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Lewis acid-catalyzed (3 + 2) annulation of bicyclobutanes with ynamides: access to 2-amino-bicyclo[2.1.1]hexenes†

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Strain-release driven annulations with bicyclo[1.1.0]butanes (BCBs) have become an attractive area of research for the synthesis of bioisosteric bicyclohexane derivatives, which play a vital role in drug discovery. Interestingly, the utilization of the inherent strain in BCBs for the synthesis of functionalized amino-bicyclo[2.1.1]hexenes, which may spatially mimic substituted benzenes and anilines, has received only scant attention. Herein, we report the $Sc(OTf)_3$-catalyzed (3 + 2) annulation of BCBs with ynamides for the facile synthesis of 2-amino-bicyclo[2.1.1]hexenes in one step under mild conditions. The reaction likely proceeds *via* nucleophilic addition facilitated by the nitrogen lone pair from the alkynyl group of the ynamides to the unsubstituted side of the BCBs, followed by the annulation of the resulting enolate with the keteniminium species. For the first time, the C–C triple bond of ynamides was utilized as the coupling partner for BCBs, resulting in products adorned with a functionalizable amino group and an integrated strained alkene moiety.

Introduction

The construction of highly strained hydrocarbons is synthetically challenging and has always attracted the interest of organic and physical chemists.[1] The incorporation of saturated building blocks into target molecules has become one of the key strategies in the fields of drug delivery and medicinal chemistry.[2] Over the years, there has been growing interest in the synthesis of different strained bicyclic scaffolds[3] and these three-dimensional architectures with conformationally restricted $C(sp^3)$-rich skeletons are becoming increasingly relevant in bioisosterism.[4] Among them, the synthesis of bicyclo[2.1.1]hexanes (BCHs) is of great interest as they can serve as bioisosteres of benzene rings (Scheme 1A).[5]

The well-known synthetic route to BCHs is the intramolecular [2 + 2] cycloaddition of 1,5-dienes.[6] Apart from that, chemists have become more interested in utilizing the strain-release driven cycloaddition of bicyclo[1.1.0]butanes (BCBs) for the synthesis of BCHs and other bicyclic frameworks.[7] But there is only one known example of the utilization of this strain-driven cycloaddition strategy for the synthesis of bicyclohexenes.[8] These bicyclohexenes may also serve as bioisosteres of benzene derivatives, and the presence of a strained alkene group in bicyclohexenes makes them synthetically more valuable as they can be further functionalized to synthesize various BCHs. Especially, an amino group directly attached to the bicyclohexene core might replicate the properties of aniline, which is medicinally important.[9–11] Therefore, we envisioned a strain-release driven annulation of BCBs with ynamides, which could lead to the synthesis of amino-bicyclohexenes in one step, thereby rendering the methodology more atom- and step-economic.

Recently, BCBs have received significant attention from organic chemists for the synthesis of strained bicyclic scaffolds owing to their higher strain energy (66.3 kcal mol^{-1}) and strained butterfly shape.[7] The most commonly utilized mode of reactivity of BCBs is the cycloaddition reaction originating from the breaking of the strained σ-bond. Among these cycloaddition processes, strain-release driven $[2\pi + 2\sigma]$ cycloaddition has been extensively investigated for the synthesis of BCH frameworks. In this context, Glorius,[12] Brown[13] and Procter[14] groups achieved independent breakthroughs by uncovering intermolecular $[2\pi + 2\sigma]$ cycloaddition between BCBs and alkenes using photocatalysis. Moreover, Li[15] and Wang[16] groups showcased the utilization of a pyridine-boryl radical system to catalyze formal $[2\pi + 2\sigma]$ cycloaddition.

