ChemComm

Check for updates

Lewis acid-catalyzed [2π+2σ] cycloaddition of dihydropyridines with bicyclobutanes†

Yujie Liang, [ID] Ronewa Nematswerani, [ID] Constantin G. Daniliuc [ID] and Frank Glorius [ID] *

Herein we report a simple BF₃-catalyzed cycloaddition of dihydropyridines with bicyclobutanes for the expedient synthesis of novel three-dimensional azacycle-fused bicyclo[2.1.1]hexane scaffolds. The reaction utilizes easily accessible starting materials and proceeds under mild, metal-free conditions with high atom efficiency.
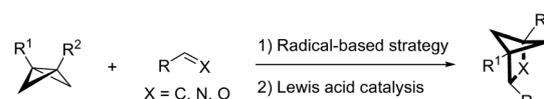
Building on the success of the "escape from flatland" concept in pharmaceutical development, there is growing interest among chemists in creating efficient methods to rapidly construct conformationally rigid, C(sp³)-enriched scaffolds. These structures hold immense potential for phenyl or pyridinyl bioisosterism, with a higher proportion of sp³-hybridized carbon atoms that is often linked to enhanced physicochemical and pharmacokinetic properties of drug candidates.[1] This is particularly true for bicyclo[2.1.1]hexanes (BCHs), which have shown promise as benzene bioisosteres due to their rigid conformation.[2] Consequently, there is a continual pursuit of new methods for the rapid construction of these ring systems with diverse substitution patterns.

To synthesize these coveted BCH building blocks in a straightforward and atom-economical way, the direct cycloaddition of bicyclobutanes (BCBs) with π-components has been the method of choice in recent years. Accordingly, these methods can be categorized into two main reaction pathways: those that proceed *via* a radical-based mechanism[3] and those that utilize Lewis acid catalysis[4] (Scheme 1a). Given the ubiquity of (hetero)arenes, the dearomative cycloaddition of (hetero)arenes with BCBs represents an attractive approach to their synthesis. In this context, Deng[5] and Feng[6] independently reported the Lewis acid-catalyzed [2π+2σ] cycloaddition reactions of BCBs with indole derivatives to afford indoline fused BCHs. In addition, through photocatalysis strategies, our group has achieved the direct cycloaddition reactions of BCBs with diverse (hetero)arenes (*e.g.* indoles, coumarins, flavones, (iso)quinolines, quinazolines and phenols) to produce
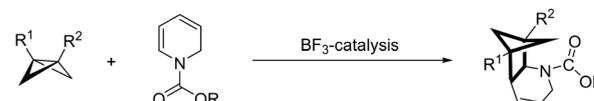
Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, 48149 Münster, Germany. E-mail: glorius@uni-muenster.de

† Electronic supplementary information (ESI) available. CCDC 2400706. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4cc06133k

highly substituted BCHs (Scheme 1b).[7] Pyridines are readily available and abundant feedstock chemicals, and the development of new cycloaddition reactions could facilitate their use in rapidly building up molecular complexity. However, due to their inherent stability from aromaticity, cycloaddition of these aromatic cores with BCBs remains challenging.[8] Inspired by the elegant work on cycloaddition reactions of dihydropyridines (synthesized in one step from pyridines) with α-substituted acroleins,[9] as well as recent advancements in Lewis acid-catalyzed BCB-based cycloaddition chemistry,[4–6] we envisioned that a Lewis acid catalytic strategy would be capable of achieving [2π+2σ] cycloaddition of dihydropyridines with BCBs (Scheme 1c). Such a method could provide straightforward access to BCHs directly fused to azacycles, which are among the most frequently encountered structural motifs in FDA-approved pharmaceuticals.[10] Driven by our ongoing interest in dearomative cycloaddition reactions of (hetero)arenes with BCBs[7] and prompted by the growing demand of conformationally restricted, saturated scaffolds in drug discovery, herein, we report that the direct cycloaddition of dihydropyridines with BCBs can be smoothly executed under simple BF₃ catalysis (Scheme 1c).

a) Strategies for cycloaddition of BCBs with π-component to form rigid BCHs scaffold

b) Our previous work: cycloaddition of BCBs with (hetero)arenes via photocatalysis

