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OF CHEMISTRY

EDGE ARTICLE

View Article Online
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Cite this: *Chem. Sci.*, 2024, **15**, 19488

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

Received 19th September 2024
Accepted 31st October 2024

DOI: 10.1039/d4sc06334a

rsc.li/chemical-science

Enantioselective dearomative formal (3+3) cycloadditions of bicyclobutanes with aromatic azomethine imines: access to fused 2,3-diazabicyclo[3.1.1]heptanes†

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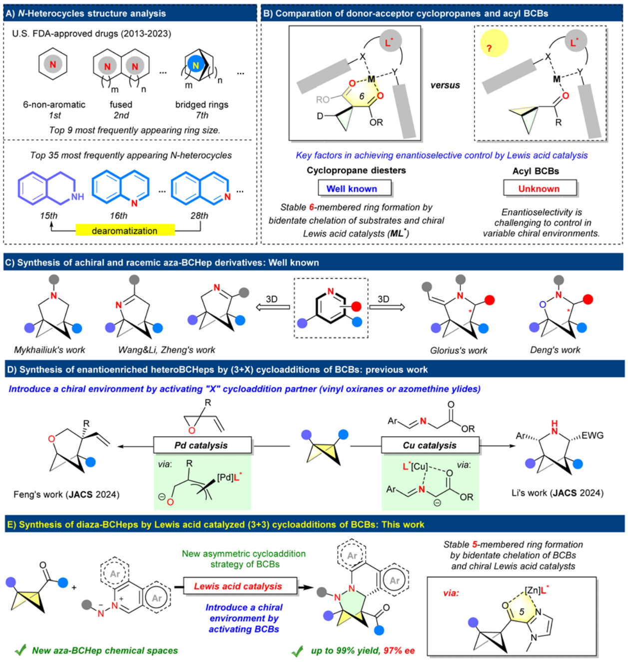
Although cycloadditions of bicyclobutanes (BCBs) have emerged as a reliable approach for producing bicyclo[*n*.1.1]alkanes such as azabicyclo[3.1.1]heptanes (aza-BCHeps), serving as saturated bioisosteres of arenes, the catalytic asymmetric variant remains underdeveloped and presents challenges. Herein, we developed several Lewis acid-catalyzed systems for the challenging dearomative (3+3) cycloaddition of BCBs and aromatic azomethine imines. This resulted in fused 2,3-diazabicyclo[3.1.1]heptanes, introducing a novel chemical space for the caged hydrocarbons. Moreover, an asymmetric Lewis acid catalysis strategy was devised for the (3+3) cycloadditions of BCBs and *N*-iminoisoquinolinium ylides, forming chiral diaza-BCHeps with up to 99% yield and 97% ee. This study showcases a unique instance of asymmetric (3+3) cycloaddition facilitated by the creation of a chiral environment *via* the activation of BCBs.

Introduction

Nitrogen heterocycles are ubiquitously present in nature and represent crucial structural elements in pharmaceuticals.[1] Njardarson's analysis of FDA-approved small-molecule drugs from 2013 to 2023 shows that 82% of the newly approved small-molecule drugs in this period contain a nitrogen heterocycle. Six-membered non-aromatic N-heterocycles are the most prevalent, followed by fused N-heterocycles, in the approved new drugs.[1b] Besides fused N-heterocycles, bridged bicyclic nitrogen heterocycles like diazabicyclo[3.2.1]octane and tropane derivatives belong to the top 35 most frequently appearing N-heterocyclic compounds.[1] Therefore, developing atom-economical and particularly catalytic asymmetric strategies to construct the aforementioned N-heterocyclic scaffolds is crucial for diverse applications, including drug discovery (Scheme 1A).

Aromatic azomethine imines are versatile and easily synthesized compounds employed as substrates in dipolar (3+3)



Scheme 1 Outline of this work. (A) Analysis of *N*-heterocycles structures. (B) Comparison of donor–acceptor cyclopropanes and acyl BCBs. (C) Synthesis of achiral and racemic aza-BCHep derivatives. (D) Synthesis of enantioenriched heteroBCHeps. (E) Synthesis of enantioenriched diaza-BCHeps.

