Chemical Science

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: D. Sarkar, S. Deswal, R. C. Das and A. T. Biju, *Chem. Sci.*, 2024, DOI: 10.1039/D4SC03893B.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemical-science

View Article Online
DOI: 10.1039/D4SC03893B

ARTICLE

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

Deeptanu Sarkar, Shiksha Deswal, Rohan Chandra Das and Akkattu T. Biju*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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 BCB 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 the 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

Construction of highly strained hydrocarbons are synthetically challenging and have always attracted the interest of organic and physical chemists.[1] The incorporation of saturated building blocks in the target molecules has become one of the key strategies in the field of drug delivery and medicinal chemistry.[2] Over the years, there has been a 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) are of great interest as they can serve as bioisostere 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 example known on 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 it 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 much attention from organic chemists for the synthesis of strained bicyclic scaffold owing to their higher strain energy (66.3 kcal/mol) and strained butterfly shape.[7] The most utilized modes of reactivity of BCBs is the cycloaddition reaction originating from breaking of the strained σ-bond. Among these cycloaddition processes, the strain-release driven [2π+2σ] cycloaddition has been extensively investigated for the synthesis of BCH frameworks. In this context, Glorius[12], Brown[13] and Procter groups[14] achieved independent breakthroughs by uncovering the intermolecular [2π+2σ] cycloaddition between BCBs and alkenes using photocatalysis. Moreover, Li[15] and Wang groups[16] showcased the utilization of the pyridine-boryl radical system to catalyze the formal [2π+2σ] cycloaddition.

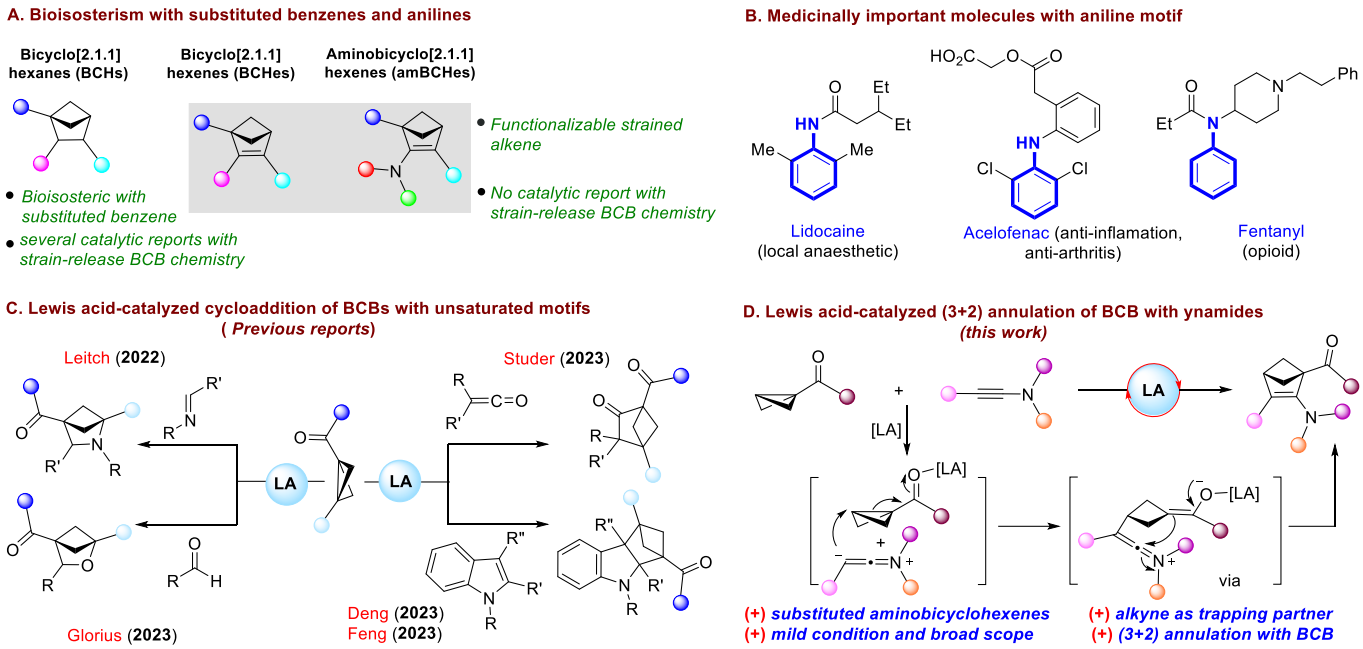
Although significant advances have been made using photocatalytic and radical-based approaches, Lewis acid catalysis has recently emerged as a simple yet effective method for catalyzing the annulation reactions of BCBs. Considering this, Leitch and co-workers[17] pioneered the Lewis acid catalysis for the formal [2π+2σ] cycloaddition reaction, employing N-arylimines and BCB to synthesize azabicyclo[2.1.1]hexanes (Scheme 1C). Later, Studer group[18] utilized the Lewis acid-catalyzed approach to illustrate the formal [2π+2σ] cycloaddition of ketenes with BCBs, yielding BCHs. Subsequently, 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.