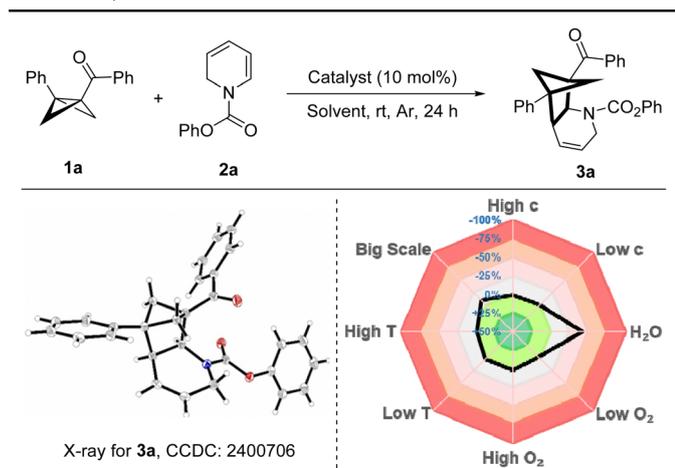c) This work: BF₃-catalyzed cycloaddition of BCBs with dihydropyridines

Scheme 1 BCB-based cycloaddition reactions for BCHs synthesis.

Initially, we chose BCB **1a** and dihydropyridine **2a** as the model substrates, and we were pleased to find that, after stirring them in DCM at room temperature for 24 h with $BF_3 \cdot Et_2O$ as catalyst, the corresponding $[2\pi+2\sigma]$ cycloaddition product **3a** was furnished in 56% yield, with no formation of a $[4\pi+2\sigma]$ cycloaddition product observed (Table 1, entry 1). The structure of **3a** was confirmed by single-crystal X-ray diffraction analysis (CCDC: 2400706†). Other Lewis acid catalysts were also tested but gave poorer results (Table 1, entries 2–6). A control experiment showed that the Lewis acid catalyst was crucial for this transformation (Table 1, entry 7). Other solvents were subsequently investigated, and MeCN was found to be superior (Table 1, entries 8–14). Performing the reaction with 1.5 equivalent of **2a** gave a similar yield (Table 1, entry 15). Using dihydropyridine **2a** as limiting reagent and slightly excess BCB did not improve the yield significantly (Table 1, entry 16).

Furthermore, using a higher loading of Lewis acid catalyst or conducting the reaction at 50 °C afforded the product **3a** in comparable yields (Table 1, entries 17 and 18). Finally, we conducted the reaction on a 0.2 mmol scale and the product **3a** can be isolated in 60% yield (Table 1, entry 19). Notably, condition-based sensitivity assessment[11] indicated that moisture supressed the reaction, while other reaction parameters such as concentration, O_2 level, reaction temperature and scale showed only negligible effects on the reaction outcome (Table 1).

With the optimized conditions in hand, an initial survey of the dihydropyridines and BCBs substrate scope was investigated (Table 2). To our delight, alkyl-substituted dihydropyridines can be accepted in this protocol (**3b**, **3c**). Although the use of a mono-substituted BCB resulted in a lower yield of product (**3d**) due to decomposition under the reaction conditions, various disubstituted ketone BCBs with electron-donating or electron-withdrawing groups reacted smoothly, producing cycloadducts in moderate to good yields (**3e**–**3o**). Among them, medicinally relevant trifluoromethyl and fluoro groups can be tolerated (**3f**, **3g**). Pleasingly, alkyl ketone BCBs can also be accommodated in this protocol (**3k**, **3l**). Other BCB substrates were also tested, for

Table 1 Optimization of the reaction conditions[a]

X-ray for 3a, CCDC: 2400706

Entry	Catalyst	Solvent	Yield (%)
1	$BF_3 \cdot Et_2O$	DCM	56
2	$Sc(OTf)_3$	DCM	42
3	$Eu(OTf)_3$	DCM	11
4	$AlCl_3$	DCM	< 5
5	TMSOTf	DCM	16
6	$Y(OTf)_3$	DCM	< 5
7	—	DCM	—
8	$BF_3 \cdot Et_2O$	MeCN	69
9	$BF_3 \cdot Et_2O$	THF	35
10	$BF_3 \cdot Et_2O$	PhMe	66
11	$BF_3 \cdot Et_2O$	EtOAc	68
12	$BF_3 \cdot Et_2O$	Acetone	67
13	$BF_3 \cdot Et_2O$	DME	43
14	$BF_3 \cdot Et_2O$	$CHCl_3$	50
15[b]	$BF_3 \cdot Et_2O$	MeCN	70
16[c]	$BF_3 \cdot Et_2O$	MeCN	70
17[d]	$BF_3 \cdot Et_2O$	MeCN	72
18[e]	$BF_3 \cdot Et_2O$	MeCN	70
19[f]	$BF_3 \cdot Et_2O$	MeCN	60

