Divergent Synthesis of Cyclobutyl and Biscyclobutenyl Amines via Lewis Acid-Catalyzed Reaction of Bicyclo[1.1.0]butanes with Triazinanes

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Abstract: In this study, we describe a Lewis acid-catalyzed divergent synthesis of cyclobutyl and biscyclobutenyl amines by exploiting the distinct reactivity exhibited by bicyclo[1.1.0]butane (BCB) ketones and esters with triazinanes. The cycloaddition of BCB ketones with triazinanes yields 2,4-diazabicyclo[4.1.1]octanes (aza-BCOs) under $B(C_6F_5)_3$ catalysis. A direct acidic treatment of the resulting aza-BCOs efficiently cleaves the aminal moiety, leading to a series of medicinally intriguing *cis*-cyclobutyl diamines. This "cycloaddition/ring-opening" process can be conducted in either a stepwise or one-pot manner. In contrast, the reaction of BCB esters with triazinanes produces a range of beautiful butterfly-shaped biscyclobutenyl amines under $In(OTf)_3$ catalysis. Both reactions feature simple operation, mild reaction conditions, and a broad substrate scope. Mechanistic studies reveal that the distinct reaction pathways originate from the different activation modes of BCBs by Lewis acid, the reaction of BCB ketones with triazinanes follows a stepwise (2+2+3) rather than (4+3) cycloaddition, and the reaction of BCB esters with triazinanes involves a Leitch's carbocation intermediate. We believe that our findings will promote the exploration of BCB chemistry to access more synthetically challenging cyclobutane frameworks.

Introduction

Cyclobutanes are privileged four-membered synthetic targets because they are versatile skeletons of natural products and pharmaceuticals with diverse biological properties,[1] and also serve as key intermediates in the synthesis of structurally complex molecules.[2] Among these, cyclobutyl amines stand out as pivotal cores in medicinal development, which can be found in a large variety of bioactive molecules, as illustrated in Scheme 1A.[3] Therefore, the development of novel strategies for synthesizing cyclobutyl amines, preferably with stereocontrol, would not only enrich the toolkit of synthetic chemists but also significantly expand the compound library available for drug discovery.

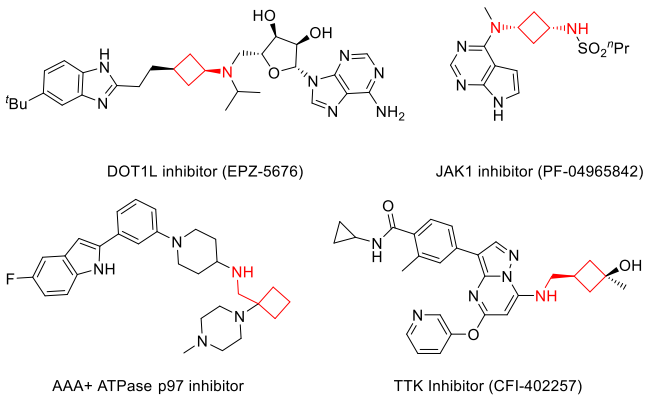
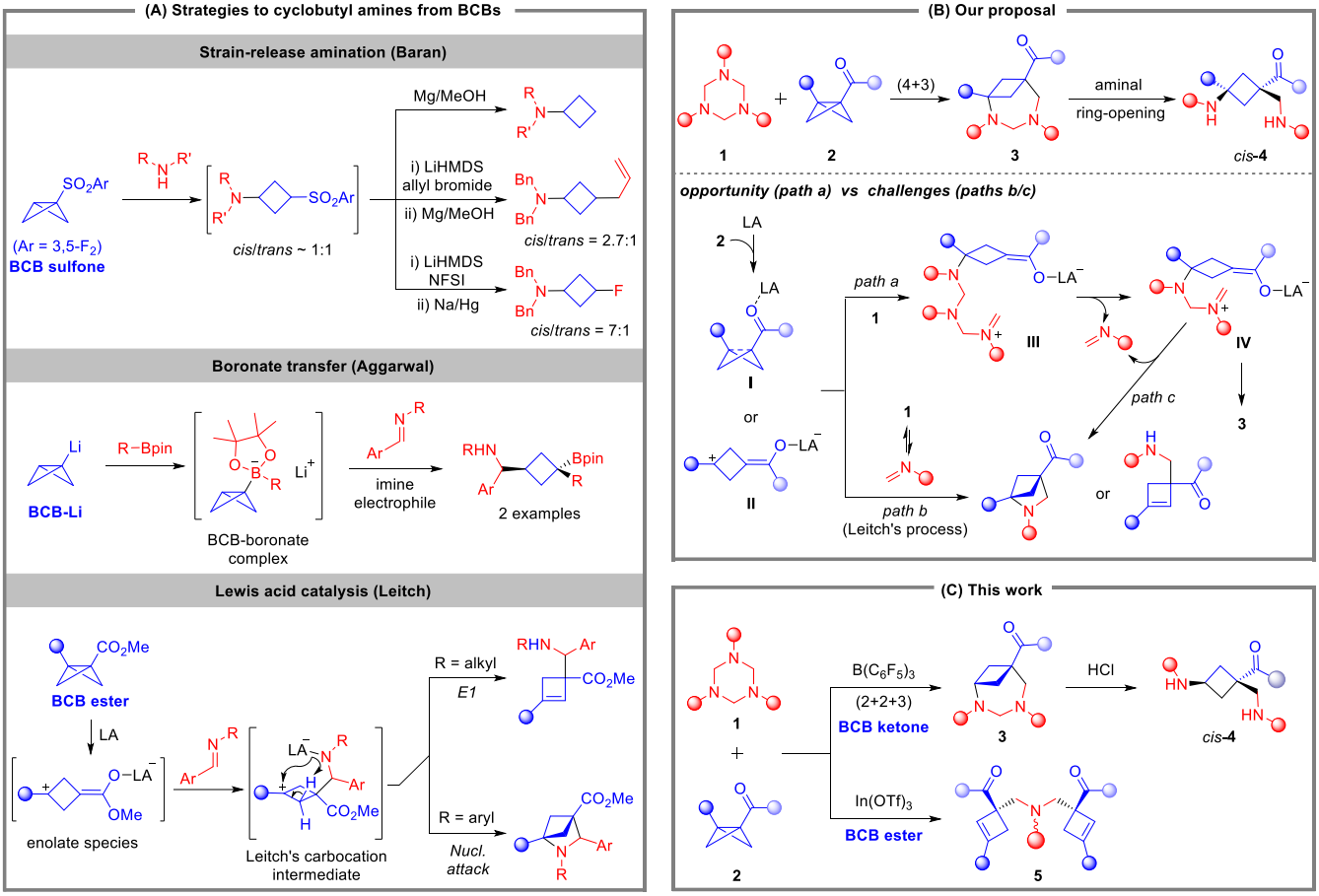


Figure 1. Importance of cyclobutyl amine scaffolds.

