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Letter

Synthesis of Chiral Tetrahydro-3-benzazepine Motifs by Iridium-Catalyzed Asymmetric Hydrogenation of Cyclic Ene-carbamates

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Cite This: *Org. Lett.* 2022, 24, 1969−1973

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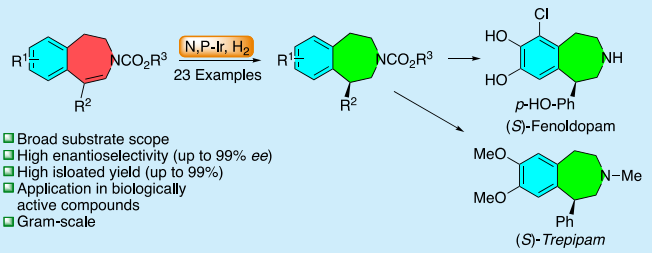
ABSTRACT: A highly efficient N,P-ligated iridium complex is presented for the simple preparation of chiral tetrahydro-3-benzazepine motifs by catalytic asymmetric hydrogenation. Substrates bearing both 1-aryl and 1-alkyl substituents were smoothly converted to the corresponding hydrogenated product with 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.[1] 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,[2] SCH-23390 is an excellent D_1 receptor antagonist,[3] and lorcaserin acts as an antiobesity drug (Figure 1).[4]

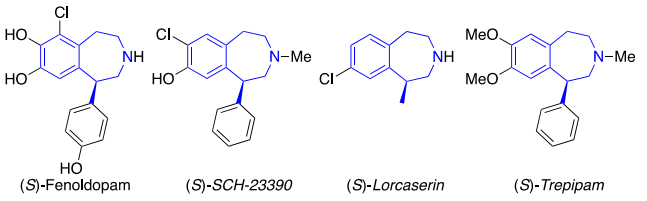
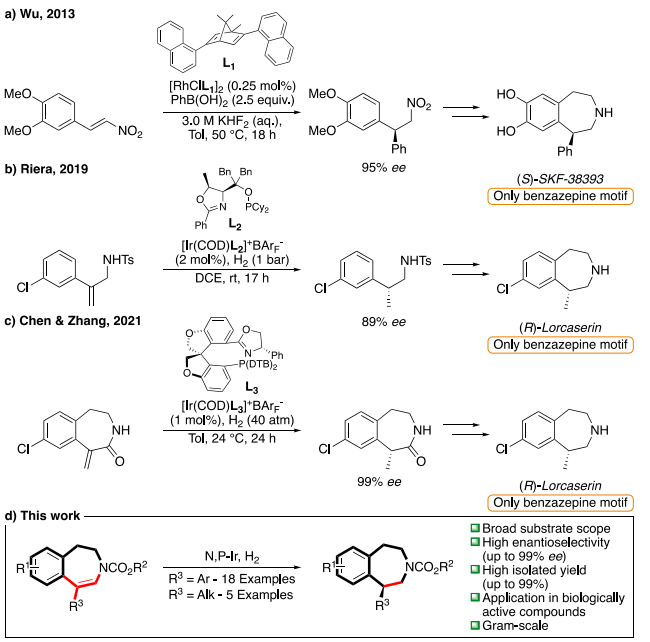


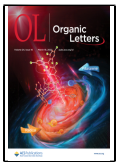
Figure 1. Representative chiral 1-substituted tetrahydro-3-benzazepine drugs.