Department of Organic Chemistry, Indian Institute of Science, Bangalore-560012, India
E-mail: atbiju@iisc.ac.in ; Homepage: https://atbiju.in/

† Electronic supplementary information (ESI) available. Details on experimental procedures, characterization data of all compounds. CCDC 2358094.

View Article Online
DOI: 10.1039/D4SC03893B

ARTICLE



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, D. Lewis acid-catalyzed (3+2) annulation of BCBs with ynamides.

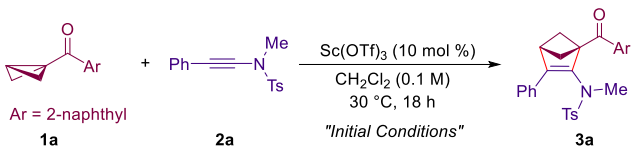
Despite the advent of strain release-driven cycloadditions of BCBs, in most cases, the coupling partners are limited to moieties with either C-C, C-N or C-O double bonds leading to the saturated BCHs, where the bicyclic skeleton cannot be further functionalized. Interestingly, the use of C-C triple bond 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 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 the drug development and drug-designing providing a straightforward route to multisubstituted 2-amino bicyclohexenes.

The choice of ynamide was based on their versatility as building blocks in different organic transformations specifically in the field of cycloaddition reactions.[23] The uniqueness of the ynamides comes from the presence of a nitrogen atom directly attached to the alkyne moiety, which makes it more active towards the cycloaddition reaction. Also, the reason of 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 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 the 2-naphthyl substituted BCB **1a** with *N*-tosyl substituted ynamide **2a** in the presence of $Sc(OTf)_3$ (10 mol%) in CH_2Cl_2

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

View Article Online
DOI: 10.1039/D4SC03803D

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, 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 parenthesis. [c] $Sc(OTf)_3$ was added at the last, see Supporting Information for details.

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, altering to other solvents such as toluene and dichloroethane (DCE) did not enhance the yield of **3a** (entry 7, 8). Since the ynamide **2a** is prone to degradation to the corresponding amide in the presence of 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, 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 the substrate scope studies.[27]

With the identified reaction conditions, we proceeded to evaluate the scope and limitations of the reaction of ynamides with BCBs. Initially, the scope of substituted ynamides were tested (Scheme 2). Reaction performed with electronically different groups at the 4-position of the aryl ring of ynamides 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 ring returned reduced yield of the annulated product. Moreover, -OMe, -Me and -Cl groups at the 3-position of the ring were also well tolerated producing the (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 ynamide 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**).

