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Highly Efficient Synthesis of Chiral Aromatic Ketones *via* Rh-Catalyzed Asymmetric Hydrogenation of β, β-disubstituted enones

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A succinct and efficient protocol was developed for the synthesis of chiral aromatic ketones *via* asymmetric hydrogenation of β,β-disubstituted enones with rhodium catalysts based on chiral bisphosphine thiourea ligands. A series of substrates (17 examples) was smoothly catalyzed to afford the corresponding chiral aromatic ketones in high conversions（>99%）with excellent enantioselectivities (up to 96% *ee*).

Optically pure aromatic ketones are widely distributed in the nature and play a significant role in the organic synthesis. Chiral β,β-disubstituted ketones are key structural subunits of many bioactive natural products and serve as prevalent building blocks in many pharmaceuticals and agrochemicals. For example, (*S*)-warfarin (**A**), a well-known anticoagulant, is commonly used to prevent heart attack, stroke and the formation of blood clot.[1] Compound **B** is an antifertility agent.[2] **C** is used in the treatment of psoriasis,[3] and **D** is an antihyperlipidemic constituent.[4] Other bioactive compounds are widely used as agrochemicals and fragrances, such as carvone (**E**) and turmerone (**F**) *et al* (Figure 1).[5-6]

Consequently, the research on efficient synthesis of chiral β,β-disubstituted ketones has attracted increasingly considerable attention. In this context, various approaches have been developed in the last decades. Representative examples of these methods are as follows: asymmetric 1,4-addition of boronic acids to enones catalyzed by Rh-Binap, [7] oxidation of C=C bond of chiral enols by Pd(II),[8] enantioselective conjugate addition of organometallic compounds to α,β-unsaturated enones,[9-13] asymmetric redox-relay oxidative Heck reaction of acyclic alkenols,[14] enantioselective β-arylation of ketones,[15] as well as asymmetric hydrogenation of β,β-disubstituted α,β-unsaturated ketones. Among these approaches, transition-metal catalyzed hydrogenation of C=C bond of enones represents a promising strategy to access these chiral compounds due to its high atom economy. However, the chemoselective reduction of enones is still a stumbling block, for both C=C bond and C=O bond could be reduced by H_2. For instance, a couple of catalytic systems would preferentially reduce C=O bond of conjugated enone.[16] Although several chiral metal complexes have been developed for the hydrogenation of β-substituted enones,[17-25] their enantioselectivities and reactivities still need to be further improved.

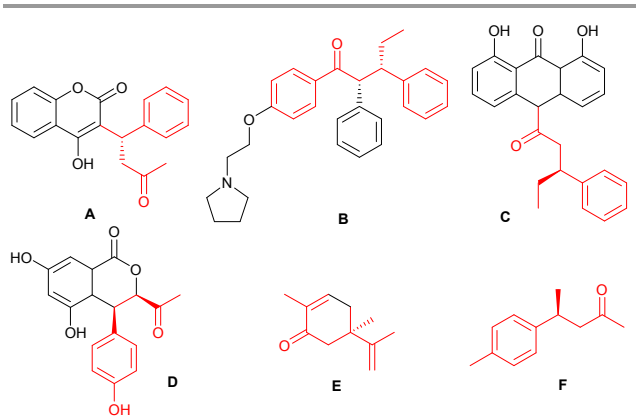

Fig. 1 Typically bioactive compounds containing chiral β,β-disubstituted ketones.

Our group has developed the bisphosphine thiourea ligand (ZhaoPhos) in 2013, wherein a covalent linker connected the ferrocene-based bisphosphine unit with the thiourea moiety.[26] The bifunctional ligand complexed with rhodium metal precursor has successfully accomplished the hydrogenation of β-amino nitroolefins,[27] unprotected imines,[28] isoquinolines and quinolones,[29] carboxylic acid derivatives,[30] and maleinimides[31] with high reactivity and excellent enantioselectivity. Inspired

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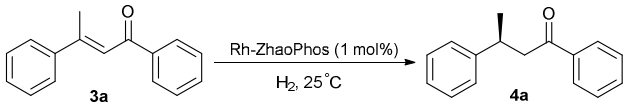
by the previous exciting results, we wonder whether Rh-ZhaoPhos could realize the asymmetric hydrogenation of β,β-disubstituted α,β-unsaturated ketones with high chemoselectivity and enantioselectivity.