Numerous racemic syntheses of 1-substituted tetrahydro-3-benzazepines have been developed, enabled mostly by intramolecular Friedel−Crafts-type alkylation,[5] ring enlargement,[6] reductive cyclization,[7] or arylation.[8] Despite their importance, fewer enantioselective methods have been developed to access enantioenriched products. The reported asymmetric methodologies mainly rely on a chiral pool approach,[9] auxiliary strategy,[10] or catalytic asymmetric synthesis.[11] 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,[11a] Riera,[11b] and Chen and Zhang[11c] 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

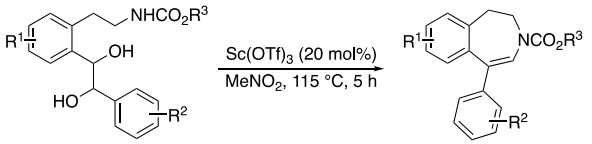


Received: February 3, 2022
Published: March 3, 2022



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.[12] The hydrogenation of cyclic ene-carbamate precursors, which can be prepared by a pinacol–pinacolone rearrangement, as outlined in Scheme 2,[13] can

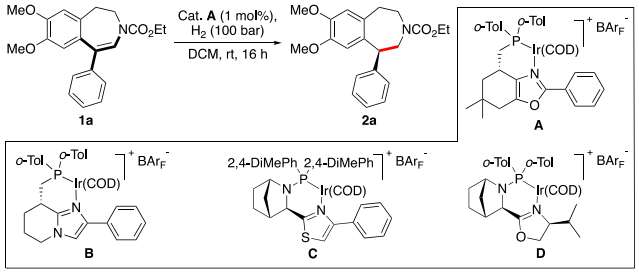
Scheme 2. Synthesis of Cyclic Ene-carbamates



potentially lead to the facile synthesis of valuable chiral 3-benzapine structures. Inspired by our previous success in the hydrogenation of cyclic motifs,[14] 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**

Table 1. Optimization of Reaction Conditions[a]



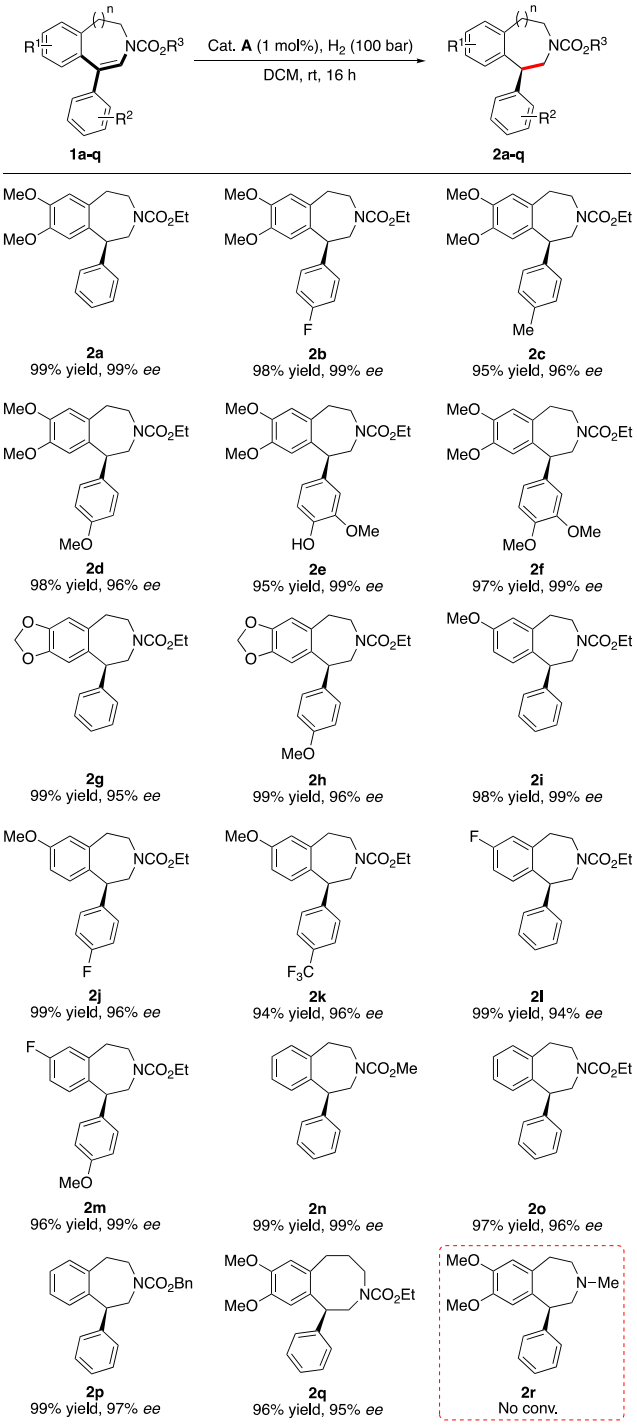
entry	deviation from above	conv. (%)	*ee* (%)
1	no	full	99 (*S*)
2	Cat. **B** instead of Cat. **A**	80	80 (*S*)
3	Cat. **C** instead of Cat. **A**	full	97 (*R*)
4	Cat. **D** instead of Cat. **A**	71	33 (*R*)
5	0.5 mol % Cat. **4A** instead of 1 mol %	73	99 (*S*)
6	50 bar H_2 instead of 100 bar	94	99 (*S*)

