OL Organic Letters

pubs.acs.org/OrgLett

Letter

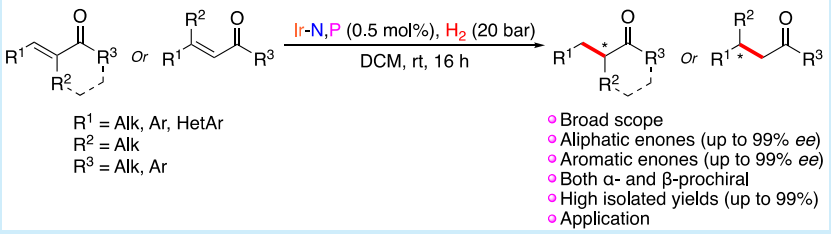
Highly Enantioselective Iridium-Catalyzed Hydrogenation of Conjugated Trisubstituted Enones

Bram B. C. Peters, Jira Jongcharoenkamol, Suppachai Krajangsri, and Pher G. Andersson*

Cite This: *Org. Lett.* 2021, 23, 242–246

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Asymmetric hydrogenation of conjugated enones is one of the most efficient and straightforward methods to prepare optically active ketones. In this study, chiral bidentate Ir−N,P complexes were utilized to access these scaffolds for ketones bearing the stereogenic center at both the α- and β-positions. Excellent enantiomeric excesses, of up to 99%, were obtained, accompanied with good to high isolated yields. Challenging dialkyl substituted substrates, which are difficult to hydrogenate with satisfactory chiral induction, were hydrogenated in a highly enantioselective fashion.

Chiral ketones bearing a stereogenic center at the α- or β-position are important compounds in organic synthesis.[1] A few reported methods to access optically active ketones include alkylation using auxiliaries,[2] catalytic asymmetric alkylation,[3] enantioselective Michael addition to unsaturated ketones,[4] or asymmetric conjugate reduction of enones.[5] However, all of the routes listed above to synthesize α- and β-chiral ketones face limitations, such as the challenge of installing/removing auxiliaries, high catalyst loading, or the use of sensitive reagents. In addition to these methods, catalytic asymmetric hydrogenation using hydrogen gas is often the method of choice, due to high enantioselectivity and atom economy. Over the years, the asymmetric olefin hydrogenation of α,β-unsaturated ketones has been reported using rhodium,[6] palladium,[7] and iridium[8] catalysts (Scheme 1).

In 2008, Hou[8c] and Bolm[8a,b] independently reported the iridium-catalyzed olefin hydrogenation of enones. Since then, several research groups have evaluated iridium catalysts using various bidentate X,P-ligands (X = N, O, S) in the asymmetric hydrogenation of α,β-unsaturated ketones resulting in moderate to high enantiomeric excesses.[8d,l] Despite the maturing of methodology for the hydrogenation of aromatic unsaturated enones, substrates having dialkyl olefin substituents are rarely reported and are hydrogenated with moderate enantioselectivity. Therefore, catalytic methodology that can hydrogenate challenging aliphatic substrates, both α- and β-prochiral, in high ee remains to be found.

In this report, the iridium-catalyzed asymmetric olefin hydrogenation of both α- and β-prochiral trisubstituted enones with high levels of stereoinduction is described. Excellent enantiomeric excesses accompanied with high isolated yields were obtained for all substrate classes (up to 96−99% ee), including aliphatic substitution patterns, which is complementary to previous reported catalytic systems for the asymmetric hydrogenation of enones.

Since limited examples on the hydrogenation of dialkyl-substituted enones have been reported, α,β-dialkyl substituted substrate **1a** was first selected as the model substrate to test the asymmetric hydrogenation of α-prochiral unsaturated ketones (Table 1). Initially, structurally diverse catalysts **A**−**D** were evaluated under 20 bar of hydrogen atmosphere in dichloromethane (DCM), resulting in poor to excellent ee (67%−99%; Table 1, entries 1−4). Although perfect enantioselection was obtained with catalyst **B**, it was accompanied with low reactivity (19% conversion). To our delight, bicyclic thiazole catalyst **E** faced higher reactivity and was very efficient, in terms of stereocontrol, giving full consumption of starting material with 99% ee of the hydrogenated product (Table 1, entry 5). The efficiency of catalyst **A** is also remarkably high, compared to the previously reported Ir−N,P catalyzed asymmetric hydrogenation of **1a**, which gave 87% ee (Scheme 1).[8b] Next, the hydrogenation of challenging β,β-dialkyl substituted enones was investigated. The use of catalysts **B**,

