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Enantioselective Hydrogenation of Endocyclic Enones: the Solution to a Historical Problem

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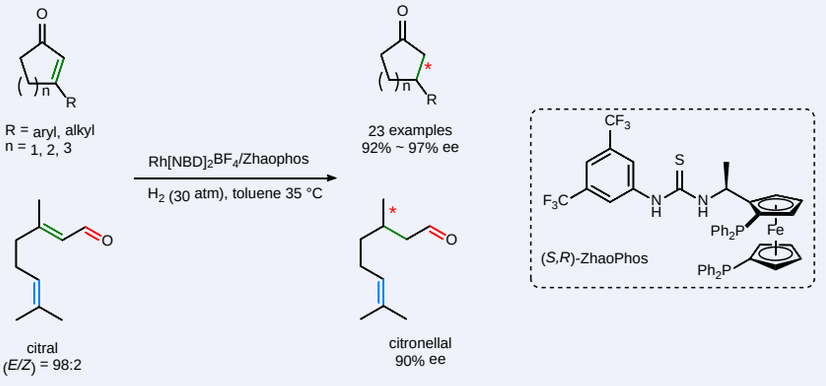
Keywords

asymmetric catalysis | hydrogenation | cyclic enone | rhodium | citral reduction

Main observation and conclusion

The enantioselective hydrogenation of endocyclic enones has been a historical problem for homogeneous catalysis. We herein report an efficient method to reduce endocyclic enones with molecular hydrogen. Catalyzed by a rhodium/Zhaophos complex, a variety of enones with five-, six- or seven-member ring were hydrogenated with high enantioselectivity (92% ~ 99% ee). Excellent chemo- and enantioselectivity demonstrated This method was successfully applied in the enantioselective hydrogenation of citral to produce enantio-enriched citronellal.

Comprehensive Graphic Content



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Background and Originality Content

Transition metal-catalyzed homogenous hydrogenation of C=C bonds, with no doubts, has played an important role in the construction of chiral compounds.[1] Over the last half century, several successful catalytic systems with numerous chiral ligands have been developed for the conversion of prochiral C=C bonds to chiral carbons.[2] A key strategy for high enantioselectivity is the coordination of the functional group of the substrates.[3] The secondary interaction assists to form two diastereomeric substrate-catalyst complexes which lead to the formation of two product enantiomers. Mechanistic studies have confirmed this secondary interaction in many successful catalytic systems such as Wilkinson/Osborn's cationic Rh complex for dehydroamino acids[3, 4], Ru/bisphosphine complexes for conjugate carboxylic acids and Noyori's RuH-NH systems for ketone reduction.[5]

In the history of asymmetric hydrogenation, endocyclic enones has always been a challenging task.[6] In our perspective, the difficulties lie in such areas: (1) as functionalized olefins, the carbonyl in endocyclic enones could not form efficient coordination to the metal due to the ring strain and therefore the enantiomeric control fails in the aforementioned catalytic systems. (2) The electron density of the C=C bonds are diluted by the conjugate carbonyl; together with steric hindrance caused by the ring, the coordination of the C=C bonds to the metal are weak.

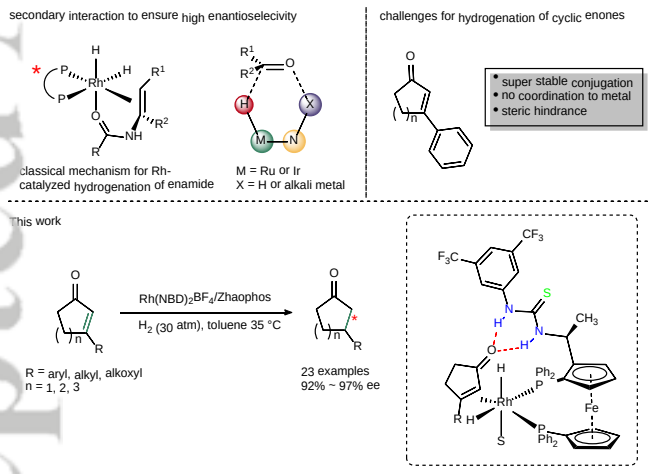


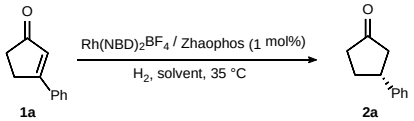
Figure 1. Challenges for asymmetric hydrogenation of cyclic enones.