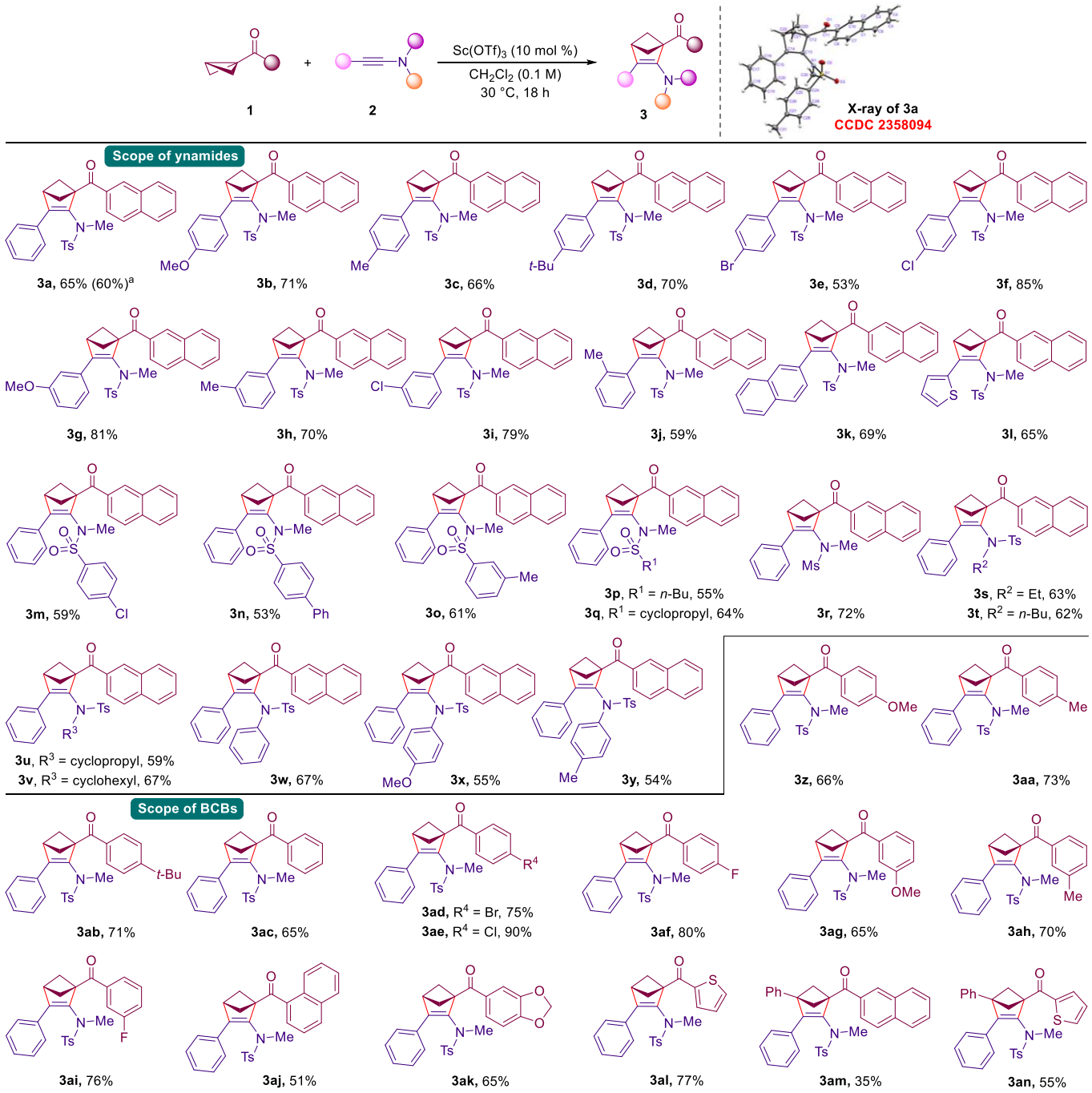
Next, the tolerance of the (3+2) annulation with substituted BCBs was tested. Instead of the 2-naphthyl moiety in **1a**, a variety of BCBs bearing aryl ketones having electron-releasing, neutral and halides at the 4-position of the ring underwent smooth (3+2) annulation with ynamide **2a**, and in all 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-amino bicyclo[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, 3ak**). Further, the 2-thienyl ketone-derived BCB reacted with **2a** to afford the (3+2) annulation product **3al** in 77% yield. Interestingly, the 1,3-disubstituted BCB ketones also afforded the target (3+2) annulated products in moderate yields under the present conditions (**3am, 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 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 in 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 BCB 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, eq 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, performing the reaction using 4-nitrophenyl substituted ynamide **2z**, the reaction furnished the (3+2) annulated product **3ao** in <10% yield (eq 2). It is reasonable to believe

