



Chiral Brønsted acid-catalyzed enantioselective synthesis of 3-azabicyclo[3.1.1]heptanes

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Abstract

Although significant progress has been made in constructing three-dimensional, C(sp³)-rich bioisosteres for pyridines, the development of catalytic enantioselective approaches to access chiral nitrogen-containing bridged scaffolds remains limited and challenging. Herein, we report a chiral Brønsted acid-catalyzed enantioselective reduction of imines harnessing Hantzsch ester as the hydrogen source under mild conditions, delivering structurally diverse chiral 3-azabicyclo[3.1.1]heptanes (27 examples) in generally good yields with high enantiocontrol (up to 93% yield, 97% ee). The reaction can be scaled up to 2 mmol with full preservation of the excellent outcomes. These saturated heterocycles serve as versatile precursors, as demonstrated by conversion to bicyclo[2.1.1]hexanes via a facile nitrogen-deletion strategy with complete retention of enantiopurity. Notably, the enantioenriched 3-aza-BCHeP can serve as a secondary amine organocatalyst, promoting the asymmetric Friedel–Crafts alkylation of indole with an α,β -unsaturated aldehyde in excellent yield and promising stereoinduction. This work establishes a practical route to access enantiopure saturated heterocyclic scaffolds, offering new three-dimensional candidates as potential pyridine isosteres in drug discovery and asymmetric catalysis.

Keywords: Chiral Brønsted acid, asymmetric transfer hydrogenation, 3-azabicyclo[3.1.1]heptane, bicyclo[2.1.1]hexane

1. Introduction

Nitrogen-containing heterocycles, especially pyridine and its derivatives, are among the most essential building blocks in medicinal chemistry and are found in many approved drugs^[1,2]. According to the “Escape from Flatland” concept proposed by Lovering and coworkers^[3,4], increasing molecular saturation can improve its physical properties, make it more selective for its target, and increase its chances of success in clinical trials^[5,6]. Over the past decade, bridged bicyclic scaffolds, particularly bicyclo[1.1.1]pentanes, bicyclo[2.1.1]hexanes (BCHs), and bicyclo[3.1.1]heptanes (BCHePs), have emerged as privileged three-dimensional, C(sp³)-enriched bioisosteres for planar aromatic rings^[7–10]. Nevertheless, the rational design of three-dimensional bioisosteres that can effectively mimic the properties of pyridine remains a significant challenge. Building on the success of using BCHePs to replace benzene rings^[11], Mykhailiuk and coworkers proposed aza-BCHeP as a promising bioisostere for pyridine (Figure 1a)^[12]. Supporting this hypothesis, several bioactive molecules incorporating the aza-BCHeP scaffold have exhibited potent biological activity or superior physicochemical profiles (Figure 1b)^[13]. Consequently, the development and application of aza-BCHePs as 3D bioisosteres have gained substantial momentum, underscoring their growing importance in drug discovery^[14–16].

Intramolecular cycloadditions have long served as a primary route for synthesizing aza-BCHePs^[17–21]. Among the earliest examples, Schieweck *et al.* reported a thermal [2+2] cycloaddition of *N*-acryloylacrylimides to afford 3-aza-BCHepdiones^[19]. For intermolecular variants, several strategies have been developed, including radical pathways^[22–26], Lewis acid-mediated substrate activation^[27–35], and transition-metal-catalyzed transformations for constructing polysubstituted aza-BCHePs^[36], with additional complementary approaches also reported^[37,38]. Beyond cycloadditions, cyclization strategies represent another major synthetic avenue to aza-BCHePs^[12,39–44].



