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Rhodium-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Carbonyl Compounds via Thiourea Hydrogen Bonding

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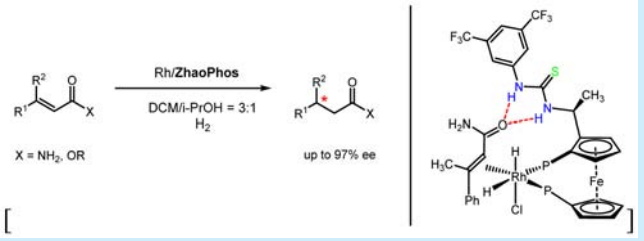
Supporting Information

ABSTRACT: The strategy of secondary interaction enables enantioselectivity for homogeneous hydrogenation. By introducing hydrogen bonding of substrates with thiourea from the ligand, α,β-unsaturated carbonyl compounds, such as amides and esters, are hydrogenated with high enantiomeric excess. The substrate scope for this chemical transformation is broad with various substituents at the β-position. Control experiments revealed that each unit of the ligand ZhaoPhos is irreplaceable. No nonlinear effect was observed for this Rh/ZhaoPhos-catalyzed asymmetric hydrogenation.



As an important noncovalent interaction, hydrogen bonding plays a crucial role in biosystem and enzyme catalysis.[1] From the inspiration of enzyme catalysis to the prosperity of small-molecule catalysis, many studies have been elaborated in the past two decades. This strategy of hydrogen bonding has been successfully applied in numerous cases of organocatalysis, which provide the synthetic community with many solutions for enantioselective synthesis.[2] Among these successful catalysts, thiourea is a special motif for hydrogen bonding. As a double hydrogen donor, thiourea could activate carbonyl compounds by lowering their LUMO energy.[3] Effective bonding with neutral functional groups, potent binding affinity, and high tunability make thiourea catalysts versatile for many kinds of organic reactions.[4] Originated in serine protease (Figure 1) catalyzed hydrolysis of amides,[1] the interaction of a

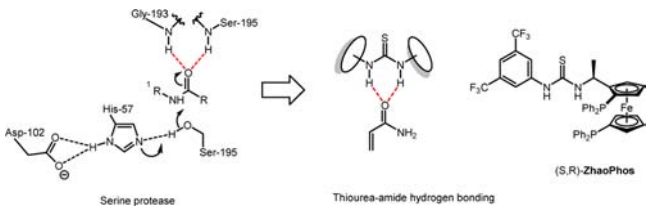


Figure 1. Double H-bonding with carbonyl.

double hydrogen donor with an amide substrate became an important paradigm for carbonyl activation in small molecule catalysis. The hydrogen bonding of (thio)urea with ketones, aldehydes, and carboxylic acid derivatives enables enantioselective chemical transformations and, therefore, emerged as an effective strategy in asymmetric catalysis.

Asymmetric hydrogenation, with 100% atom efficiency and easy workup, serves as a practical method to synthesize chiral compounds.[5] Asymmetric hydrogenation of unsaturated carboxylic acids and esters has been developed with several systems:[6] Crabtree's catalyst (iridium/P−N ligand) and the Wilkinson−Osborn system (rhodium/bisphosphine ligand) are successful representatives. To the best of our knowledge, hydrogenation of unsaturated carboxamides, however, is still a less explored field yet. Successful cases of asymmetric reduction of α,β-unsaturated amides mainly engaged with transition-metal-catalyzed conjugate addition of hydrides[7] and iridium-catalyzed direct hydrogenation by Ding.[8] We seek an efficient catalytic system to synthesize different types of chiral carboxylic acid derivatives with high enantioselectivity.

We recently developed a bisphosphine−thiourea ligand, ZhaoPhos:[9] a covalent linker connects a ferrocene-based bisphosphine unit with a thiourea moiety (Figure 1). Hydrogen bonding of thiourea with substrates enables effective secondary interaction in asymmetric catalysis. This bifunctional ligand has successfully been applied in hydrogenation of nitroolefins,[9,10] unprotected imines,[11] isoquinolines, and quinolines[12] with high reactivities and high enantioselectivities.

