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Rapid Access to Chiral 3-Oxabicyclo[3.1.1]heptanes by Iridium-Catalyzed Asymmetric Hydrogenation and Sequential Cyclization

Tong Niu, Xin-Yu Zhan, Yu-Qing Bai, Bo Wu,* and Yong-Gui Zhou*

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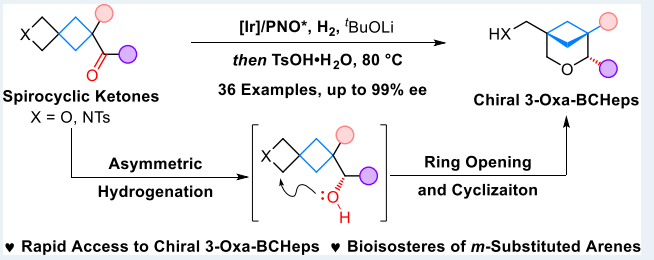
ABSTRACT: The bicyclo[3.1.1]heptanes (BCHeps) represent an essential class of three-dimensional caged scaffolds as bioisosteres of *meta*-substituted arenes in modern drug discovery. Despite significant achievements in the construction of chiral BCHeps, the synthetic strategies only limited to the asymmetric cycloaddition of bicycle[1.1.0]butanes (BCBs) and the innovative catalytic enantioselective protocols have rarely been exploited. Herein, we disclosed a synthetic strategy for the construction of chiral 3-oxa-BCHeps via the iridium-catalyzed asymmetric hydrogenation/cyclization of spirocyclic ketones. This protocol is a cascade procedure involving asymmetric hydrogenation to give the chiral spirocyclic alcohol intermediates and sequential acid-mediated ring opening and cyclization. Both spirocyclic azetidinyl ketones and spirocyclic oxetanyl ketones are compatible, delivering a wide range of chiral polysubstituted 3-oxa-BCHeps bearing amino and hydroxyl functional groups with high yields and enantioselectivities (up to 99% yield and 99% ee). The utility of this protocol is accentuated by diverse transformations and synthesis of a chiral analogue of the anticancer drug Sonidegib.



KEYWORDS: *chiral 3-oxabicyclo[3.1.1]heptanes, bioisosteres, meta-benzenes, asymmetric hydrogenation, cyclization*

INTRODUCTION

"Escaping from flatland" is a predominant concept,[1−4] which emphasizes the replacement of flat aromatic rings with three-dimensional (3D) caged scaffolds, and has gained remarkable attention in medicinal chemistry and drug discovery.[5−8] On the basis of this concept, saturated bridged bicyclic scaffolds, encompassing bicyclo[1.1.1]pentanes (BCPs), bicyclo[2.1.1]hexanes (BCHs), and bicyclo[3.1.1]heptanes (BCHeps), have been developed rapidly in mimicking planar arenes.[9−40] Among them, BCHeps represent an intriguing category of saturated 3D scaffolds as bioisosteres of *meta*-substituted benzenes[22−30] (Scheme 1a). Notably, 3-azabicyclo[3.1.1]-heptanes (3-aza-BCHeps) and 3-oxabicyclo[3.1.1]heptanes (3-oxa-BCHeps) have been demonstrated as bioisosteres of *meta*-substituted pyridines[31−37] and bioisosteres of *meta*-substituted benzenes[38−40] (Scheme 1a), respectively. Given the crucial role of chirality in influencing the biological activity and pharmacokinetic properties of drug molecules,[41−46] significant and inspiring advances have been made in the development of catalytic asymmetric methodologies to synthesize chiral BCHeps in the past two years.[47−55] These impressive strategies mainly focused on the asymmetric formal [3 + 3] cycloaddition of bicycle[1.1.0]butanes (BCBs) (Scheme 1b). In 2024, Feng, Zhang, and co-workers reported the palladium-catalyzed enantioselective cycloaddition of BCBs with vinyl oxiranes to produce chiral 2-oxa-BCHeps.[47] Subsequently, the Lewis acid-catalyzed asymmetric cycloaddition of BCBs with azomethine ylides,[48] nitrones,[49−51] diaziridines,[52] and aromatic azomethine imines[53] have been disclosed to access chiral aza-BCHeps. The synthesis of enantiopure 2-aza-BCHeps via $In(OTf)_3$/iridium relay-catalyzed asymmetric cycloaddition of BCBs with *N*-allyl carbonates was presented.[54] Recently, the chiral Brønsted acid-catalyzed cycloaddition of BCBs with indolyl methanols was developed to form enantioenriched indolo-BCHeps as potential carbazole bioisosteres.[55] Although the catalytic asymmetric cycloaddition of BCBs has been a powerful toolbox for the synthesis of chiral BCHeps, to the best of our knowledge, the catalytic asymmetric synthetic strategies except the cycloaddition of BCBs have not yet been exploited. Therefore, there is a continuing demand to explore innovative and practical asymmetric synthetic protocols for the construction of chiral BCHeps decorated with versatile functional groups.