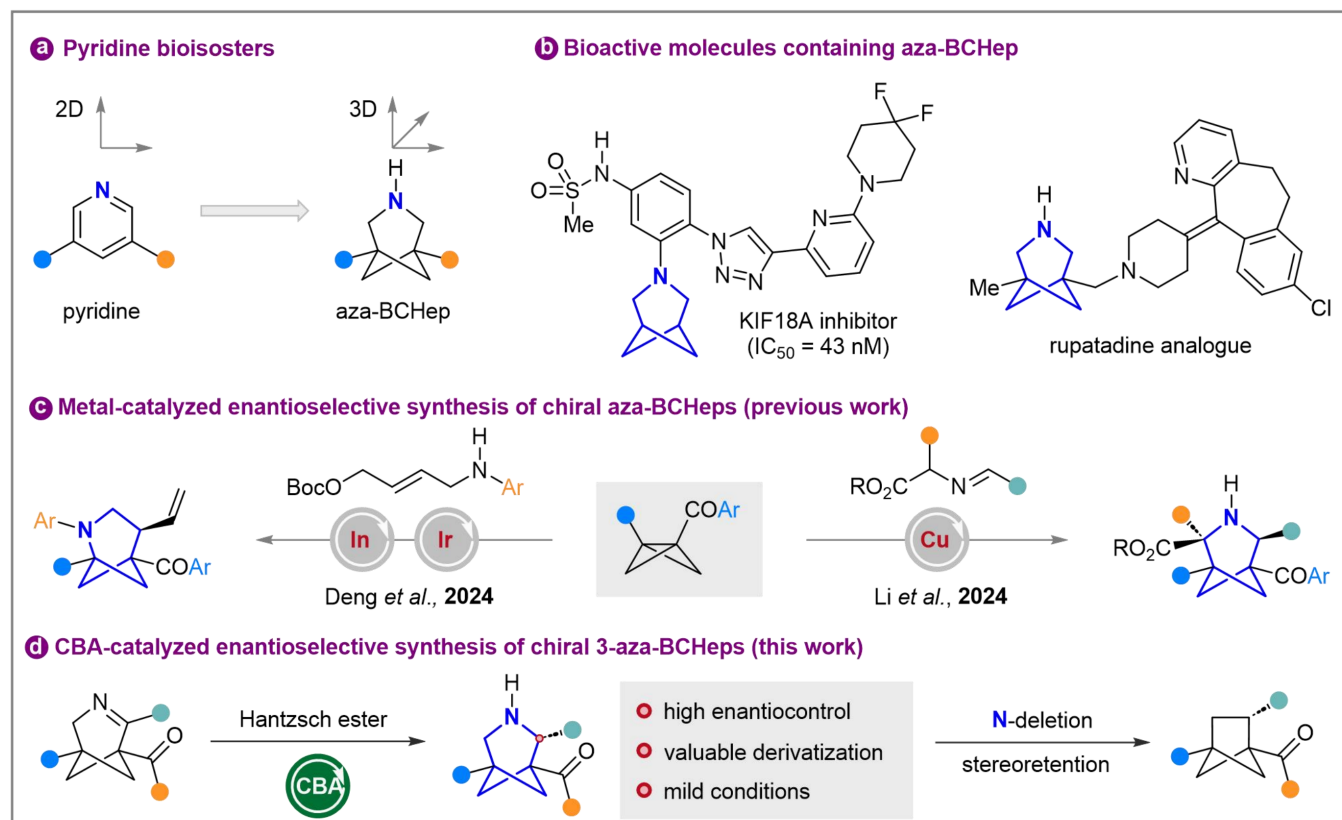


Figure 1. Background and design of the present work. CBA: chiral Brønsted acid; BCHePs: bicyclo[3.1.1]heptanes.

Despite these achievements, developing general, efficient, and catalytic asymmetric methods for enantioenriched aza-BCHePs remains a considerable challenge. Among the limited successful strategies, two main approaches have emerged. The first relies on chiral transfer from enantiopure starting materials: Hari's photoredox-catalyzed decarboxylation of chiral redox-active esters generates alkyl radicals that couple with bicyclo[1.1.0]butanes (BCBs)^[43], while Studer's Lewis acid-catalyzed formal $[2\sigma+2\sigma]$ cycloaddition employs chiral aziridines with BCBs^[46]. The second approach involves catalytic asymmetric construction. Deng's $In(OTf)_3$ /iridium relay catalysis produces 2-aza-BCHePs^[47], wherein $In(OTf)_3$ promotes BCB ring-opening followed by chiral iridium-catalyzed ring-closure. Separately, Li's copper-catalyzed asymmetric $[4\pi+2\sigma]$ cycloaddition of BCBs with azomethine ylides provides access to enantioenriched 3-aza-BCHePs (Figure 1c)^[48]. Although these pioneering studies offer valuable routes to specific chiral frameworks, a broadly applicable Brønsted acid-catalyzed asymmetric hydrogenation strategy for saturated, enantioenriched aza-BCHePs has yet to be developed.