In addition to the well-established [2+2] cycloaddition strategy,[4] the strain-release reaction of bicyclo[1.1.0]butanes (BCBs)[5] has emerged as an alternative for synthesizing different types of cyclobutanes.[6] Despite impressive progess, developing modular strategies for the synthesis of cyclobutyl amines, especially with stereocontrol and molecular complexity, remains challenging. To meet this challenge, three innovative protocols have been developed. In 2016, Baran and co-workers reported a "strain-release amination" strategy (Scheme 1A, top). This method utilized BCB sulfones as electrophiles in reactions with various amine nucleophiles to construct 3-sulfonyl cyclobutylamines.[7] Controlling cis/trans selectivity was difficult, resulting in poor stereocontrol during late-stage transformations. The direct removal of the arylsulfonyl group reduced molecular complexity. Besides, Aggarwal and co-workers developed a BCB-boronate complex from the corresponding lithiated BCB and boronic ester.[8] This complex enabled an appealing difunctionalization of the central C-C *σ*-bond with various electrophiles including imines (Scheme 1B, middle).[9] In this case, the generation of lithiated BCB required the use of hazardous *tert*-butyl lithium, and only two examples of cyclobutyl methanamines were presented albeit with good diastereoselectivity. Recently, Leitch and co-workers realized an elegant Lewis acid-catalyzed reaction of BCB esters with N-alkyl or N-aryl imines for the divergent synthesis of

cyclobutenyl methanamines (via E1 elimination) and azabicyclohexanes (aza-BCHs, via nucleophilic attack), respectively (Scheme 1C, bottom).[10] Both products were formed in parallel pathways that share a common Leitch's carbocation intermediate derived from the C-C bond formation between the Lewis acid activated BCB enolate species and the imine. Thus, the cyclobutenyl methylamines typically achieved low to moderate yields due to the competitive aza-BCHs.



Scheme 1. Strategies to cyclobutyl amines from BCBs: previous reports and this work.

1,3,5-Trisubstituted-hexahydro-1,3,5-triazines (referred to as triazinanes in this text) are stable precursors of formaldimines and have been utilized as effective aminomethylation reagents by Krische[11] and as Mannich-type reagents by Feng[12] and Kang.[13] Moreover, application of triazinanes have been further expanded as 1,n-synthons (n = 2-4) in various cycloadditions to construct a wide range of N-heterocycles.[14] Of special interest to the current study, Sun and co-workers first discovered that triazinanes could be used as 1,4-dipole precursors in the gold-catalyzed (4+1)/(4+3) cycloadditions with diazo compounds to produce five-/seven-membered N-heterocycles.[15] Besides, Werts and co-workers further developed a (4+3) cycloaddition/ring-opening strategy of donor-acceptor cyclopropanes (DACs) with triazinanes to form 1,4-diamines via (4+3) 1,3-diazepane cycloadducts.[16] Inspired by these two pioneering reports and our recent findings on high-order cycloaddition of BCBs,[17] we are intrigued by the potential of developing a (4+3) cycloaddition/ring-opening reaction of BCBs with triazinanes to produce structurally intriguing cyclobutyl diamines **4** via (4+3) aza-BCO cycloadducts **3** (Scheme 1B). This strategy would not only incorporate 1-amino and 3-methylamino functional groups into cyclobutane ring simultaneously to enhance the molecular complexity, but also result in the aminal-ring pre-fixed *cis*-configuration. Mechanistically, the complexation of Lewis acid with BCB may produce intermediate **I**[10,18,19] or enolate species **II**.[20-22] So, either an S_N1 or S_N2-like pathway is conceivable for the nucleophilc attack of triazinane **1** on BCB **2** to form intermediate **III**, which then loses one molecule of formaldimine to generate a shorter chain iminium species **IV**. Subsequent cyclization forms the desired (4+3) cycloadduct **3** (Scheme 1B, *path a*).[15,16] However, under certain conditions, triazinane **1** could decompose into formaldimines.[23] Thus, a competitive Leitch's process leading to (3+2) aza-BCH or cyclobutenyl methanamine poses a big challenge for the target (4+3) cycloaddition (Scheme 1B, *path b*).[10] Alternatively, intermediate **IV** might release another molecule of formaldimine and cyclize to afford (3+2) aza-BCHs (Scheme 1B, *path c*). In this study, we successfully realized a stepwise (2+2+3) rather than (4+3) cycloaddition of BCB ketones with triazinanes under $B(C_6F_5)_3$ catalysis, leading to aza-BCOs **3**. A direct acidic treatment of the obtained aza-BCOs resulted in efficient cleavage

of the aminal moiety, producing the designed *cis*-cyclobutyl diamines **4**. Interestingly, when BCB esters were used instead of BCB ketones to react with triazinanes under $In(OTf)_3$ catalysis, butterfly-shaped biscyclobutenyl amines **5** were unexpectedly obtained (Scheme 1C). Herein, we report these preliminary results.