3-Oxa-BCHeps have been recognized as bioisosteres of *meta*-substituted benzenes and could remarkably improve water solubility.[38−40] Although Mykhailiuk's group[38] and

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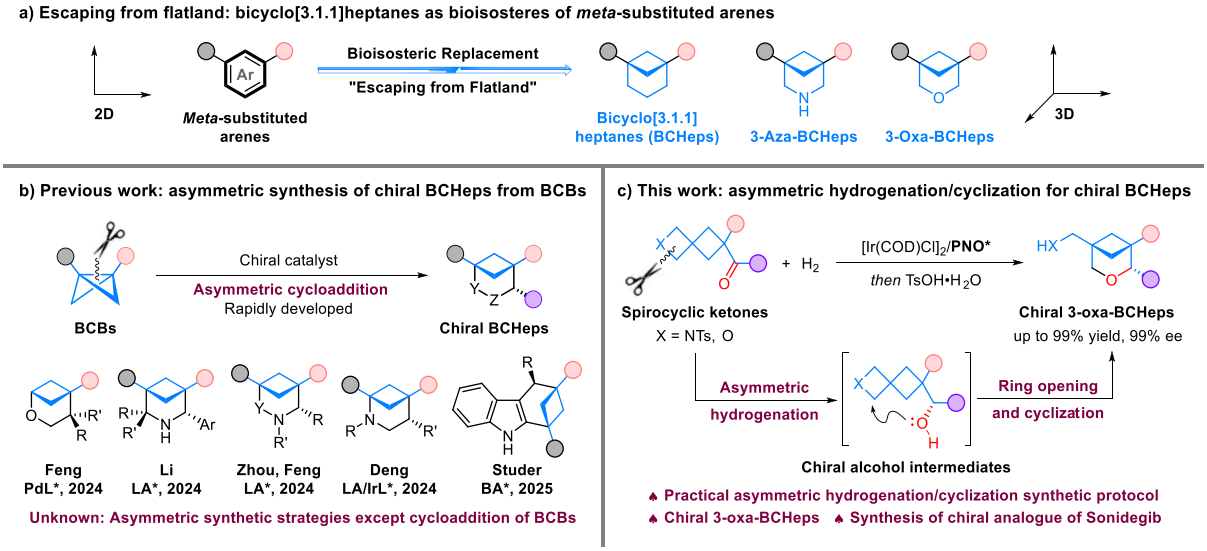
Scheme 1. Catalytic Asymmetric Synthesis of Chiral Bicyclo[3.1.1]heptanes[a]



[a](a) Bicyclo[3.1.1]heptanes as bioisosteres of *meta*-substituted arenes. (b) Asymmetric synthesis of chiral BCHeps via the cycloaddition of BCBs. (c) Asymmetric hydrogenation/cyclization to access chiral BCHeps.

Ryabchuk's group[39] reported the pioneering synthesis of achiral 3-oxa-BCHeps enabled by the acid-catalyzed ring opening and cyclization of 2-oxaspiro[3.3]heptan-6-yl methanols, the asymmetric synthesis of chiral 3-oxa-BCHeps is still elusive. In order to realize the diversity of synthetic methodologies toward chiral BCHeps and the construction of chiral 3-oxa-BCHeps, and building on our continuous interests in asymmetric hydrogenation,[56−59] we envisioned the iridium-catalyzed asymmetric hydrogenation/cyclization of spirocyclic ketones as an innovative and alternative strategy for the construction of chiral 3-oxa-BCHeps. To achieve this proposal, we need to address the following challenges. First, steric congestion in spirocyclic ketones impedes the direct insertion of iridium-hydride species into the carbonyl group. Second, the simultaneous modulation of high reactivity and enantioselectivity is remarkably dependent on the chiral catalyst. Considering that tridentate ligand-based metal catalysts possess deepened chiral binding pockets and favored outer sphere hydride transfer to facilitate the access of iridium-hydride species to sterically hindered carbonyl groups, we speculated that the tridentate ligand-based iridium catalyst could effectively tackle the aforementioned challenges. Utilizing the $[Ir(COD)Cl]_2$/planar-chiral PNO tridentate ligand as the catalyst, we herein developed an original synthetic strategy toward chiral 3-oxa-BCHeps via asymmetric hydrogenation/cyclization of spirocyclic ketones (Scheme 1c). This protocol involves asymmetric hydrogenation to give chiral spirocyclic alcohol intermediates, and sequential acid-mediated ring opening and cyclization,[60,61] providing various chiral polysubstituted 3-oxa-BCHeps bearing hydroxyl and amino functional groups with excellent yields and enantioselectivities. The synthetic utility was underscored by diverse transformations and the synthesis of a chiral analogue of the anticancer drug Sonidegib.

METHODS

General Procedure for Asymmetric Hydrogenation/Cyclization of Spirocyclic Azetidinyl Ketones 1. A mixture of $[Ir(COD)Cl]_2$ (1.0 mg, 1.0 mol %) and ligand (S_p)-**L4** (2.6 mg, 2.2 mol %) or (S_{FC})-**L8** (1.6 mg, 2.2 mol %) in 2-methyl-2-butanol (1.0 mL) was stirred in a vial at room temperature for 1 h in a glovebox to give the catalyst solution. To another vial was added lithium *tert*-butoxide (2.4 mg, 0.03 mmol), spirocyclic azetidinyl ketones **1** (0.15 mmol), 2-methyl-2-butanol (2.0 mL), and the catalyst solution (1.0 mL). Then, the mixture was transferred to an autoclave, which was then charged with a hydrogen gas (600 psi), and stirred at 70 °C for 24 or 48 h. After the careful release of the hydrogen, the autoclave was opened. Then, *p*-toluenesulfonic acid monohydrate (19.0 mg, 0.10 mmol) was added to the vial, and the mixture was stirred under 80 °C for 4 h. The volatiles were removed under reduced pressure, and the residue was purified by silica gel chromatography to give products **2**.