To address this gap, we sought to develop a catalytic asymmetric transfer hydrogenation protocol employing azabicyclo[3.1.1]heptene as the starting material, a substrate elegantly synthesized by Zheng and co-workers^[23]. Chiral Brønsted acids (CBA), renowned for their bifunctional activation mode in stereoselective transformations^[49–54], provide a particularly attractive platform. While enantioselective Brønsted acid-catalyzed transfer hydrogenation has been well established for diverse imine substrates^[55–59], the asymmetric reduction of imines embedded in conformationally rigid and strained aza-bicyclic frameworks, such as those found in 3-aza-BCHePs, remains unexplored. This unique structural environment poses a distinct challenge for efficient stereocontrol. Herein, we report a CBA-catalyzed asymmetric transfer hydrogenation of imines derived from unsaturated 3-aza-BCHePs, employing Hantzsch ester (HE) as the hydrogen source (Figure 1d). This method enables the synthesis of a broad range of highly enantioenriched 3-aza-BCHePs in generally good yields under mild reaction conditions, with excellent functional group tolerance.

2. Methods

2.1 Typical procedure for enantioselective synthesis chiral 3-aza-BCHePs

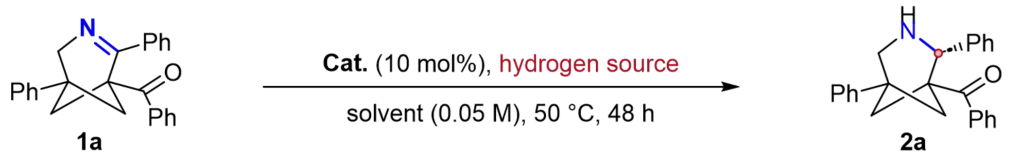
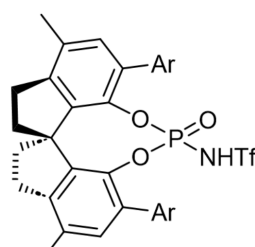
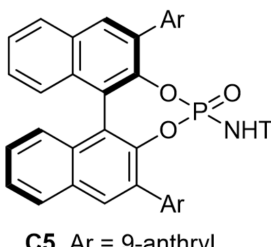
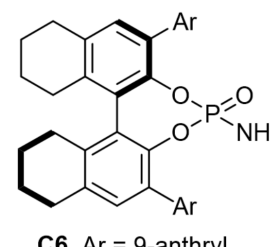
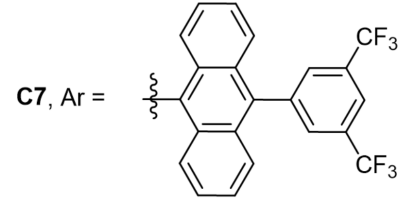
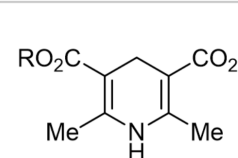
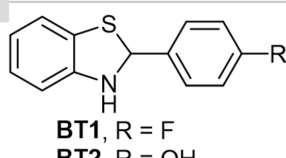
An oven-dried 25 mL Schlenk tube equipped with a magnetic stir bar was charged with imine **1** (0.2 mmol, 1.0 equiv.), HE (0.5 mmol, 2.5 equiv.), and C7 (10 mol%). The tube was evacuated and backfilled with argon three times. Mesitylene (4 mL) was then added, and the mixture was stirred at 50 °C for 72 h. After cooling to room temperature, chloranil (0.2 mmol, 1.0 equiv.) was added, and the mixture was stirred for an additional 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was washed

with aqueous NaOH (2 M, 2 × 10 mL), the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel basified with triethylamine to give product **2**. Further details are provided in the [Supplementary materials](#).