Received: December 3, 2020
Published: December 22, 2020

Scheme 1. Selected Examples of Previously Reported Iridium- and Rhodium-Catalyzed Asymmetric Hydrogenation of Unsaturated Enones and This Work

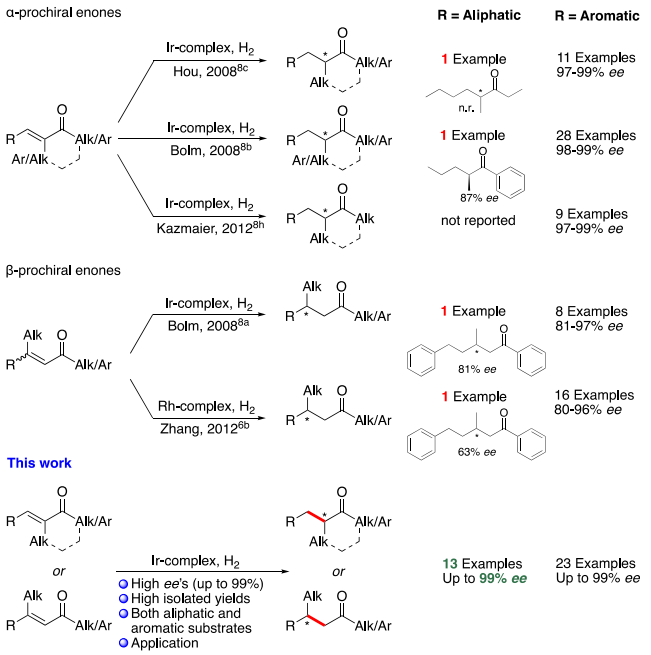
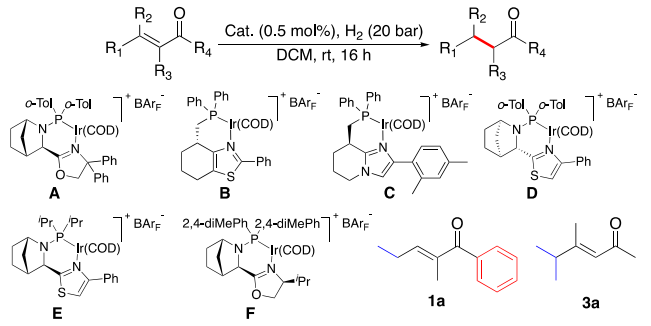


Table 1. Evaluation of Catalysts in the Hydrogenation of Aliphatic Model Substrates