[a]Reactions were performed using 0.05 mmol **1a** in 1 mL of DCM. Conversion was determined using ^{1}H NMR spectroscopy. The enantiomeric excess was determined by supercritical fluid chromatography (SFC) analysis using Chiralcel OJ-H chiral stationary phase. The stereochemistry was assigned by a comparison of the optical rotation with reported values after the reduction of **2a** by $LiAlH_4$.

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

Scheme 3. Asymmetric Hydrogenation of Aryl-Substituted Ene-carbamates[a]



[a]Reaction conditions: 0.05 mmol substrate, 1 mol % **A**, 1 mL of DCM, 100 bar H_2, 16 h, rt. The stereochemistry was tentatively assigned by assuming a similar hydrogenation pathway as that of **1a**, the absolute configuration of which was assigned by comparing the sign of the optical rotation with the literature value after the reduction of **2a** with $LiAlH_4$. Isolated yields. Enantiomeric excess was determined by SFC analysis using chiral stationary phases.

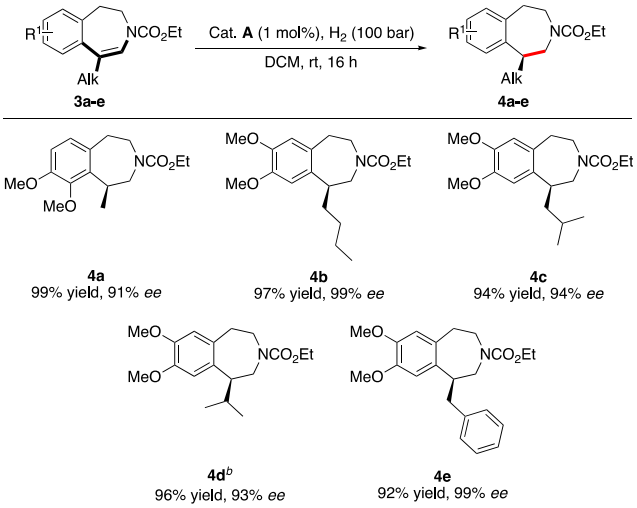
ene-carbamates (**1b–1d**) were hydrogenated with excellent enantioselectivity (96–99% *ee*) and in high isolated yield (>95%). Increasing the number of substituents did not give any change in stereoselectivity, and both phenol- and methoxy-

https://doi.org/10.1021/acs.orglett.2c00362
Org. Lett. 2022, 24, 1969–1973

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 stereochemical 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 iridium−dihydride complex.[15]

We then further explored substrates having an alkyl substituent on the ene-carbamate to access 1-alkyl tetrahydro benzazepine scaffolds (Scheme 4).[16] The methyl-substituted

Scheme 4. Asymmetric Hydrogenation of Alkyl-Substituted Ene-carbamates[a]