3. Results and Discussion

To develop an efficient asymmetric synthesis of 3-aza-BCHePs, we investigated the CBA-catalyzed transfer hydrogenation of unsaturated imine **1a** using **HE** as the hydrogen source. Initial experiments showed that the reaction was sluggish at room temperature. Optimization began with imine **1a** (0.05 mmol), **HE1** (3.0 equiv.), and catalyst **C1** (10 mol%) in mesitylene at 50 °C, affording product **2a** in 49% yield with 70% ee ([Table 1](#), entry 1). We next evaluated CBAs of different atropisomeric backbones and varied substituents to identify the superior catalyst ([Table 1](#), entries 2–6). The catalyst **C3**, which features a 4,4′-dimethyl substituted 1,1′-spirobiindane-7,7′-diol (Me-SPINOL) backbone and 9-anthryl groups at the 6,6′-positions, delivered the best performance in terms of enantioselectivity (90% ee). Given the most promising performance of 9-anthryl-derived catalyst (**C3**, entry 3), the substituent effect at the C10-position was evaluated (entry 7). Pleasingly, the installation of a 3,5-bis(trifluoromethyl)phenyl group at the C10-position of the anthryl ring further boosted both yield and enantioselectivity, furnishing **2a** in 78% yield with 94% ee (entry 7). Subsequent optimization of reaction parameters was carried out using **C7**. Evaluation of alternative reductants, including differently substituted HEs and benzothiazolines (BTs), proved less effective (entries 8–11). Reducing the loading of the original **HE1** to 2.5 equiv. maintained high reaction efficiency (81% yield, 94% ee, entry 12). A solvent survey identified mesitylene as optimal; aromatic solvents generally provided higher enantioselectivity than chlorinated or ethereal solvents (entries 13–17), suggesting that the aromatic environment plays a beneficial role in the stereodetermining step. While raising the temperature to 60 °C slightly decreased the enantioselectivity (92% ee, entry 18), extending the reaction time to 72 hours provided the optimal outcome, yielding **2a** in 89% isolated yield with 94% ee (entry 19).

Table 1. Screening reaction conditions^a.

					
 C1, Ar = 1-pyrenyl C2, Ar = 1-naphthyl C3, Ar = 9-anthryl C4, Ar = 3,5-(CF₃)₂C₆H₃  C5, Ar = 9-anthryl  C6, Ar = 9-anthryl					
 C7, Ar =  HE1, R = Et HE2, R = Me HE3, R = <i>t</i>Bu  BT1, R = F BT2, R = OH					
entry	Cat.	solvent	hydrogen source	yield (%) ^b	ee (%) ^c
1	C1	mesitylene	HE1	49	70
2	C2	mesitylene	HE1	82	76
3	C3	mesitylene	HE1	74	90
4	C4	mesitylene	HE1	85	77
5	C5	mesitylene	HE1	66	-28
6	C6	mesitylene	HE1	50	-8

7	C7	mesitylene	HE1	78	94
8	C7	mesitylene	HE2	66	93
9	C7	mesitylene	HE3	62	72
10	C7	mesitylene	BT1	8	6
11	C7	mesitylene	BT2	45	46
12 ^d	C7	mesitylene	HE1	81	94
13 ^d	C7	PhCF ₃	HE1	81	90
14 ^d	C7	toluene	HE1	78	92
15 ^d	C7	EtOAc	HE1	45	84
16 ^d	C7	THF	HE1	39	84
17 ^d	C7	CH ₂ Cl ₂	HE1	62	86
18 ^{d,e}	C7	mesitylene	HE1	80	92
19 ^{d,f}	C7	mesitylene	HE1	94 (89)	94

^a: Unless otherwise indicated, all reactions were performed with **1a** (0.05 mmol) and hydrogen source (0.15 mmol) in the presence of catalyst (10 mol%) in solvent (1.0 mL) at 50 °C under argon atmosphere for 48 h; ^b: The yields were determined by ¹H NMR spectra using triphenylmethane as an internal standard; ^c: The ee values were determined by chiral HPLC analysis; ^d: 2.5 equiv. of HE1 was used; ^e: At 60 °C; ^f: For 72 h, isolated yield was provided in parentheses. HE: Hantzsch ester.

