Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2025, **16**, 4654

All publication charges for this article have been paid for by the Royal Society of Chemistry

Silver-mediated formal [4π + 2σ] cycloaddition reactions of bicyclobutanes with nitrile imines: access to 2,3-diazobicyclo[3.1.1]heptenes†

Huijuan Liao, Jianyang Dong,* Xuechen Zhou, Qin Jiang, Zishan Lv, Fang Lei and Dong Xue *

Received 6th December 2024
Accepted 6th February 2025

DOI: 10.1039/d4sc08280j

rsc.li/chemical-science

Despite recent advances in the synthesis of aza-bicyclo[3.1.1]heptanes (aza-BCHeps, which have an sp^3-hybridized nitrogen atom) and azabicyclo[3.1.1]heptenes (aza-BCHepes, which have an sp^2-hybridized nitrogen atom), which are bioisosteres of pyridine, construction of 2,3-diazobicyclo[3.1.1]heptenes (2,3-diazo-BCHepes), which have both sp^2- and sp^3-hybridized nitrogen atoms, has yet to be achieved. Herein, we disclose a method for silver-enabled formal [4π + 2σ] cycloaddition reactions between bicyclobutanes and nitrile imines (generated from hydrazonyl chlorides) to furnish a diverse array of 2,3-diazo-BCHepes, which feature both sp^2- and sp^3-hybridized nitrogen atoms embedded in a BCHepe framework. These compounds have the potential to serve as bioisosteres of both pyridines and pyridazines. Owing to the presence of the sp^3-hybridized nitrogen, 2,3-diazo-BCHepes can be expected to exhibit geometries similar to those of aza-BCHepes and much better solubility. We demonstrated the synthetic utility of our method by carrying out a scaled-up reaction and diverse postcatalytic transformations.

Introduction

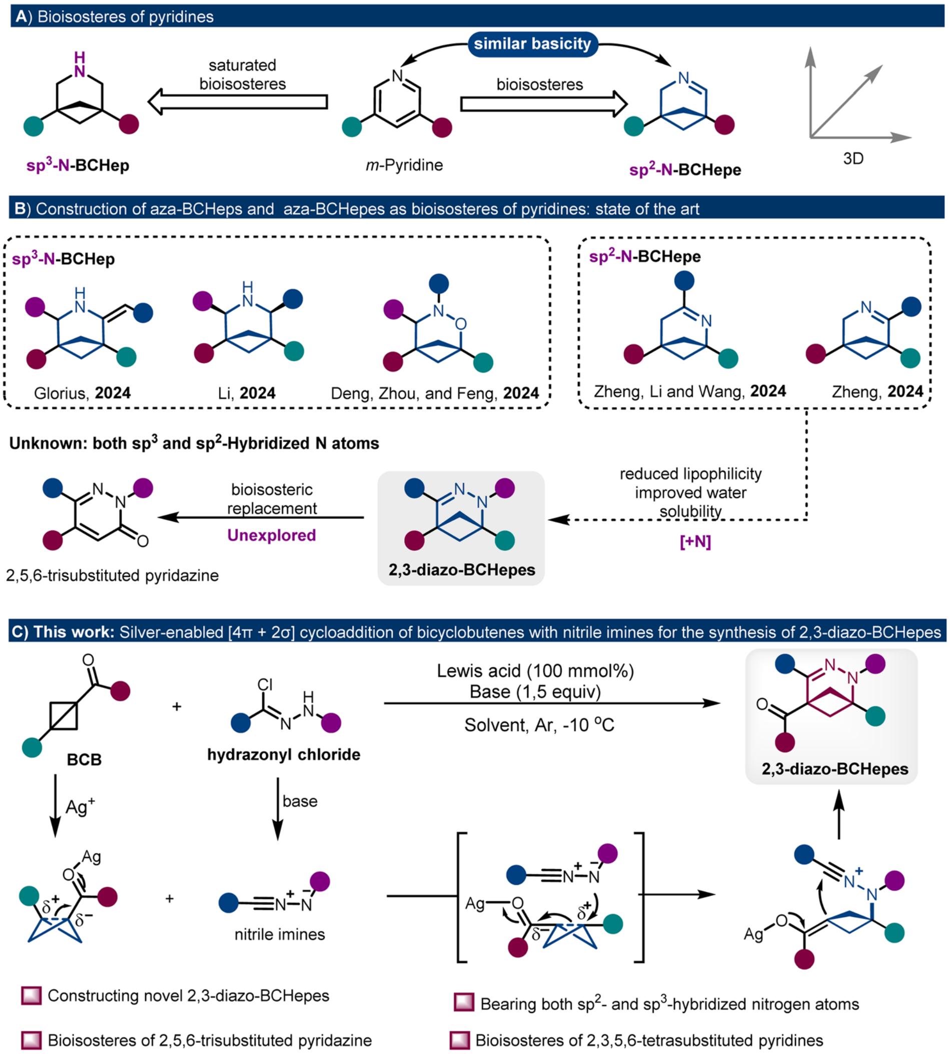
As of 2021, 88% of the drugs approved by the US Food and Drug Administration contained nitrogen heterocycles. In particular, *N*-heteroarenes such as pyridines and pyridazines are ubiquitous in pharmaceuticals and serve as fundamental building blocks in organic synthesis.[1] However, because the presence of planar moieties such as pyridine rings often results in undesirable pharmaceutical properties, medicinal chemists have been prompted to seek bioisosteres.[2] In recent years, three-dimensional saturated bridged bicyclic scaffolds such as bicyclo[1.1.1]pentanes,[3] bicyclo[2.1.1]hexanes,[4] and bicyclo[3.1.1]heptanes (BCHeps)[5] have been developed as arene surrogates because these scaffolds can mimic the structural properties of arene rings and because molecules with these scaffolds tend to have better physicochemical properties and pharmacokinetics than the parent drug molecules. Moreover, the Mykhailiuk group reported that 3-aza-BCHeps (Scheme 1A, left), which have an sp^3-hybridized nitrogen atom, are promising saturated bioisosteres of pyridines[6] and exhibit drug-like solubility, lipophilicity, and metabolic profiles.