View Article Online
DOI: 10.1039/D4SC03893B

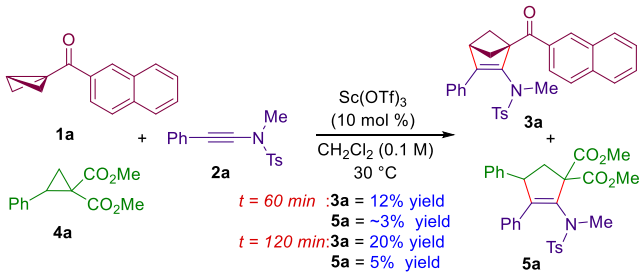
ARTICLE



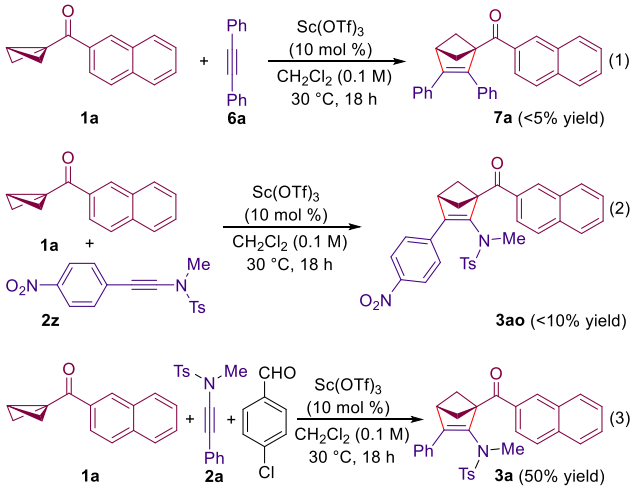
Scheme 2. Reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), $Sc(OTf)_3$ (10 mol %), CH_2Cl_2 (2.0 mL), 30 °C for 18 h. Provided are isolated yields of products. [a] Yield of **3a** in an experiment conducted on a 2.0 mmol scale.

that the presence of -NO_2 group makes **2z** less nucleophilic for the addition to Lewis acid activated BCB and thus reduces the reactivity. In addition, our efforts to intercept the enolate formed after the initial addition of ynamide to BCB (Scheme 1D) with a third component failed, and the annulated product **3a** was formed in 50% yield without the formation of product incorporating the aldehyde moiety.

Notably, the (3+2) annulated product from **1a** and the aldehyde was also not observed in this case.[19]

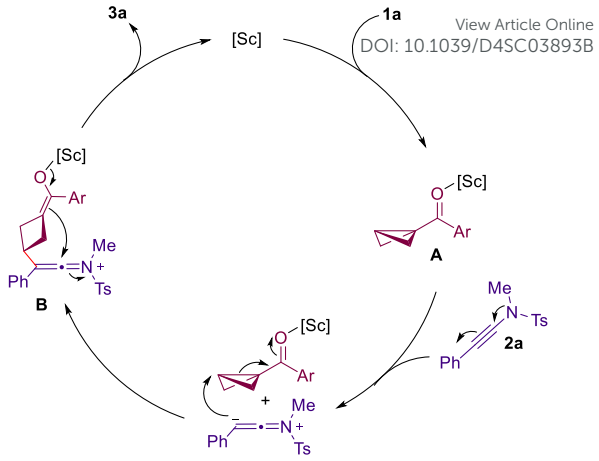


Scheme 3. Competition experiment between BCB and donor- acceptor cyclopropane



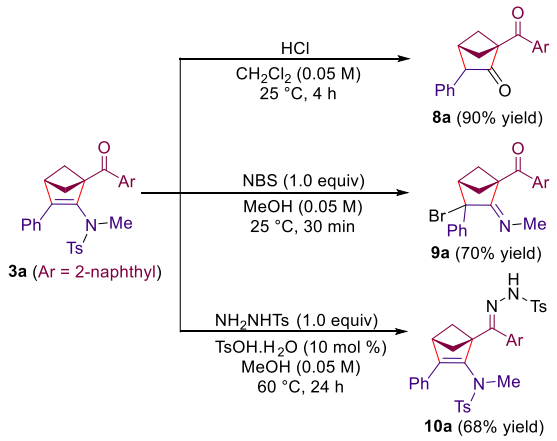
Scheme 4. Mechanistic experiments

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 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.



Scheme 5. Proposed mechanism

The functionalized 2-amino-bicyclo[2.1.1]hexenes synthesized using the present method can easily be engaged in further transformations. Hydrolysis of the enamine moiety of **3a** under acidic conditions resulted in the formation of the 1,3-diketone **8a** in 90% yield (Scheme 6). Moreover, treatment of **3a** with *N*-bromo succinimide resulted in the formation of the bromoimine derivative **9a** in 70% yield. In addition, reaction of **3a** with tosyl hydrazine afforded the hydrazone derivative **10a** in 68% yield. Notably, 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 operation. 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**.