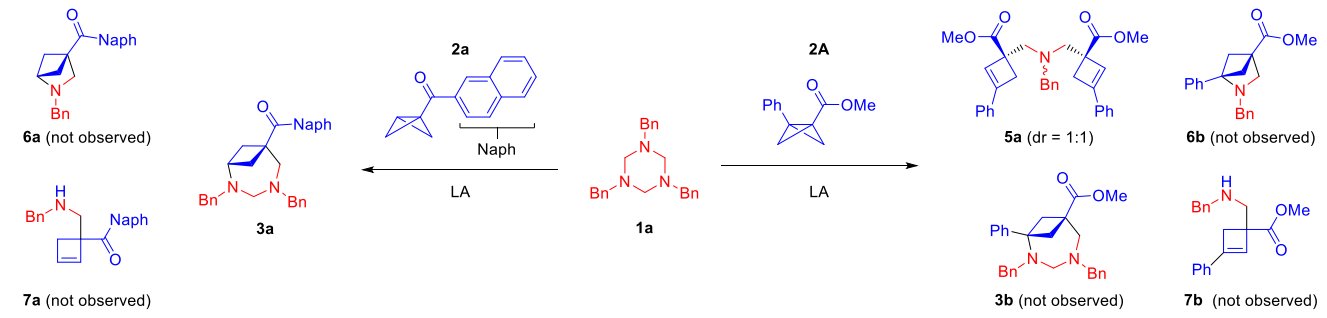
Results and Discussion

We initially examined the reaction between N-Bn triazinane **1a** and two BCBs (BCB ketone **2a** and BCB ester **2A**) under $B(C_6F_5)_3$ catalysis in dichloromethane (CH_2Cl_2) at room temperature for 24 h.[17] To our delight, for BCB ketone **2a**, the formal (4+3) cycloaddition did occur to yield the desired aza-BCO product **3a** in 44% yield, while neither (3+2) cycloadduct **6a** or cyclobutenyl methanamine **7a** was detected (Table 1, entry 1). Interestingly, for BCB ester **2A**, an unexpected butterfly-shaped biscyclobutenyl amine product **5a** rather than (4+3) cycloadduct **3b** was isolated in 58% yield without any (3+2) cycloadduct **6b** or cyclobutenyl methanamine **7b** observed (Table 1, entry 17). These outcomes motivated us to evaluate other reaction parameters for both reactions.

For the formal (4+3) cycloaddition of **1a** with **2a**, a variety of Lewis acids were screened (Table 1, entries 1-9). Although the selected Lewis acids were all effective, none showed improvement over $B(C_6F_5)_3$. Subsequently, several solvents including 1,2-dichloroethane (DCE), toluene and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were evaluated, and toluene was found to be superior (Table 1, entries 10-12). Various other reaction parameters, such as additive, temperature, concentration and catalyst loading, were further optimized (see Supporting Information and Table 1, entries 13-15). The key improvement was the addition of 4Å molecular sieves (4Å MS) to prevent the hydrolysis of triazinane **1a** and BCB ketone **2a** (Table 1, entry 13).[24,25] A control experiment revealed that no product **3a** was formed in the absence of catalyst (Table 1, entry 16). Notably, the competitive products **6a** and **7a** were not detected throughout the optimization studies. Finally, the optimal conditions were established as 10 mol% of $B(C_6F_5)_3$ catalyst in CH_2Cl_2 at room temperature, offering product **3a** in 61% yield (Table 1, entry 13).

Next, we continued to optimize the reaction of triazinane **1a** with BCB ester **2A**. This reaction exhibited good compatibility with various Lewis acid catalysts and solvents (Table 1, entries 17-28). The combination of $In(OTf)_3$ as the catalyst and HFIP as the reaction medium gave the best result (Table 1, entry 28). In contrast, 4Å MS greatly suppressed the reaction, indicating that water plays a key role in the formation of **5a** (Table 1, entry 29). Gratifyingly, by increasing the amount of **2A** to invert the **1a**/**2A** ratio, **5a** was obtained in almost quantitative yield (Table 1, entry 30). Reducing the catalyst loading to 1 mol% also produced the same result (Table 1, entry 31). A control experiment in the absence of catalyst led to no formation of product **5a** (Table 1, entry 32). Of note, the competitive products **3b**, **6b** and **7b** were not detected throughout the optimization studies. Ultimately, the optimal conditions for this reaction were established as 1 mol% of $In(OTf)_3$ catalyst in HFIP at room temperature, yielding product **5a** in 99% yield (Table 1, entry 30).

Table 1. Optimization of reaction conditions.[a]