To meet the increasing demand for 3-aza-BCHeps, the groups of Glorius,[7] Li,[8] Deng,[9] Zhou[10] and Feng[11] have recently established methods for synthesizing these compounds by means of Lewis acid-catalyzed cycloaddition reactions between bicyclo[1.1.0]butanes (BCBs) and various 1,3-dipoles (Scheme 1B). Because the sp^2-hybridized nitrogen atom of pyridines governs their basicity and hydrogen-bonding ability,[12] incorporation of an sp^2-hybridized imine nitrogen atom into the BCHep core can be expected to result in molecules that are more likely to be good mimics of pyridines; both types of compounds have unconjugated lone pair electrons on the nitrogen atom and π electrons in the C=N double bond. In this regard, the Zheng, Li and Wang groups separately reported syntheses of azabicyclo[3.1.1]heptenes (aza-BCHepes), which are regarded as perfect pyridine bioisosteres in terms of 3D conformation and basicity (Scheme 1A, right), from readily accessible vinyl azides and BCBs (Scheme 1B).[13]

Because of the ubiquity of pyridine motifs in drug molecules, exploring novel aza variants of BCHeps is an appealing strategy for drug discovery.[14] Mykhailiuk and colleagues showed that three-dimensional heteroatom-containing bioisosteres of arenes have better water solubility, higher metabolic stability, and lower lipophilicity than their arene and all-carbon bicyclic counterparts.[15] With the goal of designing a framework with a structure similar to that of aza-BCHepes but with much better solubility, we decided to try incorporating an additional

Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education and School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an, 710062, China. E-mail: jydong@snnu.edu.cn; xuedong_welcome@snnu.edu.cn

† Electronic supplementary information (ESI) available: General information, experimental procedures and characterization data of the synthesized compounds. CCDC 2394900. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4sc08280j



Scheme 1 (A) Bioisosteres of pyridines. (B) Construction of aza-BCHeps and aza-BCHepes as bioisosteres of pyridines: state of the art. (C) This work: silver-enabled [4π + 2σ] cycloaddition of bicyclobutenes with nitrile imines for the synthesis of 2,3-diazo-BCHepes.

nitrogen atom. We expected that by replacing the methylene group of aza-BCHepes with a nitrogen atom to afford 2,3-diazobicyclo[3.1.1]heptenes (2,3-diazo-BCHepes), we could obtain compounds with geometries similar to those of aza-BCHepes and much better solubility (Scheme 1B). Moreover, 2,3-diazo-BCHepes, which have both sp^2- and sp^3-hybridized nitrogen atoms, might serve as saturated bioisosteres of pyridazines (1,2-diazines), which have planar structures and have been found to have a wide range of pharmacological activities.[16] However, the construction of BCHepe frameworks with both sp^2- and sp^3-hybridized nitrogen atoms is extremely challenging (Scheme 1B).[17]

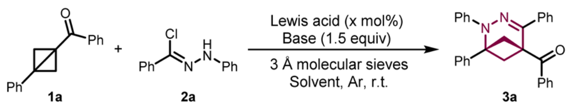
We reasoned that a [4π + 2σ] cycloaddition strategy might offer an appealing, straightforward route to 2,3-diazo-BCHepes. For this purpose, we evaluated nitrile imines, which are generally prepared by treatment of hydrazonyl halides with stoichiometric amounts of base and are versatile CNN 1,3-dipolar building blocks for the synthesis of nitrogen-containing heterocycles.[18] However, to date, research on nitrile imines has focused mainly on the construction of six-membered nitrogen heterocycles. Cycloaddition reactions of these compounds to form bridged bicyclic nitrogen heterocycles have not yet been reported.

Herein, we report the first method for silver-catalyzed formal [4π + 2σ] cycloaddition reactions of BCBs with hydrazonyl chloride-derived nitrile imines, providing a platform for the synthesis of previously inaccessible 2,3-diazo-BCHepes, which feature both sp^2- and sp^3-hybridized nitrogen atoms embedded in a BCHepe framework (Scheme 1C).