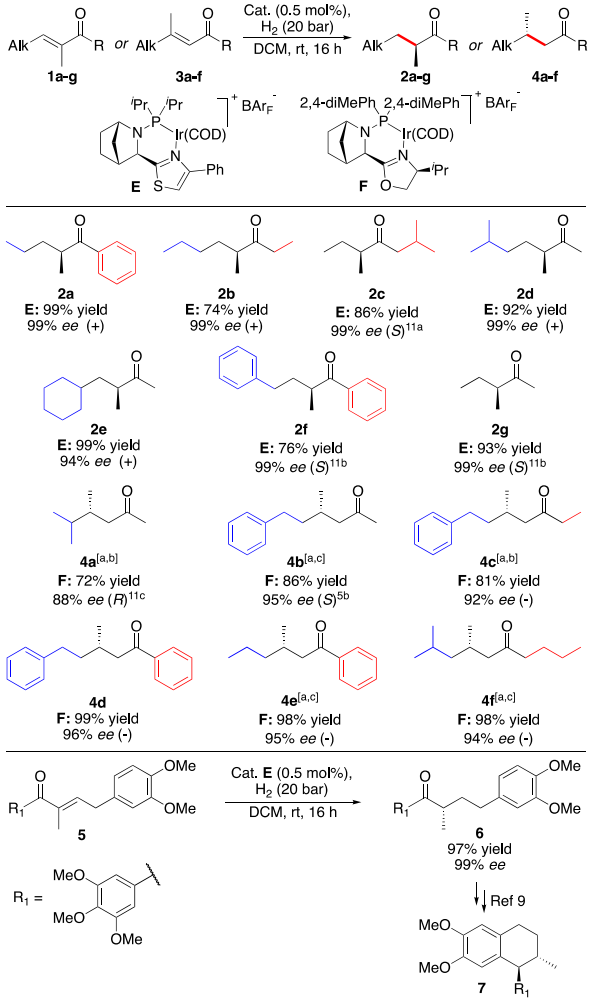
entry	substrate	catalyst	conversion (%)	enantiomeric excess, ee (%)
1	**1a**	**A**	full	94 (+)
2	**1a**	**B**	19	99 (−)
3	**1a**	**C**	78	98 (+)
4	**1a**	**D**	full	67 (−)
5	**1a**	**E**	full	99 (+)
6	**3a**	**B**	full	71 (*S*)
7	**3a**	**D**	full	11 (*S*)
8	**3a**	**E**	full	77 (*R*)
9	**3a**	**F**	full	88 (*R*)

D, and **E** on aliphatic substrate **3a** resulted in a low ee values of 71%, 11%, and 77%, respectively (Table 1, entries 6−8). Further catalyst optimization was required (see Table S2 in the Supporting Information) and with optimal oxazoline-based catalyst **F** in hand, 88% ee was obtained (Table 1, entry 9). Modification of the phosphine substituents, the oxazoline substituent, and a solvent screening did not further enhance the enantioselectivity.

As already stated, the reported hydrogenation of dialkyl-substituted enones are usually much less enantioselective, when compared to aromatic substitution patterns. Therefore, with the optimized catalysts for the hydrogenation of both classes of aliphatic conjugated trisubstituted enones in hand, the substrate scope was first further investigated for this type of substitution pattern around the olefin starting with α-prochiral substrates (Table 2).[11] Substrate **1b**, which was previously reported as not reactive (Scheme 1),[8c] was hydrogenated with equally high enantioselectivity as **1a** of 99% ee. The introduction of an *i*-butyl substituent on the olefin or the ketone scaffold gave a similar outcome of 99% ee (**1c** and **1d**). Hydrogenation of the cyclohexyl-substituted olefin **1e** proceeded with a slight decrease in ee (94%), whereas benzylic substrate **1f** and methyl-substituted enone **1g** were both well-tolerated, giving excellent selectivity of 99% ee.

Then, the substrate scope of the hydrogenation of challenging β,β-dialkyl substituted enones class was broadened using catalyst **F**. Compound **3b** was hydrogenated with 95% ee

Table 2. Asymmetric Hydrogenation of Dialkyl-Substituted Enones and Application in the Synthesis of anti-HIV Agent 7*



*Reaction conditions: 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H_2, 16 h, rt, unless stated otherwise. Absolute stereochemistry assigned by comparing optical rotation with literature values. If no reference is given then assignment is tentative. Yields given are in their isolated forms. Enantiomeric excess was determined by SFC or GC analysis, using chiral stationary phases. [a]1.0 mol % of catalyst. [b]1 bar of H_2. [c]2 bar of H_2.

https://dx.doi.org/10.1021/acs.orglett.0c04012
Org. Lett. 2021, 23, 242−246

and changing the ketone substituent to ethyl and phenyl provided good ee values of 92% and 96%, respectively (**3c** and **3d**). Compound **3d** was previously hydrogenated by iridium catalysts and rhodium catalysts (81% ee and 63% ee, respectively) with significantly lower enantiocontrol.[6b,8a] Linear *n*-propyl olefin **3e** showed good selectivity (95% ee), whereas the sterically more demanding *i*-butyl olefin substituent on substrate **3f** resulted in 94% ee.