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† Electronic supplementary information (ESI) available. CCDC 2375376 and 2375377. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d4sc06334a**

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cycloadditions to produce valuable hydroisoquinoline and related six-membered N-heterocycle frameworks.[2] These structures serve as core components in numerous natural products and pharmaceuticals.[3] In 2008, the Charette group pioneered the Lewis acid-catalyzed non-asymmetric (3+3) cycloadditions of 1,1-cyclopropane diesters with *N*-iminoquinolinium and *N*-iminoisoquinolinium ylides.[4a] Tang's group later successfully developed the asymmetric version of the aforementioned (3+3) reaction.[4b] A crucial element contributing to their success was the utilization of a carefully designed trisoxazoline (TOX)-nickel catalyst to create a stable chiral environment by coordinating with two chelating, electron-withdrawing groups on cyclopropanes (Scheme 1B).[5] Until now, there have been five literature reports on asymmetric (3+3) cycloadditions with aromatic azomethine imines.[4b,6] However, these reports are mainly focused on constructing fused six-membered N-heterocycles. Cycloaddition reactions using these versatile 1,3-dipoles to form bridged bicyclic nitrogen heterocycles, especially enantioenriched bridged bicyclic cycloadducts, have not been reported yet.

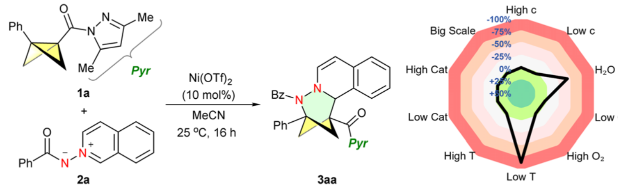
Recently, bicyclo[3.1.1]heptanes (BCHeps) and aza-BCHeps have attracted increasing attention from chemists and medicinal chemists for serving as bioisosteres of *meta*-substituted benzenes and pyridines, respectively.[7] Significantly, Mykhailiuk's studies show that heteroatom (N- or O-) incorporated analogs of caged hydrocarbons (bicyclo[2.1.1]hexanes (BCHs)[8] and BCHeps) often demonstrate enhanced water solubility, improved metabolic stability, and reduced lipophilicity.[7d,9] In this context, the (3+3) cycloadditions of bicyclobutanes (BCBs)[10] have emerged as a vital synthetic platform for building BCHep and hetero-BCHep skeletons, owing to the pioneering scientific contributions of Molander,[11] Waser,[12] Li,[13] Wang,[14] Zheng,[15] Deng,[16] Glorius[17] and our group.[18] Several strategies, including photocycloaddition,[11,12] pyridine-boryl radical catalysis,[13,14] Ti-catalyzed radical-relay process,[15] Lewis acid catalysis,[16,18] and silver-promoted tandem (3+3)/(3+2)/retro-(3+2) cycloaddition,[17] have been developed for efficient (3+3) cycloadditions of BCBs (Scheme 1C). Despite significant progress, the access to enantioenriched (hetero)BCHeps through catalytic asymmetric cycloadditions of BCBs remains limited and presents a persistent challenge. Very recently, our group developed the first asymmetric (3+3) cycloadditions of BCBs with vinyl oxiranes using palladium catalysis.[19] The Li group pioneered the synthesis of enantioenriched 3-aza-BCHeps through copper-catalyzed cycloadditions of BCBs with azomethine ylides.[20] The strategies employed by both groups focus exclusively on creating a stable chiral environment by activating the "*X*" component in the (3 + *X*) reaction of BCBs (Scheme 1D).

Based on our interest in BCB chemistry,[21] we envisioned that the asymmetric (3+3) cycloaddition of BCBs with aromatic azomethine imines might serve as a new approach to enantiomerically enriched fused 2,3-diazabicyclo[3.1.1]heptanes (*N*,*N*-BCHeps) through a chiral Lewis acid catalyst *via* activating the BCBs (Scheme 1E).[22] However, this hypothesis encountered significant challenges. (a) For instance, although Deng's group has successfully established the non-asymmetric (3+3) cycloadditions of BCBs with nitrones,[16] the analogous reaction with aromatic azomethine imines remains unexplored because an energy barrier exists in the cycloaddition process, requiring dearomatization with aromatic azomethine imines.[23] (b) Achieving enantioselective control in the cycloaddition of BCBs with a single electron-withdrawing group, as opposed to donor–acceptor cyclopropanes containing two chelating, electron-withdrawing groups,[4] poses greater challenges in establishing chiral environments by forming a chiral catalyst–substrate complex with varying conformations. (c) Another key challenge in the Lewis acid catalyzed asymmetric (3+3) version is identifying optimal chiral catalysts that can overcome the strong racemic background reaction, thereby enabling the simultaneous construction of two congested quaternary centers and a chiral aza-trisubstituted carbon center with excellent ee values.[24]