Results and discussion

To evaluate the feasibility of the cycloaddition reaction and to optimize the conditions, we used phenyl(3-phenylbicyclo[1.1.0]butan-1-yl)methanone (**1a**) and hydrazonyl chloride **2a** as model substrates (Table 1). First, we screened reactions involving various metal Lewis acids (20 mol%) with K_3PO_4 as the base in dichloromethane containing 3 Å molecular sieves at room

Table 1 Optimization of reaction conditions[a]



Entry	Lewis acid (mol%)	Base	Solvent	Yield (%)
1	$Sc(OTf)_3$ (20)	K_3PO_4	DCM	Trace
2	AgOTf (20)	K_3PO_4	DCM	12
3	$Eu(OTf)_3$ (20)	K_3PO_4	DCM	NR
4	$AgBF_4$ (20)	K_3PO_4	DCM	15
5	$AgBF_4$ (50)	K_3PO_4	DCM	20
6	$AgBF_4$ (100)	K_3PO_4	DCM	34
7	$AgBF_4$ (100)	Na_2CO_3	DCM	9
8	$AgBF_4$ (100)	K_2CO_3	DCM	7
9	$AgBF_4$ (100)	Et_3N	DCM	NR
10	$AgBF_4$ (100)	K_3PO_4	CH_3CN	NR
11	$AgBF_4$ (100)	K_3PO_4	THF	NR
12	$AgBF_4$ (100)	K_3PO_4	DCE	33
13[b]	$AgBF_4$ (100)	K_3PO_4	DCM	40
14[b,c]	$AgBF_4$ (100)	K_3PO_4	DCM	65
15[b,c,d]	$AgBF_4$ (100)	K_3PO_4	DCM	64
16[b,c,d]	—	K_3PO_4	DCM	NR
17[b,c,d]	$AgBF_4$ (100)	—	DCM	21
18[b,c,d,e]	$AgBF_4$ (100)	K_3PO_4	DCM	23

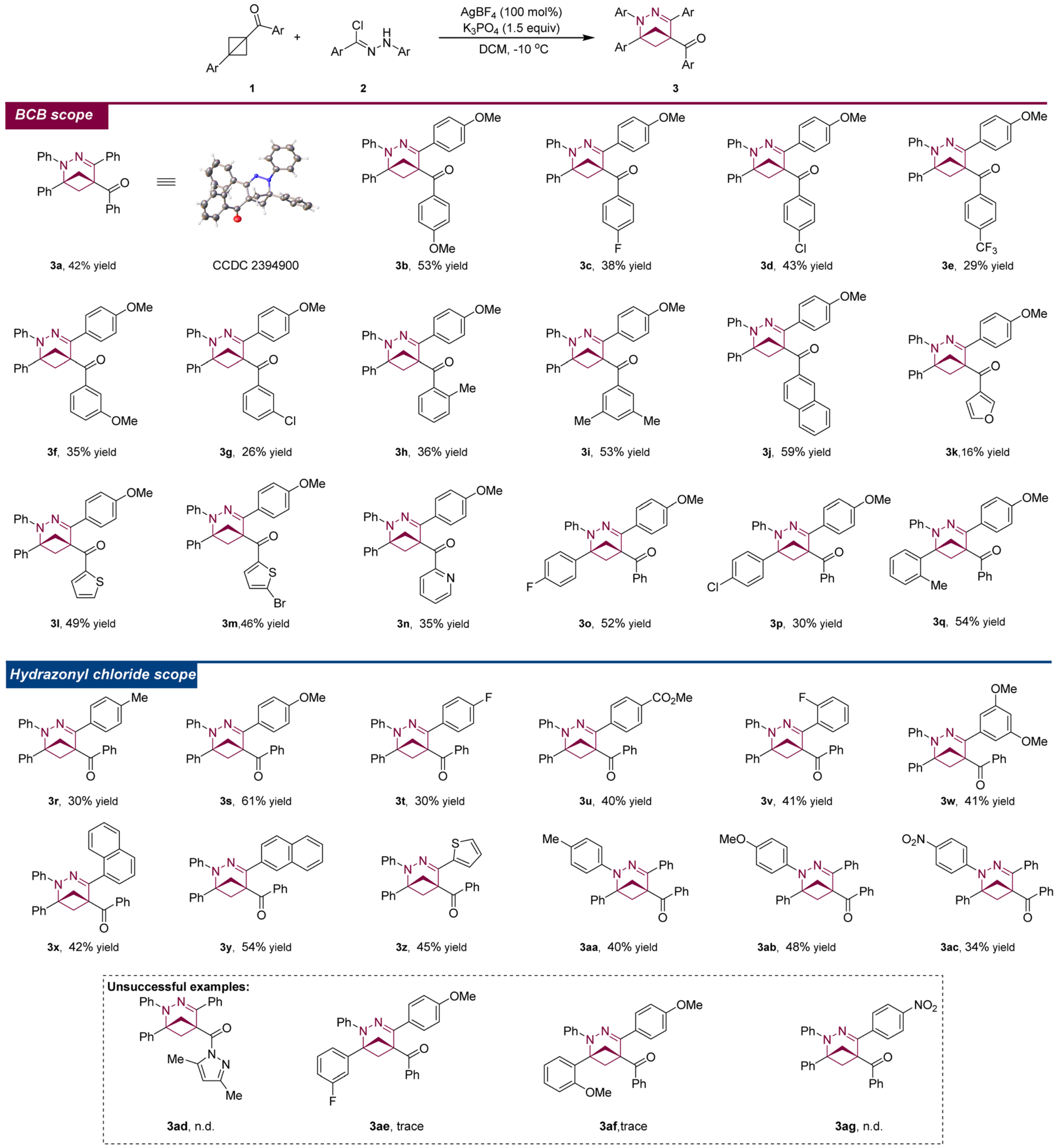
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), Lewis acid (20–100 mol%), base (0.15 mmol), solvent (1 mL), 3 Å molecular sieves (50 mg), Ar atmosphere, room temperature (r.t.), 16 h. Yields were determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. DCM, dichloromethane; NR, no reaction. [b] Reaction temperature, −10 °C. [c] 3 equiv of **1a**. [d] Reaction time, 1 h. [e] Without 3 Å molecular sieves.

