Highly Enantioselective Iridium-Catalyzed Hydrogenation of Conjugated Trisubstituted Enones

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

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. A few reported methods to access optically active ketones include alkylation using auxiliaries, catalytic asymmetric alkylation, enantioselective Michael addition to unsaturated ketones, or asymmetric conjugate reduction of enones. 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, palladium, and iridium catalysts (Scheme 1).

In 2008, Hou and Bolm 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. 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). Next, the hydrogenation of challenging β,β-dialkyl substituted enones was investigated. The use of catalysts B,
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 phospine 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 reported as not reactive (Scheme 1),12 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).
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. 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.

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). 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, 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

| Substrate | Reaction Conditions | Yield | Enantiomeric Excess |
|-----------|-------------------|-------|---------------------|
| 8a        | 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H₂, 16 h, rt | 99% yield | 99% ee |
| 8b        | 0.5 mol % catalyst, 5 bar of H₂ | 99% yield | 99% ee |
| 8c        | 1.0 mol % of catalyst | 99% yield | 99% ee |
| 8d        | 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H₂, 16 h, rt | 99% yield | 99% ee |
| 8e        | 0.5 mol % catalyst, 5 bar of H₂ | 99% yield | 99% ee |
| 8f        | 1.0 mol % of catalyst | 99% yield | 99% ee |
| 8g        | 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H₂, 16 h, rt | 99% yield | 99% ee |
| 8h        | 0.5 mol % catalyst, 5 bar of H₂ | 99% yield | 99% ee |
| 8i        | 1.0 mol % of catalyst | 99% yield | 99% ee |
| 8j        | 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H₂, 16 h, rt | 99% yield | 99% ee |
| 8k        | 0.5 mol % catalyst, 5 bar of H₂ | 99% yield | 99% ee |
| 8l        | 1.0 mol % of catalyst | 99% yield | 99% ee |
| 8m        | 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H₂, 16 h, rt | 99% yield | 99% ee |
| 8n        | 0.5 mol % catalyst, 5 bar of H₂ | 99% yield | 99% ee |
| 8o        | 1.0 mol % of catalyst | 99% yield | 99% ee |
| 8p        | 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H₂, 16 h, rt | 99% yield | 99% ee |
| 8q        | 0.5 mol % catalyst, 5 bar of H₂ | 99% yield | 99% ee |
| 8r        | 1.0 mol % of catalyst | 99% yield | 99% ee |
| 8s        | 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H₂, 16 h, rt | 99% yield | 99% ee |
| 8t        | 0.5 mol % catalyst, 5 bar of H₂ | 99% yield | 99% ee |
| 8u        | 1.0 mol % of catalyst | 99% yield | 99% ee |

*Reaction conditions: 0.2 mmol of substrate, 0.5 mol % catalyst, 2 mL of solvent, 20 bar of H₂, 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. 1.3 mmol scale. 0.75 mol % of catalyst. 1.0 mol % of catalyst. 5 bar of H₂. 2 bar of H₂.

### Associated Content

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04012.
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. Sarpong, R.; Alkylidene Carbonyl Compounds. Iridium(I)-Catalyzed Asymmetric Hydrogenation of Cyclic Enones. Angew. Chem., Int. Ed. 2008, 47, 947−950.
   (c) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. Organocatalytic Transfer Hydrogenation of Cyclic Enones. J. Am. Chem. Soc. 2006, 128, 12662−12663.

2. (d) Paterson, I.; Steadman nee Doughty, V. A.; McLeod, L. P.; Ma, S.; Grinberg, N.; Roschangar, F.; Yee, N. K.; Wang, G.; Desrosiers, J.-N.; Qu, B.; Chen, A.; Rudzinski, D. M.; Samankumara, M. A.; Li, Z.; Reeves, J. T.; Fandrick, K. R.; Patel, N. D.; Desroisiers, 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 (+)-concanamycin F: the strategic use of boron-mediated aldol reactions of chiral ketones. Tetrahedron: Asymmetry 2011, 22, 2443−2446.

3. (e) Silva, R. M.; Okano, L. T.; Rodrigues, J. A. R.; Clososki, G. C. Extractive biocatalysis in the asymmetric reduction of α,β-unsaturated carbonyl compounds with reductases from Nicotiana tabacum. Tetrahedron: Asymmetry 2004, 15, 2443−2446.

4. (f) Martin, N. J. A; List, B. Highly Enantioselective Transfer Hydrogenation of α,β-Unsaturated Ketones. J. Am. Chem. Soc. 2006, 128, 13366−13369.
   (g) Han, Z. S.; Zhang, L.; Xu, Y.; Steiber, J. D.; Marsini, M. A.; Li, Z.; Reeves, J. T.; Pandrick, K. R.; Patel, N. D.; Desroisiers, 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 Structurally 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.

5. (i) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. Iridium-Catalyzed highly enantioselective synthesis of optically active ketones by iridium-catalyzed asymmetric hydrogenation of β-disubstituted enones. Chem. Commun. 2017, 53, 9258−9261.

6. (j) Biosca, M.; Coll, M.; Lagarde, F.; Brémond, E.; Routaboul, J.; }

**Organic Letters**

**pubs.acs.org/OrgLett**

**Letter**

**245**

https://dx.doi.org/10.1021/acs.orglett.0c04012

**Org Lett. 2021, 23, 242−246**
Manoury, E.; Pâmes, 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.

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.

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.

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

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.

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.; Giacovelli, G.; Giavenzana, T.; Malpezi, 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-sultans under Mild Conditions: And efficient synthesis 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.; Druehling, 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 androstane as Substitutes in Organic Reactions. 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 Grignard 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.