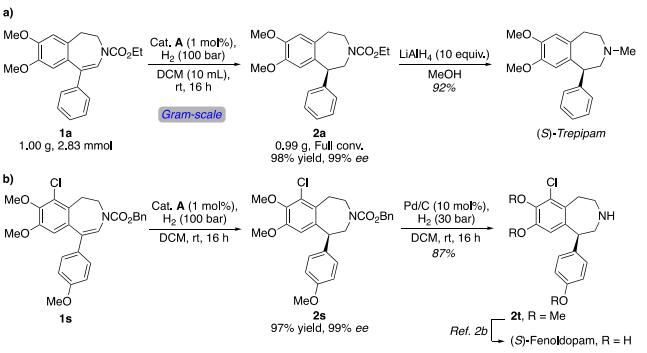


[a]Reaction conditions: 0.05 mmol substrate, 1 mol % **A**, 1 mL of DCM, 100 bar H_2, 16 h, rt, unless stated otherwise. The stereochemistry was tentatively assigned by assuming a similar hydrogenation pathway to **1a**, the absolute configuration of which was assigned by comparing the sign of the optical rotation with the literature value after the reduction of **2a** with $LiAlH_4$. Isolated yields. Enantiomeric excess was determined by SFC analysis using chiral stationary phases. [b]2 mol % **A** was used.

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

Scheme 5. Gram-Scale Asymmetric Hydrogenation and Applications



excess of $LiAlH_4$ 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.[2b] To the best of our knowledge, no asymmetric synthesis of fenoldopam was previously disclosed.[2b,17]

Because the absolute configuration of trepipam is reported, we were able to confirm the stereochemical 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.[18] 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 enantiomerical 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

https://doi.org/10.1021/acs.orglett.2c00362
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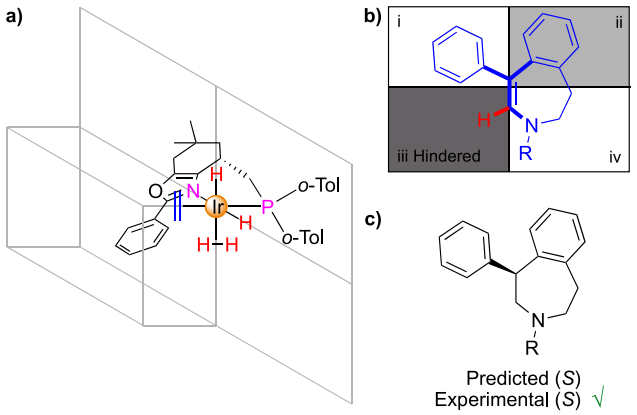

Figure 2. Stereoselectivity model. (a) Coordination of oxazole ligand and olefin to the iridium center. (b) Quadrant model based on the steric influence of the ligand seen from the olefin. (c) Predicted and experimental stereochemical outcomes for the hydrogenation of enecarbamates.

iridium-catalyzed asymmetric hydrogenation of cyclic enecarbamates. 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.

■ ACKNOWLEDGMENTS

We thank the Swedish Research Council (VR), the Knut and Alice Wallenberg foundation (KAW 2016:0072 and KAW 2018:0066), and Stiftelsen Olle Engkvist Byggmästare for their financial support. We deeply appreciate the generous financial support from the Development and Promotion of Science and Technology Talents Project (DPST; 022/2558 for W.I.) under the Institute for the Promotion of Teaching Science and Technology (IPST), Thailand Science Research and Innovation (TSRI), Chulabhorn Research Institute (grant no. 2536703/42320), and Center of Excellence on Environmental Health and Toxicology (EHT).