Although significant advances have been made using photocatalytic and radical-based approaches, Lewis acid catalysis has recently emerged as a simple yet effective method for catalyzing the annulation reactions of BCBs. Considering this, Leitch and co-workers[17] pioneered Lewis acid catalysis for the formal $[2\pi + 2\sigma]$ cycloaddition reaction, employing *N*-arylimines and BCBs to synthesize azabicyclo[2.1.1]hexanes

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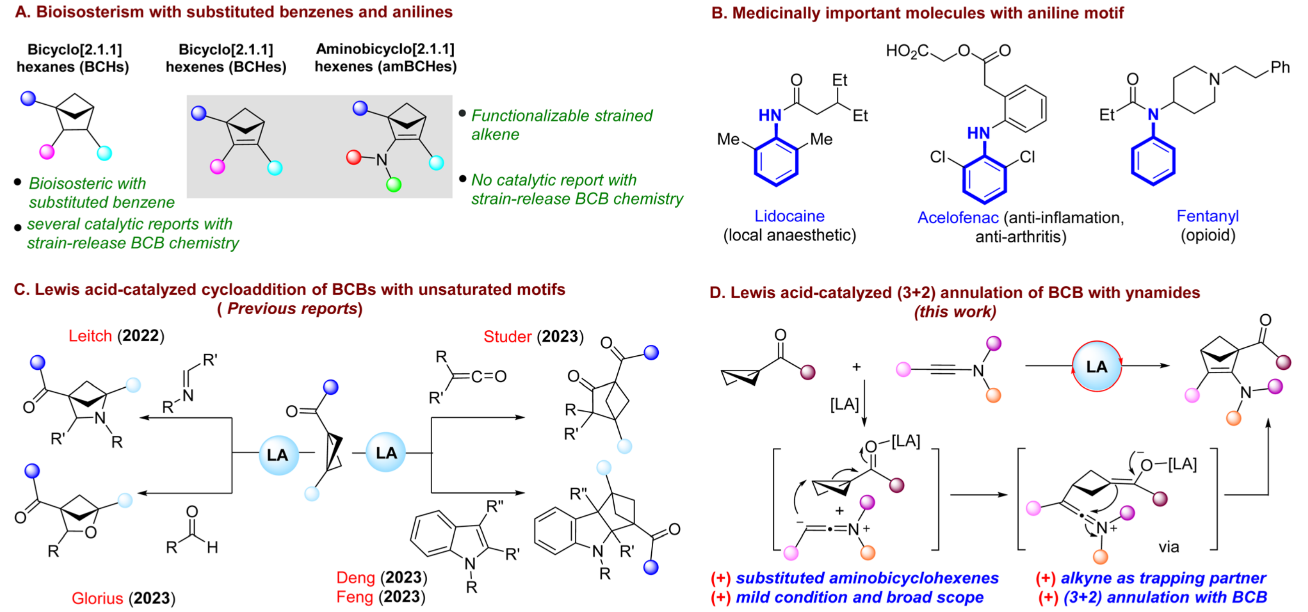


Scheme 1 (A) Bioisosterism with substituted benzenes and anilines, (B) medicinal importance of aniline derivatives, (C) previous reports on Lewis acid-catalyzed cycloaddition reactions involving BCBs, and (D) Lewis acid-catalyzed (3 + 2) annulation of BCBs with ynamides.

(Scheme 1C). Later, the Studer group[18] utilized a Lewis acid-catalyzed approach to illustrate the formal [2π + 2σ] cycloaddition of ketenes with BCBs, yielding BCHs. Subsequently, the Glorius group[19] demonstrated the incorporation of aldehydes as coupling partners in the formal [2π + 2σ] cycloaddition of BCBs. Moreover, Deng[20] and Feng[21] groups independently disclosed the dearomative [2π + 2σ] cycloaddition of indoles with BCBs *via* Lewis acid catalysis for the synthesis of bicyclo[2.1.1] hexanes.