With the optimized reaction conditions in hand, we evaluated the substrate scope of this asymmetric transfer hydrogenation. As depicted in Figure 2, the model reaction of substrate **1a** proceeded smoothly on a 0.2 mmol scale, providing **2a** in improved isolated yield with excellent enantioselectivity. We then examined a broad range of substituted 3-aza-BCHeps to test the robustness and generality of the protocol. First, variations at the *para*, *meta* and *ortho*-positions of the aryl group attached to the imine were explored. Installation of an electron-donating (**2b**), electron-neutral (**2d**), or electron-withdrawing (**2e–2h**) group at the *para*-position of the aromatic ring had minimal impact on the reaction outcome, affording the corresponding chiral 3-aza-BCHeps in 85–92% yields with 90–96% ee; a slight erosion in enantioselectivity was observed only with the *para*-methoxy group (**2c**). *meta*-substituted hydrogenation products (**2i–2l**) exhibited comparable efficiency and enhanced enantiocontrol, whereas *ortho*-substitution led to a significant decrease in both reactivity and stereoselectivity (**2m**), likely due to steric hindrance. Replacement of the phenyl ring with a 2-thienyl group or alkyl chain also proved viable (**2n–2o**). Subsequently, the substituent effect of the bridgehead aryl group was investigated. The electronic nature of the *para*-substituent exerted negligible influence on the transformation, with the corresponding products (**2p–2s**) obtained in 79–93% yields with 90–95% ee. However, removal of this aryl group caused a significant erosion in both yield and enantioselectivity (**2t**). Furthermore, replacement of the benzoyl group at the other bridgehead with 2-thienyl or acetyl groups afforded products (**2u–2v**) with excellent stereoselectivity. Finally, substrates decorated with two substituted aryl moieties were examined in this transformation. Functional groups including methyl, fluoro, chloro, and methoxy, regardless of the *para*- or *meta*-position on the phenyl ring, were well accommodated with no obvious influence on the efficacy (**2w–2aa**). The absolute configuration of product **2a** was determined by X-ray crystallographic analysis, and those of other products in Figure 2 were assigned by analogy. In summary, the protocol demonstrates a broad substrate scope, accommodating diverse electronic and steric profiles with generally high yields and excellent enantiocontrol, highlighting its synthetic utility for accessing enantioenriched 3-aza-BCHeps.

To demonstrate the practical utility of our method, we first evaluated its scalability. Under the standard conditions, a scale-up reaction of substrate **1a** (2 mmol) provided 3-aza-BCHep **2a** in 95% yield with 94% ee. Similarly, **2f** was synthesized efficiently on scale (1 mmol), affording the product in 84% yield with 96% ee (Figure 3a). With sufficient quantities of these chiral building blocks available, a series of synthetic transformations were performed. Treatment of **2a** with *O*-(diphenylphosphinyl)hydroxylamine (DPPH) under nitrogen-deletion conditions afforded the saturated BCH **3a** in 86% yield^[60–62], with complete preservation of enantioselectivity (94% ee) (Figure 3b), and the configuration of **3a** was confirmed by single crystal X-ray diffraction analysis. The same strategy was successfully applied to substrates **2b**, **2g**, and **2j**, affording the corresponding products in good yields with full enantiopurity retention, demonstrating the reliability of this scaffold as a precursor to other high-value bridged systems. Subsequent transformations of **2a** gave alcohol **4** (91%) as a pair of diastereoisomers upon reduction with NaBH₄, and afforded terminal alkene **5** (73%) via Wittig olefination (Figure 3c). Moreover, **2h** underwent late-stage derivatization via a Buchwald–Hartwig coupling with apixaban, furnishing the drug-conjugated product **6** in 73% yield (Figure 3d). To further explore the catalytic potential of these scaffolds, we evaluated 3-aza-BCHeps **2f** and **4** as novel chiral secondary amine organocatalysts. In the asymmetric Friedel–Crafts alkylation of indoles with an α,β -unsaturated aldehyde, these catalysts delivered the desired product **7** in up to 93% yield with 68% ee

(Figure 3e). Collectively, these results validate the 3-aza-BChep framework as a promising new entry for asymmetric organocatalysis. Collectively, these developments in scalable synthesis, strategic skeletal editing, derivatization, and catalytic application validate 3-aza-BCheps as highly versatile three-dimensional molecular building blocks for synthetic and medicinal chemistry.

