scheme 5C).[64] By treating **4al** with α-chloroethyl chloroformate in CH_2Cl_2 at room temperature followed by reflux in MeOH, the remote N^1-Bn protecting group was selectively removed to **10**, while the free N^1-H group of **10** inhibited the proximal N^2-Bn deprotection under the same or even harsh reaction conditions. Interestingly, when the free N^1-H group of **10** was substituted, treatment of **11** with α-chloroethyl chloroformate in 1,2-dichloroethane (DCE) at 80 °C followed by reflux in MeOH smoothly deprotected the proximal N^2-Bn group to **12**. Thus, after a second N^2-H substitution of **12**, various **13** bearing different N-pharmacophores including sulfonyl and triazole groups could be readily assembled. The structure of **13b** was assigned by X-ray structure analysis, which unambiguously confirmed the N^1/N^2-Bn deprotection sequence (CCDC 2338181).[60] These transformations demonstrated the potential synthetic utility of our protocol.

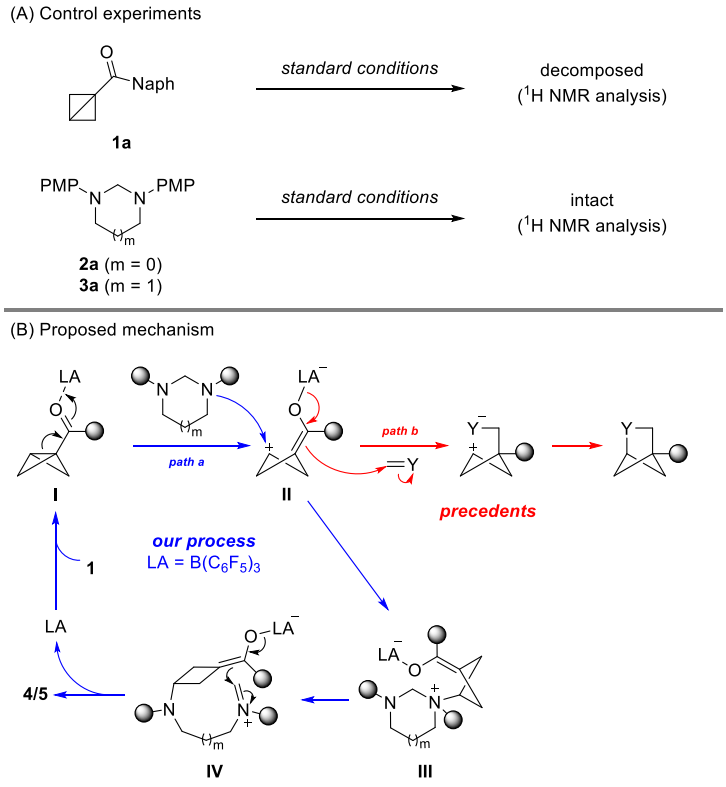
Scheme 5. Further investigations



To gain more insights into the mechanistic details, two control experiments were performed (Scheme 6A). When BCB **1a** or imidazolidine/hexahydropyrimidine **2a**/**3a** was subjected to the standard reaction

conditions, **1a** totally decomposed and **2a/3a** remained intact, thereby suggesting that Lewis acid $B(C_6F_5)_3$ activates BCB rather than imidazolidine/hexahydropyrimidine substrate. Thus, a plausible ionic stepwise mechanism is proposed for our process (Scheme 6B, *path a*). Initially, complexation of Lewis acidic $B(C_6F_5)_3$ catalyst with BCB **1** generates species **I**, which undergoes enolization to intermediate **II**. Subsequent nucleophilic addition of imidazolidine/hexahydropyrimidine **2/3** to the carbocation center of **II** forms ammonium species **III**. Importantly, it is obviously different from the pioneering precedents by Leitch,[44] Studer[45] and Glorius[48] that triggered the reaction with nucleophilic attack from the anion moiety of intermediate **II** (Scheme 6B, *path b*). Subsequent aminal ring opening affords zwitterionic iminium species **IV**, followed by intramolecular cyclization to afford the target product **4/5** with the release of $B(C_6F_5)_3$ catalyst.

Scheme 6. Mechanistic investigation



Conclusion

In summary, we have developed a modular and efficient approach for the formal (n+3) (n = 5,6) cycloaddition of BCBs with imidazolidines/hexahydropyrimidines under $B(C_6F_5)_3$ catalysis, offering two series of synthetically challenging medium-bridged rings, 2,5-diazabicyclo[5.1.1]nonanes and 2,6-diazabicyclo[6.1.1]decanes. The reaction proceeds under mild reaction conditions and tolerates a broad range of BCBs and imidazolidines/hexahydropyrimidines. The potential synthetic utility of the reaction has also been highlighted by a scale-up experiment and various synthetic transformations of products. As we know, this methodology represents the first Lewis acid catalyzed high order (n+3) (n > 3) cycloaddition of BCBs.[65] Given the novel reactivity of this transformation and the high demand for conformationally restricted bicyclic molecules in drug design and development, we envision that this methodology will have an impact in both synthetic and medicinal chemistry. Further studies will be reported in due course.

Methods

Typical procedure for the synthesis of 4aa from 1a and 2a. In a reaction vial equipped with a magnetic stir bar, **1a** (31.2 mg, 0.15 mmol, 1.50 equiv) and **2a** (28.4 mg, 0.10 mmol, 1.00 equiv) were added into CH_2Cl_2 (1.0 mL). $B(C_6F_5)_3$ (10.2 mg, 0.02 mmol, 20 mol%) was then added. The reaction vial was sealed, and the resulting mixture was stirred at 40 ºC for 2 h. The reaction was cooled down to room temperature, concentrated under reduced pressure and purified by flash column chromatography (eluent: hexanes/EtOAc = 5:1) on silica gel to afford the corresponding product **4aa** as a yellow solid in 81% yield (39.9 mg).

Data availability

The data that support the findings of this study are available in this article and Supplementary Information (experimental procedures and characterization data). Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under a deposition

number CCDC 2327804 (**4ab**), CCDC 2327802 (**5b**) and CCDC 2338181 (**13b**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

Acknowledgments

The authors are grateful for the financial support from the National Natural Sciences Foundation of China (22201221).

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Contributions

S. Peng supervised the project. L. Yang and H. Wang performed the experiments. S. Peng wrote the manuscript and analysed the experimental data. All authors discussed the results, checked the data and agreed to the manuscript.

Ethics declarations

Competing interests

The authors declare no competing financial interest.

Supplementary information

Experimental procedures along with characterizing data, copies of NMR spectra, and X-ray crystallographic data (PDF)

Crystal data for compounds **4ab**, **5b** and **13b** (CIF)

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