Reports of the maneuvers on AH of this class of substrates are limited. Although unfunctionalized olefins are hydrogenated with chiral analogues of Crabtree's complex, only sporadic reports on AH of cyclic has been documented.[7] Hydrogenation catalyzed by a cationic ruthenium complex could give (+)-*cis*-methyl dihydrojasmonate with a dr value of 88:12.[8] A rhodium/Segphos complex was applied in the asymmetric hydrogenation of 6-member-ring endocyclic enones, but the moderate regioselectivity or ee was still an issue.[9] In 2008, asymmetric hydrogenation of cyclic enones was achieved by Jaekel and coworkers using a hydroformylation catalyst and this catalytic system could be applied in the synthesis of enantioenriched citronellal.[10] Efforts by Börner and co-workers were reported to develop a series of *P*-chirogenic Xantphos and their application of asymmetric hydrogenation of isophorone with high enantioselectivity[11], although broad reaction scope was not disclosed. In comparison, functionalized cyclic enones such as N-acyl enamides, with higher reactivity and easier enantiomeric control, could also be hydrogenated smoothly with a rhodium catalyst.[12] An alternative strategy, transfer hydrogenation, was reported by Macmillan[13] and List[14] respectively using organocatalysts. But the relatively low catalytic efficiency slowed down its large-scale application.

Results and Discussion

We began the initial investigations with the hydrogenation of model substrate 3-phenylcyclopent-2-en-1-one (**1a**) to evaluate several chiral bisphosphine ligands. A variety of bisphosphine ligands with different backbones were surveyed under relatively harsh conditions (60 atm H_2, 35°C, 48 hours). To our disappointment, commercially available chiral bisphosphine ligands, no matter electron-rich or not, failed in the rhodium catalyzed hydrogenation of this endocyclic enone (Table S1 in the supporting information). The rhodium complexes with these ligands showed insufficient reactivities and poor enantioselectivities. Gratefully, a thiourea-containing bisphosphine, Zhaophos that was developed by our group, succeeded in this chemical transformation. Catalyzed by a Rh/Zhaophos complex, 3-phenylcyclopent-2-en-1-one (**1a**) was hydrogenated to the cyclopentanone bearing a stereocenter at the β-position with a full conversion and 95% ee. After screening the reaction parameters, the optimized condition was obtained (97% ee in toluene, 30 atm H_2, 35 °C). To our delight, no ketone reduction was observed. Lowering the hydrogen pressure or the reaction temperature, however, would lead to a decrease in conversion. Explanations for the reason of the superiority of Zhaophos to other bisphosphine ligands include: (1) the hydrogen bond between thiourea and the carbonyl might activate the substrate by lowering the HOMO, (2) the secondary interaction between the substrate and the catalyst would enhance the enantiodiscrimination (the interaction model could be found in figure 1).

Table 1. Screening of reaction conditions for the asymmetric hydrogenation of 3-phenylcyclopent-2-en-1-one. [a]



Entry	Solvent	H_2 / atm	Time	Conversion	ee
1	CH_2Cl_2	60	48 h	>99%	95%
2	DCE	60	48 h	12%	86%
3	THF	60	48 h	65%	95%
4	MeOH	60	48 h	10%	86%
5	^{i}PrOH	60	48 h	19%	94%
6	EtOAc	60	48 h	92%	96%
7	toluene	60	48 h	>99%	96%
8	toluene	30	48 h	>99%	97%
9	toluene	30	24 h	>99%	97%
10	toluene	10	24 h	97%	97%
11[b]	toluene	30	24 h	45%	96%

[a] reaction conditions: $Rh(NBD)_2BF_4$/ligand/**1a** (0.1 mmol) ratio of 1/1.1/100, 1.0 mL solvent. The conversion was determined by ^{1}H NMR and the ee value was determined by HPLC analysis using a chiral stationary phase. [b] The reaction was carried out at 25 °C.