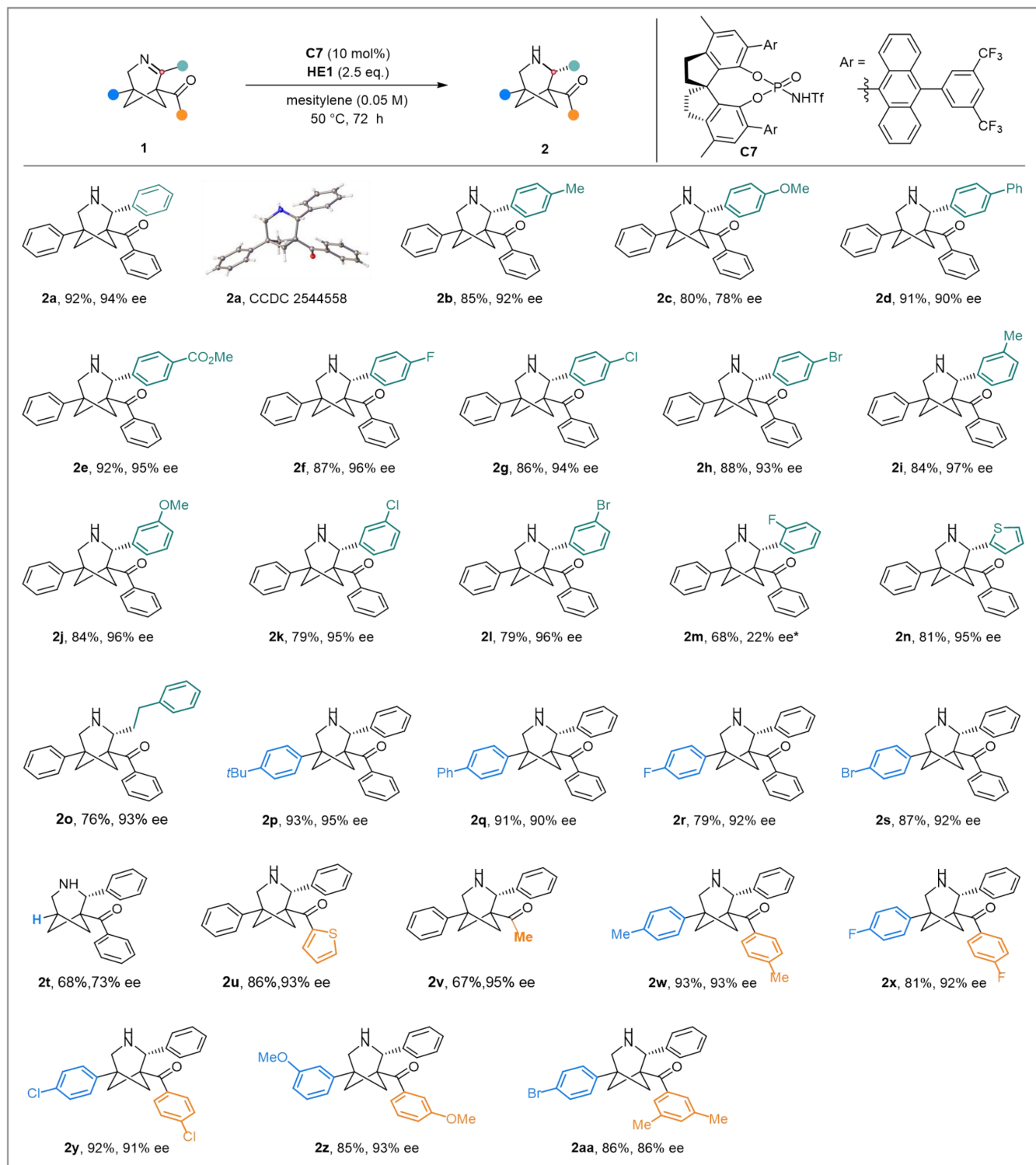


Figure 2. Substrate scope of 3-aza-BCheps. All reactions were performed with **1** (0.2 mmol), **HE1** (0.5 mmol) and **C7** (10 mol%) in mesitylene (4.0 mL) at 50 °C under argon atmosphere. Isolated yields are shown. *Reaction was conducted for 168 hours. BCheps: bicyclo[3.1.1]heptanes; HE: Hantzsch ester.