General Procedure for Asymmetric Hydrogenation/Cyclization of Spirocyclic Oxetanyl Ketones 3. A mixture of $[Ir(COD)Cl]_2$ (0.8 mg, 0.75 mol %) and ligand (S_p)-**L4** (2.0 mg, 1.65 mol %) or (S_{FC})-**L8** (1.2 mg, 1.65 mol %) in 2-methyl-2-butanol (1.0 mL) was stirred in a vial at room temperature for 1 h in a glovebox to give the chiral catalyst solution. To another vial was added lithium *tert*-butoxide (1.8 mg, 0.0225 mmol), spirocyclic oxetanyl ketones **3** (0.15 mmol), 2-methyl-2-butanol (1.0 mL), and the catalyst solution (1.0 mL). Then, the mixture was transferred to an autoclave, which was then charged with the hydrogen gas (600 psi) and stirred at 70 °C for 48 h. After the careful release of the hydrogen gas, the autoclave was opened. Then, *p*-toluenesulfonic acid monohydrate (19.0 mg, 0.10 mmol) was added to the vial, and the reaction mixture was stirred under 80 °C for 4 h. The volatiles were removed under reduced pressure, and the crude residue was purified by silica gel column chromatography to give the desirable products **4**.

RESULTS AND DISCUSSION

To examine the feasibility of the proposed protocol, a series of spirocyclic azetidinyl ketones **1** and spirocyclic oxetanyl ketones **3** were conveniently synthesized from readily available 3,3-bis(bromomethyl)-1-tosylazetidine or 3,3-bis(bromomethyl)-oxetane through two methods with moderate to

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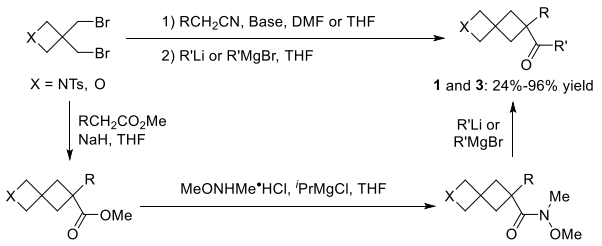
ACS Catal. 2025, 15, 18563−18571

good yields (Scheme 2). One is the alkylation of nitriles with dibromide, followed by nucleophilic addition and hydrolysis.

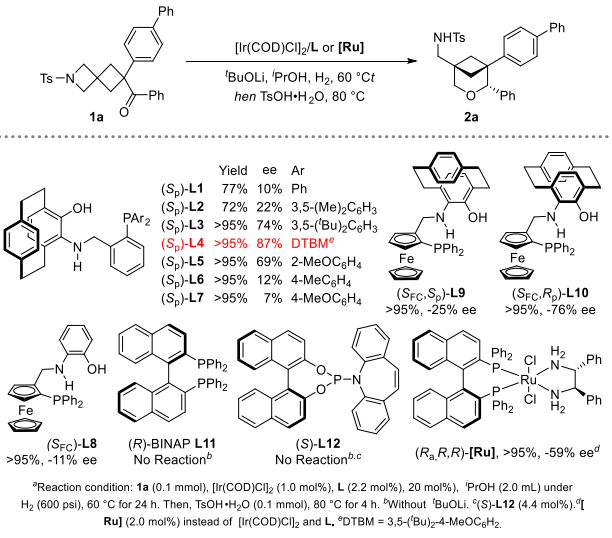
Scheme 2. Synthesis of Spirocyclic Ketones



The other is the synthesis of ester intermediates, the subsequent conversion of the esters into amides, and nucleophilic addition and elimination of amides.

With the spirocyclic ketones in hand, we focused on the development of a rapid synthetic strategy for access to chiral 3-oxa-BCHeps via the asymmetric hydrogenation/cyclization of spirocyclic ketones. At the outset, spirocyclic azetidinyl ketone **1a** was chosen as the model substrate and chiral ligands were evaluated (Scheme 3). Initially, several planar-chiral PNO

Scheme 3. Evaluation of Chiral Ligands

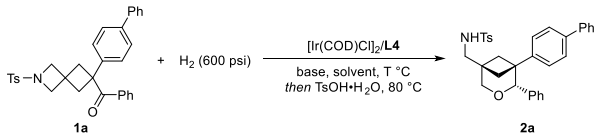


[a]Reaction condition: **1a** (0.1 mmol), [Ir(COD)Cl]$_2$ (1.0 mol%), **L** (2.2 mol%), 20 mol%), ^{i}PrOH (2.0 mL) under H_2 (600 psi), 60 °C for 24 h. Then, TsOH•H_2O (0.1 mmol), 80 °C for 4 h. [b]Without ^{t}BuOLi. [c](*S*)-**L12** (4.4 mol%). [d][**Ru**] (2.0 mol%) instead of [Ir(COD)Cl]$_2$ and **L**. [e]DTBM = 3,5-(^{t}Bu)$_2$-4-MeOC$_6$H$_2$.