Initially, β,β-disubstituted conjugated enones were prepared through Horner-Wadsworth-Emmons reaction using aromatic ketones as starting material according to the reported procedure (see supplementary information).[20]

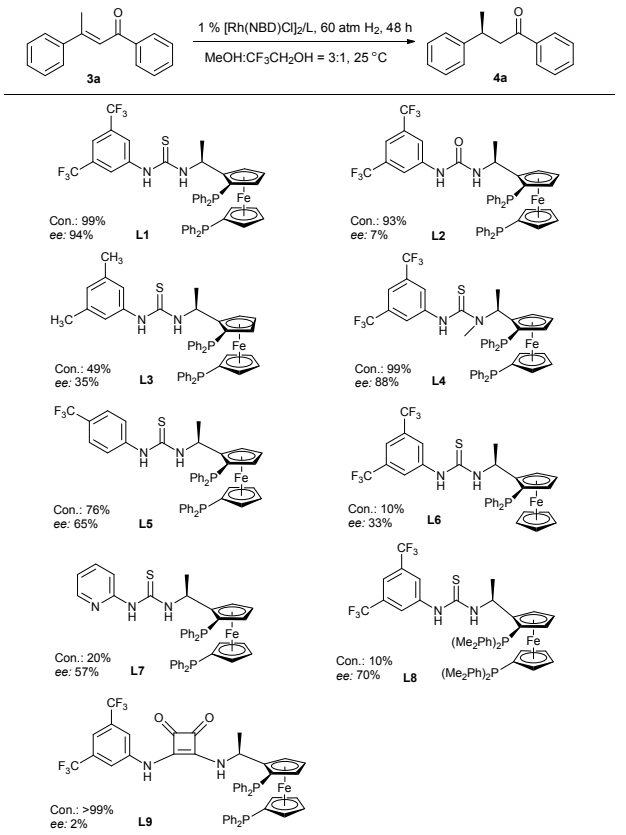
Then (*E*)-1,3-diphenylbut-2-en-1-one **3a** was chosen as a model substrate. The hydrogenation of **3a** in the presence of the ZhaoPhos-Rh complex, generated *in situ* from $[Rh(NBD)Cl]_2$ (1.0 mol%; NBD = 2,5-norbornadiene) and ZhaoPhos (1.0 equivalent of Rh), in trifluoroethanol under 30 atm of hydrogen pressure at room temperature for 24 h, gave (*S*)-**4a** with 75% conversion and 65% *ee* (Table 1, entry 1). When the pressure of hydrogen was increased to 60 atm, full conversion and 65% *ee* was afforded (entry 2). With this encouraging result, we examined the catalytic activity of ZhaoPhos with different metal sources (entries 3-5). $[Rh(COD)Cl]_2$ and $[Rh(NBD)_2]BF_4$ provided higher conversion (>99%) with lower enantioselectivity. On the contrary, $[Rh(COD)_2]BF_4$ showed both lower conversion and enantioselectivity. In most cases, solvent played a crucial role in the Rh-ZhaoPhos system. Consequently, various types of solvents were screened, using methol, ethanol and isopropanol as solvent gave **4a** with 92% *ee* (entries 6-8), while trifluoroethanol afforded the highest

Table 1 Optimization of the reaction conditions [a]