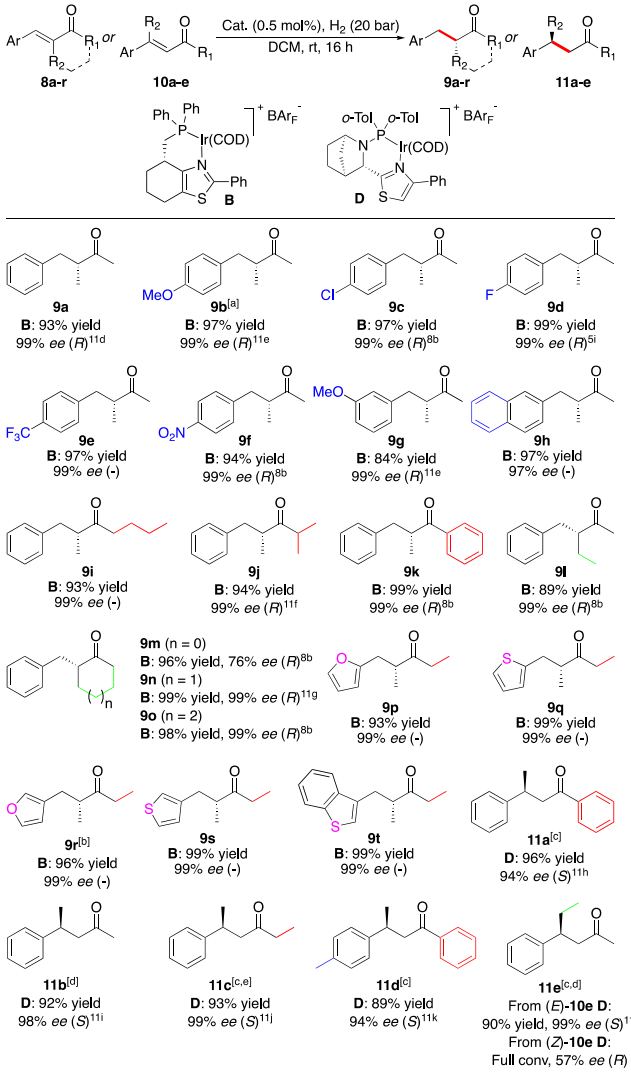
To demonstrate the synthetic utility, this developed catalytic system for dialkyl-substituted enones was applied in the partial synthesis of anti-HIV agent **7** (Table 2). Hydrogenation of α,β-dialkyl substituted enone **5** yielded key intermediate α-chiral ketone **6** in 98% ee (97% isolated yield), which has previously been synthesized via a stereoselective alkylation, using an auxiliary strategy.[9]

Then, aromatic enones were evaluated and our library of ligands were shown to be well-tolerated in the hydrogenation of model substrate **8a**, in terms of selectivity, showing excellent ee values of up to 99% (see Table S3 in the Supporting Information). Catalyst **B** was chosen for further studies on the class of α-prochiral aromatic enones (Table 3).[11] The introduction of various electron-donating or electron-withdrawing substituents on the aromatic ring gave equal results and substrates **8b**−**8g** gave uniformly excellent ee values of 99%. Moreover, the scalability of the methodology was demonstrated by the hydrogenation of **8b** on a 1.3 mmol scale (99% yield). Changing the substituent to 2-naphthalene **8h** led to a slight decrease in enantioselectivity (97% ee). Thereafter, substrates with a variety of substituents on the ketone side chain were hydrogenated and *n*-butyl, *i*-propyl, and phenyl ketones all yielded the desired product in perfect ee of 99% (**8i**−**8k**). An increase in the bulk of the α-substituent to ethyl (**8l**) gave a similar result. The ring size of cyclic enones with an exocyclic olefin was shown to affect the enantioselectivity. Whereas cyclopentanone derivative **8m** was hydrogenation in moderate ee of 76%, six-membered and seven-membered cyclic enones were hydrogenated in excellent ee of 99% (**8n**−**8o**). Furthermore, heterocyclic substrates **8p**−**8t** were also well-tolerated (99% ee, 93%−99% yield).