We applied the optimized conditions to explore the reaction scope. Various aryl cyclic enones underwent hydrogenation smoothly to yield chiral *β*-aryl chiral cyclic ketones (figure 2). The substitution groups on the benzene ring, no matter electron-donating or electron-withdrawing, showed limited impact on both yields and enantioselectivities. Heteroaromatic substituents, such as thiophene, did not make this reaction sluggish (**2p**). Alkyl cyclic enones (**2q** and **2r**) could also be reduced with high enantioselectivities. If the ring size expand from five-member ring to six- or seven-member ring, no significant influence on the reactivity or

enantioselectivity was observed (**2s** and **2t**).

Cyclic enones were normally selected as model substrates to study chemo- and enantioselective hydrogenation of important *α,β*-unsaturated ketones or aldehydes in industry.[15] We envisioned that this catalytic system could be applied in the production of value-added chiral aldehydes such as enantio-enriched citronellal. Asymmetric hydrogenation of citral to produce enantiopure citronellal was regarded as commercially practical. In addition, this transformation from citral to citronellal, which has been a historical problem in fragrance industry, was also a key step for menthol production. We envisioned that our catalytic system could be applied in the preparation of enantio-enriched citronellal.

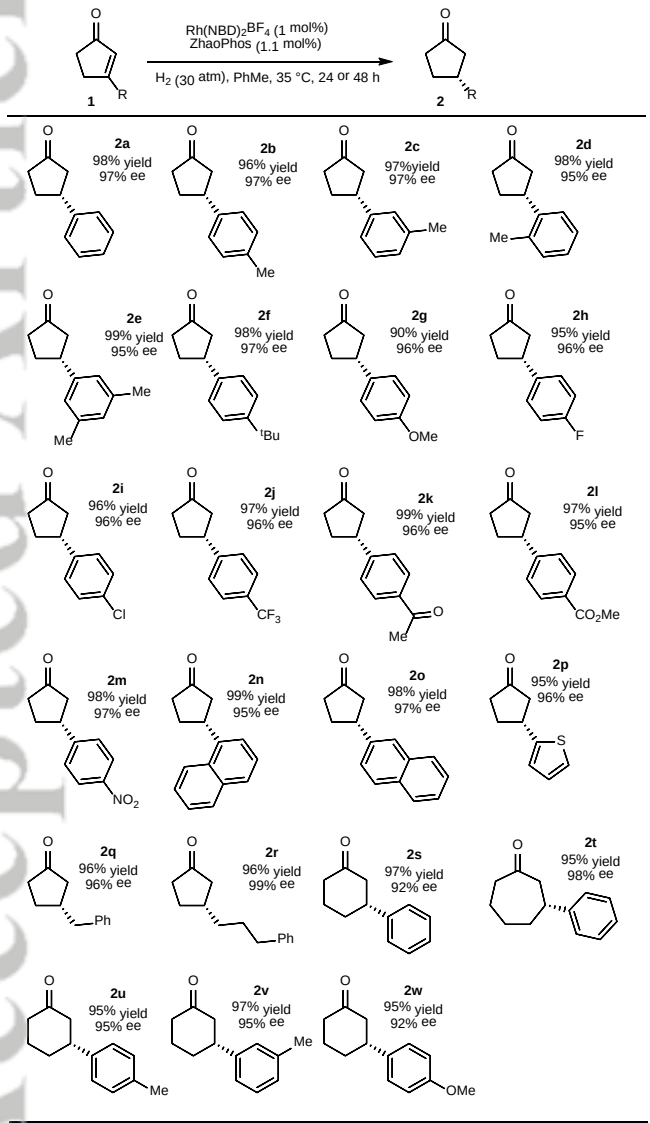
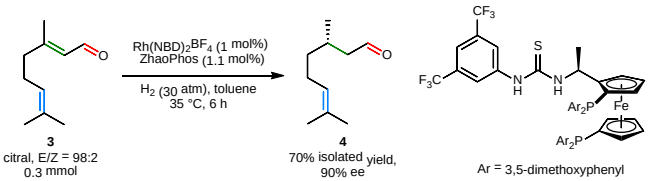


Figure 2. Substrate scope for asymmetric hydrogenation of cyclic enones.