Despite the advent of strain release-driven cycloadditions of BCBs, in most cases, the coupling partners are limited to moieties with either C–C, C–N or C–O double bonds leading to saturated BCHs, where the bicyclic skeleton cannot be further functionalized. Interestingly, the use of C–C triple bond containing coupling partners for annulation with BCBs has received only scant attention.[22] Encouraged by this, we envisaged a Lewis acid-catalyzed annulation of BCBs with the C–C triple bond of ynamides, which could lead to the formation of functionalized 2-amino-bicyclo[2.1.1]hexenes with a strained alkene integrated in the bicyclic scaffold readily available for further synthetic transformations. This is likely to open a new synthetic avenue in drug development and drug design, providing a straightforward route to multisubstituted 2-amino-bicyclohexenes.

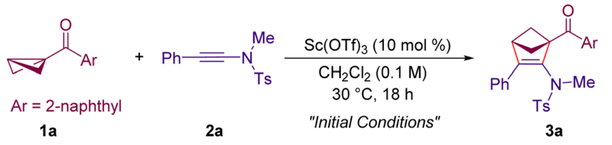
The choice of ynamides was based on their versatility as building blocks in different organic transformations specifically in the field of cycloaddition reactions.[23] The uniqueness of ynamides comes from the presence of a nitrogen atom directly attached to the alkyne moiety, which makes them more active towards the cycloaddition reaction. Also, regioselectivity can be attributed to the zwitterionic resonance structure of ynamides. While this manuscript was under preparation, Chen, Zhou and co-workers have reported an elegant Lewis acid-catalyzed (3 + 2) annulation of BCBs with ynamides for the synthesis of polysubstituted 2-amino-bicyclo[2.1.1]hexenes.[24] Notably, Chen, Zhou and co-workers used *N*-mesyl ynamide substrates along with a Na_2SO_4 additive under their optimized conditions, and we utilized *N*-tosyl ynamides without additives, and both reactions are catalyzed by $Sc(OTf)_3$.

Results and discussion

Inspired by the idea of using ynamides as the olefin partner, the present studies were initiated by treating 2-naphthyl substituted BCB **1a** with *N*-tosyl substituted ynamide **2a** in the presence of $Sc(OTf)_3$ (10 mol%) in CH_2Cl_2 at 30 °C (Table 1, entry 1).[25] Interestingly, the desired (3 + 2) annulation product **3a** was obtained in 61% yield. Intrigued by this result, various Lewis acids were examined for this (3 + 2) annulation. Disappointingly, the Lewis acid screening did not improve the yield of **3a** (entries 2–5). Switching the reaction solvent to $CHCl_3$ resulted in 60% yield of the desired 2-amino-bicyclohexene product (entry 6). However, changing to other solvents such as toluene and dichloroethane (DCE) did not enhance the yield of **3a** (entries 7 and 8). Since the ynamide **2a** is prone to degradation to the corresponding amide in the presence of a Lewis acid, an experiment was performed with 4 Å MS as an additive.[26] This reaction also did not help in improving the yield of **3a** (entry 9). Reducing the reaction concentration by half led to a 49% yield of **3a** (entry 10). Moreover, reducing or increasing the loading of $Sc(OTf)_3$ did not enhance the yield of **3a** (entries 11 and 12). Notably, when $Sc(OTf)_3$ was added at the end to the reaction flask, **3a** was formed in an improved yield of 65% (entry 13). This condition was used for substrate scope studies.[27]

With the identified reaction conditions, we proceeded to evaluate the scope and limitations of the reaction of ynamides

Table 1 Optimization of the reaction conditions[a]



Entry	Variation of the initial conditions[a]	Yield of **3a**[b] (%)
1	None (**2a** was added at the end)	62 (61)
2	$Yb(OTf)_3$ instead of $Sc(OTf)_3$	50
3	$Bi(OTf)_3$ instead of $Sc(OTf)_3$	20
4	TMS-OTf instead of $Sc(OTf)_3$	51
5	$Eu(OTf)_3$ instead of $Sc(OTf)_3$	38
6	$CHCl_3$ instead of CH_2Cl_2	60
7	Toluene instead of CH_2Cl_2	53
8	DCE instead of CH_2Cl_2	43
9	4 Å MS as the additive	56
10	0.05 M CH_2Cl_2 instead of 0.1 M CH_2Cl_2	49
11	5 mol% $Sc(OTf)_3$ instead of 10 mol%	59
12	15 mol% $Sc(OTf)_3$ instead of 10 mol%	62
13[c]	$Sc(OTf)_3$ added at the end	65 (65)