tridentate ligands[62,63] developed by our group were tested. Pleasingly, the desired 3-oxa-BCHeps bearing the amino group **2a** was obtained in 77% yield and 10% ee using planar-chiral PNO ligand **L1**, followed by the sequential acid-mediated cyclization. To improve the enantioselectivity, we speculated that the adjustment of steric hindrance and electron properties of the phosphine group in the tridentate ligand would be helpful to get rid of the dilemma. Encouragingly, with the enhancement of steric hindrance, a higher ee (74%) was obtained with **L3**. The ligand **L4** bearing 3,5-di-*tert*-butyl-4-methoxy-phenyl (DTBM) group could give an excellent yield and the highest enantioselectivity (>95% yield, 87% ee). Other PNO tridentate ligands **L8**−**L10** have no positive impact on the enantioselectivity. The asymmetric hydrogenation shut down with chiral bisphosphine ligand **L11** and phosphoramidite ligand **L12**. When the BINAP/1,4-diamine-ruthenium complex (R_a,*R*,*R*)-[Ru] was applied, the ee value of **2a** was only 59%.

Subsequently, the influence of solvents on reactivity and enantioselectivity was evaluated with **L4** as the chiral ligand (Table 1). Utilizing lithium *tert*-butoxide as a base under 60

Table 1. Condition Optimization[a]



entry	solvent	base	T (°C)	yield (%)[b]	ee (%)[c]
1	THF	^{t}BuOLi	60	>95	59
2	DCE	^{t}BuOLi	60	39	83
3	toluene	^{t}BuOLi	60	67	92
4	EtOH	^{t}BuOLi	60	22	24
5	^{i}PrOH	^{t}BuOLi	60	>95	87
6	^{t}BuOH	^{t}BuOLi	60	>95	94
7	^{t}AmOH	^{t}BuOLi	60	>95	95
8	^{t}AmOH	^{t}BuONa	60	55	86
9	^{t}AmOH	^{t}BuOK	60	<5	
10	^{t}AmOH	NaOH	60	22	79
11	^{t}AmOH	K_2CO_3	60	<5	
12	^{t}AmOH	Cs_2CO_3	60	<5	
13	^{t}AmOH	^{t}BuOLi	50	>95	96
14	^{t}AmOH	^{t}BuOLi	70	>95	97
15	^{t}AmOH	^{t}BuOLi	80	>95	95
16[d]	^{t}AmOH	^{t}BuOLi	70	98	96

[a]Reaction conditions: **1a** (0.1 mmol), [Ir(COD)Cl]$_2$ (1.0 mol %), (S_p)-**L4** (2.2 mol %), base (20 mol %), and solvent (2.0 mL) under H_2 (600 psi) and 60 °C for 24 h. Then, TsOH·H_2O (0.1 mmol) under 80 °C for 4 h. [b]Yield was measured by analysis of ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as the internal standard. [c]Determined by chiral HPLC. [d]Hydrogenation was conducted at 0.15 mmol scale and 70 °C for 24 h, isolated yield.

°C, the asymmetric hydrogenation proceeded smoothly in tetrahydrofuran, and moderate ee was afforded (entry 1). When the solvent switched to dichloroethane, 3-oxa-BCHep **2a** was furnished in a low yield but 83% ee (entry 2). In toluene, a moderate yield and higher ee of **2a** (92%) was achieved (entry 3). After that, several alcohols were tested for this process. Although poor results were given in ethanol, other alcohols, such as isopropanol, *tert*-butanol, and 2-methyl-2-butanol, appeared to be adequate solvents for this asymmetric hydrogenation and the sequential cyclization process (entries 4−7). All things considered, 2-methyl-2-butanol could afford preferable results (>95% yield, 95% ee) and was chosen as the most suitable solvent for this reaction. During the screening of bases, while lithium *tert*-butoxide performed well in the reaction, when sodium *tert*-butoxide or sodium hydroxide (entries 8 and 10) was employed as the base, **2a** could only be afforded with low yields and unsatisfying enantioselectivities. Other bases, such as potassium *tert*-butoxide, potassium carbonate, and cesium carbonate, were found to be inadequate in this reaction (entries 9, 11−12). Furthermore, the reaction temperature of asymmetric hydrogenation was also evaluated. Even though parallel results were given under 50−80 °C (entries 7, 13−15), a slightly higher ee could be achieved under 70 °C (entry 14). At last, a 0.15 mmol scale experiment was conducted with [Ir(COD)Cl]$_2$, planar-chiral tridentate ligand **L4**, lithium *tert*-butoxide, 2-methyl-2-butanol, and H_2 (600 psi) under 70 °C for 24 h, followed by the treatment with