The binding affinity of (thio)urea with carboxylic acid derivatives is in a range similar to that with nitro groups or sulfonates,[13] which inspires us to explore the application of ZhaoPhos in homogeneous hydrogenation of unsaturated carbonyl compounds. We envision that the secondary interaction of hydrogen bonding between thiourea and carbonyl substrates could play a dual role: (1) H-bond activates the substrate by decreasing the LOMO; (2) the binding between the ligand and substrate enhances the enantiomeric control. We report herein a successful example of rhodium/

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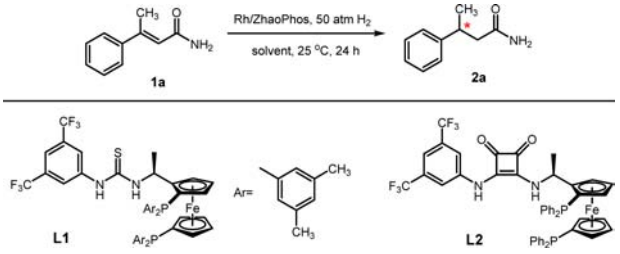
ZhaoPhos-catalyzed asymmetric hydrogenation of α,β-unsaturated carbonyl compounds.

Initially, we chose *trans*-β-methylcinnamide as the target and $[Rh(COD)Cl]_2$ as the metal precursor since this rhodium(I) dimer showed excellent performance in hydrogenation of nitroolefins and (iso)quinolines with ZhaoPhos in our previous studies. After screening of various types of solvent, we found that dichloromethane gave the best enantioselectivity. Solvent pairs were also tested. Solvent pairs were also tested, and we finally selected a mixture of dichloromethane and 2-propanol with a volume ratio 3:1 as the solvent (Table 1, entry9). When

Table 1. Condition Optimization[a]



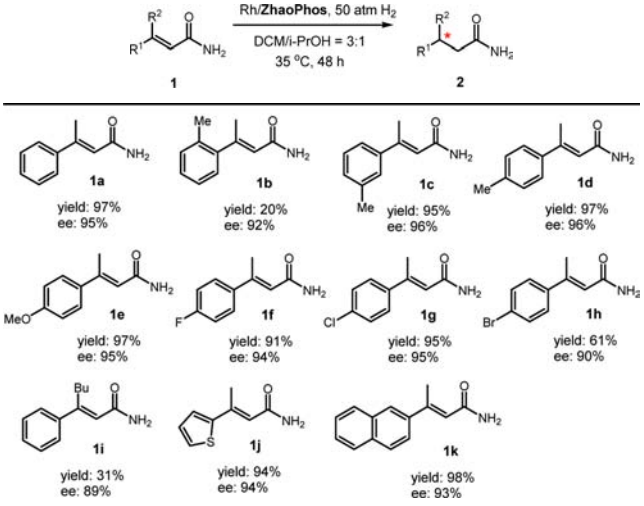
entry	solvent	ligand	conv[b] (%)	ee[c] (%)
1	MeOH	ZhaoPhos	24	65
2	i-PrOH	ZhaoPhos	50	86
3	DCM	ZhaoPhos	42	94
4	DCE	ZhaoPhos	18	90
5	dioxane	ZhaoPhos	<5	74
6	acetone	ZhaoPhos	trace	
7	ethyl acetate	ZhaoPhos	36	91
8	DCM/Tol = 3:1	ZhaoPhos	69	91
9	DCM/*i*-PrOH = 3:1	ZhaoPhos	58	95
10[d]	DCM/*i*-PrOH = 3:1	ZhaoPhos	99	95
11[d]	DCM/*i*-PrOH = 3:1	**L1**	63	90
12[d]	DCM/*i*-PrOH = 3:1	**L2**	38	36

[a]Reaction conditions: **1a** (0.1 mmol) in 1.0 mL of solvent, **1**/$[Rh(COD)Cl]_2$/**L** = 100/0.50/1.0. [b]Conversion was determined by ^{1}H NMR analysis; no side product was observed. [c]Enantiomeric excess was determined by HPLC with a chiral stationary phase. [d]Conducted at 35 °C for 48 h.

we increased the temperature and elongated the reaction time, the desired conversion (99%) and high enantioselectivity (95%) were obtained under 50 atm hydrogen gas pressure (entry 10). Similar to the previous hydrogenation cases with a Rh/ZhaoPhos system,[9−12] this reaction is solvent-dependent. More bulky substituents on phosphine do not bring higher enantioselectivity but lower conversion (entry 11). Squaramide, which usually plays a role as an alternative for (thio)urea in hydrogen-bonding catalysis, fails to show any advantages over thiourea (entry 12).

The substrate scope of Rh/ZhaoPhos-catalyzed hydrogenation of α,β-unsaturated amides is shown in Table 2. β,β-Disubstituted acrylamides were reduced with high enantioselectivities. Various substituents with different electronic effects do not bring significant changes in enantioselectivities. Steric effects, however, show an influence on the reactivity of this chemical transformation: compared to the *meta*- or *para*-position, the methyl group at the *ortho*-position on the phenyl slows the reaction rate significantly. The thienyl group, a representative of heteroaryl, also works smoothly in this homogeneous hydrogenation reaction.