■ REFERENCES

(1) For reviews, see: (a) Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. Recent Progress in Development of Dopamine Receptor Subtype-Selective Agents: Potential Therapeutics for Neurological and Psychiatric Disorders. *Chem. Rev.* **2007**, *107*, 274−302. (b) Zhang, J.; Xiong, B.; Zhen, X.; Zhang, A. Dopamine D_1 receptor ligands: Where are we now and where are we going. *Med. Res. Rev.* **2009**, *29*, 272−294. (c) Danyliuk, I. Y.; Vas'kevich, R. I.; Vas'kevich, A. I.; Vovk, M. V. Hydrogenated Benzazepines: Recent Advances in the Synthesis and Study of Biological Activity. *Chem. Heterocycl. Compd.* **2019**, *55*, 802−814.

(2) (a) Ladd, D. L.; Weinstock, J.; Wise, M.; Gessner, G. W.; Sawyer, J. L.; Flaim, K. E. Synthesis and Dopaminergic Binding of 2-Aryldopamine Analogues: Phenethylamines, 3-Benzazepines, and 9-(Aminomethyl)fluorenes. *J. Med. Chem.* **1986**, *29*, 1904−1912. (b) Weinstock, J.; Ladd, D. L.; Wilson, J. W.; Brush, C. K.; Yim, N. C. F.; Gallagher, G.; McCarthy, M. E.; Silvestri, J.; Sarau, H. M. Synthesis and Renal Vasodilator Activity of Some Dopamine Agonist 1-Aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diols: Halogen and Methyl Analogues of Fenoldopam. *J. Med. Chem.* **1986**, *29*, 2315−2325.

(3) Hyttel, J. SCH 23390 − the First Selective Dopamine D-1 Antagonist. *Eur. J. Pharmacol.* **1983**, *91*, 153−154.

(4) (a) Smith, B. M.; Smith, J. M.; Tsai, J. H.; Schultz, J. A.; Gilson, C. A.; Estrada, S. A.; Chen, R. R.; Park, D. M.; Prieto, E. B.; Gallardo, C. S.; Sengupta, D.; Thomsen, W. J.; Saldana, H. R.; Whelan, K. T.; Menzaghi, F.; Webb, R. R.; Beeley, N. R. A. Discovery and SAR of New Benzazepines as Potent and Selective 5-HT_{2C} Receptor Agonists for the Treatment of Obesity. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1467−1470. (b) Smith, B. M.; Smith, J. M.; Tsai, J. H.; Schultz, J. A.; Gilson, C. A.; Estrada, S. A.; Chen, R. R.; Park, D. M.; Prieto, E. B.; Gallardo, C. S.; Sengupta, D.; Dosa, P. I.; Covel, J. A.; Ren, A.; Webb, R. R.; Beeley, N. R. A.; Martin, M.; Morgan, M.; Espitia, S.; Saldana, H. R.; Bjenning, C.; Whelan, K. T.; Grottick, A. J.; Menzaghi, F.; Thomsen, W. J. Discovery and Structure-Activity Relationship of (1*R*)-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (Lorcaserin), a Selective Serotonin 5-HT_{2C} Receptor Agonist for the Treatment of Obesity. *J. Med. Chem.* **2008**, *51*, 305−313.

(5) For selected examples, see: (a) Fuchs, J. R.; Funk, R. L. Intramolecular Electrophilic Aromatic Substitution Reactions of 2-Amidoacroleins: A New Method for the Preparation of Tetrahydroisoquinolines, Tetrahydro-3-benzazepines, and Hexahydro-3-benzazocines. *Org. Lett.* **2001**, *3*, 3349−3351. (b) Zhu, Q.; Wang, J.; Bian, X.; Zhang, L.; Wei, P.; Xu, Y. Novel Synthesis of Antiobesity Drug Lorcaserin Hydrochloride. *Org. Process Res. Dev.* **2015**, *19*, 1263−1267. (c) Giri, R.; Namballa, H. K.; Sarker, A.; Alberts, I.; Harding, W. W.