Entry	Precursors	Solvent	Con. (%)[b]	*Ee* (%)[c]
1[d]	$[Rh(NBD)Cl]_2$	CF_3CH_2OH	75	65
2	$[Rh(NBD)Cl]_2$	CF_3CH_2OH	>99	65
3	$[Rh(COD)Cl]_2$	CF_3CH_2OH	>99	15
4	$[Rh(NBD)_2]BF_4$	CF_3CH_2OH	>99	45
5	$[Rh(COD)_2]BF_4$	CF_3CH_2OH	66	56
6	$[Rh(NBD)Cl]_2$	MeOH	97	92
7	$[Rh(NBD)Cl]_2$	EtOH	87	92
8	$[Rh(NBD)Cl]_2$	^{i}PrOH	77	92
9	$[Rh(NBD)Cl]_2$	EtOAc	40	85
10	$[Rh(NBD)Cl]_2$	CH_2Cl_2	30	81
11	$[Rh(NBD)Cl]_2$	toluene	36	89
12	$[Rh(NBD)Cl]_2$	dioxane	10	23
13	$[Rh(NBD)Cl]_2$	acetone	43	88
14	$[Rh(NBD)Cl]_2$	MeOH: CF_3CH_2OH =1:1	>99	85
15	$[Rh(NBD)Cl]_2$	MeOH: CF_3CH_2OH =3:1	>99	94
16	$[Rh(NBD)Cl]_2$	MeOH: CF_3CH_2OH =9:1	98	93
17[e]	$[Rh(NBD)Cl]_2$	MeOH: CF_3CH_2OH =3:1	95	93
18[f]	$[Rh(NBD)Cl]_2$	MeOH: CF_3CH_2OH =3:1	91	93

[a] Unless otherwise mentioned, all reactions were carried out with a Rh/L/**3a** ratio of 1/1.1/100 in 1.0 mL of solvent at 25 °C under 60 atm of hydrogen for 48 h. [b] Determined by ^{1}H NMR spectroscopy, no side product was observed. [c] The *ee* value was determined by HPLC on a chiral phase. [d] Under 30 atm of H_2 for 24 h. [e] Under 50 atm of H_2. [f] Under 30 atm of H_2.



[a] All reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature under 60 atm of hydrogen for 48 h. [b] Determined by 1H NMR spectroscopy. [c] The *ee* value was determined by HPLC on a chiral phase.

Scheme 1 Screening ligands for Rh-catalyzed asymmetric hydrogenation of **3a** [a, b, c]

conversion (>99%). When we turned our eyes to a mixture solution of methanol and trifluoroethanol (V:V = 3:1), the best result, full conversion and 94% *ee* could be obtained (entry 15). The pressure of hydrogen was also tuned and the conversion was proportionate to the pressure without erosion of the enantioselectivity (entries 15, 17 and 18). The absolute configuration of **4a** was confirmed as *S* by comparison of the observed optical rotation with reported data.

Moreover, other eight species of ZhaoPhos analogues developed by our group were also screened with $[Rh(NBD)Cl]_2$ as metal precursor. In contrast with the result of ZhaoPhos (**L1**), bisphosphine ureas **L2** and **L9** only gave 7% and 2% *ee*, respectively. This sharp contrast implied that thiourea was an inevitably active moiety to the series of ligands. Compared to **L3** with 3, 5-dimethyl on the phenyl ring, **L5** with electron-withdrawing group, trifluoromethyl, increased the enantioselectivity to 65%. After the 3,5-bis(trifluoro-methyl) phenyl group was replaced by a pyridyl ring, **L7** showed lower yield (20%) and *ee* value (57%). Furthermore, whether monophosphine ligand **L6** or bisphosphine thiourea ligand with a bulky group **L8** resulted in lower reactivity. However, **L4** bearing very similar structure as **L1**, provided 99% conversion and 88% *ee*. These results revealed that bisphosphine moiety,

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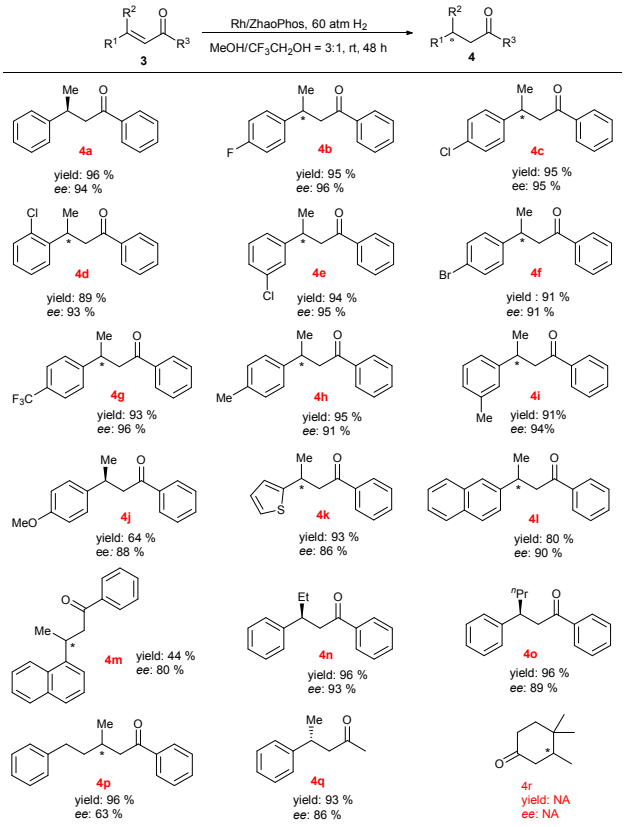