Results and discussion

Our study commences by exploring the non-asymmetric cycloadditions of Glorius's BCB **1a** (ref. 25) with isoquinoline azomethine imine **2a**. After screening of various reaction parameters, we found that the desired (3+3) reaction occurred with $Ni(OTf)_2$ as the catalyst in acetonitrile at room temperature (conditions A); the *N*,*N*-BCHep **3aa** was obtained in almost quantitative yield (Table 1, entry 1). Control experiments revealed that the solvent had substantial effect on the yield but no improvement over acetonitrile was seen (entries 2–6). Although other metal Lewis acids can produce the desired product with reduced yield (entries 7–10), main-group Lewis acids like BF_3 did not yield **3aa** (entry 11). Control experiments demonstrated that the reaction did not occur at 80 °C without

Table 1 Optimization of the reaction conditions[a]



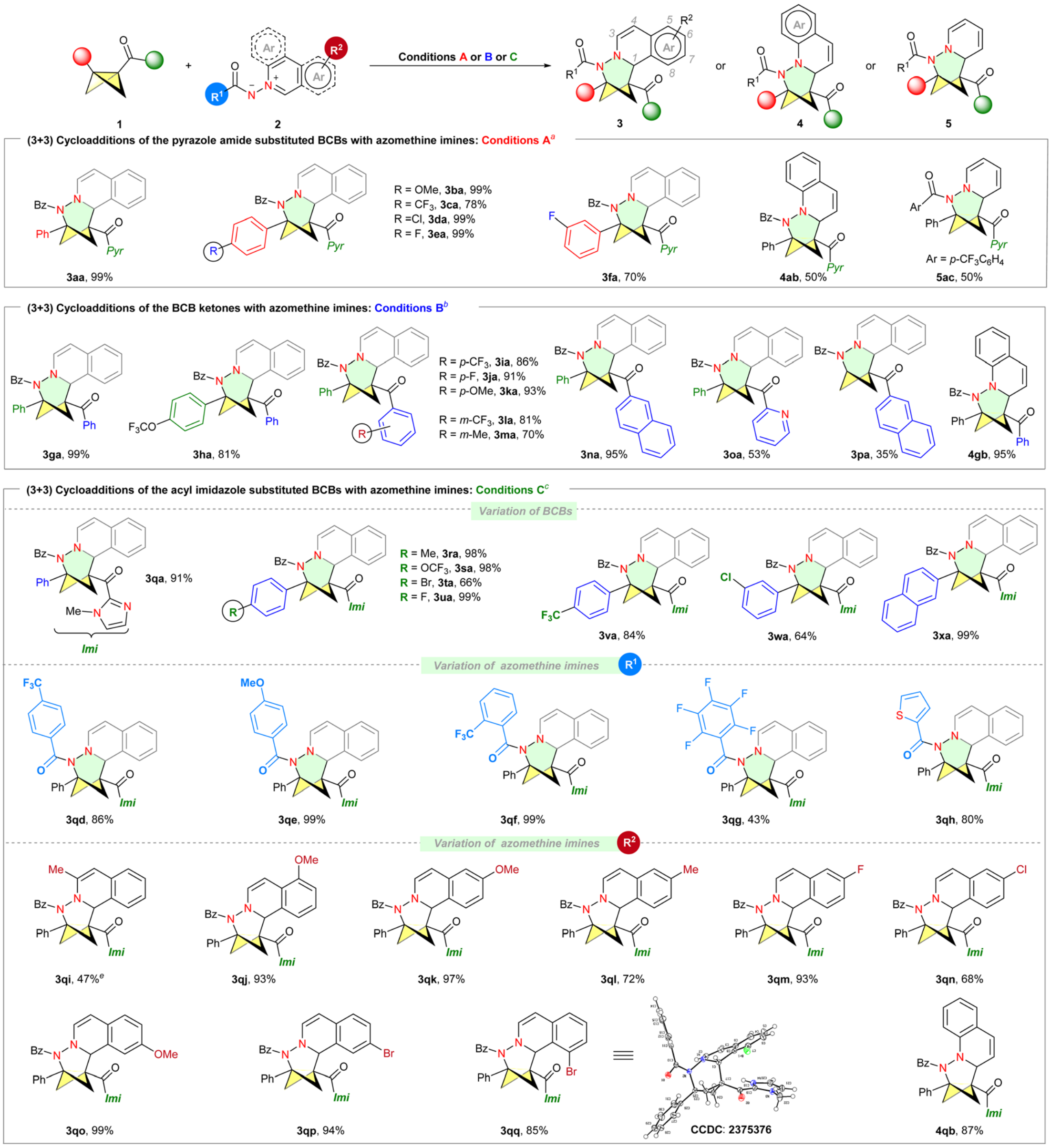
Entry	Variation	Yield[b] (%)
1	None	>99
2	Toluene instead of MeCN	25
3	EtOAc instead of MeCN	23
4	1,4-Dioxane instead of MeCN	22
5	DCE instead of MeCN	63
6	CH_2Cl_2 instead of MeCN	35
7[c]	$Sc(OTf)_3$ instead of $Ni(OTf)_2$	25
8[c]	$Fe(OTf)_2$ instead of $Ni(OTf)_2$	30
9[c]	$Zn(OTf)_2$ instead of $Ni(OTf)_2$	20
10[c]	$Co(OTf)_2$ instead of $Ni(OTf)_2$	33
11[c]	$BF_3 \cdot Et_2O$ instead of $Ni(OTf)_2$	0
12[d]	Without $Ni(OTf)_2$	0