temperature under argon for 16 h (entries 1–4). To our delight, desired product 2,3-diazo-BCHepe **3a** was obtained in 15% yield (as indicated by ^1H NMR spectroscopy) when $AgBF_4$ was the Lewis acid; the other tested acids gave lower yields. Subsequent variation of the $AgBF_4$ loading revealed that 100 mol% $AgBF_4$ gave a slightly better yield (entries 5 and 6). We also found that replacing K_3PO_4 with other bases gave lower yields (entries 7–9). Subsequent screening of various solvents for $AgBF_4$-catalyzed reactions revealed that dichloromethane was superior (entries 10–12). Notably, decreasing the reaction temperature to −10 °C increased the yield to 40% (entry 13). Performing the reaction with 3 equiv of **1a** at −10 °C gave **3a** in 65% yield (entry 14); and, notably, decreasing the reaction time to 1 h gave **3a** in 64% yield (entry 15). Control experiments showed that the reaction did not occur in the absence of a Lewis acid (entry 16) and that the yield of **3a** was 21% in the absence of a base (entry 17). Moreover, when the 3 Å molecular sieves were omitted, **3a** was obtained in only 23% yield (entry 18). Ultimately, the optimal conditions were determined to be as follows: **1a** (3.0 equiv), **2a** (1.0 equiv), and $AgBF_4$ (100 mol%) in dichloromethane at −10 °C under argon for 1 h (entry 15). The structure of **3a** was confirmed by X-ray diffraction analysis of a single crystal (Scheme 2).

Using the optimized conditions, we evaluated the substrate scope with respect to the BCB (Scheme 2, top panel). Aryl BCB ketones bearing an electron-neutral, electron-donating, or electron-withdrawing substituent on the aryl ring at the bridgehead position (aryl ketone bridgehead substituent) were reactive, delivering the desired products (**3a–3i**) in 26–53% yields. Specifically, phenyl BCB ketones bearing a *para* methoxy group, fluorine or chlorine atom, or trifluoromethyl group delivered corresponding products **3b–3e** in 29–53% yields. In addition, phenyl BCB ketones with a *meta* methoxy group or chlorine atom were also suitable substrates, affording **3f** and **3g**, respectively, in 35% and 26% yields. Notably, an *ortho*-methyl-substituted substrate afforded desired product **3h** in 36% yield. Moreover, a multisubstituted phenyl BCB ketone gave 2,3-diazo-BCHepe **3i** in 53% yield. In addition to phenyl BCB ketones, other aryl BCB ketones were compatible with the reaction conditions: 2,3-diazo-BCHepes with a naphthalene (**3j**), furan (**3k**), thiophene (**3l** and **3m**), or pyridine (**3n**) moiety were obtained in 16–59% yields. However, a BCB ketone bearing an acyl pyrazole group failed to produce the desired product (see unsuccessful examples, **3ad**), probably because the acyl pyrazole was less reactive toward cycloaddition than the ketones. Finally, substituted aryl rings at the other bridgehead position of the BCB ketone were also well tolerated. Specifically, we obtained moderate yields of 2,3-diazo-BCHepes with a *para* fluorine or chlorine atom on the aryl ring (**3o** and **3p**). Notably, an *ortho*-methyl-substituted phenyl BCB ketone also underwent the reaction, affording **3q** in 54% yield. However, *meta*-fluorine and *ortho*-methoxy-substituted phenyl BCB ketones failed to produce the desired products (see unsuccessful examples, **3ae** and **3af**).

Subsequently, we evaluated the substrate scope with respect to the hydrazonyl chloride by carrying out reactions with **1a** (Scheme 2, bottom panel). Initially, the aryl residue bound to the carbon atom of the hydrazonyl chloride was varied. Hydrazonyl chlorides with an electron-neutral, electron-donating, or electron-withdrawing substituent at the *para* position of the aryl ring were reactive, delivering the desired products (**3r–3u**) in 30–61% yields. However, *para*-nitro-substituted hydrazonyl chloride failed to produce the desired products (see unsuccessful examples, **3ag**). Notably, an *ortho*-fluorophenyl-substituted hydrazonyl chloride afforded desired product **3v** in 41% yield. Moreover, a multisubstituted hydrazonyl chloride gave 2,3-diazo-BCHepe **3w** in 41% yield. In addition to phenyl hydrazonyl chlorides, other aryl hydrazonyl chlorides were compatible with the reaction conditions: specifically, 2,3-diazo-BCHepes with a naphthalene (**3x** and **3y**) or thiophene (**3z**) moiety were obtained in 42–54% yields. Finally, substituted aryl rings on the nitrogen atom of the hydrazonyl chloride were amenable to the reaction: we were able to obtain products bearing an electron-donating group methyl group (**3aa**) or methoxy group (**3aa** and **3ab**) or an electron-withdrawing nitro group (**3ac**).