Finally, β-prochiral aromatic enone **10a** was evaluated in the hydrogenation to the corresponding saturated ketone. Fortunately, catalyst **D**, which has successfully been applied in the hydrogenation of β-prochiral unsaturated esters,[10] gave higher chiral induction of 94% ee in the hydrogenation of substrate **10a** (see Table S4 in the Supporting Information). Changing the carbonyl side chain to a methyl and ethyl group increased the enantioselectivity to 98% and 99% ee, respectively (**10b** and **10c**). The presence of an electron-donating methyl group at the *para* position (**10d**) of the aryl substituent on the olefin was hydrogenated in similar ee (94%), compared to the unsubstituted equivalent **10a**. Increasing the length of the β-alkyl group to ethyl did not affect either the conversion or the enantioselectivity and compound (*E*)-**10e** was hydrogenated in 99% ee. The isomeric purity of the olefin turned out to be important for the enantioselection of the catalyst. Whereas the hydrogenation of (*E*)-**10e** produces (*S*)-**11e**, an opposite enantiomeric outcome was formed when (*Z*)-**10e** was hydrogenated (57% ee), demonstrating that the reaction is enantiodivergent.

In conclusion, an efficient protocol for the synthesis of α- and β-chiral ketones via asymmetric hydrogenation of conjugated unsaturated enones by Ir−N,P catalysis is described. Although dialkyl-substituted enones have previously been hydrogenated with moderate enantioinduction, efficient hydrogenation of these challenging substrates was achieved by using the conditions described in this study giving 88%−99% ee. The method was successfully applied in the synthesis of an anti-HIV agent. Furthermore, various (hetero)aromatic-substituted enones were well-tolerated, resulting in 94%−99% ee of the corresponding chiral ketones.

Table 3. Asymmetric Hydrogenation of Aromatic-Substituted Enones*



*Reaction conditions: 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H_2, 16 h, rt, unless stated otherwise. Absolute stereochemistry assigned by comparing optical rotation with literature values. If no reference is given then assignment is tentative. Yields given are in their isolated forms. Enantiomeric excess was determined by SFC or GC analysis, using chiral stationary phases. [a]1.3 mmol scale. [b]0.75 mol % of catalyst. [c]1.0 mol % of catalyst. [d]5 bar of H_2. [e]2 bar of H_2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04012.

https://dx.doi.org/10.1021/acs.orglett.0c04012
Org. Lett. 2021, 23, 242−246

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

AUTHOR INFORMATION

Corresponding Author

Pher G. Andersson − *Department of Organic Chemistry, Stockholm University, 106 91 Stockholm, Sweden; School of Chemistry and Physics, University of KwaZulu-Natal, Private Bag, X54001 Durban, South Africa;* orcid.org/0000-0002-1383-8246; Email: Pher.Andersson@su.se

Authors

Bram B. C. Peters − *Department of Organic Chemistry, Stockholm University, 106 91 Stockholm, Sweden;* orcid.org/0000-0001-7788-3866

Jira Jongcharoenkamol − *Department of Organic Chemistry, Stockholm University, 106 91 Stockholm, Sweden*

Suppachai Krajangsri − *Department of Organic Chemistry, Stockholm University, 106 91 Stockholm, Sweden*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c04012

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors 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. J. J. thanks the Chulabhorn Graduate Institute, Chulabhorn Royal Academy, Thailand for an exchange scholarship to Stockholm University.

REFERENCES

(1) (a) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. Asymmetric Total Syntheses of Platensimycin. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942−3945. (b) Leal, R. A.; Beaudry, D. R.; Alzghari, S. K.; Sarpong, R. Synthesis of the Pentacyclic Skeleton of the Indole Alkaloid Arboflorine. *Org. Lett.* **2012**, *14*, 5350−5353. (c) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. Total Synthesis of the Antimicrotubule Agent (+)-Discodermolide Using Boron-Mediated Aldol Reactions of Chiral Ketones. *Angew. Chem., Int. Ed.* **2000**, *39*, 377−380. (d) Paterson, I.; Steadman nee Doughty, V. A.; McLeod, M. D.; Trieselmann, T. Stereocontrolled total synthesis of (+)-concanamycin F: the strategic use of boron-mediated aldol reactions of chiral ketones. *Tetrahedron* **2011**, *67*, 10119−10128. (e) Han, Y.-X.; Jiang, Y.-L.; Li, Y.; Yu, H.-X.; Tong, B.-Q.; Niu, Z.; Zhou, S.-J.; Liu, S.; Lan, Y.; Chen, J.-H.; Yang, Z. Biomimetically inspired asymmetric total synthesis of (+)-19-dehydroxyl arisandilactone A. *Nat. Commun.* **2017**, *8*, 14233.