[a] Conditions A: **1a** (1.0 equiv.), **2a** (1.2 equiv.), $Ni(OTf)_2$ (10 mol%) in CH_3CN (0.05 M) at room temperature for 16 h. [b] NMR yield with CH_2Br_2 as an internal standard. [c] Performed in CH_2Cl_2. [d] Run at 80 °C.

the presence of the Lewis acid catalyst (entry 12). Condition-based sensitivity screening was performed,[26] revealing that low temperature inhibited the reaction. The reaction showed moderate sensitivity to moisture, with concentration, scale, catalyst loading, high temperature, and O_2 level having no significant impact on the reaction (Table 1).

With the optimized conditions in hand, we investigated the BCB scope (Scheme 2, top). Different substituents at the phenyl moiety, such as the methoxy group, halides and the CF_3 group, were well tolerated (**3aa–fa**, 70–99% yield). As a trend, electron-rich **1b** afforded relatively better results than electron deficient **1c** and **1f.** In addition to isoquinoline azomethine imine **2a**, both quinoline azomethine imine **2b** and *N*-aminopyridinium ylide **2c** are compatible with conditions A, yielding the corresponding products smoothly (**4ab** and **5ac**). During our investigation of BCB ketones under conditions A, we discovered that a (3+3) cycloadduct **3ga** was obtained with a 9% NMR yield. To our delight, excellent yield (99% yield of **3ga**) was achieved in CH_3CN at 50 °C using $Sc(OTf)_3$ as the catalyst (conditions B, see Table S2 in the ESI†).

The substrate scope of BCBs containing benzoyl groups was subsequently explored under conditions B (Scheme 2, middle). The steric and electronic properties of *para*-substituents on the phenyl group of BCBs had minor impact on the yields (**3ga–ka**, 81–99% yield). BCBs with substituents at the *meta*-position of the phenyl group were well tolerated (**3la–ma**). Besides phenyl