According to the Mykhailiuk group's strategy for designing benzene bioisosteres, the similarity between the geometric properties of bioisosteres and the substituted benzene moieties that they are modeled after is of great significance.[19] To further explore the potential utility of 2,3-diazo-BCHepes as bioisosteres, we compared their geometric properties with those of



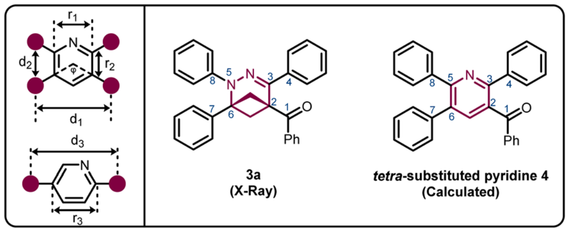
Scheme 2 Exploration of substrate scope. Reaction conditions: **1** (0.3 mmol), **2** (0.1 mmol), K_3PO_4 (0.15 mmol), $AgBF_4$ (0.1 mmol, 100 mol%), 3 Å molecular sieves (50 mg), DCM (1 mL), −10 °C, Ar, 1 h. For details, see the ESI†.

structurally related pyridines (Table 2). We compared the d, r and φ exit vectors obtained from X-ray data for **3a** with the corresponding vectors for tetrasubstituted pyridine **4** calculated by means of density functional theory. The vectors for **3a** were indeed very close to those for **4**, indicating that the 2,3-diazo-BCHepe mimicked the pyridine ring well.

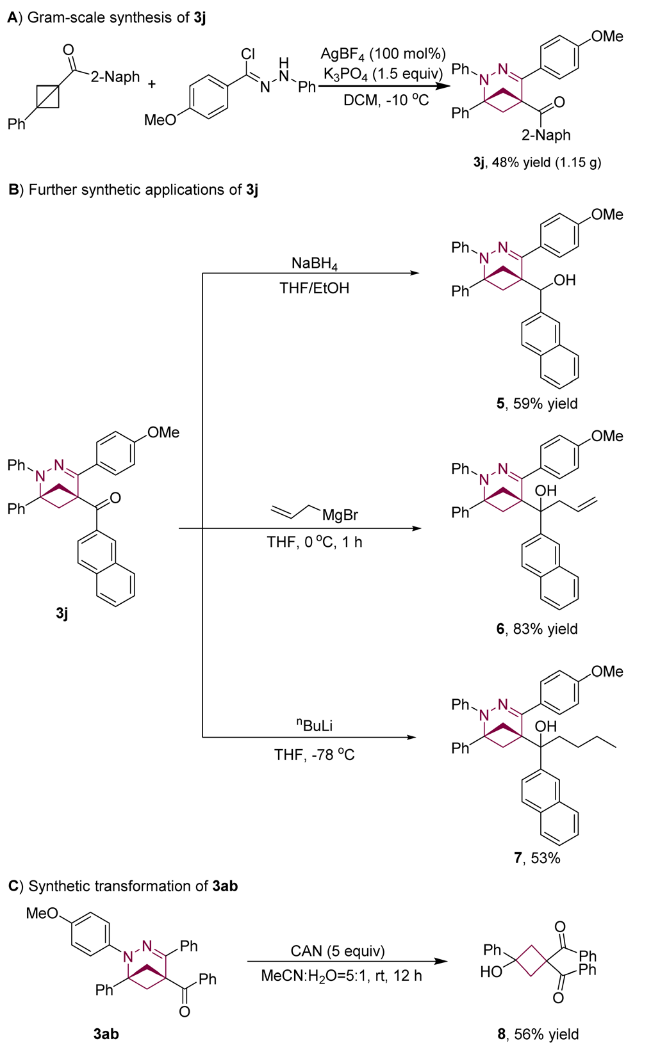
To demonstrate the utility of our cycloaddition method, we performed a 5 mmol-scale reaction to generate 2,3-diazo-BCHepe **3j** and observed only a slight decrease in the yield (Scheme 3A). Moreover, we carried out several transformations of **3j** (Scheme 3B). Specifically, selective reduction of the ketone of **3j** afforded alcohol **5** in 59% yield. Additionally, reaction of **3j** with allylMgBr or n-butyl lithium produced tertiary alcohol **6** or **7** in 83% and 53% yields, respectively. As shown in Scheme 3C, oxidation of **3ab** and subsequent hydrolysis generated alcohol **8** in 56% yield.

Having explored the reaction's substrate scope and the utility of the products for various transformations, we conducted