Based on experimental observations and precedents in CBA catalysis^[63–69], we propose a plausible mechanism for the asymmetric transfer hydrogenation (Figure 4). The imine substrate **1a** is first activated by catalyst **C7** through hydrogen bonding, generating

intermediate **I**. The stereoselective hydride transfer then proceeds via a proposed transition state **II**, which assembles the activated iminium ion, the HE, and the catalyst in a well-organized network of non-covalent interactions. This key step facilitates the facial-selective reduction, delivering the enantioenriched amine **2a** and generating the Brønsted acid–pyridine complex **III**. Finally, a proton transfer event releases the pyridine byproduct and regenerates the active CBA catalyst, thereby closing the catalytic cycle.

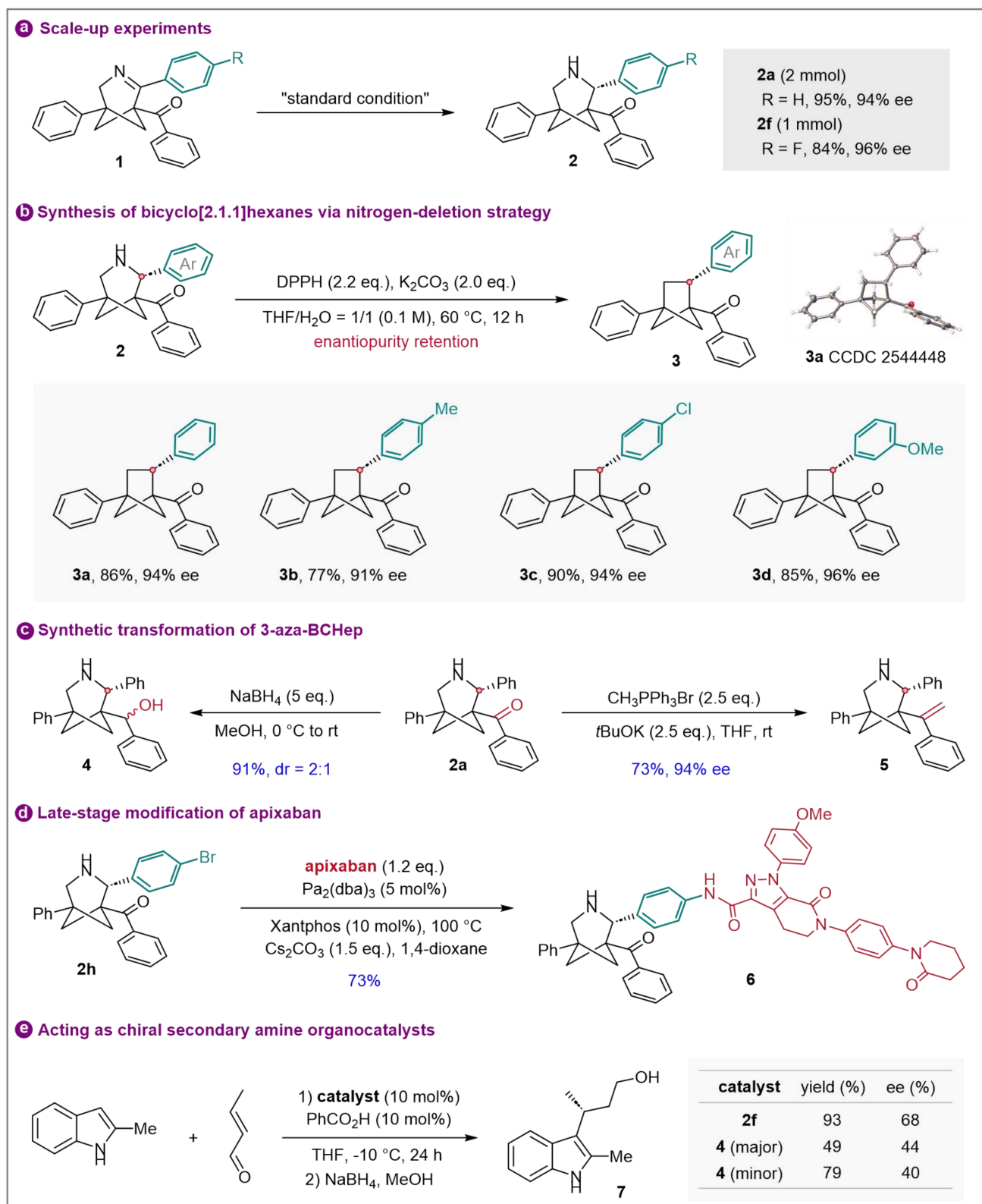


Figure 3. Scale-up experiments and further synthetic applications.