[a] Initial conditions: **1a** (0.1 mmol), **2a** (2.0 equiv., addition at the end), $Sc(OTf)_3$ (10 mol%), CH_2Cl_2 (0.1 M), 30 °C, and 18 h. [b] The ^1H NMR yield of the crude products determined with the aid of 1,3,5-trimethoxybenzene as an internal standard. Isolated yield in parentheses. [c] $Sc(OTf)_3$ was added at the last; see the ESI for details.

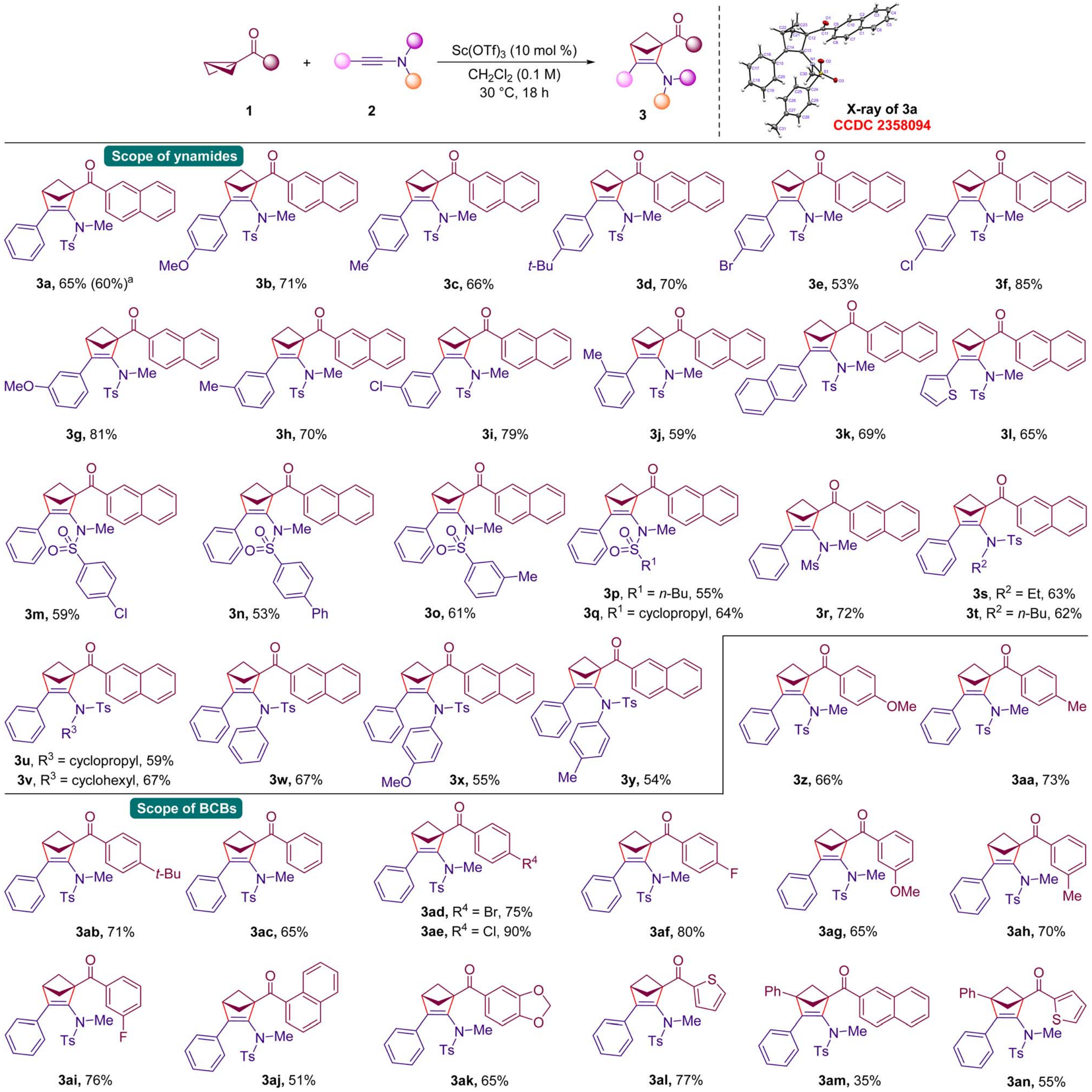
with BCBs. Initially, the scope of substituted ynamides was tested (Scheme 2). A reaction with ynamides bearing electronically different groups at the 4-position of the aryl ring readily afforded the (3 + 2) annulation product in good yields (**3a–3f**). The reaction leading to the formation of **3a** was scalable on a 2.0 mmol scale in 60% yield, indicating the practical nature of the present annulation. In the case of the unsubstituted product **3a**, the structure was further confirmed by the X-ray analysis of the crystals.[28] Ynamides with strongly electron-withdrawing groups such as $-NO_2$ at the 4-position of the ring returned a reduced yield of the annulated product. Moreover, –OMe, –Me and –Cl groups at the 3-position of the ring were also well tolerated producing (3 + 2) adducts in good yields (**3g–3i**). Substituting the 2-position of the ring with a methyl group produced the product **3j** in 59% yield. The reaction conducted using 2-naphthyl and 2-thienyl substituted ynamides afforded the expected products **3k** and **3l** in 69% and 65% yields, respectively. Additionally, the *N*-tosyl moiety of the ynamides can be changed to differently substituted aryl sulphonamides and linear as well as cyclic alkyl sulphonamides and in all cases, the (3 + 2) annulated products were formed in reasonable yields (**3m–3q**). The protecting group on ynamides can be varied using mesyl (Ms) instead of the tosyl group, and the desired product **3r** was formed in 72% yield.[29] Notably, the methyl group on ynamide nitrogen can also be varied with ethyl, *n*-butyl, cyclopropyl, cyclohexyl and substituted aryl moieties without affecting the reactivity, and in all cases, the target products were formed in moderate to good yields (**3s–3y**).