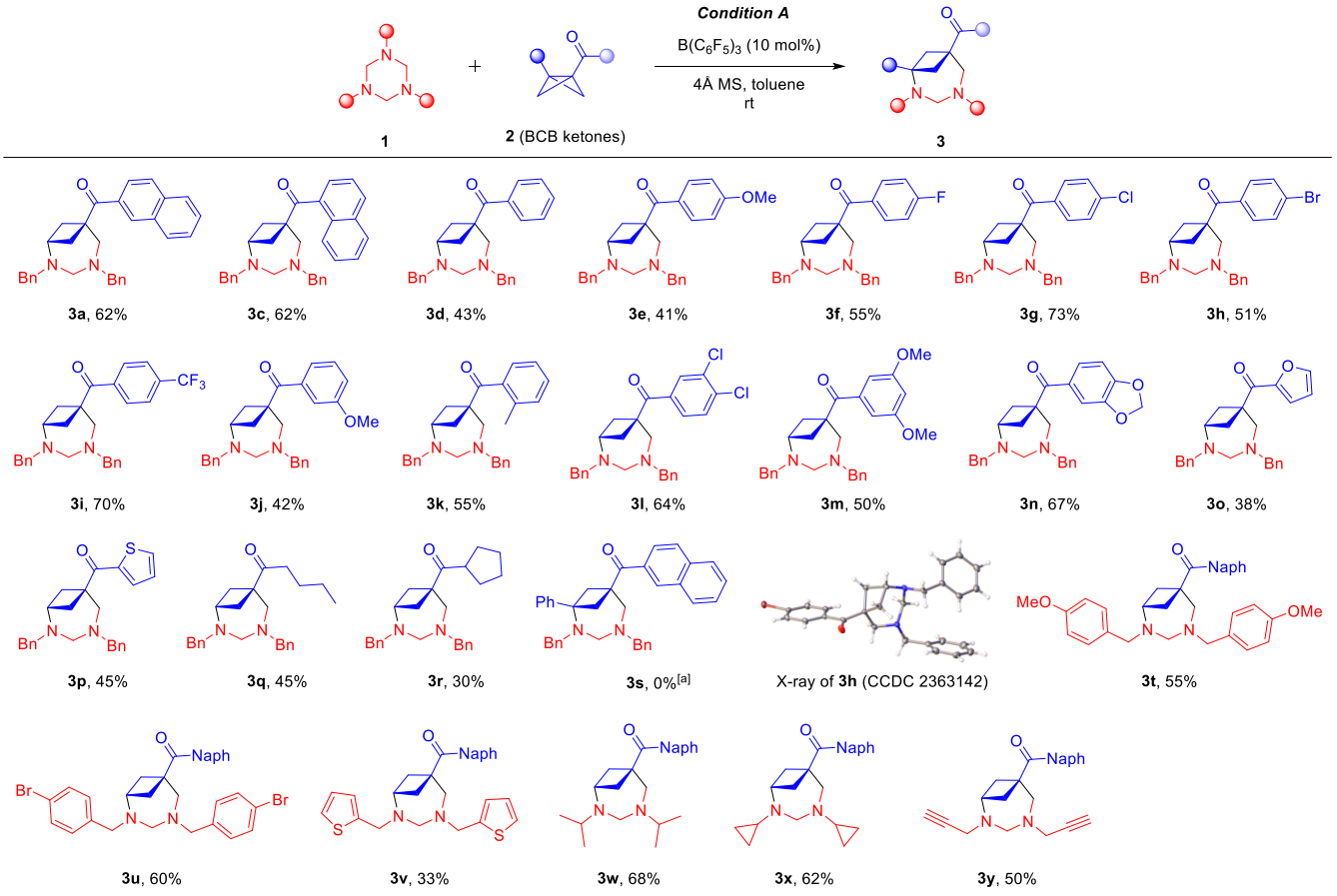
entry	catalyst	solvent	yield (**3a**)[b]	entry	catalyst	solvent	yield (**5a**)[b]
1	$B(C_6F_5)_3$	CH_2Cl_2	44	17	$B(C_6F_5)_3$	CH_2Cl_2	58
2	TMSOTf	CH_2Cl_2	43	18	TMSOTf	CH_2Cl_2	46
3	BF_3•OEt_2	CH_2Cl_2	31	19	BF_3•OEt_2	CH_2Cl_2	50
4	$Ga(OTf)_3$	CH_2Cl_2	36	20	$Ga(OTf)_3$	CH_2Cl_2	43
5	$Sc(OTf)_3$	CH_2Cl_2	29	21	$Sc(OTf)_3$	CH_2Cl_2	58
6	$Yb(OTf)_3$	CH_2Cl_2	29	22	$Yb(OTf)_3$	CH_2Cl_2	58
7	$Bi(OTf)_3$	CH_2Cl_2	41	23	$Bi(OTf)_3$	CH_2Cl_2	53
8	$In(OTf)_3$	CH_2Cl_2	35	24	$In(OTf)_3$	CH_2Cl_2	62
9	$Cu(OTf)_2$	CH_2Cl_2	28	25	$Cu(OTf)_2$	CH_2Cl_2	60
10	$B(C_6F_5)_3$	DCE	47	26	$In(OTf)_3$	DCE	59
11	$B(C_6F_5)_3$	toluene	52	27	$In(OTf)_3$	toluene	58
12	$B(C_6F_5)_3$	HFIP	-	28	$In(OTf)_3$	HFIP	63
13[c]	$B(C_6F_5)_3$	toluene	62	29[c]	$In(OTf)_3$	HFIP	49

14[c,d]	$B(C_6F_5)_3$	toluene	57	30[f]	$In(OTf)_3$	HFIP	99
15[c,e]	$B(C_6F_5)_3$	toluene	52	31[f,g]	$In(OTf)_3$	HFIP	99
16	-	toluene	-	32	-	HFIP	-

[a] Reaction conditions: **1a** (0.2 mmol), **2a**/**2A** (0.3 mmol), catalyst (10 mol%), solvent (2.0 mL), rt, 24 h. [b] Isolated yields. [c] 4Å MS (100 mg) was added. [d] Catalyst (20 mol%) was used. [e] At 0 °C. [f] **2A** (0.5 mmol). [g] Catalyst (1 mol%).