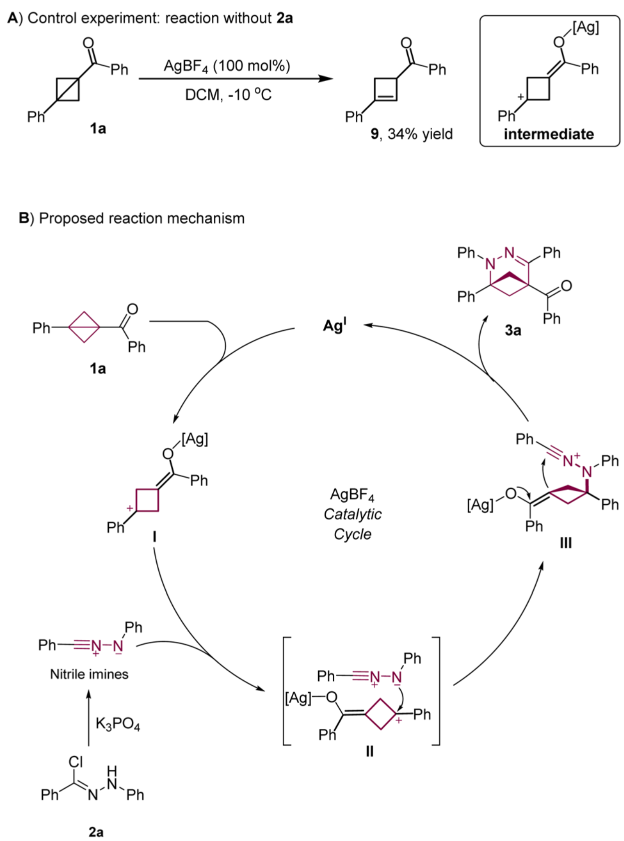
Table 2 2,3-Diazo-BCHepe **3a** as a promising bioisostere of tetra-substituted pyridine **4**



Parameters	X-ray of **3a** $X^{a,b}$ distance a, b, c, d: position of carbon	Values calculated for tetra-substituted pyridine
d_1	$4.74^{1.7}$ Å	$4.95^{1.7}$ Å
r_1	$2.12^{2.6}$ Å, $2.29^{3.5}$ Å	$2.44^{2.6}$ Å, $2.34^{3.5}$ Å
d_2	$3.06^{1.4}$ Å	$3.06^{1.4}$ Å
r_2	$1.52^{2.3}$ Å, $1.50^{5.6}$ Å	$1.41^{2.3}$ Å, $1.41^{5.6}$ Å
d_3	$5.63^{4.7}$ Å	$5.75^{4.7}$ Å
r_3	$2.65^{3.6}$ Å, $2.69^{2.5}$ Å	$2.78^{3.6}$ Å, $2.76^{2.5}$ Å
$\varphi^{(8,5,3,4)}$	114.0°	109.0°
$\varphi^{(7,6,2,1)}$	121.1°	115.1°



Scheme 3 Gram-scale synthesis of **3j** and synthetic transformations of **3j** and **3ab**.



Scheme 4 Control experiment and the proposed mechanism.

mechanistic studies to evaluate the validity of the proposed reaction pathway shown in Scheme 1D. When **1a** was subjected to the optimized conditions in the absence of **2a**, cyclobutene **9** was obtained in 34% yield (Scheme 4A), indicating that direct activation of **1a** by $AgBF_4$ to form a cationic intermediate was feasible. On the basis of this result and literature reports,[7–11] we propose that the reaction proceeds *via* the mechanism shown in Scheme 4B. Initially, deprotonation of hydrazonyl chloride **2a** and concomitant loss of HCl afford a 1,3-dipolar nitrile imine. Compound **1a** is activated by coordination between $AgBF_4$ and the carbonyl group to give cationic intermediate **I**, which is trapped by the nitrile imine to form δ-carbanionic intermediate **III** *via* intermediate **II**. Subsequent transannular cyclization of **III** delivers 2,3-diazo-BCHepe **3a** and regenerates the $AgBF_4$ catalyst.

Conclusions

In summary, we have established a method for $AgBF_4$-enabled formal [4π + 2σ] cycloaddition reactions between BCBs and nitrile imines derived from hydrazonyl chlorides. This method serves as a versatile platform for *de novo* construction of highly sought after 2,3-diazo-BCHepes, which have both sp^2- and sp^3-hybridized nitrogen atoms embedded in a BCHepe framework. This method was used for cycloadditions of a wide range of disubstituted BCBs with hydrazonyl chlorides as nitrile imine precursors, affording access to 2,3-diazo-BCHepes for the first time. The synthetic value of this method was demonstrated through a gram-scale reaction and synthetic transformations of two of the products. 2,3-Diazo-BCHepes have the potential to serve as bioisosteres of both pyridazines and pyridines. With their sp^3-hybridized nitrogen atoms, 2,3-diazo-BCHepes can be expected to be more water soluble, more metabolically stable, and less lipophilic than 3-aza-BCHepes. We anticipate that the method reported herein will find applications in the discovery of active pharmaceutical ingredients with nitrogen-containing bicyclic scaffolds.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for **3a** (CCDC 2394900) have been deposited at the Cambridge Crystallographic Data Centre.

Author contributions

J. Y. D. and D. X. conceived and directed the project. H. J. L. discovered and developed the reaction. H. J. L., X. C. Z., Q. J., Z. S. L. and F. L. performed the experiments and collected the data. All authors discussed and analyzed the data. J. Y. D. and D. X. wrote the manuscript with contribution from other authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (22171174 and 22401177), the Fundamental Research Funds for the Central Universities (GK202401008), the Innovation Capability Support Program of Shaanxi (2023-CX-TD-28), the Fundamental Science Research Project of Shaanxi for Chemistry, Biology (22JHZ002), the Young Talent Fund of Association for Science and Technology in Shaanxi, China (20240606), and the Key Research and Development Program of Shaanxi (2024SF2-GJHX32).