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

Generous financial support by the Science and Engineering Research Board (SERB), Government of India (File Number: SCP/2022/000837) is greatly acknowledged. D. S. thanks IISc for the fellowship and S.D. and R.C.D. thank MHRD for the PMRF scholarship. We thank Mr. Khush Jain and Ms. Safa Shajahan for the help in preparing the ynamide substrates. We thank Mr. Kishorkumar Sindogi (IISc) for collecting the X-ray data of **3a**. We thank Dr. Avishek Guin and Dr. Subrata Bhattacharjee for the useful discussions.

Notes and references

1. A. Greenberg and J. F. Liebman, "Strained Organic Molecules"; *Academic Press: New York*, 1978.
2. (a) M. A. Subbaiah and N. A. Meanwell, *J. Med. Chem*. 2021, **64**, 14046; (*b*) M. R. Bauer, P. Di Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. I. Storer and B. C. Whitehurst, *RSC Med. Chem.* 2021, **12**, 448; (*c*) M. A. Dallaston, S. D. Houston and C. M. Williams, *Chem.-Eur. J*. 2020, **26**, 11966.
3. For recent reviews on BCB, see: (*a*) Q.-Q. Hu, J. Chen, Y. Yang, H. Yang and L. Zhou, *Tetrahedron Chem*. 2024, **9**, 100070; (*b*) M. Golfmann and J. C. L. Walker, *Commun. Chem.* 2023, **6**, 9; (*c*) C. B. Kelly, J. A. Milligan, L. J. Tilley and T. M. Sodano, *Chem. Sci*. 2022, **13**, 11721; For examples on bicyclic pentanes and other bicyclic scaffolds, see: (*d*) J. M. Anderson, N. D. Measom, J. A. Murphy and D. L. Poole, *Angew. Chem., Int. Ed.* 2021, **60**, 24754; (*e*) X. Ma and P. Luu Nhat, *Asian J. Org. Chem*. 2020, **9**, 8; (*f*) G. M. Locke, S. S. R. Bernhard and M. O. Senge, *Chem. Eur. J*. 2019, **25**, 4590. (*g*) B. A. Chalmers, H. Xing, S. Houston, C. Clark, S. Ghassabian, A. Kuo, B. Cao, A. Reitsma, C.-E. P. Murray, J. E. Stok, G. M. Boyle, C. J. Pierce, S. W. Littler, D. A. Winkler, P. V. Bernhardt, C. Pasay, J. J. De Voss, J. McCarthy, P. G. Parsons, G. H. Walter, M. T. Smith, H. M. Cooper, S. K. Nilsson, J. Tsanaktsidis, G. P. Savage and C. M. Williams, *Angew. Chem., Int. Ed*. 2016, **55**, 3580; (*h*) M. D. Levin, P. Kaszynski and J. Michl, *Chem. Rev.* 2000, **100**, 169; (*i*) T. Iida, J. Kanazawa, T. Matsunaga, K. Miyamoto, K. Hirano and M. Uchiyama, *J. Am. Chem. Soc.* 2022, **144**, 21848.
4. (*a*) F. Lovering, *Med Chem Comm* 2013, **4**, 515. (b) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem*. 2009, **52**, 6752.
5. (*a*) J. Tsien, C. Hu, R. R. Merchant and T. Qin, *Nat. Rev. Chem*., 2024, **8**, 605; (b) P. K. Mykhailiuk, *Org. Biomol. Chem*., 2019, **17**, 2839.