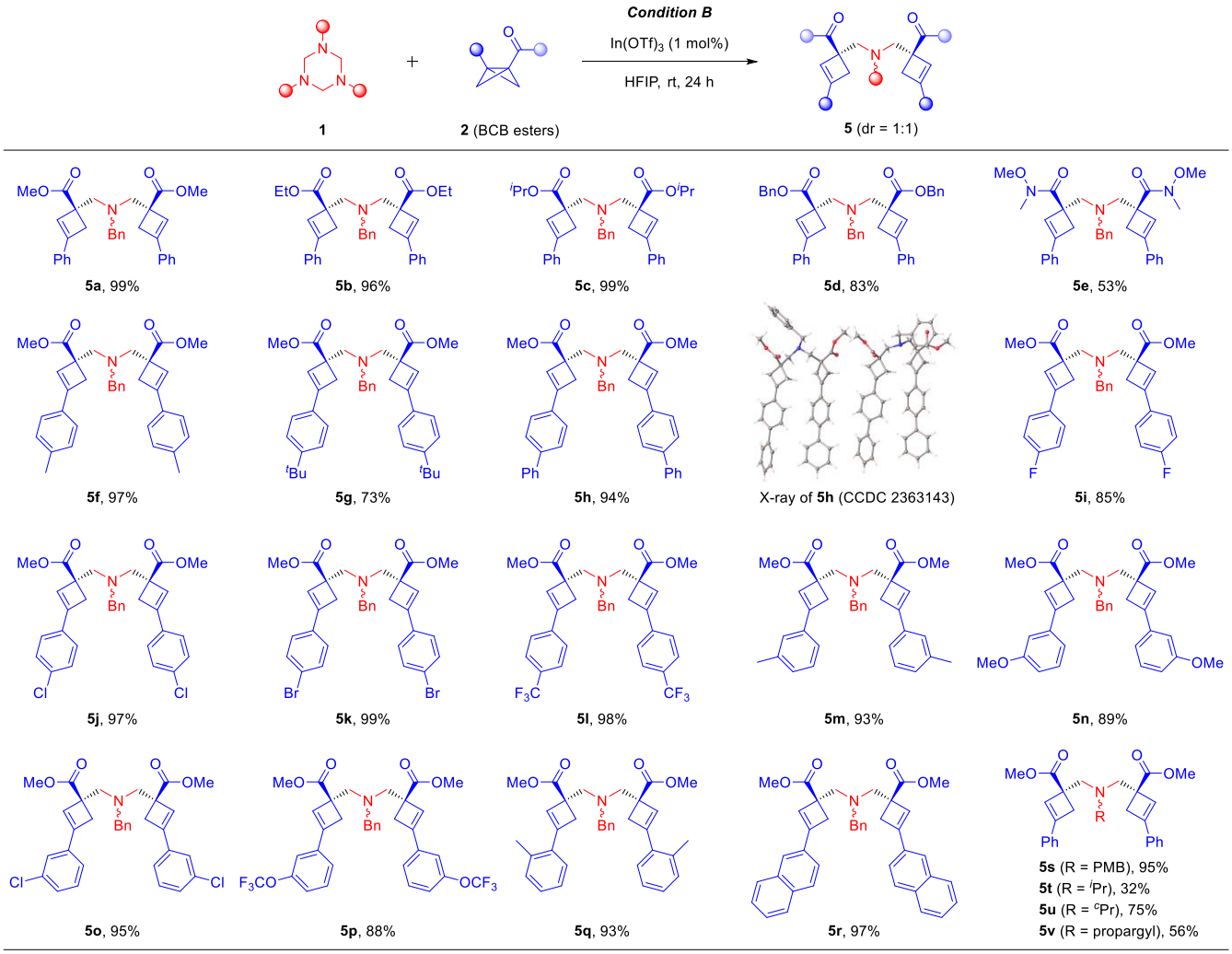
With the above two sets of optimal reaction conditions established, we first examined the substrate generality and limitations for the synthesis of aza-BCOs under condition A (Scheme 2). A diverse range of aryl BCB ketones successfully underwent this transformation (**3a** and **3c**-**p**). In these cases, replacing the 2-naphthyl BCB ketone with the bulkier 1-naphthyl one did not affect the reaction, yielding the corresponding cycloadduct **3c** in 62% yield. The phenyl BCB ketone as well as those bearing a single electron-donating (methyl, methoxy) or electron-withdrawing (halogen, trifluoromethyl) substituent at random position of the phenyl ring was compatible with this transformation, producing the target aza-BCOs in moderate to good yields (**3d**-**k**). Particularly noteworthy is **3h**, which contains an Ar-Br moiety available for further modifications via cross-couplings. The structure of **3h** was comfirmed by X-ray structure analysis (CCDC 2363142).[26] Moreover, both multi-substituted aryl and heteroaromatic (furan, thiophene) BCB ketones participated well in the reaction to furnish the desired products **3l**-**p** in 38-67% yields. Encouragingly, alkyl BCB ketones, such as *n*-butyl- and cyclopentyl-substituted ones, were also suitable for the reaction, affording the aimed cycloadducts in 45% (**3q**) and 30% (**3r**) yields, respectively. Unfortunately, when 1,3-disubstituted BCB ketone was employed under condition A, no product **3s** was detected.

The scope with respect to triazinanes was further explored under condition A. Several other N-benzyl triazinanes bearing an electron-donating (methoxy), electron-withdrawing (bromo) or heteroaromatic (thiophene) group were well-tolerated, affording the desired products in 55% (**3t**), 60% (**3u**) and 33% (**3v**) yields, respectively. N-alkyl congeners, such as N-isopropyl and N-cyclopropyl ones, worked well to furnish the target aza-BCOs in good yields (**3w** 68% and **3x** 62%). Notably, the N-propargyl triazinane was also a viable reaction partner, giving rise to the expected product **3y** with high degrees of molecular complexity in 50% yield.



Scheme 2. Scope of triazinanes with BCB ketones. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $B(C_6F_5)_3$ (10 mol%), toluene (2.0 mL), 4Å MS (100 mg), rt, 24 h. Isolated yields. [a] BCB ketone was 78% recovered.

Next, we continued our studies under condition B to examine the substrate scope of the $In(OTf)_3$-catalyzed reaction of triazinanes with BCB esters for the synthesis of biscyclobutenyl amines (Scheme 3). This protocol is amenable to a variety of 1,3-disubstituted BCB esters, including methyl (**5a**), ethyl (**5b**), isopropyl (**5c**) and benzyl (**5d**) esters. Notably, the BCB Weinreb amide, which offers potential for further downstream modifications, was also compatible with this transformation (**5e** 53%). BCB esters bearing various substituents at the *para*-position of the aryl ring, including alkyl (**5f**, **5g**), phenyl (**5h**), halide (**5i**-**k**) and trifluoromethyl (**5l**), all participated well in the reaction to afford the target products in 73-99% yields. The structure and relative configuration of **5h** were comfirmed by X-ray structure analysis (CCDC 2363143).[26] Furthermore, BCB esters with substituents at the *meta*-position of the aryl ring, including methyl (**5m**), methoxy (**5n**), chloro (**5o**) and trifluoromethyloxy (**5p**) that is popular in drugs and agrochemicals, were well-tolerated under the current conditions, providing the aimed products in good yields. Additionally, the reaction proceeded very smoothly with two sterically more demanding *ortho*-methylphenyl and 2-naphthyl BCB esters, and the corresponding products **5q** and **5r** were isolated in 93% and 97% yields, respectively. The scope of triazinanes was then examined. N-PMB (*para*-methoxybenzyl) and N-alkyl (isopropyl, cyclopropyl) triazinanes worked well, providing the target products **5s** (95%), **5t** (32%) and **5u** (95%). Notably, the N-propargyl triazinane was also tolerated, and desired product **5v** was obtained in 56% yield.