Synthesis and Dopamine Receptor Pharmacological Evaluations on Ring C *ortho* Halogenated 1-Phenylbenzazepines. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127305.
(6) Xing, S.; Gu, N.; Wang, X.; Liu, J.; Xing, C.; Wang, K.; Zhu, B. Substitution-Controlled Selective Formation of Hexahydrobenz[*e*]-isoindoles and 3-Benzazepines via $In(OTf)_3$-Catalyzed Tandem Annulations. *Org. Lett.* **2018**, *20*, 5680−5683.
(7) Krull, O.; Wünsch, B. Synthesis and Structure/NMDA Receptor Affinity Relationships of 1-Substituted Tetrahydro-3-benzazepines. *Bioorg. Med. Chem.* **2004**, *12*, 1439−1451.
(8) Singh, K. N.; Singh, P.; Sharma, E.; Kaur, M.; Deol, Y. S. Aryne-Mediated Arylation of the 3-Benzazepine Scaffold: One-Pot Synthesis of 1-Aryl-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines. *Synthesis* **2015**, *47*, 3212−3220.
(9) (a) Damsen, H.; Niggemann, M. Calcium-Catalyzed Synthesis of 1,2-Disubstituted 3-Benzazepines. *Eur. J. Org. Chem.* **2015**, *2015*, 7880−7883. (b) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. Enantiospecific Synthesis of (+)-(*R*)-1-Phenyl-3-methyl-1,2,4,5-tetrahydrobenz[*d*]azepine From (+)-(*S*)-*N*-Methyl-1-phenyl Ethanolamine (Halostachine) via Arene Chromium Tricarbonyl Methodology. *Tetrahedron Lett.* **1989**, *30*, 3581−3584. (c) Smilovic, I. G.; Cluzeau, J.; Richter, F.; Nerdinger, S.; Schreiner, E.; Laus, G.; Schottenberger, H. Synthesis of Enantiopure Antiobesity Drug Lorcaserin. *Bioorg. Med. Chem.* **2018**, *26*, 2686−2690.
(10) (a) Sarkar, S.; Schepmann, D.; Wünsch, B. Asymmetric synthesis of Enantiomerically Pure 1,4-Di- and 1,1,4-Trisubstituted Tetrahydro-1*H*-3-benzazepines. *Tetrahedron: Asymmetry* **2011**, *22*, 1411−1422. (b) Masood Husain, S.; Fröhlich, R.; Wünsch, B. A Very Short Asymmetric Synthesis of Enantiomerically Pure Methyl Substituted Tetrahydro-3-benzazepines. *Tetrahedron: Asymmetry* **2008**, *19*, 1613−1616. (c) Husain, S. M.; Heim, M. T.; Schepmann, D.; Wünsch, B. Asymmetric Synthesis and σ Receptor Affinity of Enantiomerically Pure 1,4-Disubstituted Tetrahydro-1*H*-3-benzazepines. *Tetrahedron: Asymmetry* **2009**, *20*, 1383−1392. (d) Wirt, U.; Schepmann, D.; Wünsch, B. Asymmetric Synthesis of 1-Substituted Tetrahydro-3-benzazepines as NMDA Receptor Antagonists. *Eur. J. Org. Chem.* **2007**, *2007*, 462−475. (e) Sarkar, S.; Schepmann, D.; Köhler, J.; Fröhlich, R.; Wünsch, B. Aymmetric Synthesis of Potent and Selective σ_1 Receptor Ligands with Tetrahydro-3-benzazepine Scaffold. *Eur. J. Org. Chem.* **2012**, *2012*, 5980−5990.