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (10 mol%), solvent (1 mL), Ar, rt, 24 h. Yields were determined by ^1H NMR analysis of the crude mixture using CH_2Br_2 as an internal standard. [b] Using **2a** (0.15 mmol). [c] Using **1a** (0.12 mmol) and **2a** (0.1 mmol). [d] Using catalyst (20 mol%). [e] Reaction conducted at 50 °C. [f] Reaction condition: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (10 mol%), solvent (2 mL), Ar, rt, 24 h. Isolated yield is showed.
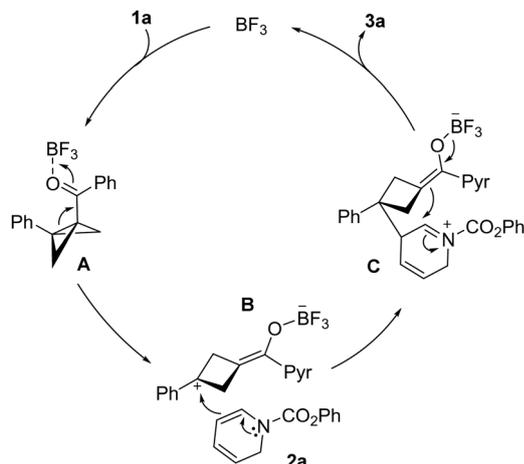
Table 2 Substrate scope investigation[a]
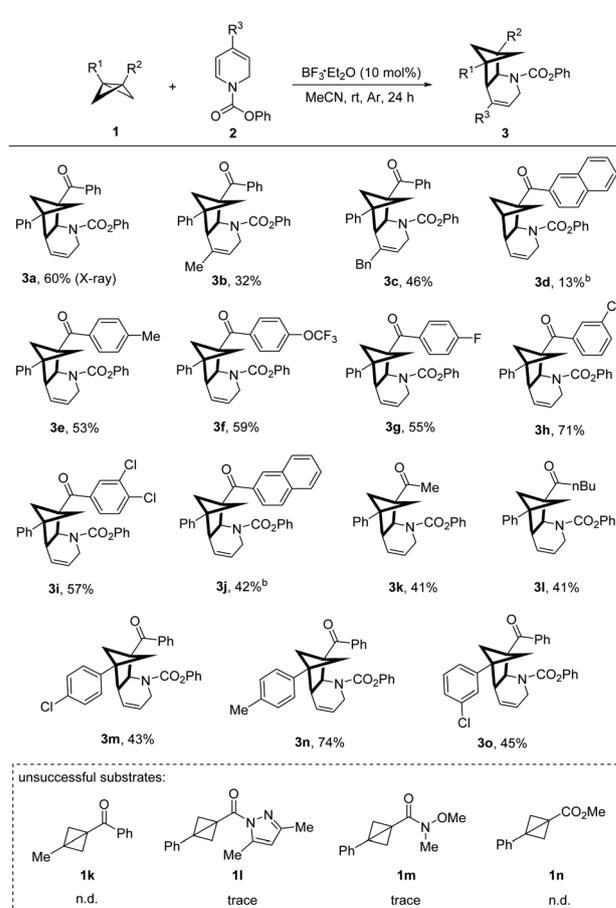
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $BF_3 \cdot Et_2O$ (10 mol%), MeCN (2 mL), Ar, rt, 24 h. Isolated yields are shown. [b] Using DCM as solvent. n.d. = not detected. See the ESI for experimental details.
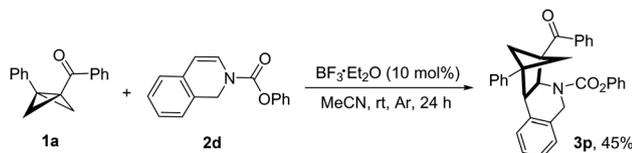
Scheme 2 Cycloaddition of dihydroisoquinoline with BCB.

Scheme 3 Proposed mechanism.

examples, substrates **1k**, **1l**, and **1m** produced little or no product, with a significant amount of starting material remaining. Substrate **1n**, however, decomposed under the reaction conditions, resulting in an uncharacterized complex mixture. In addition to dihydropyridines, we were delighted to find that, dihydroisoquinoline could also undergo the corresponding [2π+2σ] cycloaddition (Scheme 2).

Based on the observed regioselectivity and literature reports,[4–6] a plausible reaction mechanism is proposed (Scheme 3). Initially, the BCB substrate **1a** coordinates with the Lewis acid catalyst to form complex **A**, which then undergoes enolization to yield species **B**. Subsequently, the electron-rich dihydropyridine **2a** nucleophilically attacks **B** to generate enolate and iminium intermediate **C**. Finally, intramolecular cyclization gives product **3a** and regenerates the BF₃ catalyst.