(2) Lim, D.; Coltart, D. M. Simple and Efficient Asymmetric α-Alkylation and α,α-Bisalkylation of Acyclic Ketones by Using Chiral N-Amino Cyclic Carbamate Hydrazones. *Angew. Chem., Int. Ed.* **2008**, *47*, 5207−5210.

(3) Uchida, T.; Katsuki, T. Construction of a new type of chiral bidentate NHC ligands: copper-catalyzed asymmetric conjugate alkylation. *Tetrahedron Lett.* **2009**, *50*, 4741−4743.

(4) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. Highly Enantioselective Conjugate Additions to α,β-Unsaturated Ketones Catalyzed by a (Salen)Al Complex. *J. Am. Chem. Soc.* **2005**, *127*, 1313−1317.

(5) (a) Lipshutz, B. H.; Servesko, J. M. CuH-Catalyzed Asymmetric Conjugate Reductions of Acyclic Enones. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789−4792. (b) Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Itoh, J.-I.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. Asymmetric Conjugate Reduction of α,β-Unsaturated Ketones and Esters with Chiral Rhodium(2,6-bisoxazolinylphenyl) Catalysts. *Chem. - Eur. J.* **2006**, *12*, 63−71. (c) Monguchi, D.; Beemelmanns, C.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. Catalytic asymmetric conjugate reduction with ethanol: A more reactive system Pd(II)-^{i}Pr-DUPHOS complex with molecular sieves 4A. *J. Organomet. Chem.* **2008**, *693*, 867−873. (d) Voigtritter, K. R.; Isley, M. A.; Moser, R.; Aue, D. H.; Lipshutz, B. H. Regioselective reductions of β,β-disubstituted enones catalyzed by nonracemically ligated copper hydride. *Tetrahedron* **2012**, *68*, 3410−3416. (e) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. Organocatalytic Transfer Hydrogenation of Cyclic Enones. *J. Am. Chem. Soc.* **2006**, *128*, 12662−12663. (f) Martin, N. J. A; List, B. Highly Enantioselective Transfer Hydrogenation of α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **2006**, *128*, 13368−13369. (g) Han, Z. S.; Zhang, L.; Xu, Y.; Sieber, J. D.; Marsini, M. A.; Li, Z.; Reeves, J. T.; Fandrick, K. R.; Patel, N. D.; Desrosiers, J.-N.; Qu, B.; Chen, A.; Rudzinski, D. M.; Samankumara, L. P.; Ma, S.; Grinberg, N.; Roschangar, F.; Yee, N. K.; Wang, G.; Song, J. J.; Senanayake, C. H. Efficient Asymmetric Synthesis of Structually Diverse P-Stereogenic Phosphinamides for Catalyst Design. *Angew. Chem., Int. Ed.* **2015**, *54*, 5474−5477. (h) Shimoda, K.; Kubota, N.; Hamada, H. Asymmetric reduction of α,β-unsaturated carbonyl compounds with reductases from *Nicotiana tabacum*. *Tetrahedron: Asymmetry* **2004**, *15*, 2443−2446. (i) Silva, R. M.; Okano, L. T.; Rodrigues, J. A. R.; Clososki, G. C. Extractive biocatalysis in the asymmetric reduction of α-alkyl, β-aryl enones by Baker's yeast. *Tetrahedron: Asymmetry* **2017**, *28*, 939−944.