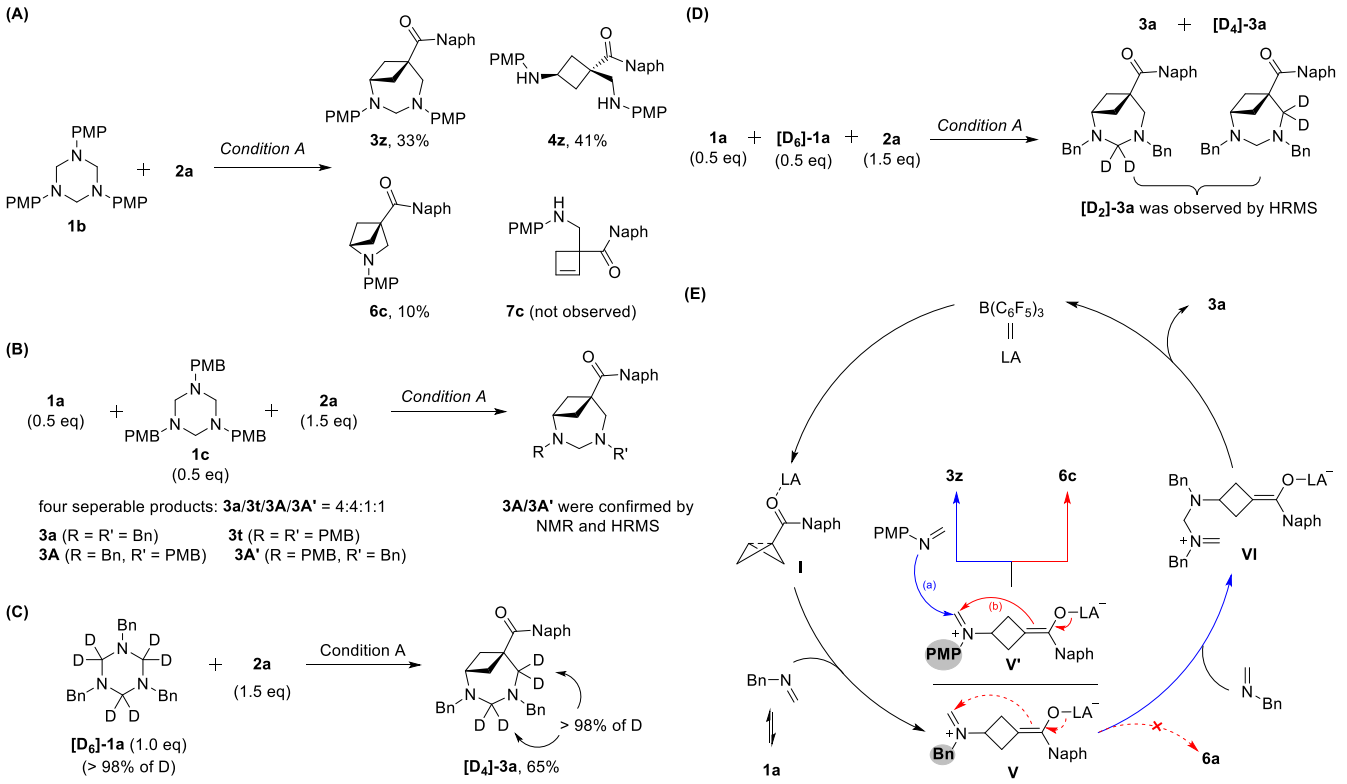


Scheme 3. Scope of triazinanes with BCB esters. Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol), $In(OTf)_3$ (1 mol%), HFIP (2.0 mL), rt, 24 h. Isolated yields.

Interestingly, when N-PMP (*para*-methoxyphenyl) triazinane **1b** was used to react with BCB ketone **2a** under condition A, the reaction became rather complex (Scheme 4A). Three major products were isolated, the target aza-BCO **3z** (33%), the ring-opening *cis*-cyclobutyl diamine **4z** (41%) and the (3+2) aza-BCH **6c** (10%), while the cyclobutenyl amine **7c** was not detected. This result has two significant implications: first, the formation of **6c** without **7c** suggests that Leitch's carbocation species is not involved, and an S_N2-like nucleophilic addition of triazinane to Lewis acid-activated BCB ketone **I** is more likely; second, the formation of **6c** indicates that the cycloaddition might proceed via a stepwise (2+2+3) rather than (4+3) process.[23a-c] Several

control and deuterium-labeling experiments were further performed to gain insights into the cycloaddition pathway. A competition reaction of **1a** and **1c** with **2a** under condition A produced four separable products, including **3a**, **3t** and two cross-cycloadducts **3A**/**3A'** (Scheme 4B). The structures of **3A**/**3A'** were characterized by NMR and HRMS analysis. Additionally, the reaction of **[D$_6$]-1a** with **2a** afforded the fully deuterated product **[D$_4$]-3a** (Scheme 4C). Upon treatment of **1a** and **[D$_6$]-1a** with **2a**, the reaction delivered an inseparable mixture including **[D$_2$]-3a** detected by HRMS analysis (Scheme 4D). These experiments demonstrate that the formation of aza-BCOs proceeds through iterative additions of formaldimines to B(C$_6$F$_5$)$_3$-activated BCB ketone **I**, supporting a (2+2+3) rather than (4+3) cycloaddition pathway.

Based on the above results, a plausible mechanism is proposed (Scheme 4E). Initially, B(C$_6$F$_5$)$_3$ activates BCB ketone **1a** to form complex **I**. The nucleophilic addition of formaldimine via an S$_N$2-like pathway produces intermediate **V**. Subsequent reaction with another molecule of formaldimine affords intermediate **VI**. Finally, intramolecular cyclization furnishes product **3a** with the release of B(C$_6$F$_5$)$_3$ catalyst. For intermediate **V**, the preferred intermolecular addition of another formaldimine than the intramolecular attack of the enolate on the iminium group (**VI** vs **6a**) is probably due to the higher nucleophilicity of the Bn-N atom of formaldimine compared to the enolate. Thus, when N-PMP formaldimine with lower nucleophilicity is employed, the intramolecular cyclization of intermediate **V'** becomes competitive with the intermolecular addition of another N-PMP formaldimine to **V'**, leading to products **6c** and **3z** simultaneously (*path a* vs *path b*, Scheme 4E).