In our perspective, AH of citral to produce enantio-pure citronellal has many challenges. First, compared to their acyclic counterparts, cyclic enones are configurationally stabilized due to the ring strain. The enantiomeric induction of acyclic *α,β*-unsaturated carbonyl compounds was therefore less effective. Second, chemoselectivity for C=C bonds over aldehyde C=O bond and regioselectivity for the conjugate C=C bond over the other one has to be achieved in a single chemical transformation.

Since AH of C=C bonds without secondary interaction was normally an enantiodivergent process[16], we therefore selected geranial as the targeting substrate. Over-reduction (either the aldehyde or the other C=C bond) was indeed a tough challenge during the condition optimization. Low hydrogen pressure and shorter reaction time was applied in order to achieve desired chemo- and regioselectivity. With a minor-modified Zhaophos[17], geranial could be hydrogenated to give citronellal with high enantioselectivity (90%) and high yield (70%). The over-reduction to alcohol was the main reason for the loss in yield.



Scheme 1. Challenge in the AH of citral.

Conclusions

In summary, we report a synthetic method of AH of endocyclic enones, which has been a challenge for a long time. Catalyzed by a rhodium/Zhaophos complex, a series of cyclic enones, no matter has a 5-, 6- or 7-member ring, could be hydrogenated with high enantioselectivities. This catalytic system could be successfully applied in the enantioselective conversion of citral to enantio-enriched citronellal.

Experimental

In an argon-filled glovebox, a solution of Zhaophos (9.6 mg, 0.011 mmol) and $Rh(NBD)_2BF_4$ (3.7 mg, 0.01 mmol) in 1.0 mL anhydrous toluene was stirred at room temperature for 40 min. 100 uL of the resulting solution was transferred via syringe into a vial that was charged with a solution of **1** (0.1 mmol) in 0.9 mL anhydrous toluene. This vial was placed into an autoclave, which was then purged with H_2 (3 times) and pressurized with 30 atm of H_2. The mixture was stirred at 35 °C (oil bath) for the indicated period of time. After the indicated period of time, the hydrogen gas was carefully released in a fume hood. The products were purified by flash chromatography and the enantiomeric excess was determined by HPLC analysis.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

Acknowledgement

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Entry for the Table of Contents

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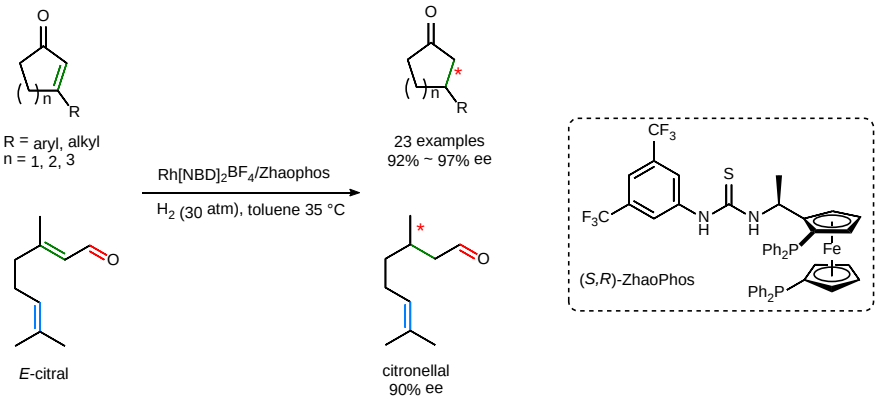

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