In conclusion, we have developed a new BF₃-catalyzed cycloaddition reaction between dihydropyridines and bicyclobutanes to create novel azacycle-fused BCH scaffolds. The reaction utilizes easily accessible starting materials and proceeds under mild conditions, further enriching the synthetic toolkit for rapid access to structurally diverse rigid scaffolds.

Data availability

The data supporting this article has been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (b) T. J. Ritchie and S. J. F. Macdonald, *Drug Discovery Today*, 2009, **14**, 1011–1020; (c) F. Lovering, *Med. Chem. Commun.*, 2013, **4**, 515–519; (d) D. Trauner, *Angew. Chem., Int. Ed.*, 2018, **57**, 4177–4191; (e) P. K. Mykhailiuk, *Org. Biomol. Chem.*, 2019, **17**, 2839–2849; (f) M. A. M. Subbaiah and N. A. Meanwell, *J. Med. Chem.*, 2021, **64**, 14046–14128.
2 (a) A. Denisenko, P. Garbuz, S. V. Shishkina, N. M. Voloshchuk and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2020, **59**, 20515–20521; (b) A. Denisenko, P. Garbuz, N. M. Voloshchuk, Y. Holota, G. Al-Maali, P. Borysko and P. K. Mykhailiuk, *Nat. Chem.*, 2023, **15**, 1155–1163; (c) K. J. Woelk, K. Dhake, N. D. Schley and D. C. Leitch, *Chem. Commun.*, 2023, **59**, 13847–13850; (d) M. Zanini, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2024, **63**, e202410207; (e) J. Tsien, C. Hu, R. R. Merchant and T. Qin, *Nat. Rev. Chem.*, 2024, **8**, 605–627; (f) T. Qin, M. He and W. Zi, *Nat. Synth.*, 2024, DOI: 10.1038/s44160-024-00659-6; (g) E. F. Plachinski, R. Z. Qian, R. Villanueva, D. L. Poole, T. Rosenthal and T. P. Yoon, *J. Am. Chem. Soc.*, 2024, **146**, 31400–31404.
3 (a) 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**, 7988–7994; (b) M. Xu, Z. Wang, Z. Sun, Y. Ouyang, Z. Ding, T. Yu, L. Xu and P. Li, *Angew. Chem., Int. Ed.*, 2022, **61**, e202214507; (c) Y. Liang, R. Kleinmans, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2022, **144**, 20207–20213; (d) S. Agasti, F. Beltran, E. Pye, N. Kaltsoyannis, G. Crisenza and D. J. Procter, *Nat. Chem.*, 2023, **15**, 535–541; (e) Y. Liu, S. Lin, Y. Li, J.-H. Xue, Q. Li and H. Wang, *ACS Catal.*, 2023, **13**, 5096–5103; (f) H. Yan, Y. Liu, X. Feng and L. Shi, *Org. Lett.*, 2023, **25**, 8116–8120; (g) M. Robichon, T. Kratz, F. Beyer, J. Zuber, C. Merten and T. Bach, *J. Am. Chem. Soc.*, 2023, **145**, 24466–24470; (h) J. L. Tyler, F. Schäfer, H. Shao, C. Stein, A. Wong, C. G. Daniliuc, K. N. Houk and F. Glorius, *J. Am. Chem. Soc.*, 2024, **146**, 16237–16247; (i) Q. Fu, S. Cao, J. Wang, X. Lv, H. Wang, X. Zhao and Z. Jiang, *J. Am. Chem. Soc.*, 2024, **146**, 8372–8380; (j) H. Ren, T. Li, J. Xing, Z. Li, Y. Zhang, X. Yu and J. Zheng, *Org. Lett.*, 2024, **26**, 1745–1750; (k) J. Jeong, S. Cao, H.-J. Kang, H. Yoon, J. Lee, S. Shin, D. Kim and S. Hong, *J. Am. Chem. Soc.*, 2024, **146**, 27830–27842; (l) Y. Liu, Z. Wu, J.-R. Shan, H. Yan, E.-J. Hao and L. Shi, *Nat. Commun.*, 2024, **15**, 4374–4383; (m) S. Dutta, Y.-L. Lu, J. E. Erchinger, H. Shao, E. Studer, F. Schäfer, H. Wang, D. Rana, C. G. Daniliuc, K. N. Houk and F. Glorius, *J. Am. Chem. Soc.*, 2024, **146**, 5232–5241.
4 (a) K. Dhake, K. J. Woelk, J. Becica, A. Un, S. E. Jenny and D. C. Leitch, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204719; (b) Y. Liang, F. Paulus, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2023, **62**, e202305043; (c) N. Radhoff, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2023, **62**, e202304771; (d) Z. Lin, H. Ren, X. Lin, X. Yu and J. Zheng, *J. Am. Chem. Soc.*, 2024, **146**, 18565–18575; (e) S. Hu, Y. Pan, D. Ni and L. Deng, *Nat. Commun.*, 2024, **15**, 6128–6137; (f) Q.-Q. Hu, L.-Y. Wang, X.-H. Chen, Z.-X. Geng, J. Chen and L. Zhou, *Angew. Chem., Int. Ed.*, 2024, **63**, e202405781; (g) J.-Y. Su, J. Zhang, Z.-Y. Xin, H. Li, H. Zheng and W.-P. Deng, *Org. Chem. Front.*, 2024, **11**, 4539–4545; (h) K. Zhang, S. Tian, W. Li, X. Yang, X.-H. Duan, L.-N. Guo and P. Li, *Org. Lett.*, 2024, **26**, 5482–5487; (i) D. Sarkar, S. Deswal, R. C. Das and A. T. Biju, *Chem. Sci.*, 2024, **15**, 16243–16249; (j) S. Nicolai and J. Waser, *Chem. Sci.*, 2024, **15**, 10823–10829; (k) J.-J. Wang, L. Tang, Y. Xiao, W.-B. Wu, G. Wang and J.-J. Feng, *Angew. Chem., Int. Ed.*, 2024, **63**, e202405222; (l) S. Dutta, C. G. Daniliuc, C. Mück-Lichtenfeld and A. Studer, *J. Am. Chem. Soc.*, 2024, **146**, 27204–27212; (m) W.-B. Wu, B. Xu, X.-C. Yang, F. Wu, H.-X. He, X. Zhang and J.-J. Feng, *Nat. Commun.*, 2024, **15**, 8005–8014; (n) X.-G. Zhang, Z.-Y. Zhou, J.-X. Li, J.-J. Chen and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2024, **146**, 27274–27281; (o) Y. Xiao, F. Wu, L. Tang, X. Zhang, M. Wei, G. Wang and J.-J. Feng, *Angew. Chem., Int. Ed.*, 2024, **63**, e202408578; (p) J. Zhang, J.-Y. Su, H. Zheng, H. Li and W.-P. Deng, *Angew. Chem., Int. Ed.*, 2024, **63**, e202318476; (q) F. Wu, W.-B. Wu, Y. Xiao, Z. Li, L. Tang, H.-X. He, X.-C. Yang, J.-J. Wang, Y. Cai, T.-T. Xu, J.-H. Tao, G. Wang and J.-J. Feng, *Angew.*