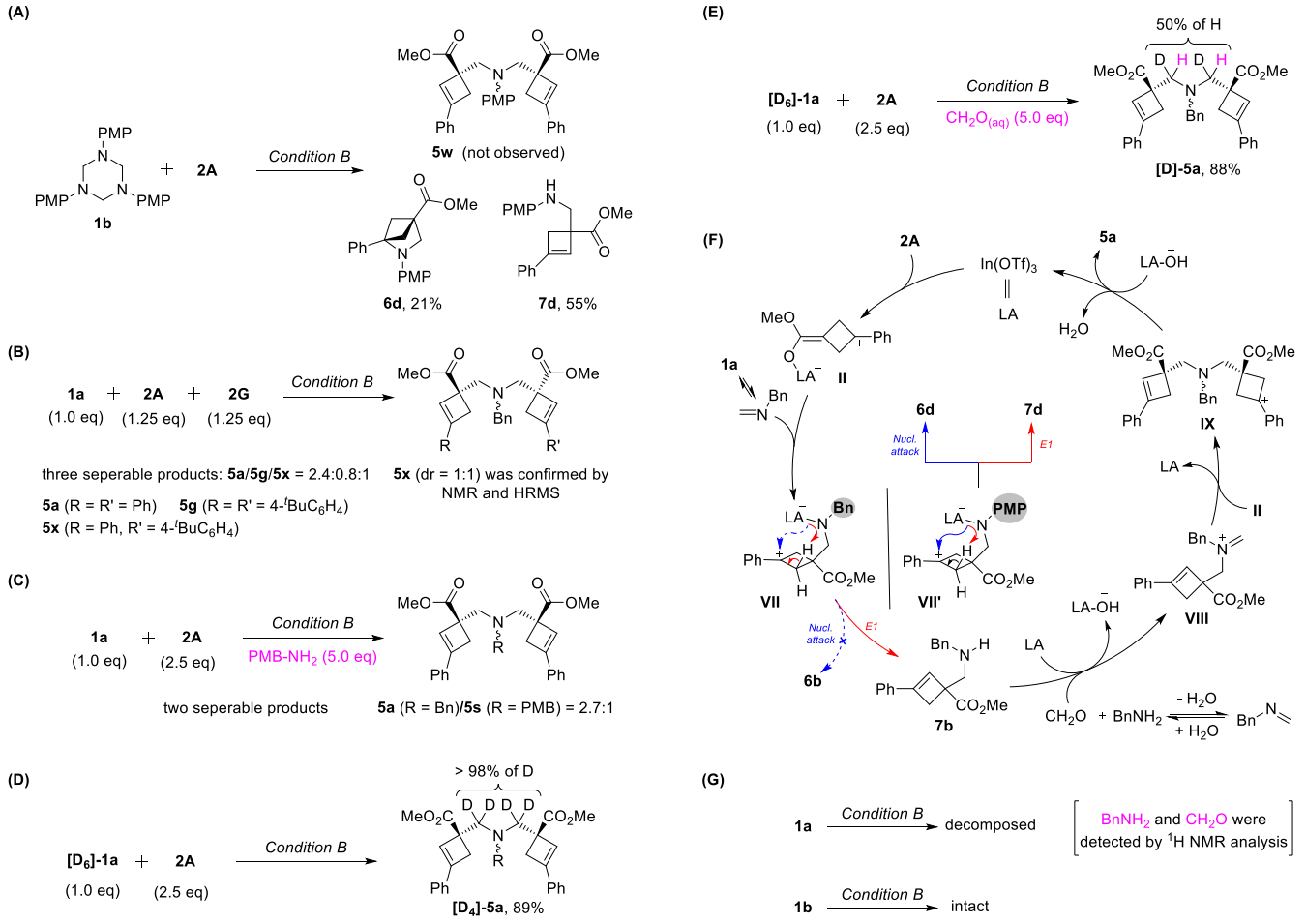
Scheme 4. Mechanistic studies for the reaction of BCB ketone with triazinane.

In contrast, when N-PMP triazinane **1b** and BCB ester **2A** were used under condition B, no biscyclobutenyl amine **5w** was formed. Instead, two Leitch's products were obtained, the (3+2) aza-BCH **6d** (40%) and the cyclobutenyl methanamine **7d** (50%) (Scheme 5A). This result suggests that Leitch's carbocation species is involved in this reaction. Moreover, a competition reaction of **1a** with **2A** and **2G** was performed under condition B, leading to three seperable products including the cross-over product **5x** confirmed by NMR and HRMS analysis (Scheme 5B). This result indicates iterative additions of Lewis acid-induced enolate **II** to N-imine and N-iminium electrophiles. Furthermore, the reaction of **1a** with **2A** in the presence of PMB-NH$_2$ generated two seperable products **5a** and **5s**, providing evidence for the exchange between PMB-NH$_2$ and triazinane **1a** (Scheme 5C). In addition, the reaction of **[D$_6$]-1a** with **2A** afforded the fully deuterated product **[D$_4$]-5a** (Scheme 5D). Treatment of **[D$_6$]-1a** with **2A** in the presence of formaldehyde produced **[D]-5a** with 30% of hydrogen incorporation (Scheme 5E). These results demonstrate that under condition B, triazinane decomposes to formaldimine that further hydrolyzes to aniline and formaldehyde, which is consistent with the result that 4Å MS significantly suppressed the reaction (Table 1, entry 29).

Based on the above results, we propose a possible mechanism (Scheme 5F). Initially, complexation of the In(OTf)$_3$ catalyst with BCB ester **2A** generates zwitterionic enolate intermediate **II**. Then, nucleophilic addition of enolate to formaldimine is preferred than

the S_N1-like attack of formaldimine to the cation carbon center of enolate, leading to Leitch's carbocation species **VII**. The selectivity may originate from the coordination of formaldimine to Lewis acid.[10] This key intermediate **VII** undergoes an intramolecular E1 elimination to cyclobutenyl methanamine **7b** rather than a nucleophilic ring-closing to **6b**, which is mainly attributed to the more basicity of Bn-N atom. N-Bn triazinane **1a** decomposes to formaldimine that further hydrolyzes to benzylamine and formaldehyde in the presence of water. A Lewis acid-promoted condensation of **7b** with formaldehyde generates an iminium species **VIII** and a hydroxide ion.[27] A second nucleophilic addition of enolate **II** to iminium affords carboncation species **IX**. Finally, deprotonation of **IX** by the hydroxide ion offers the target product **5a**, regenerating Lewis acid and water.

