Synthesis of Chiral Tetrahydro-3-benzazepine Motifs by Iridium-Catalyzed Asymmetric Hydrogenation of Cyclic Ene-carbamates
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ABSTRACT: A highly efficient N,P-ligated iridium complex is presented for the simple preparation of chiral tetrahydro-3-benzazepine motifs by catalytic asymmetric hydrogenation. Substrates bearing both 1-aryl and 1-alkyl substituents were smoothly converted to the corresponding hydrogenated product with excellent enantioselectivity (91−99% ee) and in isolated yield (92−99%). The synthetic value of this transformation was demonstrated by a gram-scale hydrogenation and application in the syntheses of trepipam and fenoldopam.

Benzazepines represent common structural motifs in biologically active compounds. Widespread applications have been found in drug molecules, and various substituted tetrahydro-3-benzazepines have been evaluated pharmacologically in the past. Among these, several 1-substituted tetrahydro-3-benzazepines have tested positively as drug candidates against various diseases. For example, fenoldopam shows blood-pressure-reducing abilities, SCH-23390 is an excellent D1 receptor antagonist, and lorcaserin acts as an antiobesity drug (Figure 1).

Numerous racemic syntheses of 1-substituted tetrahydro-3-benzazepines have been developed, enabled mostly by intramolecular Friedel–Crafts-type alkylation, ring enlargement, reductive cyclization, or arylation. Despite their importance, fewer enantioselective methods have been developed to access enantioenriched products. The reported asymmetric methodologies mainly rely on a chiral pool approach, auxiliary strategy, or catalytic asymmetric synthesis. However, the catalytic asymmetric approaches that have been developed thus far do not focus on the synthesis of benzazepine motifs but rather show a single application of the obtained chiral products in the synthesis of a benzazepine. For example, the elegant contributions of Wu, Riera, and Chen and Zhang can all yield chiral 1-substituted benzazepine motifs after several transformations but have only been demonstrated once (Scheme 1a−c).

Scheme 1. Representative Catalytic Approaches to Chiral 1-Substituted Tetrahydro-3-benzazepine Motifs and This Work

a) Wu, 2013
b) Riera, 2019
c) Chen and Zhang, 2021
d) This work
Over the past decades, asymmetric hydrogenation using hydrogen gas has proven to be one of the most efficient methods for installing chirality due to the high reactivity, enantioselectivity, and atom economy. The hydrogenation of cyclic ene-carbamate precursors, which can be prepared by a pinacol-pinacolone rearrangement, as outlined in Scheme 2, can potentially lead to the facile synthesis of valuable chiral 3-benzazepine structures. Inspired by our previous success in the hydrogenation of cyclic motifs, we were encouraged to elaborate a novel asymmetric strategy for the preparation of chiral 3-benzazepines (Scheme 1d). In addition, the obtained methodology was applied in the synthesis of biologically relevant compounds.

Initially, several structurally diverse chiral N,P-ligated iridium complexes were evaluated in the hydrogenation of model substrate 1a (Table 1, entries 1–4). To our delight, catalyst A was shown to be very efficient and provided full and clean conversion toward the desired product 2a with 99% ee when 1 mol % of catalyst was used in dichloromethane (DCM) under 100 bar of hydrogen atmosphere. Decreasing the catalyst loading or the hydrogen pressure negatively affected the conversion, whereas the high enantioselectivity was retained (entries 5 and 6).

Having established an effective catalytic system, we began to investigate the generality of this iridium-catalyzed asymmetric hydrogenation of cyclic ene-carbamates (Scheme 3). Starting with electron-rich dimethoxy-substituted benzazepine motifs, both the model substrate 1a and different para-substituted 1-aryl-ene-carbamates (1b–1d) were hydrogenated with excellent enantioselectivity (96–99% ee) and in high isolated yield (>95%). Increasing the number of substituents did not give any change in stereoselectivity, and both phenol- and methoxy-
derived benzazepines 2e and 2f were obtained in 99% ee. Changing the dimethoxy substituent pattern to a 1,3-benzodioxole motif was well tolerated, giving 95 and 96% ee for the hydrogenation of 1g and 1h, respectively. Decreasing the electron density on the benzazepine motif to monomethoxy did not affect the enantioselectivity, and substrates 1i–1k were hydrogenated smoothly. Further decreasing the electronic properties to a fluorine-substituted core motif slightly decreased the enantioselectivity to 94% ee (2l); however, introducing a methoxy group to the para position of the 1-aryl substituent enhanced the stereoselective outcome to 96% ee (2m). The size of the carbamate group had little effect on the reactivity or selectivity, and methyl-, ethyl-, and benzyl-ene-carbamates 1n–1p were all hydrogenated with excellent enantioselectivities of 96–99% ee. Changing the ring size had a minor effect, and the eight-membered cyclic carbamate 2q was obtained with 95% ee. Unfortunately, the hydrogenation of N-methyl enamine 2r was found to inhibit the hydrogenation. The amine most likely forms a strong chelate with the catalyst, preventing hydrogenation from occurring. Alternatively, it might deprotonate the acidic hydrogenation.