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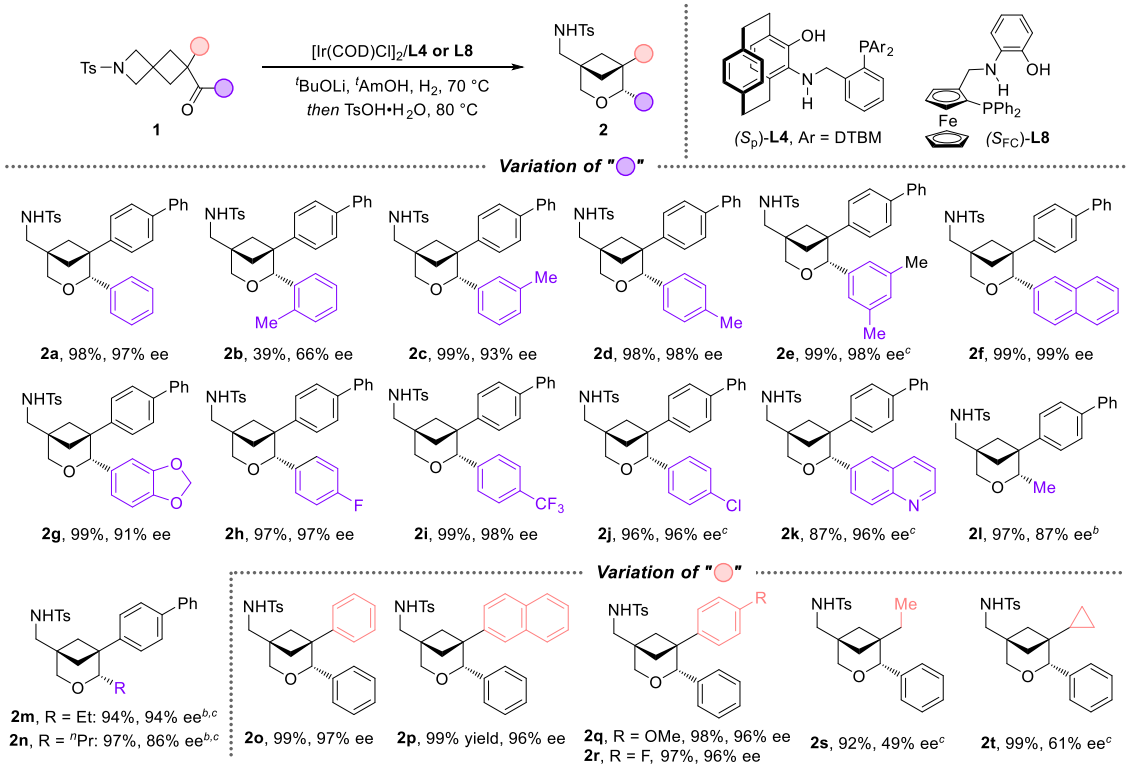
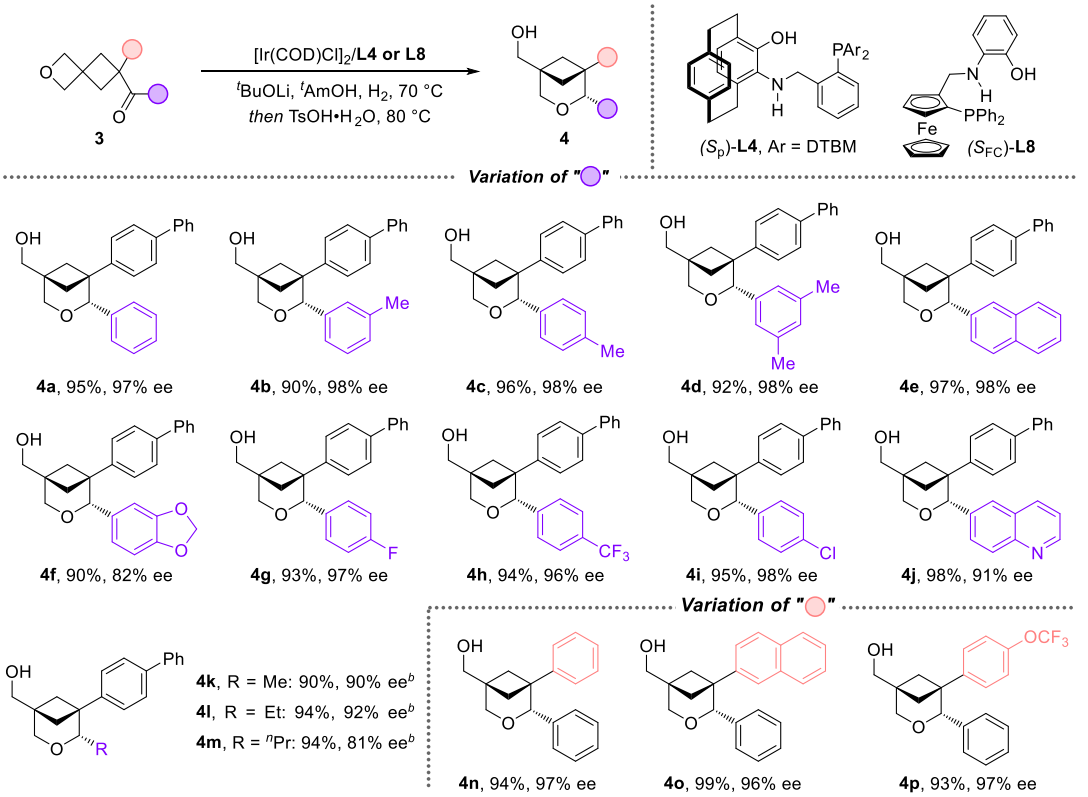
Scheme 4. Substrate Scope of Spirocyclic Azetidinyl Ketones 1



[a]Reaction condition: **1** (0.15 mmol), $[Ir(COD)Cl]_2$ (1.0 mol%), **L4** (2.2 mol%), ^{t}BuOLi (20 mol%), ^{t}AmOH (3.0 mL) under H_2 (600 psi), 70 °C for 24 h. Then, TsOH•H_2O (0.1 mmol), 80 °C for 4 h. [b]**L8** instead of **L4**. [c]Hydrogenation reaction time was extended to 48 h

Scheme 5. Substrate Scope of Spirocyclic Oxetanyl Ketones 3



[a]Reaction condition: **3** (0.15 mmol), $[Ir(COD)Cl]_2$ (0.75 mol%), **L4** (1.65 mol%), ^{t}BuOLi (15 mol%), ^{t}AmOH (2.0 mL) under H_2 (600 psi), 70 °C for 48 h. Then, TsOH•H_2O (0.1 mmol), 80 °C for 4 h. [b]**L8** instead of **L4**.