(11) (a) Huang, K.-C.; Gopula, B.; Kuo, T.-S.; Chiang, C.-W.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to β-Nitroolefins: Formal Synthesis of (*S*)-SKF 38393. *Org. Lett.* **2013**, *15*, 5730−5733. (b) Cabré, A.; Verdaguer, X.; Riera, A. Enantioselective Synthesis of β-Methyl Amines *via* Iridium-Catalyzed Asymmetric Hydrogenation of *N*-Sulfonyl Allyl Amines. *Adv. Synth. Catal.* **2019**, *361*, 4196−4200. (c) Ye, X.-Y.; Liang, Z.-Q.; Jin, C.; Lang, Q.-W.; Chen, G.-Q.; Zhang, X. Design of Oxa-spirocyclic PHOX Ligands for the Asymmetric Synthesis of Lorcaserin *via* Iridium-Catalyzed Asymmetric Hydrogenation. *Chem. Commun.* **2021**, *57*, 195−198. (d) Hostmann, T.; Molloy, J. J.; Bussmann, K.; Gilmour, R. Light-Enabled Enantiodivergence: Stereospecific Reduction of Activated Alkenes Using a Single Organocatalyst Enantiomer. *Org. Lett.* **2019**, *21*, 10164−10168. (e) Roagna, G.; Ascough, D. M. H.; Ibba, F.; Vicini, A. C.; Fontana, A.; Christensen, K. E.; Peschiulli, A.; Oehlrich, D.; Misale, A.; Trabanco, A. A.; Paton, R. S.; Pupo, G.; Gouverneur, V. Hydrogen Bonding Phase-Transfer Catalysis with Ionic Reactants: Enantioselective Synthesis of γ-Fluoroamines. *J. Am. Chem. Soc.* **2020**, *142*, 14045−14051. (f) Li, B.; Aliyu, M. A.; Gao, Z.; Li, T.; Dong, W.; Li, J.; Shi, E.; Tang, W. General Synthesis of Chiral α,α-Diaryl Carboxamides by Enantioselective Palladium-Catalyzed Cross-Coupling. *Org. Lett.* **2020**, *22*, 4974−4978.
(12) Selected reviews: (a) Chirik, P. J. Iron- and Cobalt-Catalyzed Alkene Hydrogenation: Catalysis with Both Redox-Active and Strong Field Ligands. *Acc. Chem. Res.* **2015**, *48*, 1687−1695. (b) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. Asymmetric Hydrogenation of Olefins Using Chiral Crabtree-type Catalysts: Scope and Limitations. *Chem. Rev.* **2014**, *114*, 2130−2169. (c) Etayo, P.; Vidal-Ferran, A. Rhodium-Catalysed Asymmetric Hydrogenation as a Valuable Synthetic Tool for the Preparation of Chiral Drugs. *Chem. Soc. Rev.* **2013**, *42*, 728−754.
(13) Ieawsuwan, W.; Pingaew, R.; Kunkaewom, S.; Ploypradith, P.; Ruchirawat, S. Scandium(III)-Triflate-Catalyzed Pinacol-Pinacolone Rearrangement and Cyclization of 1,2-Diaryl-1,2-Ethanediol: A Versital Synthesis of 1-Aryl-2,3-Dihydro-1*H*-3-Benzazepines. *Asian J. Org. Chem.* **2019**, *8*, 1441−1447.
(14) Selected examples: (a) Zheng, J.; Jongcharoenkamol, J.; Peters, B. B. C.; Guhl, J.; Ponra, S.; Ahlquist, M. S. G.; Andersson, P. G. Iridium-Catalysed Enantioselective Formal Deoxygenation of Racemic Alcohols *via* Asymmetric Hydrogenation. *Nat. Catal.* **2019**, *2*, 1093−1100. (b) Liu, J.; Krajangsri, S.; Singh, T.; De Seriis, G.; Chumnanvej, N.; Wu, H.; Andersson, P. G. Regioselective Iridium-Catalyzed Asymmetric Monohydrogenation of 1,4-Dienes. *J. Am. Chem. Soc.* **2017**, *139*, 14470−14475. (c) Zhou, T.; Peters, B.; Maldonado, M. F.; Govender, T.; Andersson, P. G. Enantioselective Synthesis of Chiral Sulfones by Ir-Catalyzed Asymmetric Hydrogenation: A Facile Approach to the Preparation of Chiral Allylic and Homoallylic Compounds. *J. Am. Chem. Soc.* **2012**, *134*, 13592−13595.