(6) (a) Scheuermann née Taylor, C. J.; Jaekel, C. Enantioselective Hydrogenation of Enones with a Hydroformylation Catalyst. *Adv. Synth. Catal.* **2008**, *350*, 2708−2714. (b) Zhang, T.; Jiang, J.; Yao, L.; Geng, H.; Zhang, X. Highly efficient synthesis of chiral aromatic ketones *via* Rh-catalyzed asymmetric hydrogenation of β,β-disubstituted enones. *Chem. Commun.* **2017**, *53*, 9258−9261.

(7) Wang, D.-S.; Wang, D.-W.; Zhou, Y.-G. Pd-Catalyzed Asymmetric Hydrogenation of C = C Bond of α,β-Unsaturated Ketones. *Synlett* **2011**, *2011*, 947−950.

(8) (a) Lu, S.-M.; Bolm, C. Highly Chemo- and Enantioselective Hydrogenation of Linear α,β-Unsaturated Ketones. *Chem. - Eur. J.* **2008**, *14*, 7513−7516. (b) Lu, S.-M.; Bolm, C. Highly Enantioselective Synthesis of Optically Active Ketones by Iridium-Catalyzed Asymmetric Hydrogenation. *Angew. Chem., Int. Ed.* **2008**, *47*, 8920−8923. (c) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. Iridium-Catalyzed highly Enantioselective Hydrogenation of the C = C Bond of α,β-Unsaturated Ketones. *Angew. Chem., Int. Ed.* **2008**, *47*, 10133−10136. (d) Tian, F.; Yao, D.; Liu, Y.; Xie, F.; Zhang, W. Iridium-Catalyzed Highly Enantioselective Hydrogenation of Exocyclic α,β-Unsaturated Carbonyl Compounds. *Adv. Synth. Catal.* **2010**, *352*, 1841−1845. (e) Liu, X.; Han, Z.; Wang, Z.; Ding, K. SpinPhox/Iridium(I)-Catalyzed Asymmetric Hydrogenation of Cyclic α-Alkylidene Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2014**, *53*, 1978−1982. (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) Elías-Rodríguez, P.; Borràs, C.; Carmona, A. T.; Faiges, J.; Robina, I.; Pàmies, O.; Diéguez, M. Pyrrolidine-Based P,O Ligands from Carbohydrates: Easily Accessible and Modular Ligands for the Ir-Catalyzed Asymmetric Hydrogenation of Minimally Functionalized Olefins. *ChemCatChem* **2018**, *10*, 5414−5424. (h) Maurer, F.; Huch, V.; Ullrich, A.; Kazmaier, U. Development of Catalysts for the Stereoselective Hydrogenation of α,β-Unsaturated Ketones. *J. Org. Chem.* **2012**, *77*, 5139−5143. (i) Li, Q.; Wan, P.; He, Y.; Zhou, Y.; Li, L.; Chen, B.; Duan, K.; Cao, R.; Zhou, Z.; Qiu, L. Enantioselective Hydrogenation of the Double Bond of Exocyclic α,β-Unsaturated Carbonyl Compounds Catalzed by Iridium/H_8-BINOL-Derived Phosphine-Oxazoline Complexes. *Asian J. Org. Chem.* **2014**, *3*, 774−783. (j) Biosca, M.; Coll, M.; Lagarde, F.; Brémond, E.; Routaboul, L.;

Manoury, E.; Pàmies, O.; Poli, R.; Diéguez, M. Chiral ferrocene-based P,S ligands for Ir-catalyzed hydrogenation of minimally functionalized olefins. Scope and limitations. *Tetrahedron* **2016**, *72*, 2623−2631. (k) Zheng, Z.; Cao, Y.; Chong, Q.; Han, X.; Ding, J.; Luo, C.; Wang, X.; Zhu, D.; Zhou, Q.-L.; Ding, K. Chiral Cyclohexyl-Fused Spirobiindanes: Practical Synthesis, Ligand Development and Asymmetric Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 10374−10381. (l) Wang, X.; Han, Z.; Wang, Z.; Ding, K. Catalytic Asymmetric Synthesis of Aromatic Spiroketals by SpinPhox/Iridium(I)-Catalyzed Hydrogenation and Spiroketalization of α,α'-Bis(2-hydroxyarylidene) Ketones. *Angew. Chem., Int. Ed.* **2012**, *51*, 936−940.