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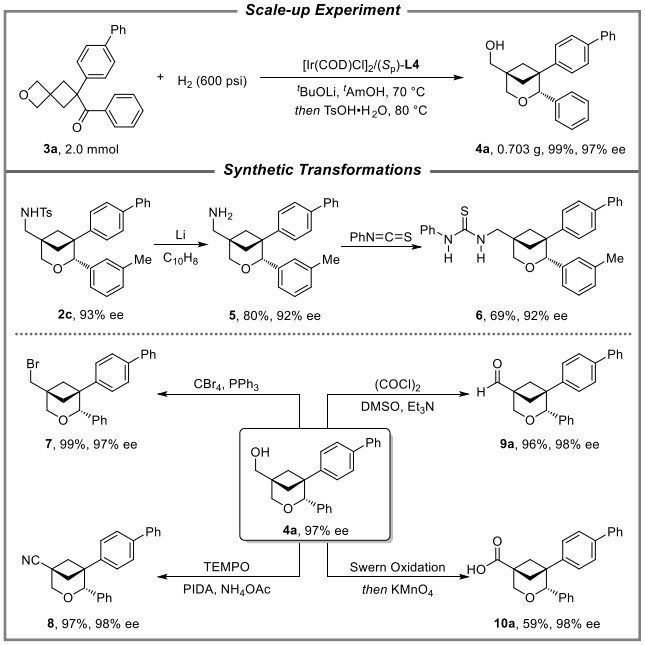
a *p*-toluenesulfonic acid monohydrate at 80 °C for 4 h (entry 16). The results were comparable to those under the 0.10 mmol scale.

After the establishment of the optimal reaction conditions, we set out to investigate the substrate scope of the asymmetric hydrogenation and sequential cyclization of spirocyclic azetidinyl ketones **1**. As shown in Scheme 4, first, substrates **1** with different aryl groups that are adjacent to carbonyl were synthesized and applied in the reaction. We were pleased to find that the *meta*- and *para*-tolyl groups showed great compatibility, and 3-oxa-BCHeps **2c** and **2d** were both obtained with high yields and excellent ee. However, the hydrogenation and cyclization of **1b** bearing *ortho*-tolyl were not satisfactory, and 39% yield and 66% ee were offered. We presumed that these outcomes may be attributed to the unsuited steric hindrance of the *ortho*-tolyl group with the chiral environment of the iridium catalyst. For substrates **1e** and **1f** containing 3,5-demethylphenyl and 2-naphthyl groups, the chiral 3-oxa-BCHeps **2e** and **2f** with excellent yields and ee could be afforded as well. When an electron-donating piperonyl group was introduced (**2g**), the enantioselectivity decreased a bit to 91%. Furthermore, substrates **1h**, **1i**, and **1j** containing electron-withdrawing groups were compatible with the mild reaction conditions as well, affording the chiral 3-oxa-BCHeps **2h**, **2i**, and **2j** with high yields and ee (96−99% yields, 96−98% ee). For spirocyclic azetidinyl ketone **1k** with a heteroaryl group, excellent enantioselectivity could be achieved but with a slightly lower yield. Next, the aryl groups adjacent to carbonyl were replaced by alkyl groups. By the utilization of ligand **L8** instead of **L4**, the asymmetric hydrogenation and sequential cyclization of spirocyclic azetidinyl ketones **1l**−**1n** were investigated. As the results show, this protocol furnished the corresponding 3-oxa-BCHeps **2l**, **2m**, and **2n** with high yields and acceptable enantioselectivities. In addition, we evaluated different groups substituted to the 6-position of the azaspiro[3.3]heptanes. Aryl groups with different steric hindrances and electron properties has a minor influence on the reactivity and enantioselectivity. For the ethyl-substituted **1s** and cyclopropyl-substituted **1t**, the products **2s** and **2t** were obtained in 49% and 61% ee, respectively.

To further demonstrate the universality of this asymmetric hydrogenation and sequential cyclization strategy toward chiral 3-oxa-BCHeps, another kind of substrate, spirocyclic oxetanyl ketones **3** were considered (Scheme 5). Similarly, under the established optimal reaction conditions, different aryl groups adjacent to the carbonyl of **3** were first evaluated. Pleasingly, the tuning of the steric hindrance of the aryl group has nearly no influence on the reactivity and enantioselectivity. Chiral 3-oxa-BCHeps bearing hydroxyl group **4a**−**4e** were furnished with high yields and ee (90−97% yields, 97−98% ee). For substrates **3f**−**3j**, no significant effect was observed regardless of the electronic properties, steric hindrance, or positions of substituents. Alike the spirocyclic azetidinyl ketones **1**, the chiral ligand for alkyl-substituted ketones **3k**−**3m** was changed to ferrocene-based planar-chiral **L8**. Satisfactory results were obtained for **4k** and **4l** (90−94% yields, 90−92% ee), but the ee of **4m** diminished to 81%. What is more, chiral 3-oxa-BCHep **4p** bearing a trifluoromethoxy group was synthesized through this protocol with 93% yield and 97% ee.