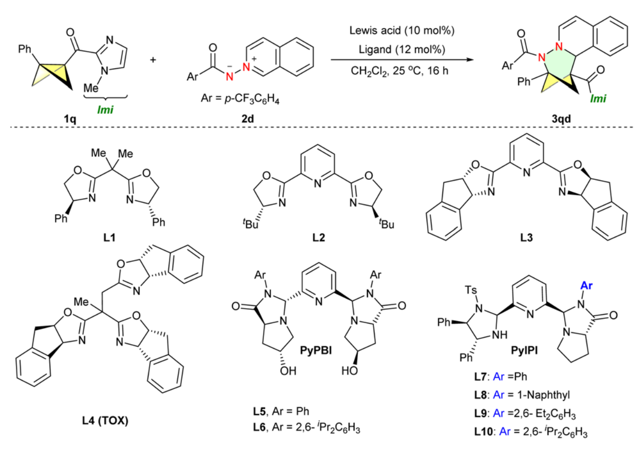
Scheme 2 Substrate scope investigation.[a–d] [a]Conditions A: **1a–f** (0.2 mmol), **2a–c** (0.24 mmol), $Ni(OTf)_2$ (10 mol%) in CH_3CN (4 mL) at room temperature for 16 h. [b]Conditions B: **1g–p** (0.2 mmol), **2a–b** (0.24 mmol), $Sc(OTf)_3$ (10 mol%) in CH_3CN (4 mL) at 50 °C for 16 h. [c]Conditions C: **1q–x** (0.2 mmol), **2a–b** (or **2d–q**) (0.24 mmol), $Fe(OTf)_2$ (10 mol%) in CH_2Cl_2 (4 mL) at room temperature for 12 h. [d]Isolated yield. [e]Run at 40 °C.

ketones, naphthyl (**3na**) and heteroaryl ketones (**3oa**) were also suitable for this (3+3) reaction, yielding the corresponding *N*,*N*-BCHeps in moderate to excellent yield. The (3+3) cycloaddition of monosubstituted BCB **1p** with **2a** produced the desired product **3pa**, although the yield was low. Quinoline azomethine imine **2b** was successfully employed in the reaction, resulting in the formation of **4gb** with a yield of 95%. Additionally, we further investigated the scope of substrates containing BCBs with an acyl imidazole group by employing the Fe(OTf)$_2$ catalyst (conditions C, Scheme 2, bottom). BCBs **1q–1w** featuring various substituted phenyl rings (*p*-Me, *p*-OCF$_3$, *p*-Br, *p*-F, *p*-CF$_3$, *m*-Cl) furnished the corresponding cycloadducts (**3qa–wa**) in very high yields (64–99%). Naphthyl-substituted BCB **1x** also reacted smoothly. Of note, in contrast to Glorius's observation that a BCB with a strong electron-withdrawing trifluoromethyl group on the phenyl ring resulted in a poor yield of the product,[25] our study indicates that the electronic properties of substituents on the phenyl group had minimal influence on the yields, suggesting that a benzylic carbocation intermediate may not be involved in our catalytic system.

We then evaluated the compatibility of aromatic azomethine imines **2** bearing various benzoyl protecting groups. The benzoyl protecting group of *N*-iminoisoquinolinium ylides exhibited good tolerance towards both electron-withdrawing and electron-donating substituents (R^1), with the exception of **2g**. Azomethine imine **2h** with a thiophene-2-carbonyl group was well tolerated. Unfortunately, the (3+3) reactions are not compatible with *N*-tosyliminoisoquinolinium ylides. Furthermore, the current (3+3) protocol is amenable to a series of azomethine imines **2** bearing different R^2 substituents, including alkyl (**3qi** and **3ql**), OMe (**3qj–qk**, **3qo**) and halogen (**3qm–qn** and **3qp–qq**)[27] groups at the C3 and C5–C8 positions of isoquinoline moieties, and led to the corresponding polysubstituted *N*,*N*-BCHeps in good yield (47–99%). The azomethine imine **2b** was successfully employed in the reaction, resulting in the formation of **4qb** with a yield of 87%.