Next, the tolerance of (3 + 2) annulation with substituted BCBs was tested. Instead of the 2-naphthyl moiety in **1a**, a variety of BCBs bearing aryl ketones having electron-releasing and neutral groups and halides at the 4-position of the ring underwent smooth (3 + 2) annulation with ynamide **2a**, and in all cases, the target products were formed in moderate to good yields (**3z–3af**). Moreover, substitution at the 3-position of the aryl ring was also tolerated well and the corresponding 2-aminobicyclo[2.1.1]hexenes were formed in good yields (**3ag–3ai**). In addition, disubstitution on the aryl ring did not affect the reactivity of the (3 + 2) annulation (**3aj** and **3ak**). Further, the 2-thienyl ketone-derived BCB reacted with **2a** to afford the (3 + 2) annulation product **3al** in 77% yield. Interestingly, 1,3-disubstituted BCB ketones also afforded the target (3 + 2) annulated products in moderate yields under the present conditions (**3am** and **3an**). Disappointingly, BCBs with phenyl and $-CO_2Me$ moieties at the 1,3-positions did not afford the desired (3 + 2) annulated products under the optimized conditions.

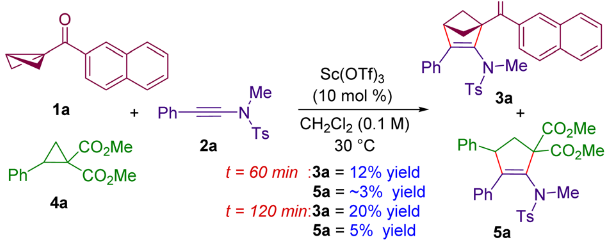
Given the similarity in the reactivity of BCBs with donor–acceptor cyclopropanes under Lewis acid conditions,[30] a competition experiment was performed with ynamide **2a** with BCB **1a** and cyclopropane **4a** (Scheme 3). Performing the reaction under optimized conditions and quenching the reaction after 60 minutes revealed that the (3 + 2) annulation product **3a** from BCB **1a** was formed in 12% yield, whereas the annulation product **5a** derived from cyclopropane **4a** was formed in ∼3% yield. Moreover, **3a** and **5a** were formed in 20% and 5% yields respectively when the reaction was quenched after 120 minutes. This is an indication that the BCB **1a** works ∼4 times faster than the DA cyclopropane **4a** in its reaction with ynamides, thereby shedding light on the better reactivity of BCBs over DA cyclopropanes. This is because of the high strain energy of BCBs compared to DA cyclopropanes.

To gain insight into the mechanism of the reaction, a few experiments were performed. When the reaction of BCB **1a** was carried out with diphenyl acetylene **6a** instead of the ynamide **2a**, the desired (3 + 2) annulation product **7a** was not formed (Scheme 4, eqn (1)). This study indicates that **6a** is not nucleophilic enough to add to the Lewis acid activated BCB and sheds light on the importance of the nucleophilicity of ynamides in the present (3 + 2) annulation. Moreover, when using 4-nitrophenyl substituted ynamide **2z**, the reaction furnished the (3 + 2) annulated product **3ao** in <10% yield (eqn (2)). It is reasonable to believe that the presence of the $-NO_2$ group makes **2z** less nucleophilic for the addition to a Lewis acid activated BCB and thus reduces its reactivity. In addition, our efforts to intercept the enolate formed after the initial addition of the ynamide to the BCB (Scheme 1D) with a third component failed, and the annulated product **3a** was formed in 50% yield without the formation of a product incorporating the aldehyde moiety. Notably, the (3 + 2) annulated product from **1a** and the aldehyde were also not observed in this case.[19]

Based on the preliminary mechanistic experiments and literature precedents,[20,21] a plausible mechanism is presented in Scheme 5. It is reasonable to assume that the BCB **1a** is activated by $Sc(OTf)_3$ to form the Lewis acid–BCB complex **A**. This activation facilitates a nitrogen lone pair assisted nucleophilic attack (most likely an S_N2-type pathway) from the alkynyl moiety of the ynamide **2a**, onto the unsubstituted side of the activated



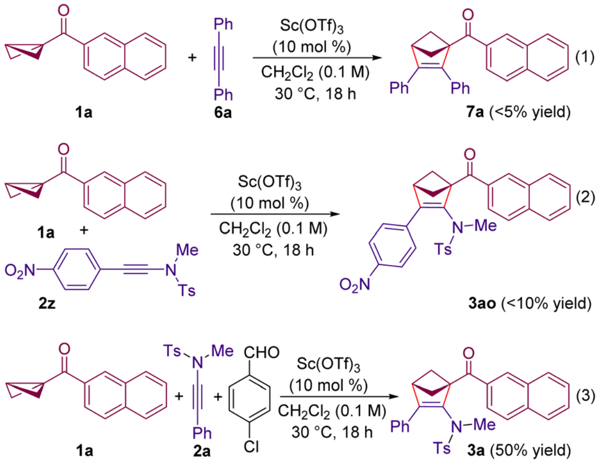
Scheme 2 Reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), Sc(OTf)$_3$ (10 mol%), CH_2Cl_2 (2.0 mL), and 30 °C for 18 h. Provided are the isolated yields of products. ^{a}Yield of **3a** in an experiment conducted on a 2.0 mmol scale.