Notes and references

1 P. Bhutani, G. Joshi, N. Raja, N. Bachhav, P. K. Rajanna, H. Bhutani, A. T. Paul and R. Kumar, *J. Med. Chem.*, 2021, **64**, 2339–2381.

2 M. A. M. Subbaiah and N. A. Meanwell, *J. Med. Chem.*, 2021, **64**, 14046–14128.

3 (*a*) R. Gianatassio, J. M. Lopchuk, J. Wang, C. M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. C. Zhu and J. J. Zhu, *Science*, 2016, **351**, 241–246; (*b*) J. Kanazawa, K. Maeda and M. Uchiyama, *J. Am. Chem. Soc.*, 2017, **139**, 17791–17794; (*c*) X. H. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers and D. W. C. MacMillan, *Nature*, 2020, **580**, 220–226; (*d*) S. J. Yu, C. C. Jing, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2020, **59**, 3917–3921; (*e*) Y. Y. Yang, J. Tsien, J. M. E. Hughes, B. K. Peters, R. R. Merchant and T. Qin, *Nat. Chem.*, 2021, **13**, 950–955; (*f*) H. D. Pickford, J. Nugent, B. Owen, J. J. Mousseau and R. C. Smith, *J. Am. Chem. Soc.*, 2021, **143**, 9729–9736; (*g*) S. Shin, S. Lee, W. Choi, N. Kim and S. Hong, *Angew. Chem., Int. Ed.*, 2021, **60**, 7873–7879; (*h*) W. Z. Dong, E. Yen-Pon, L. B. Li, A. Bhattacharjee, A. Jolit and G. A. Molander, *Nat. Chem.*, 2022, **14**, 1068–1077; (*i*) W. C. Huang, S. Keess and G. A. Molander, *J. Am. Chem. Soc.*, 2022, **144**, 12961–12969; (*j*) S. Livesley, A. J. Sterling, C. M. Robertson, W. R. F. Goundry, J. A. Morris, F. Duarte and C. Aissa, *Angew. Chem., Int. Ed.*, 2022, **61**, e202111291; (*k*) R. Bychek and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2022, **61**, e202205103; (*l*) I. F. Yu, J. L. Manske, A. Diéguez-Vázquez, A. Misale, A. E. Pashenko, P. K. Mykhailiuk, S. V. Ryabukhin, D. M. Volochnyuk and J. F. Hartwig, *Nat. Chem.*, 2023, **15**, 685–693.

4 (*a*) A. Denisenko, P. Garbuz, S. V. Shishkina, N. M. Voloshchuk and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2020, **59**, 20515–20521; (*b*) R. Kleinmans, T. Pinkert, S. Dutta, T. O. Paulisch, H. Keum, G. Daniliuc and F. Glorius, *Nature*, 2022, **605**, 477–482; (*c*) R. Y. 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; (*d*) Y. J. Liang, R. Kleinmans, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2022, **144**, 20207–20213; (*e*) K. Dhake, K. J. Woelk, J. Becica, A. Un, S. E. Jenny and D. Leitch, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204719; (*f*) S. Agasti, F. Beltran, E. Pye, N. Kaltsoyannis, M. Crisenza and D. J. Procter, *Nat. Chem.*, 2023, **15**, 535–541; (*g*) 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; (*h*) Y. J. Liang, F. Paulus,

C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2023, **62**, e202305043; (*i*) D. S. Ni, S. Hu, X. Tan, Y. Yu, Z. H. Li and L. Deng, *Angew. Chem., Int. Ed.*, 2023, **62**, e202308606; (*j*) N. Radhoff, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2023, **62**, e202304771; (*k*) L. Tang, Y. J. Xiao, F. Wu, J. L. Zhou, T. T. Xu and J. J. Feng, *Angew. Chem., Int. Ed.*, 2023, **27**, e202310066; (*l*) Y. Liu, S. Lin, Y. Li, J. H. Xue, Q. J. Li and H. G. Wang, *ACS Catal.*, 2023, **13**, 5096–5103; (*m*) Q. Q. Fu, S. S. Cao, J. H. Wang, X. X. Lv, H. Wang, X. W. Zhao and Z. Y. Jiang, *J. Am. Chem. Soc.*, 2024, **146**, 8372–8380; (*n*) S. Dutta, D. Lee, K. Ozols, C. G. Daniliuc, R. Shintani and F. Glorius, *J. Am. Chem. Soc.*, 2024, **146**, 2789–2797; (*o*) J. L. Tyler, F. Schäfer, H. L. Shao, C. Stein, A. Wong, C. G. Daniliuc, K. N. Houk and F. Glorius, *J. Am. Chem. Soc.*, 2024, **146**, 16237–16247; (*p*) Q. Q. Hu, L. Y. Wang, X. H. Chen, Z. X. Geng, J. Chen and L. Zhou, *Angew. Chem., Int. Ed.*, 2024, e202405781; (*q*) J. J. Wang, L. Tang, Y. J. Xiao, W. B. Wu, G. Q. Wang and J. J. Feng, *Angew. Chem., Int. Ed.*, 2024, **63**, e202405222; (*r*) Y. H. Liu, Z. X. Wu, J. R. Shan, H. P. Yan, E. J. Hao and L. Shi, *Nat. Commun.*, 2024, **15**, 4374–4382.