To elucidate the potential utility of this asymmetric hydrogenation and sequential cyclization strategy toward enantiopure 3-oxa-BCHeps, a scale-up experiment of spirocyclic oxetanyl ketone **3a** was carried out at 2.0 mmol scale. Consistent results were afforded compared to those obtained under 0.15 mmol scale. These outcomes confirmed the validity of this newly developed protocol and encouraged us to explore its preparative utility (Scheme 6). The chiral 3-oxa-BCHep **2c**

Scheme 6. Scale-Up Experiment and Synthetic Transformations



underwent deprotection by the treatment of lithium and naphthalene to give chiral amine **5** with an 80% yield and retentive ee value. Then, amine **5** could be further converted to chiral thiourea **6** with 69% yield. This newly developed chiral thiourea might be utilized as a chiral organocatalyst and would exhibit potential applications in asymmetric catalysis.[64−66] For hydroxyl-containing 3-oxa-BCHep **4a**, four different kinds of transformations were performed. First, the Appel reaction allowed the conversion of chiral alcohol **4a** into bromide **7** (99% yield, 97% ee). Second, **4a** could be transformed into chiral nitrile **8**, and the ee value could be maintained. The Swern oxidation of chiral alcohol **4a** furnished the aldehyde **9a** in 96% yield and 98% ee. Finally, carboxylic acid **10a** was synthesized from aldehyde **9a** through the oxidation of potassium permanganate.

To illustrate the potential of chiral 3-oxa-BCHeps as *meta*-benzene bioisosteres, the chiral analogue (*S*)-**11** of marketed anticancer drug Sonidegib[67] was synthesized from the chiral **4p** (Scheme 7). After Swern oxidation and subsequent Pinnick oxidation, chiral carboxylic acid **10b** was furnished in a good yield with 96% ee. The obtained acid **10b** went through condensation with 6-(2,6-dimethylmorpholino)pyridin-3-amine to give chiral analogue (*S*)-**11** with 80% yield and the retentive ee. Furthermore, the chiral analogue (*S*)-**11** was tested for CYP inhibition. For CYP2C9 and CYP2C19 inhibition, the chiral analogue (*S*)-**11** showed improvement compared with the benzene-containing Sonidegib. For CYP1A2, CYP2D6, and CYP3A4 inhibition, parallel properties were found between chiral (*S*)-**11** and Sonidegib.

Furthermore, with the single-crystal X-ray structure[68] of **4b** (see details in the Supporting Information), the detailed geometric properties of chiral 3-oxa-BCHeps obtained through

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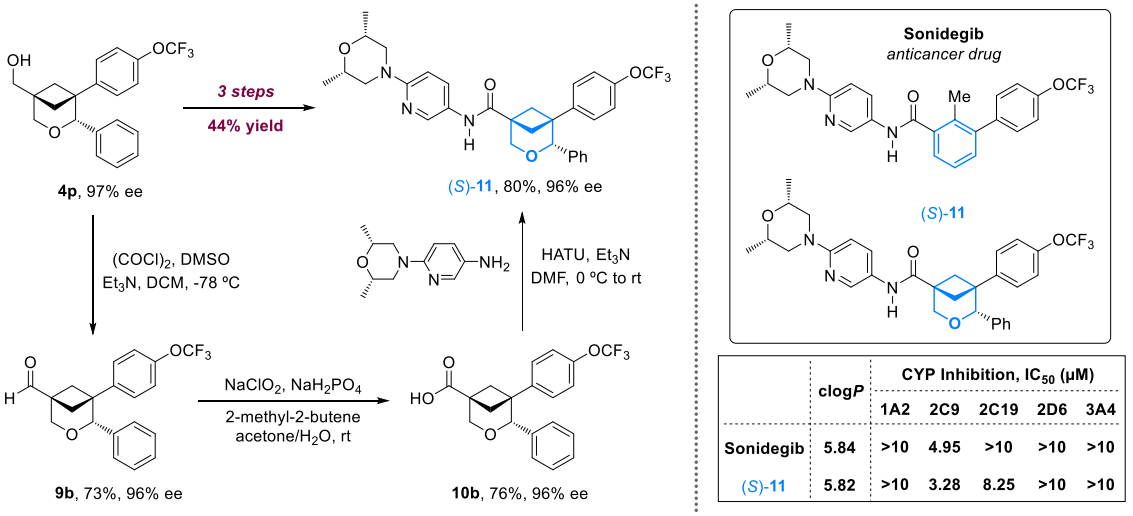
Scheme 7. Synthesis and Property Assessment of Chiral Analogue of Sonidegib



	clog*P*	CYP Inhibition, IC_{50} (μM)				
		1A2	2C9	2C19	2D6	3A4
Sonidegib	5.84	>10	4.95	>10	>10	>10
(*S*)-11	5.82	>10	3.28	8.25	>10	>10

this protocol came to light. As shown in Figure 1, geometric properties, including two substituent vector angles and two C−C distances, were considered. The exit vector angle α is 8.9°, and the out-of-plane vector angle ϕ is 119.3° (Figure 1a). C−C distances r and d were 2.118 and 4.769 Å (Figure 1b), respectively. These values are excellent in accordance with those of *meta*-substituted benzenes.[23,38,39] The analogous geometric properties further validate chiral 3-oxa-BCHeps **2** and **4** as bioisosteres of *meta*-substituted benzenes.