After establishing the non-asymmetric (3+3) cycloadditions of BCBs with aromatic azomethine imines, we proceeded to develop the asymmetric (3+3) version. BCB **1q** containing bidentate chelating groups and **2d** with the 4-(trifluoromethyl) benzoyl-protecting group were selected as the model substrates. In the presence of Co(OTf)$_2$ and **L1**, a 6% ee was detected (Table 2, entry 1), prompting us to explore different oxazoline-based chiral ligands for the cycloaddition reaction (entries 2–4). The use of **L2** led to an enhancement in enantiomeric excess (22% ee, entry 2). Nevertheless, when transitioning to alternative ligands such as **L3–L4**, the outcomes were unsatisfactory. The TOX ligand **L4** provided excellent enantioselective control in Tang's (3+3) cycloadditions of cyclopropanes,[4b] but it resulted in racemic **3qd** in the current cycloadditions of BCBs. Recently, Xie and Guo developed two novel tridentate nitrogen ligands, PyBPI and PyIPI, which exhibited effective stereoselective control in Lewis acid catalysis.[28] Thus these ligands were synthesized and evaluated (**L5–L10**). While PyBPI **L6** showed poor results in the enantioselective dearomative (3+3) reaction, the PyIPI ligand **L10** produced **3qd** with a promising ee value (entry 6 *versus* entry 10). After systematically screening various reaction parameters (entries 11–17), we successfully conducted the enantioselective (3+3) reaction using **L10**, resulting in the synthesis of the target compound (*R*)-**3qd** with a 78% NMR yield and 92% ee when Zn(OTf)$_2$ was utilized in place of Co(OTf)$_2$.

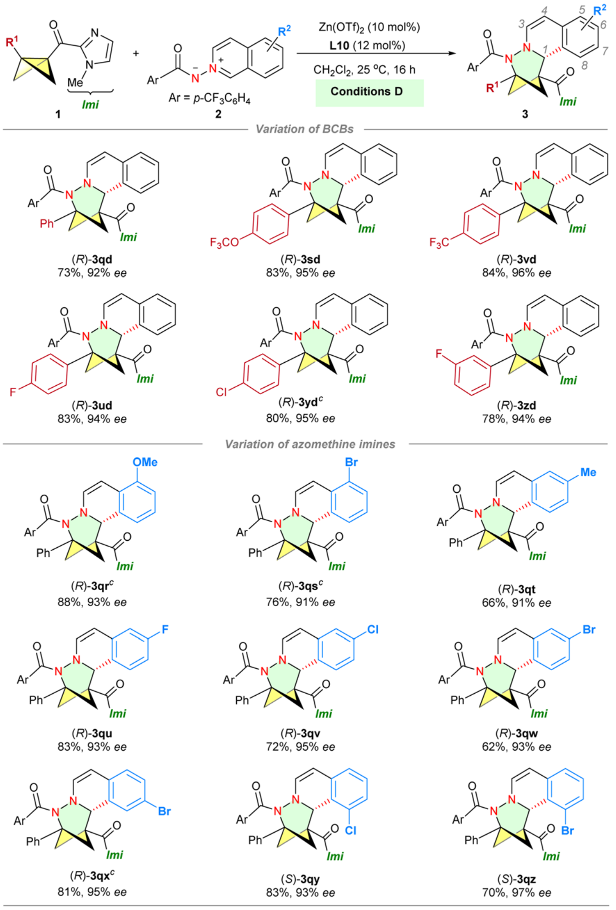
Table 2 Optimization of the asymmetric (3+3) reaction conditions[a]



Entry	Lewis acid	Ligand	Yield[b] (%)	ee[c]
1	Co(OTf)$_2$	**L1**	79	6
2	Co(OTf)$_2$	**L2**	68	22
3	Co(OTf)$_2$	**L3**	18	17
4	Co(OTf)$_2$	**L4**	87	1
5	Co(OTf)$_2$	**L5**	73	0
6	Co(OTf)$_2$	**L6**	78	16
7	Co(OTf)$_2$	**L7**	81	13
8	Co(OTf)$_2$	**L8**	77	34
9	Co(OTf)$_2$	**L9**	85	64
10	Co(OTf)$_2$	**L10**	85	70
11	Fe(OTf)$_2$	**L10**	65	88
12	Ni(OTf)$_2$	**L10**	83	28
13	Sc(OTf)$_3$	**L10**	63	0
14	**Zn(OTf)$_2$**	**L10**	**78**	**92**
15[d]	Zn(OTf)$_2$	**L10**	99	88
16[e]	Zn(OTf)$_2$	**L10**	29	86
17[f]	Zn(OTf)$_2$	**L10**	90	51

[a] **1q** (0.1 mmol), **2d** (0.12 mmol), Lewis acid (10 mol%) and ligand (12 mol%) in CH$_2$Cl$_2$ (2 mL) at room temperature for 16 h. [b] NMR yield with CH$_2$Br$_2$ as an internal standard. [c] Based on chiral HPLC analysis. [d] Performed in 1,4-dioxane. [e] Run at 0 °C. [f] Run at 40 °C.