6. (*a*) A. Denisenko, P. Garbuz, N. M. Voloshchuk, Y. Holota, G. Al-Maali, P. Borysko and P. K. Mykhailiuk, *Nat. Chem*. 2023, **15**, 1155; (*b*) S. Paul, D. Adelfinsky, C. Salome, T. Fessard and M. K. Brown, *Chem. Sci*. 2023, **14**, 8070; (*c*) A. Denisenko, P. Garbuz, Y. Makovetska, O. Shablykin, D. Lesyk, G. AlMaali, R. Korzh, I. V. Sadkova and P. K. Mykhailiuk, *Chem. Sci*. 2023, **14**, 14092. (*d*) A. Denisenko, P. Garbuz, S. V. Shishkina, N. M. Voloshchuk and P. K. Mykhailiuk, *Angew. Chem., Int. Ed*. 2020, **59**, 20515.
7. For reviews, see: (a) A. Fawcett, *Pure Appl. Chem*. 2020, **92**, 751; (b) J. Turkowska, J. Durka and D. Gryko, *Chem. Commun*. 2020, **56**, 5718; (c) M. A. A. Walczak, T. Krainz and P. Wipf, *Acc. Chem. Res*. 2015, **48**, 1149; for examples, see: (d) Q. Fu, S. Cao, J. Wang, X. Lv, H. Wang, X. Zhao and Z. Jiang, *J. Am. Chem. Soc*. 2024, **146**, 8372; (e) Y. Liang, R. Nematswerani, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed*. 2024, **63**, e202402730; (f) J. Zhang, J.-Y. Su, H. Zheng, H. Li and W.-P. Deng, *Angew. Chem., Int. Ed*. 2024, **63**, e202318476; (g) T. V. T. Nguyen, A. Bossonnet, M. D. Wodrich and J. Waser, *J. Am. Chem. Soc*. 2023, **145**, 25411; (h) T. Yu, J. Yang, Z. Wang, Z. Ding, M. Xu, J. Wen, L. Xu and P. Li, *J. Am. Chem. Soc*. 2023, **145**, 4304; (i) H. Wang, H. Shao, A. Das, S. Dutta, H. T. Chan, C. Daniliuc, K. N. Houk and F. Glorius, *Science* 2023, **381**, 75; (j) Y. Zheng, W. Huang, R. K. Dhungana, A. Granados, S. Keess, M. Makvandi and G. A. Molander, *J. Am. Chem. Soc*. 2022, **144**, 23685. (k) P. Wipf and M. A. A. Walczak, *Angew. Chem. Int. Ed*. 2006, **45**, 4172.
8. M. Xu, Z. Wang, Z. Sun, Y. Ouyang, Z. Ding, T. Yu, L. Xu and P. Li, *Angew. Chem. Int. Ed*. 2022, **61**, e202214507.
9. (*a*) T. M. Sodano, L. A. Combee and C. R. J. Stephenson, *ACS Med. Chem. Lett*. 2020, **11**, 1785. (b) D. Staveness, T.M. Sodano, K. Li, E.A. Burnham, K.D. Jackson and C. R. J. Stephenson, *Chem.,* 2019, **5**, 215.
10. (*a*) T. Kahl, K. W. Schröder, F. Lawrence, W. Marshall, H. Höke and R. Jäckh, *Wiley*, 2012, Vol. 3, Chapter 465, 465; (*b*) J. Schranck and A. Tlili, *ACS Catal*. 2018, **8**, 405.
11. (*a*) A. S. Kalgutkar and D. Dalvie, *Annu. Rev. Pharmacol. Toxicol*. 2015, **55**, 35; (*b*) A. S. Kalgutkar, *J. Med. Chem*. 2020, **63**, 6276.
12. R. Kleinmans, T. Pinkert, S. Dutta, T. O. Paulisch, H. Keum, C. G. Daniliuc and F. Glorius, *Nature* 2022, **605**, 477.