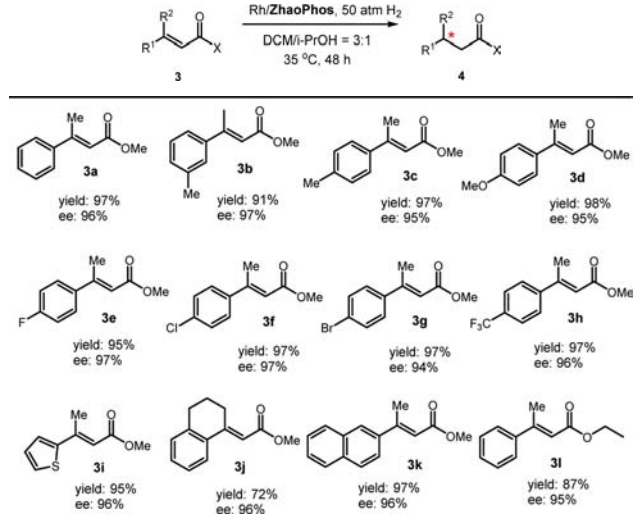
Table 2. Substrate Scope of Rhodium-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Amides[a]



[a]Reaction conditions: **1** (0.2 mmol) in 1.0 mL of solvent, **1**/$[Rh(COD)Cl]_2$/**L** = 100/0.50/1.0; yields were obtained after isolation; ee's were determined by HPLC with a chiral stationary phase.

With the success of hydrogenation of unsaturated amides in hand, we sought an expansion of substrate scope into other unsaturated carbonyl compounds. When the optimized conditions were applied in reactions of esters, high conversions with high enatioselectivities were obtained. The scope of β,β-disubstituted ester substrates includes various substituents on the β-phenyl ring with different electronic and steric effects, which is in accordance with hydrogenation of unsaturated amides. A broad substrate scope of this Rh/ZhaoPhos catalytic system suggests its potential application in synthetic chemistry (Table 3).

Table 3. Substrate Scope of Rhodium-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Esters and Ketone[a]



[a]Reaction conditions: **3** (0.2 mmol) in 1.0 mL of solvent, **3**/$[Rh(COD)Cl]_2$/**L** = 100/0.50/1.0; yields were obtained after isolation; ee's were determined by HPLC with a chiral stationary phase.

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To investigate the cooperation of the thiourea moiety and ferrocene-based bisphosphine skeleton, a series of analogues of ZhaoPhos were prepared and applied in the model reaction. (Experimental details are shown in the Supporting Information.) In accordance with previous studies on hydrogenation of nitroolefins,[9] unprotected inmines,[11] and (iso)quinolines,[12] control experiments revealed that (1) each unit within ZhaoPhos is irreplaceable for high conversion and high enantioselectivity in catalytic chemical transformation and (2) a covalent linker enables the incorporation.

We previously proposed a hydride-transfer mechanism for asymmetric hydrogenation of (iso)quinolines with rhodium/ZhaoPhos complex,[12] which involves an outersphere model[14] rather than the traditional innersphere mechanism.[15] When deuterium gas was used to conduct this hydrogenation, D atoms were added at α- and β-positions. No obvious H atoms were observed to be added to the C=C bond (see the Supporting Information). This result supports a traditional innersphere mechanism, which has been well studied and widely accepted in rhodium-catalyzed hydrogenation. Based on these results, we propose a ligand–substrate coordinating complex involving a secondary interaction between the thiourea and the carbonyl substrate (Figure 2).

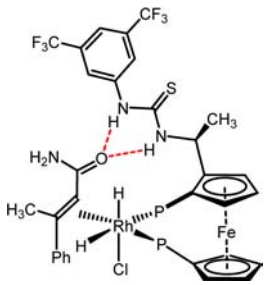

Figure 2. Proposed hydrogen bonding between the reactive Rh species and carbonyl substrate.

A nonlinear effect, which can be observed in catalytic asymmetric reactions, suggests potential dimerization or high-order aggregation of catalysts.[16] However, no nonlinear effect was observed in hydrogenation of *trans*-β-methylcinnamide (see the Supporting Information). It supports an assumption that no catalyst self-aggregation or ligand–substrate agglomeration occurs prior to the catalytic cycle.

In summary, we developed a synthetic method to approach β-chiral carbonyl compounds. Catalyzed by a Rh/ZhaoPhos complex, α,β-unsaturated carbonyl substrates were hydrogenated with high enantioselectivities. A secondary interaction between the thiourea ligand and carbonyl of the substrates is believed to be crucial for the success. In addition, we did not observe nonlinear effect in this catalytic chemical transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01812.

Experimental procedures, characterization data (PDF)

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§J.W. and J.J. contributed equally.

Notes

The authors declare no competing financial interest.

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