(9) Liu, X.; Chen, P.; Li, X.; Ba, M.; Jiao, X.; Guo, Y.; Xie, P. Design, synthesis and biological evaluation of substituted (+)-SG-1-derivatives as novel anti-HIV agents. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 1699−1703.

(10) Li, J.-Q.; Quan, X.; Andersson, P. G. Highly Enantioselective Iridium-Catalyzed Hydrogenation of α,β-Unsaturated Esters. *Chem. - Eur. J.* **2012**, *18*, 10609−10616.

(11) (a) Caporusso, A. M.; Giacomelli, G.; Lardicci, L. Metal catalysis in organic reactions. Part 9. Iron-induced reaction of organoaluminium compounds with aliphatic alk-1-ynes. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3139−3145. (b) Fischer, J.; Kilpert, C.; Klein, U.; Steglich, W. Stereochemistry of [3.3]-sismatropic rearrangements in the oxazole series. *Tetrahedron* **1986**, *42*, 2063−2074. (c) Duncan, A. P.; Leighton, J. P. Enantioselective Cu-Catalyzed Conjugate Addition of Diethylzinc to Acyclic Aliphatic Enones. *Org. Lett.* **2004**, *6*, 4117−4119. (d) Abate, A.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Giovenzana, T.; Malpezzi, L.; Serra, S. Chirality and Frangrance Chemistry: Stereoisomers of the Commercial Chiral Odorants Muguesia and Pamplefleur. *J. Org. Chem.* **2005**, *70*, 1281−1290. (e) Zagozda, M.; Plenkiewicz, J. Enantioselective reductions of α,β-unsaturated ketones by *Geotrichum candidum, Mortierella isabellina* and *Rhodotorula rubra* yeast. *Tetrahedron: Asymmetry* **2006**, *17*, 1958−1962. (f) Oppolzer, W.; Darcel, C.; Rochet, P.; Rosset, S.; de Brabander, J. Non-destructive Removal of the Bornanesultam Auxiliary in α-Substituted *N*-Acylbornane-10,2-sultanis under Mild Conditions: And efficient snthesis of enantiomerically pure ketones and aldehydes. *Helv. Chim. Acta* **1997**, *80*, 1319−1337. (g) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. Enantioselective alkylation of ketones via chiral, nonracemic lithioenamines. An asymmetric synthesis of. alpha. -alkyl and. alpha.,.alpha.'-dialkyl cyclic ketones. *J. Am. Chem. Soc.* **1981**, *103*, 3081−3087. (h) Luo, Y.; Carnell, A. J. Chemoenzymatic Synthesis and Application of Bicyclo[2.2.2]octadiene Ligands: Increased Efficiency in Rhodium-Catalyzed Asymmetric Conjugate Additions by Electronic Tuning. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750−2754. (i) Brown, H. C.; Srebnik, M.; Bakshi, R. K.; Cole, T. E. Chiral synthesis via organoboranes. 10. Preparation of. alpha.-chiral acyclic ketones of exceptionally high enantiomeric excess from optically pure borinic esters. *J. Am. Chem. Soc.* **1987**, *109*, 5420−5426. (j) López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. Copper-Catalyzed Enantioselective Conjugate Addition of Griganrd Reagents to Acyclic Enones. *J. Am. Chem. Soc.* **2004**, *126*, 12784−12785. (k) Huang, R.-Z.; Lau, K. K.; Li, Z.; Liu, T.-L.; Zhao, Y. Rhodium-Catalyzed Enantioconvergent Isomerization of Homoallylic and Bishomoallylic Secondary Alcohols. *J. Am. Chem. Soc.* **2018**, *140*, 14647−14654. (l) Endo, K.; Ogawa, M.; Shibata, T. Multinuclear Catalyst for Copper-Catalyzed Asymmetric Conjugate Addition of Organozinc Reagents. *Angew. Chem., Int. Ed.* **2010**, *49*, 2410−2413.

https://dx.doi.org/10.1021/acs.orglett.0c04012
Org. Lett. 2021, 23, 242−246