(15) (a) Pearson, R. G. The Transition-Metal-Hydrogen Bond. *Chem. Rev.* **1985**, *85*, 41−49. (b) Morris, R. H. Brønsted-Lowry Acid Strength of Metal Hydride and Dihydrogen Complexes. *Chem. Rev.* **2016**, *116*, 8588−8654. (c) Zhu, Y.; Fan, Y.; Burgess, K. Carbene-Metal Hydrides Can Be Much Less Acidic Than Phosphine-Metal Hydrides: Significance in Hydrogenations. *J. Am. Chem. Soc.* **2010**, *132*, 6249−6253.
(16) For the synthesis of alkyl-substituted ene-carbamates **3a**−**e**, see the Supporting Information.
(17) For achiral syntheses of Fenoldopam, see ref 2b and: Weinstock, J.; Wilson, J. W.; Ladd, D. L.; Brush, C. K.; Pfeiffer, F. R.; Kuo, G. Y.; Holden, K. G.; Yim, N. C. F.; Hahn, R. A.; Wardell, J. R., Jr.; Tobia, A. J.; Setler, P. E.; Sarau, H. M.; Ridley, P. T. Separation of Potent Central and Renal Dopamine Agonist Activity in Substituted 6-Chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepines. *J. Med. Chem.* **1980**, *23*, 973−975.
(18) (a) Brandt, P.; Hedberg, C.; Andersson, P. G. New Mechanistic Insights into the Iridium-Phosphanooxazoline-Catalyzed Hydrogenation of Unfunctionalized Olefins: A DFT and Kinetic Study. *Chem.—Eur. J.* **2003**, *9*, 339−347. (b) Church, T. L.; Rasmussen, T.; Andersson, P. G. Enantioselectivity in the Iridium-Catalyzed Hydrogenation of Unfunctionalized Olefins. *Organometallics* **2010**, *29*, 6769−6781. (c) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. Asymmetric Hydrogenation of Trisubstituted Olefins with Iridium-Phosphine Thiazole Complexes: A Further Investigation of the Ligand Structure. *J. Am. Chem. Soc.* **2006**, *128*, 2995−3001. (d) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. Optically Active Iridium Imidazol-2-ylidene-oxazoline Complexes: Preparation and Use in Asymmetric Hydrogenation of Arylalkenes. *J. Am. Chem. Soc.* **2003**, *125*, 113−123. (e) Fan, Y.; Cui, X.; Burgess, K.; Hall, M. B. Electronic Effects Steer the Mechanism of Asymmetric Hydrogenations of Unfunctionalized Aryl-Substituted Alkenes. *J. Am. Chem. Soc.* **2004**, *126*, 16688−16689. (f) Rageot, D.; Woodmansee, D. H.; Pugin, B.; Pfaltz, A. Proline-Based P,O Ligand/Iridium Complexes as Highly Selective Catalysts: Asymmetric Hydrogenation of Trisubstituted Alkenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 9598−9601. (g) Mazuela, J.; Norrby, P.-O.; Andersson, P. G.; Pàmies, O.; Diéguez, M. Pyranoside Phosphite-Oxazoline Ligands for the Highly Versatile and Enantioselective Ir-Catalyzed Hydrogenation of Minimally Functionalized Olefins. A Combined Theoretical and Experimental Study. *J. Am. Chem. Soc.* **2011**, *133*, 13634−13645. (h) Gruber, S.; Pfaltz, A. Asymmetric Hydrogenation with Iridium C,N and N,P Ligand Complexes: Characterization of Dihydride Intermediates with a Coordinated Alkene. *Angew. Chem., Int. Ed.* **2014**, *53*, 1896−1900.

https://doi.org/10.1021/acs.orglett.2c00362
Org. Lett. 2022, 24, 1969−1973