DOI: 10.1039/D4SC03893B

13. R. Guo, Y.-C. Chang, L. Herter, C. Salome, S. E. Braley, T. C. Fessard and M. K. Brown, *J. Am. Chem. Soc.* 2022, **144**, 7988.
14. S. Agasti, F. Beltran, E. Pye, N. Kaltsoyannis, G. E. M. Crisenza and D. J. Procter, *Nat. Chem*. 2023, **15**, 535.
15. T. Yu, J. Yang, Z. Wang, Z. Ding, M. Xu, J. Wen, L. Xu and P. Li, *J. Am. Chem. Soc.* 2023, **145**, 4304.
16. Y. Liu, S. Lin, Y. Li, J.-H. Xue, Q. Li and H. Wang, *ACS Catal*. 2023, **13**, 5096.
17. K. Dhake, K. J. Woelk, J. Becica, A. Un, S. E. Jenny and D. C. Leitch, *Angew. Chem. Int. Ed.* 2022, **61**, e202204719.
18. N. Radhoff, G. C. Daniliuc and A. Studer, *Angew. Chem. Int. Ed.* 2023**, 62**, e202304771.
19. Y. Liang, F. Paulus, C. G. Daniliuc and F. Glorius, *Angew. Chem. Int. Ed.* 2023, **62**, e202305043.
20. D. Ni, S. Hu, X. Tan, Y. Yu, Z. Li and L. Deng, *Angew. Chem. Int. Ed.* 2023, **62**, e202308606.
21. (*a*) L. Tang, Y. Xiao, F. Wu, J.-L. Zhou, T.-T. Xu and J.-J Feng, *Angew. Chem. Int. Ed*. 2023, **62**, e202310066; see also: (*b*) J.-J. Wang, L. Tang, Y. Xiao, W.-B. Wu, G. Wang and J.-J. Feng, *Angew. Chem. Int. Ed*. 2024, **63**, e202405222.
22. For a single example of the annulation of pyridinyl BCBs with phenyl acetylene proceeding in a radical pathway, see ref. 8. For a (3+2) annulation involving BCBs for the access to aminobicyclo[2.1.1]hexanes, see: H. Ren, T. Li, J. Xing, Z. Li, Y. Zhang, X. Yu and J. Zheng, *Org. Lett*., 2024, **26**, 1745.
23. Ynamide reviews: (*a*) J. Ficini, *Tetrahedron* 1976, **32**, 1449; (*b*) C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar and L. Wei, *Tetrahedron* 2001, **57**, 7575; (*c*) K. A. Dekorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev*., 2010, **110**, 5064. (d) Y.-B. Chen, P.-C. Qian and L.-W. Ye, *Chem. Soc. Rev***.**, 2020, **49**, 8897. (e) L. Hu and J. Zhao, *Acc. Chem. Res.* 2024, **57**, 855. (f) C.C. Lynch, A. Sripada and C. Wolf, *Chem. Soc. Rev***.**, 2020, **49**, 8543.
24. During the preparation of this manuscript, Chen, Zhou and co-workers reported the Lewis acid-catalyzed (3+2) annulation of BCBs with ynamides for the synthesis of polysubstituted 2-amino bicyclo[2.1.1]hexenes. For details, see: Q.-Q. Hu, L.-Y. Wang, X.-H. Chen, Z.-X. Geng, J. Chen and L. Zhou, *Angew. Chem. Int. Ed*. 2024, **63**, e202405781.
25. For related BCB works from our group, see: (*a*) A. Guin, S. Bhattacharjee, M. S. Harariya and A. T. Biju, Chem. Sci., 2023, **14**, 6585; (*b*) Guin, A.; Deswal, S.; M. S. Harariya and Biju, A. T. *Chem. Sci*., 2024, **15**, 12473.
26. W. D. Mackay, M. Fistikci, R. M. Carris and J. S. Johnson, *Org. Lett.*, 2014, **16**, 1626.
27. For details, see the Supporting Information.
28. CCDC 2358094 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
29. The reaction of **1a** with *N*-benzyl *N*-mesyl ynamide substrate used by Chen, Zhou and co-workers (ref 24) under the optimized conditions afforded the 2-amino bicyclo[2.1.1]hexene product in 50% yield.
30. (*a*) A. U. Augustin and D. B. Werz, *Acc. Chem. Res*., 2021, **54**, 1528; (*b*) V. Pirenne, B. Muriel and J. Waser, *Chem. Rev*., 2021, **121**, 227; (*c*) D. B. Werz and A. T. Biju, *Angew. Chem., Int. Ed*., 2020, **59**, 3385; (*d*) P. Singh, R. K. Varshnaya, R. Dey and P. Banerjee, *Adv. Synth. Catal*., 2020, **362**, 1447; (*e*) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed*., 2014, **53**, 5504; (*f*) H.-U. Reissig and R. Zimmer, *Chem. Rev*., 2003, **103**, 1151.

Dr Akkattu T. Biju
Professor
Phone: +91-80-2293-2646
Fax: +91-80-2360-0529
e-mail: atbiju@iisc.ac.in
https://orgchem.iisc.ac.in/atbiju/

Indian Institute of Science
Department of Organic Chemistry
Bangalore-560012
INDIA

24th August 2024

Dear Prof. (Dr.) Yudin,

Sub: Submission of the revised version of the manuscript entitled **"Lewis acid-catalyzed (3+2) annulation of bicyclobutanes with ynamides: Access to 2-amino bicyclo[2.1.1]hexenes"** (Manuscript ID: SC-EDG-06-2024-003893).

Data Availability Statement

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 Supporting Information of the manuscript

Please do not hesitate to contact me in case you need additional information.

Thanks a lot!

Best regards
AT Biju