5 J. Y. Dong, H. J. Liao and D. Xue, *Synthesis*, 2024, **56**, A–J.

6 D. Dibchak, M. Snisarenko, A. Mishuk, O. Shablykin, L. Bortnichuk, O. Klymenko-Ulianov, Y. Kheylik, I. V. Sadkova, H. S. Rzepa and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2023, **62**, e202304246.

7 (*a*) Y. J. Liang, R. Nematswerani, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2024, **63**, e202402730; (*b*) P. Bellotti and F. Glorius, *J. Am. Chem. Soc.*, 2023, **145**, 20716–20732.

8 X. Wang, R. Gao and X. Li, *J. Am. Chem. Soc.*, 2024, **146**, 21069–21077.

9 J. Zhang, J. Y. Su, H. L. Zheng, H. Li and W. P. Deng, *Angew. Chem., Int. Ed.*, 2024, e202318476.

10 X. G. Zhang, Z. Y. Zhou, J. X. Li, J. J. Chen and Q. L. Zhou, *J. Am. Chem. Soc.*, 2024, **146**, 27274–27281.

11 W. Wu, B. Xu, X. Yang, F. Wu, H. He, X. Zhang and J. Feng, *Nat. Commun.*, 2024, **15**, 8005.

12 K. K. Rajbongshi, B. Dam and B. K. Patel, Pyridines dihydropyridines and piperidines: an outline on synthesis and biological activities, in *N-Heterocycles: Synthesis and Biological Evaluation*, ed. K. L. Ameta, R. Kant, A. Penoni, A. Maspero and L. Scapinello, Springer Nature Singapore, 2022, pp. 1–49.

13 (*a*) Z. R. Lin, H. S. Ren, X. B. Lin, X. H. Yu and J. Zheng, *J. Am. Chem. Soc.*, 2024, **146**, 18565–18575; (*b*) Y. Liu, S. Lin, Z. Ding, Y. Li, Y. Tang, J. Xue, Q. Li, P. Li and H. Wang, *Chem*, 2024, **10**, 3699–3708.

14 (*a*) M. Baumann and I. R. Baxendale, *Beilstein J. Org. Chem.*, 2013, **9**, 2265–2319; (*b*) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; (*c*) S. De, A. Kumar S K, S. K. Shah, S. Kazi, N. Sarkar, S. Banerjee and S. Dey, *RSC Adv.*, 2022, **12**, 15385–15406.

15 (*a*) V. V. Levterov, Y. Panasyuk, V. O. Pivnytska and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2020, **59**, 7161–7167; (*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*) V. V. Levterov, Y. Panasiuk, K. Sahun, O. Stashkevych, V. Badlo, O. Shablykin, I. Sadkova, L. Bortnichuk, O. Klymenko-Ulianov, Y. Holota, L. Lachmann, P. Borysko, K. Horbatok, I. Bodenchuk, Y. Bas, D. Dudenko and P. K. Mykhailiuk, *Nat. Commun.*, 2023, **14**, 5608–5607.

16 (*a*) C. G. Wermuth, *Med. Chem. Commun.*, 2011, **2**, 935–941; (*b*) A. M. Subbaiah and N. A. Meanwell, *J. Med. Chem.*, 2021, **64**, 14046–14128; (*c*) N. A. Meanwell and A. Heterocycl, *Chem*, 2017, **123**, 245–361.

17 J. Zhang, J. Su, H. Zheng, H. Li and W. Deng, *ACS Catal.*, 2024, **14**, 17837–17849.

18 For selected examples of cycloaddition reactions of nitrile imines, see:(*a*) L. K. Garve, M. Petzold, P. G. Jones and D. B. Werz, *Org. Lett.*, 2016, **18**, 564–567; (*b*) S. M. Gomha, T. A. Farghaly, A. R. Sayed, M. M. Abdalla and J. Heterocycl, *Chem*, 2016, **53**, 1505–1511; (*c*) H. Gazzeh, S. Boudriga, M. Askri, A. Khatyr, M. Knorr, C. Strohmann, C. Golz, Y. Rousselin and M. M. Kubicki, *RSC Adv.*, 2016, **6**, 49868–49875; (*d*) A. Alizadeh and L. Moafi, *Chim. Acta.*, 2016, **99**, 457–461; (*e*) Y. Miura and N. Yoshioka, *Chem. Phys. Lett.*, 2015, **626**, 11–14; (*f*) M. Yıldırım and Y. Dürüst, *Tetrahedron*, 2011, **67**, 3209–3215; (*g*) A. L. Gerten, M. C. Slade, K. M. Pugh and L. M. Stanley, *Org. Biomol. Chem.*, 2013, **11**, 7834–7837; (*h*) C. X. Guo, W. Z. Zhang, N. Zhang and X. B. Lu, *J. Org. Chem.*, 2017, **82**, 7637–7642; (*i*) M. P. Sibi, L. M. Stanley and C. P. Jasperse, *J. Am. Chem. Soc.*, 2005, **127**, 8276–8277; (*j*) A. Singh, A. L. Loomer and G. P. Roth, *Org. Lett.*, 2012, **14**, 5266–5269; (*k*) G. Wang, X. H. Liu, T. Y. Huang, Y. L. Kuang, L. L. Lin and X. M. Feng, *Org. Lett.*, 2013, **15**, 76–79.

19 P. K. Mykhailiuk, *Org. Biomol. Chem.*, 2019, **17**, 2839–2849.