We then further explored substrates having an alkyl substituent on the ene-carbamate to access 1-alkyl tetrahydro benzazepine scaffolds (Scheme 4). The methyl-substituted ene-carbamate 3a was hydrogenated with 91% ee. Increasing the alkyl-chain length to n-butyl enhanced the enantioselectivity to 99% ee (4b). Both i-butyl- and i-propyl-substituted benzazepines were obtained with slightly decreased enantioselectivities of 94 and 93% ee, respectively (4c and 4d). On the contrary, the benzyl-substituted benzazepine 4e was accessed with an excellent enantioselectivity of 99% ee. Satisfactorily, all chiral alkyl-substituted benzazepines 4a–e could be isolated in high yields.

To demonstrate the scalability of this asymmetric protocol, we carried out the gram-scale hydrogenation of ene-carbamate 1a with the same reactivity and selectivity, and the desired chiral benzazepine 2a was obtained in 98% yield with 99% ee (Scheme 5a). Treating the obtained hydrogenated product 2a with an excess of LiAlH4 in MeOH reduced the carbamate group to methylamine to elaborate (S)-trepipam in 92% yield, exemplifying the synthetic utility of this asymmetric hydrogenation methodology. Further application was demonstrated by the synthesis of blood-pressure-reducing agent (S)-fenoldopam (Scheme 5b). The hydrogenation of 1s proceeded smoothly, giving the corresponding tetrahydro-3-benzazepine 2s with 99% ee. Subsequent hydrogenation of the isolated product in the presence of Pd/C led to the cleavage of the Cbz-group. Thereafter, 2t could be transformed to (S)-fenoldopam, as previously described. To the best of our knowledge, no asymmetric synthesis of fenoldopam was previously disclosed.

Because the absolute configuration of trepipam is reported, we were able to confirm the stereoselective outcome of the hydrogenation by comparing the sign of optical rotation of our synthetic trepipam with that reported. This confirmed the absolute configuration of product 2a to be the (S)-enantiomer. On the basis of computational and experimental studies, a quadrant model has been developed to predict the stereochemical outcome in the iridium-catalyzed asymmetric hydrogenation of olefins using bidentate N,P-ligands. It is suggested that olefins preferentially coordinate trans to phosphorus and that steric interactions between the ligand and the olefin are the origin of the enantioselection (Figure 2a). As a consequence of the encumbered chiral ligand around the iridium center, the coordinated olefin experiences steric hindrance from either the lower or the upper left quadrant. To minimize steric interactions, the smallest hydrogen substituent of the olefin arranges itself to point toward the bulk of the ligand, which in this case occupies the lower left quadrant iii. Thereby, the coordinated enantiotopic face is locked. The quadrant model, where the hydride is delivered from the bottom, then predicts the enantiotopic outcome of the hydrogenation (Figure 2b). Because the absolute configuration of 2a was confirmed to be the (S)-enantiomer, we were able to validate the developed quadrant model that indeed predicted the stereochemical outcome for the hydrogenation of this class of cyclic ene-carbamates correctly (Figure 2c).

In summary, we herein described the straightforward and operationally simple synthesis of chiral 3-benzazepines by the
iridium-catalyzed asymmetric hydrogenation of cyclic ene-carbamates. A series of 1-aryl- and 1-alkyl-substituted benzazepines were accessed with excellent enantioselectivity (91−99% ee) and in high isolated yield (92−99%). The methodology was shown to be scalable to at least a gram scale. Furthermore, the synthetic utility was highlighted in the enantioselective preparation of trepipam and fenoldopam.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00362.

Experimental procedures, characterization data of new compounds, separation of chiral products, and NMR spectra of new compounds (PDF)

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**Notes**

The authors declare no competing financial interest.

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