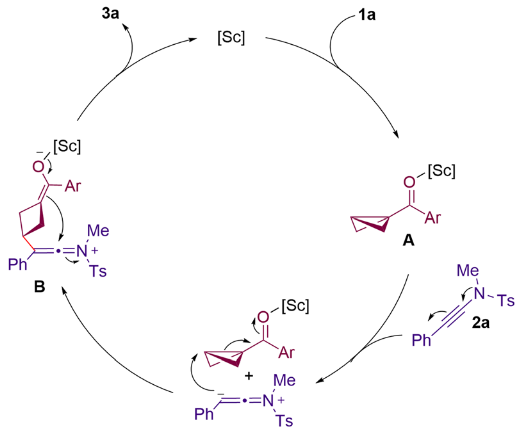
Scheme 3 Competition experiment between a BCB and donor–acceptor cyclopropane.

BCB. This results in the formation of intermediate **B**, which possesses an enolate BCB fraction and a keteniminium moiety. Subsequently, the keto-enolate undergoes an intramolecular addition to the keteniminium ion to afford the desired 2-amino-bicyclo[2.1.1]hexene product **3a**. Our preliminary studies on trapping the enolate **B** with electrophiles such as aldehydes failed.

The functionalized 2-amino-bicyclo[2.1.1]hexenes synthesized using the present method can easily be engaged in further transformations. The hydrolysis of the enamine moiety of **3a** under acidic conditions resulted in the formation of the 1,3-

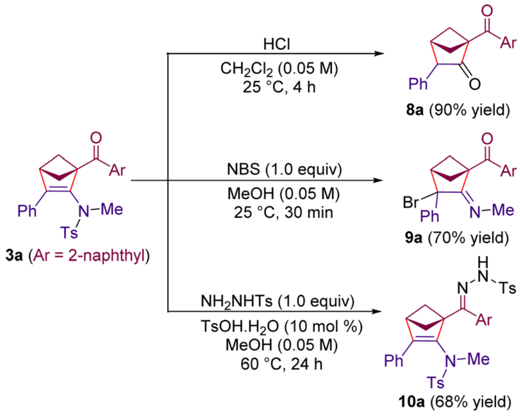


Scheme 4 Mechanistic experiments.



Scheme 5 Proposed mechanism.

diketone **8a** in 90% yield (Scheme 6). Moreover, the treatment of **3a** with *N*-bromosuccinimide resulted in the formation of the bromoimine derivative **9a** in 70% yield. In addition, the reaction of **3a** with tosyl hydrazine afforded the hydrazone derivative **10a** in 68% yield. Notably, the hydrogenation of the C=C double bond and the reduction of the ketone moiety in related *N*-mesylated 2-amino-bicyclo[2.1.1]hexene products are reported by Chen, Zhou and co-workers.[24]



Scheme 6 Product functionalization.

Conclusions

In conclusion, we have demonstrated the $Sc(OTf)_3$-catalyzed (3 + 2) annulation of BCBs with ynamides leading to the formation of biologically relevant 2-amino-bicyclo[2.1.1]hexenes under mild conditions in a one-pot process. The reaction likely proceeds in a stepwise manner initiated by the nucleophilic addition of ynamides to the unsubstituted side of the BCBs, followed by the annulation of the ensuing enolate with the keteniminium species. Differently substituted keto-BCBs and a variety of electronically dissimilar ynamides underwent this smooth (3 + 2) annulation. Further studies on related annulation reactions involving BCBs are currently ongoing in our laboratory.

Data availability

Details on experimental procedures, mechanistic experiments, characterization data of all the 2-amino-bicyclo[2.1.1]hexenes and X-ray data of **3a**. The details are available in the ESI† of the manuscript.

Author contributions

D. S. and A. T. B. designed the project. D. S. optimized the reaction conditions. D. S., S. D. and R. C. D. examined the substrate scope and analysed the data. D. S. performed the mechanistic experiments. R. C. D. wrote the first draft of the manuscript with inputs from D. S. and S. D., and A. T. B. edited the manuscript. All authors have given approval to the final version of the manuscript. A. T. B. directed the research.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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