With the identified reaction conditions D in hand, we examined the scope of this enantioselective (3+3) reaction (Scheme 3). Initially, the variation in BCB was evaluated. BCBs bearing trifluoromethyloxy (**1s**) and trifluoromethyl (**1v**) substituents on the aryl ring, which are popular in pharmaceuticals and agrochemicals, were found to be compatible in the reaction, resulting in the desired product with 95–96% ee ((*R*)-**3sd–vd**). The presence of halogen substituents at the *para*- or *meta*-position of the benzene ring did not negatively impact the reaction outcome ((*R*)-**3ud**, **3yd** and **3zd**). The *N*-iminoisoquinolinium ylides **2** bearing methoxy, halogen (F, Cl, Br), or methyl groups at the C5–C8 positions of isoquinoline moieties yielded the desired products **3qr–3qz** with high efficiency and outstanding enantioselectivity.[27] Notably, in some instances, poor yields (<30% NMR yield) of the cycloadducts (**3qs** and **3qx**)

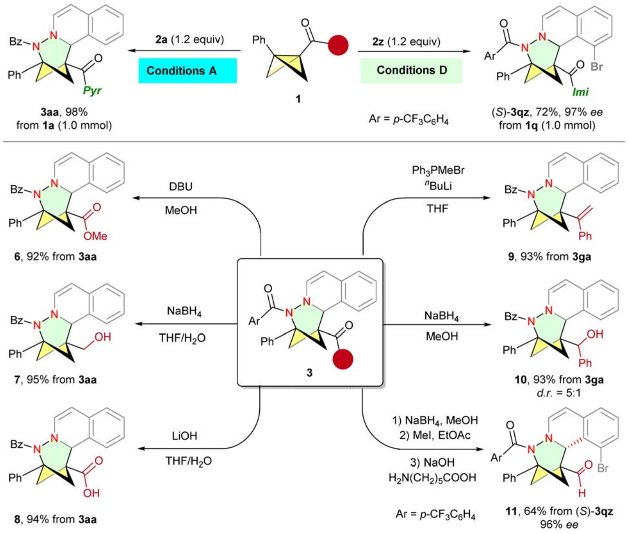


Scheme 3 Enantioselective (3+3) cycloadditions of BCBs with azomethine imines.[a,b] [a]Conditions D: **1** (0.2 mmol), **2** (0.24 mmol), $Zn(OTf)_2$ (10 mol%) and **L10** (12 mol%) in CH_2Cl_2 (4 mL) at room temperature for 16 h. [b]Isolated yield. [c]Performed in CH_2Cl_2/1,4-dioxane (10/1, v/v) instead of CH_2Cl_2 for better solubility.

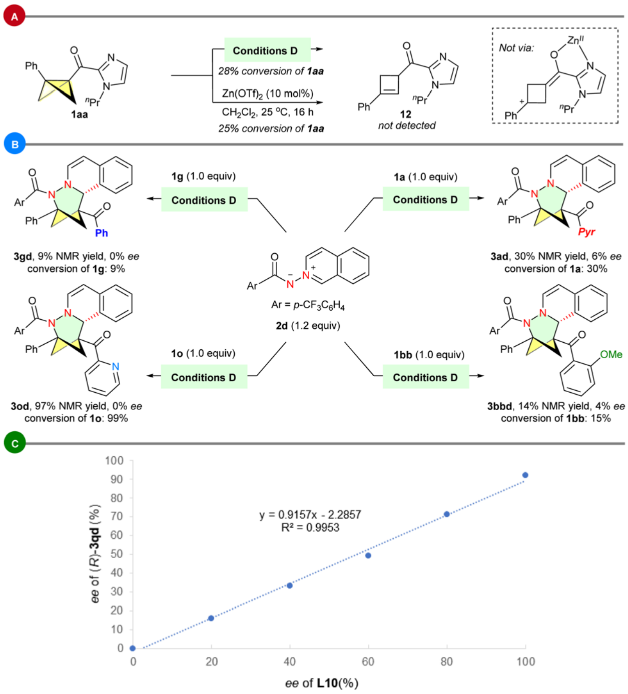
under conditions D may be attributed to the low solubility of azomethine imines in CH_2Cl_2. However, high yields (76–81% yield) and stereoselectivity (91–95% ee) were successfully attained in CH_2Cl_2/1,4-dioxane (10/1).