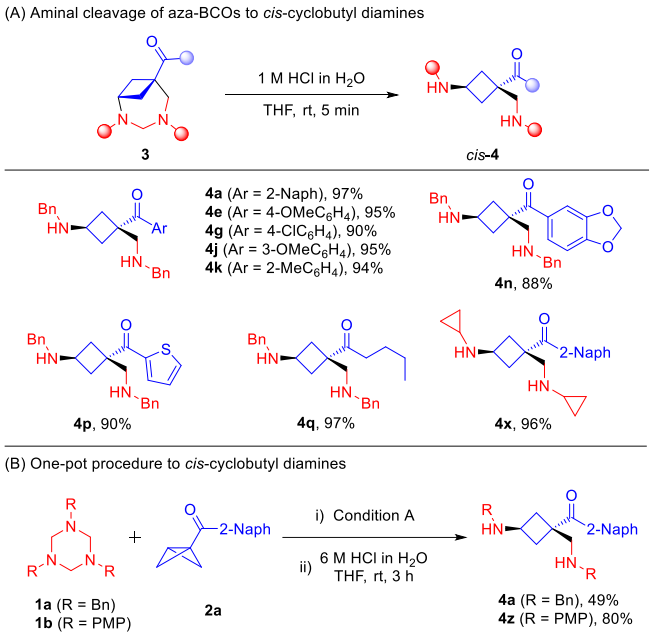
When N-PMP formaldimine with lower basicity was employed, the intramolecular nucleophilic ring-closing of intermediate **VII'** became competitive with the E1 elimination, leading to products **6d** and **7d** simultaneously. No biscyclobutenyl amine **5w** was observed for this reaction, because N-PMP triazinane **1b** could not hydrolyze to generate formaldehyde under condition B. This was demonstrated by the results of ^{1}H NMR analysis, showing that N-Bn triazinane **1a** under condition B decomposed to benzylamine and formaldehyde, while no formaldehyde was observed for N-PMP triazinane **1b** (Scheme 5G).



Scheme 5. Mechanistic studies for the reaction of BCB ester with triazinane.

Encouraged by the above success, we then focused on the ring-opening of aza-BCOs (Scheme 6). Gratifyingly, cleavage of the aminal group proved to be feasible under acidic conditions (1 M HCl in THF/H_2O), and the transformation of **3a** to the corresponding *cis*-cyclobutyl diamine **4a** was effectively accomplished in 96% yield. A series of selected aza-BCOs from Scheme 2 were examined, all of which were successfully transformed to the ring-opening *cis*-cyclobutyl diamines in high yields (Scheme 6A). To prove our hypothesis of a one-pot procedure transforming BCBs into *cis*-cyclobutyl diamines, we reacted the model N-Bn triazinane **1a** with BCB ketone **2a** under condition A followed by treatment with acid, providing the target product **4a** in 49% yield, albeit with a longer reaction time and more acidic reaction conditions (Scheme 6B). In addition, we noticed that N-PMP cycloadduct **3z** was relatively unstable and slowly decomposed to **4z** on silica gel or in $CDCl_3$, thus the one-pot procedure was more suitable for the reaction of N-PMP triazinane **1b** with **2a**, leading to product **4z** in 80% yield. These results validated the feasibility of our conceptual

"cycloaddition/ring-opening" strategy for the synthesis of *cis*-cyclobutyl diamines from BCBs and triazinanes.



Scheme 6. Ring-opening of aza-BCOs to *cis*-cyclobutyl diamines.

Conclusion

In summary, we have developed two complementary approaches for the divergent synthesis of cyclobutyl and biscyclobutenyl amines by exploiting the distinct reactivity exhibited by BCB ketones and esters with triazinanes under Lewis acid catalysis. The cycloaddition reaction of BCB ketones with triazinanes leads to aza-BCOs, and a direct acidic treatment efficiently cleaves the aminal moiety, resulting in *cis*-cyclobutyl diamines. Either a stepwise or one-pot manner is suitable for the "cycloaddition/ring-opening" strategy. In contrast, the reaction of BCB esters with triazinanes yields a series of beautiful butterfly-shaped biscyclobutenyl amines under $In(OTf)_3$ catalysis. Mechanistic studies indicate that the distinct reaction pathways originate from the different activation modes of BCBs by Lewis acid, the cycloaddition of BCB ketones with triazinanes proceeds via a stepwise (2+2+3) rather than (4+3) pathway, and the reaction of BCB esters with triazinanes involves a Leitch's carbocation intermediate. The obtained two series of products provide a unique platform for exploration of new cyclobutane-based drug candidates, especially given the *cis*-configuration of cyclobutyl diamines and the functional group compatibility of both products. Work is ongoing to explore the mechanistic details, and to apply these techniques towards cyclobutane-based bioactive molecule synthesis. Further studies will be reported in due course.

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[26] CCDC 2363142 (**3h**) and CCDC 2363143 (**5h**) contain the supplementary crystallographic data for this work, which can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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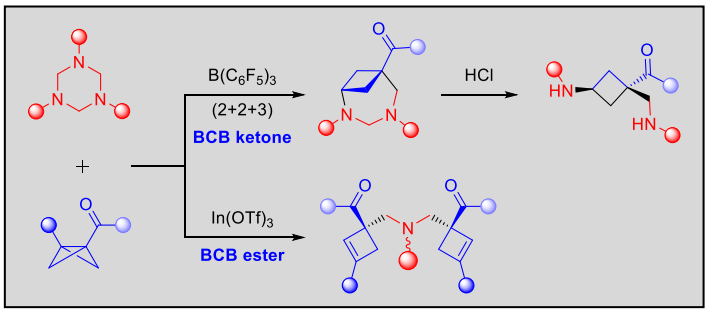

A Lewis acid-catalyzed divergent synthesis of cyclobutyl and biscyclobutenyl amines is realized by exploiting the distinct reactivity exhibited by bicyclo[1.1.0]butane (BCB) ketones and esters with triazinanes. The first (2+2+3) cycloaddition of BCB ketones with triazinanes yields 2,4-diazabicyclo[4.1.1]octanes (aza-BCOs) under $B(C_6F_5)_3$ catalysis, and a direct acidic treatment efficiently cleaves the aminal moiety, resulting in *cis*-cyclobutyl diamines. In contrast, the reaction of BCB esters with triazinanes produces butterfly-shaped biscyclobutenyl amines under $In(OTf)_3$ catalysis. Mechanistic studies reveal that the distinct reaction pathways originate from the different activation modes of BCBs by Lewis acid.