[a] All reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature under 60 atm of hydrogen for 48 h. [b] The yield of the isolated product was calculated by deduction the consumed starting material. [c] Determined by chiral HPLC analysis. [d] The hydrogenated product 3r didn't detect at all; NA referred to "not available".

Scheme 2 Asymmetric hydrogenation of β,β-disubstituted α,β-unsaturated ketones by the Rh-ZhaoPhos complex [a, b, c]

thiourea subunit and trifluoromethyl group at the 3- and 5-positions on the phenyl ring were the three key elements of the effective catalyst, which promoted the coordination of the ligand with substrates, facilitated the reaction, maintained the geometry of intermediates, and hampered the racemization. The chemo- and enantioselective hydrogenation of conjugated enones was therefore catalyzed by 1 mol% **L1** in the mixture solvent of MeOH and CF_3CH_2OH (V:V = 3:1) under 60 atm of H_2 at 25 °C for 48 h.

In order to explore the practicability of this protocol, various substrates with different groups at the β-position of conjugated enones **3** were reduced under the optimal conditions (Scheme 2). In most cases, whether electron-donating groups or electron-withdrawing groups on the phenyl ring, substrates **3a**-**3j** were hydrogenated with high yields and excellent enatioselectivities (Scheme 2, **4a**-**4j**). Substrates with *meta*- or *para*-substituets on the phenyl ring resulted in better results (94-95% yield and 95-96% *ee*) than that of *ortho*-substituted compound (**4c** and **4e** *vs.* **4d**). Unexpectedly, the *para*-methoxy substituted substrate **3j** was reduced in fairly lower yield (64%) and moderate reactivity (88% *ee*). When the phenyl ring was replaced by a fused-aryl group, 2-naphthyl, 80% yield and 90% ee (**4l**) were obtained. However, when the phenyl group was substituted by 1-naphthyl group, **4m** was achieved only in 44% yield with 80% *ee*. The diverse results between **4d** and **4c** & **4e** as well as between **4l** and **4m** might be attributed to the sterically hindered effects related to the cooperation of catalyst and substrates. The hetero aromatic ring substituted substrate **3k** afforded excellent *ee* value as well. Substrates with different R^2 and R^3 were also hydrogenated *via* the catalytic system. If the R^2 were methyl, ethyl or propyl group, the yields and enantioselectives were almost identical (**4a** *vs.* **4n**-**4o**). But both R^1 and R^3 were all alkyl groups, significant changes of the conversion and enantioselectivity were observed. For example, when R^1 was changed to phenyl ethyl group, full conversion and only 63% *ee* were observed (**4p**); and R^3 was replaced by methyl group, 93% yield and 86% *ee* were obtained (**4q**). These outcomes implied that the catalytic system was not applicable to the substrates with alkyl substituents at α- or β-position.

In conclusion, we have developed a succinct and efficient protocol for the synthesis of chiral aromatic ketones *via* asymmetric hydrogenation of β,β-disubstituted α,β-unsaturated ketones catalyzed by Rh-ZhaoPhos under mild conditions. In most cases, the enantiomerically pure products, versatile precursors in chemical synthesis, were achieved with high conversion and excellent enantioselectivity. This catalytic system is compatible with various functional groups. A further study is in progress with the aim of exploring the mechanism of this novel catalytic system and expanding substrate scope.

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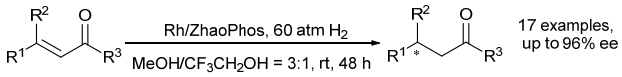

A series of chiral aromatic ketones were achieved with excellent enantioselectivities via Rh-ZhaoPhos catalyzed asymmetric hydrogenation of β,β-disubstituted enones.