To showcase the synthetic utility of these cycloadducts, we initially performed scale-up experiments. Both non-asymmetric and asymmetric systems were successfully scaled up to a 1.0 mmol scale using standard conditions, while preserving efficiency and selectivity. The pyrazole amide group of **3aa** can be easily converted into various valuable functional groups, such as ester **6** and carboxylic acid **8**, smoothly. Primary alcohol **7** and secondary alcohol **10** can be obtained with excellent yield through the $NaBH_4$ reduction of **3aa** and **3ga**, respectively. The reaction of **3ga** with the Wittig reagent afforded **9** in 93% yield. Finally, cleavage of the imidazole moiety gave rise to the desired aldehyde **11** in 64% yield and 96% ee (Scheme 4).

Control experiments were conducted to gain insight into this asymmetric transformation. When subjecting BCB **1aa** to conditions D with or without ligand **L10**, we did not observe the rapid decomposition of **1aa**, nor did we observe the corresponding side product cyclobutene **12** (Scheme 5A). This result suggests that the benzylic carbocation enolate intermediate may not be involved in the reaction, aligning with the electronic effect observed in BCB substrates. BCBs containing electron-withdrawing groups (*e.g.*, *p*- and *m*-CF_3) on the phenyl ring also yield good results. While BCB **1g** and **1o** generated the corresponding products **3gd** and **3od** with 0% ee, the (3+3) reactions of **1a** or **1bb**, which contain a bidentate chelating group, with **2d** produced **3ad** with 6% ee and **3bbd** with 4% ee,



Scheme 4 Scale-up and derivatizations.



Scheme 5 Control experiments and non-linear effect study. (A) Subjecting BCB to condition D, with or without the ligand. (B) (3+3) cycloadditions of BCBs that contain a bidentate chelating group. (C) Non-linear effect study.

respectively. The results indicate that forming a stable chiral environment through the chelation of a bidentate acyl imidazole group on BCB with a Zn-Lewis acid catalyst is essential for achieving enantioselective control (Scheme 5B). Furthermore, the correlation between the enantiomeric purities of ligands **L10** and (*R*)-**3qd** was assessed. The study uncovered a linear correlation, indicating that the active catalyst/ligand is monomeric in nature (Scheme 5C).[28e]

Conclusions

In conclusion, we have established a dearomative (3+3) cycloaddition for synthesizing novel diaza-BCHep derivatives from BCBs and aromatic azomethine imines. The good to high overall yields and excellent enantioselectivities are governed by the catalysts and reaction conditions. This straightforward approach operates under mild conditions and exhibits good functional group tolerance. The synthetic utility and practicality were also highlighted by the scale-up experiment and diverse synthetic transformations of the cycloadducts. Notably, this study presents a rare example of Lewis acid-catalyzed asymmetric (3+3) cycloadditions of BCBs, paving the way for the enantioselective synthesis of other valuable bicyclo[*n*.1.1] alkanes through chiral Lewis acid catalysis.

Data availability

The data supporting this article have been included as part of the ESI.† All detailed procedures, characterization data and NMR spectra are available in the ESI.†

Author contributions

X.-C. Y. and F. W. performed all of the experiments and analysed their results. W.-B. W., X. Z. and J.-J. F. wrote the manuscript. J.-J. F. conceived the catalytic system and directed the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the Fundamental Research Funds for the Central Universities, National Natural Science Foundation of China (22471068), Natural Science Foundation of Hunan Province (2024JJ6126) and China Postdoctoral Science Foundation (2024M750865) for financial support. The ^{1}H, ^{13}C NMR spectroscopy, HRMS (ESI) and single crystal X-ray diffraction were performed at the Analytical Instrumentation Center of Hunan University.

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