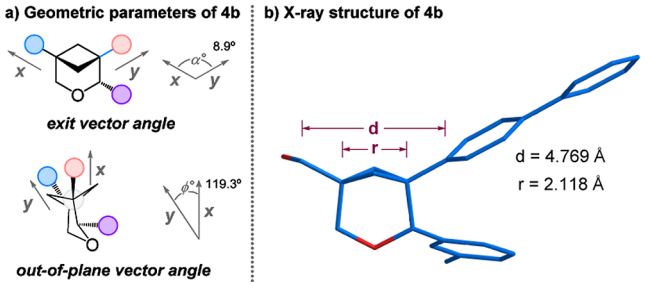
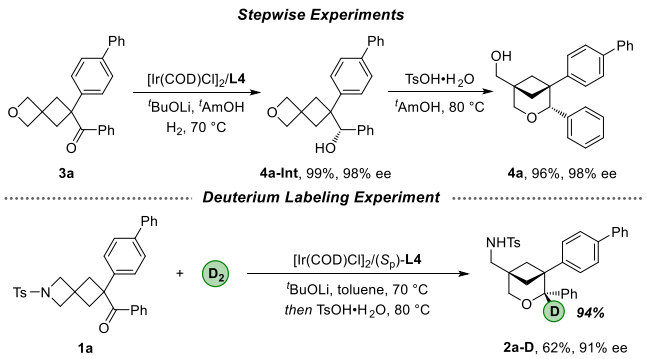


Figure 1. Geometric properties of chiral 3-oxa-BCHep **4b**. (a) Geometric parameters of **4b**. (b) X-ray structure of 4b.

To shed light on this iridium-catalyzed asymmetric hydrogenation and sequential cyclization, mechanism study experiments were conducted (Scheme 8).

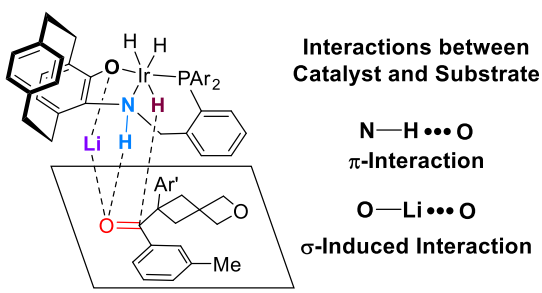
Scheme 8. Mechanism Study Experiments



First, we performed stepwise experiments to investigate the detailed reaction pathway. Chiral spirocyclic alcohol intermediate **4a-Int** was obtained in 99% isolated yield and 98% ee from spirocyclic oxetanyl ketone **3a** under the conditions of asymmetric hydrogenation with $[Ir(COD)Cl]_2$ and PNO ligand **L4**. Afterward, **4a-Int** and *p*-toluenesulfonic acid monohydrate in 2-methyl-2-butanol were heated to 80 °C for 4 h to afford 3-oxa-BCHeps **4a**, the yield and enantioselectivity were consistent with those gained in Scheme 4. These results illustrated that **4a-Int** should be the intermediate of the iridium-catalyzed asymmetric hydrogenation and sequential cyclization produced the desired chiral 3-oxa-BCHeps. Besides, for further clarification, the deuterium labeling experiment was carried out. Under a deuterium atmosphere instead of the hydrogen gas, **2a-D** with 94% deuterium incorporation was observed when toluene was used as the solvent. The deuterium labeling experiment further demonstrated the cyclization was accomplished by the attack of azetidine or oxetane with a hydroxyl group, which was generated through iridium-catalyzed asymmetric hydrogenation.

With the confined absolute configuration of **4b** and previous literature reports,[62,63,69,70] the enantiocontrol model of an iridium-catalyzed hydrogenation of spirocyclic ketone is proposed in Scheme 9. The superior chiral environment of the chiral ligand and both the O−Li···O and N−H···O interactions between the chiral catalyst and substrate would be beneficial for the excellent control of enantioselectivity.

Scheme 9. Proposed Enantiocontrol Model



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CONCLUSION

In conclusion, an unprecedented iridium-catalyzed asymmetric hydrogenation/cyclization strategy has been established for the rapid synthesis of the chiral 3-oxa-BCHeps. This approach is compatible for both spirocyclic azetidinyl ketones and spirocyclic oxetanyl ketones, providing a series of chiral polysubstituted 3-oxa-BCHeps bearing amino and hydroxyl functional groups with excellent yields and enantioselectivities. The synthetic potential and utility of this protocol were verified by the scale-up reaction, diverse transformations, and synthesis of chiral analogue of anticancer drug Sonidegib. Moreover, the stepwise experiments and deuterium labeling experiments were conducted to elucidate the detailed reaction mechanism. We anticipate that this catalytic asymmetric strategy will open up new opportunities in the structurally versatile construction of chiral bicyclic bioisosteres. Further efforts are currently ongoing in our laboratory toward the application of this methodology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c05947.

Detailed experimental procedures, characterization of new compounds, spectra, and X-ray data (PDF)
Data for **4b** (2417371) (CIF)
Data for **4l** (2418087) (CIF)

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Notes

The authors declare no competing financial interest.

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