4. Conclusion

In summary, we have developed a practical and efficient Brønsted acid-catalyzed asymmetric transfer hydrogenation for the synthesis of enantioenriched 3-aza-BCHePs. This method facilitates the transformation of readily accessible unsaturated precursors into chiral saturated architectures under mild conditions, characterized by a broad substrate scope and exceptional enantioselectivity. The high degree of stereocontrol is rationalized by a proposed mechanism involving a well-defined non-covalent interaction network. The synthetic utility of the resulting aza-BCHePs is highlighted by their stereospecific conversion into BCHs via nitrogen deletion, their diverse downstream functionalization, and their successful application as a novel class of chiral secondary amine organocatalysts. Overall, this work provides a robust and step-economical route to an important class of three-dimensional, sp^3 -rich bioisosteres, thereby expanding the synthetic toolkit for both drug discovery and asymmetric catalysis.

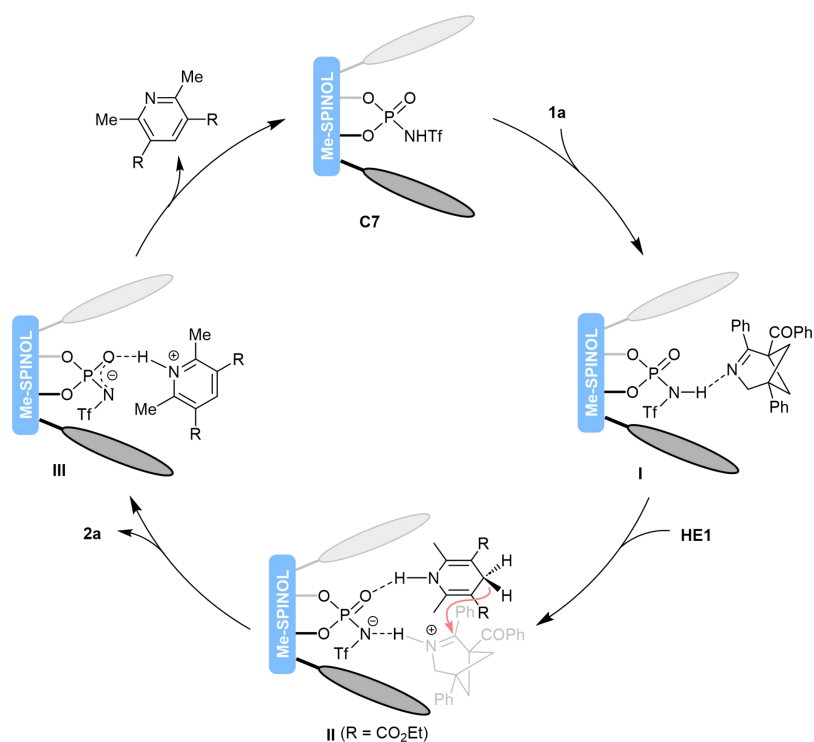


Figure 4. Proposed reaction pathway.

Supplementary materials

The supplementary material for this article is available at: [Supplementary materials](#).

Declarations

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Authors contribution

Tan B, Ding WY: Conceptualization, supervision, writing-original draft.
 Deng MX: Investigation, data curation, writing-original draft.
 Liu HH: Investigation, formal analysis.
 Xiang SH: writing-original draft.

Conflicts of interest

Bin Tan is an Editorial Board Member of *Chiral Chemistry*. The other authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data reported in this paper are available in the main text or supplementary information, including methods, NMR data, HRMS data, HPLC spectra Crystal data and NMR spectra. Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2544558 (**2a**) and CCDC 2544448 (**3a**).

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