Chem., Int. Ed., 2024, **63**, e202406548; (*r*) X. Wang, R. Gao and X. Li, *J. Am. Chem. Soc.*, 2024, **146**, 21069–21077.

5 D. Ni, S. Hu, X. Tan, Y. Yu, Z. Li and L. Deng, *Angew. Chem., Int. Ed.*, 2023, **62**, e202308606.

6 L. Tang, Y. Xiao, F. Wu, J.-L. Zhou, T.-T. Xu and J.-J. Feng, *Angew. Chem., Int. Ed.*, 2023, **62**, e202310066.

7 (*a*) R. Kleinmans, T. Pinkert, S. Dutta, T. O. Paulisch, H. Keum, C. G. Daniliuc and F. Glorius, *Nature*, 2022, **605**, 477–482; (*b*) R. Kleinmans, S. Dutta, K. Ozols, H.-L. Shao, F. Schäfer, R. E. Thielemann, H. T. Chan, C. G. Daniliuc, K. N. Houk and F. Glorius, *J. Am. Chem. Soc.*, 2023, **145**, 12324–12332; (*c*) S. Dutta, D. Lee, K. Ozols, C. G. Daniliuc, R. Shintani and F. Glorius, *J. Am. Chem. Soc.*, 2024, **146**, 2789–2797.

8 J. Ma, F. Strieth-Kalthoff, T. Dalton, M. Freitag, J. L. Schwarz, K. Bergander, C. Daniliuc and F. Glorius, *Chem*, 2019, **5**, 2854–2864.

9 M. Hatano, Y. Goto, A. Izumiseki, M. Akakura and K. Ishihara, *J. Am. Chem. Soc.*, 2015, **137**, 13472–13475.

10 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.

11 L. Pitzer, F. Schäfers and F. Glorius, *Angew. Chem., Int. Ed.*, 2019, **58**, 8572–8576.