Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900251

Link to VoR: http://dx.doi.org/10.1002/adsc.201900251

Very Important Publication **COMMUNICATION**

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Synthesis of Tridentate Chiral Spiro Aminophosphine-oxazoline Ligands and Application to Asymmetric Hydrogenation of α-Keto Amides

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract: A new type of tridentate chiral spiro aminophosphine-oxazoline ligands (SpiroOAP) have been synthesized through four steps. The SpiroOAP ligands are highly efficient for the asymmetric hydrogenation of α-keto amides, providing a variety of synthetically useful α-hydroxy amides with excellent enantioselectivity (up to 98% ee) and turnover numbers (up to 10,000).

Keywords: Tridentate ligand, Chiral spiro catalyst; Asymmetric hydrogenation, Iridium, α-Keto amides.

Transition metal-catalyzed asymmetric hydrogenation of unsaturated compounds is an efficient and convenient method for the synthesis of chiral molecules in optical form, which had been applied in wide field such as pharmaceuticals, pesticides, flavors, and fragrances. Since Knowles and co-workers[1] reported that the chiral phosphine can control the enantioselectivity of rhodium-catalyzed hydroge-nation of dehydroamino acid derivatives, many chiral ligands have been developed for the asymmetric hydrogenation of various unsaturated compounds such as olefins, ketones, and imines. The breakthrough in the asymmetric hydrogenation of simple ketone was made by Noyori and co-workers[2] in the 1990s with the catalyst BINAP-ruthenium-diamine complexes. Inspired by this work, many diphosphine ligands have been developed for the asymmetric hydrogenation of ketones in the last two decades[3]. For enhancing the stability of the catalyst, tridentate phosphine ligands containing nitrogen moiety, such as PNP[4] and PNN[5] were designed and applied for the asymmetric hydrogenation of ketones. During our studies on the iridium-catalyzed asymmetric hydrogenation of ketones, we have synthesized tridentate chiral spiro ligands SpiroPAP and SpiroSAP, which show excellent enantio-selectivity and unprecedented activity (up to 4.5 million TON)[6] in the hydrogenation of simple ketones and β-keto esters. However, when we applied these two tridentate ligands for the asymmetric hydrogenation of α-keto amides, only up to 82% ee and 84% ee were obtained, respectively. For improving the enantioselectivity and activity of the iridium catalyst, we designed a new type of tridentate chiral spiro phosphine ligands, SpiroOAP (**1**), by introducing an oxazoline moiety into the molecule (Figure 1). We hope to increase the enantioselectivity of the catalysts in the asymmetric hydrogenation of α-keto amides by varying the substituent and configuration on the oxazoline ring of the ligands.

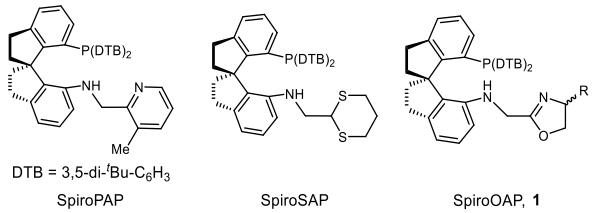

Figure 1. Tridentate chiral spiro ligands

The tridentate chiral spiro phosphine ligands SpiroOAP were synthesized from the ligands SpiroAP[7]. The reductive amination of SpiroAP with ethyl glyoxalate afforded the ester **2** in 96% yield. The ester **2** was hydrolyzed to the acid **3** in 89% yield with LiOH. The condensation of the acid **3** with enantiomerically pure 2-amino alcohols in the presence of HOBt (1-hydroxybenzotriazole) and EDCI-HCl (1-(3-dimethylaminopropyl)-3-ethylcarbo-diimide hydrochloride) gave the amides **4** in 73-97%

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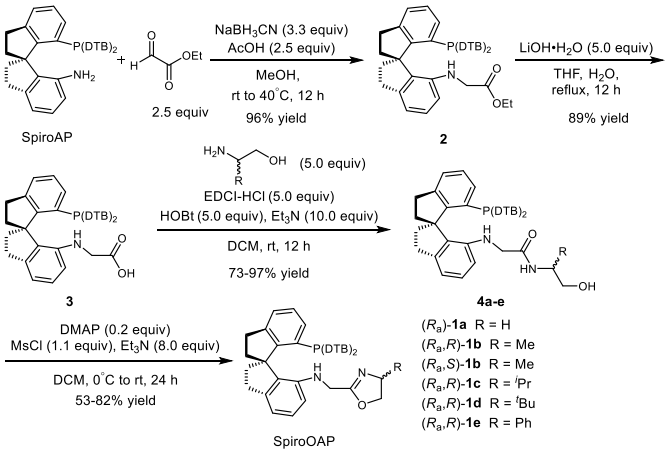
yield. The cyclization of the amides **4** provided the target ligands SpiroOAP in 53-82% yield. The ligands SpiroOAP are stable and can be purified by silica gel column chromatography (Scheme 1).



Scheme 1. Synthesis of ligands SpiroOAP (**1**).

Optical α-hydroxy amides are important motifs for the synthesis of biologically active compounds[8]. Chiral α-hydroxy ketones, which can be obtained from the optical α-hydroxy Weinreb amides through a nucleophilic addition with Grignard reagents, are a class of flavors[9] (Figure 2). Transition metal-catalyzed asymmetric hydrogenation of α-keto amides is a straightforward access to optical α-hydroxy amides. However, in a sharp contrast to β-keto esters[10], α-keto esters[11] and α-keto acids[12], the asymmetric hydrogenation of α-keto amides has been less studied. Only a few examples were reported on the asymmetric hydrogenation of α-keto amides with high enantioselectivity.[13] However, these methods still suffered from low efficiency or limited substrate scope. Therefore, efficient chiral ligands with high enantioselectivity, high activity, and wide substrate scope are desired for the catalytic asymmetric hydrogenation of α-keto amides.

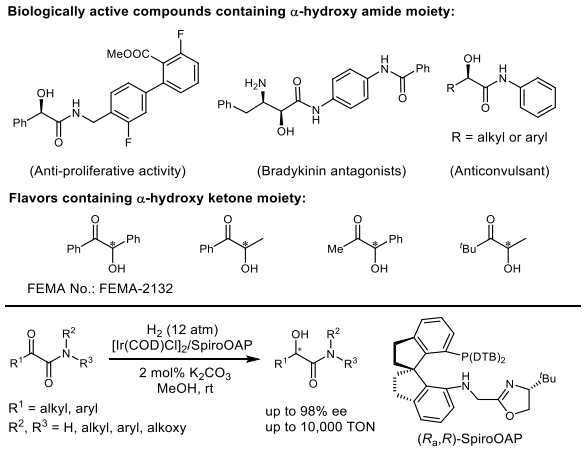
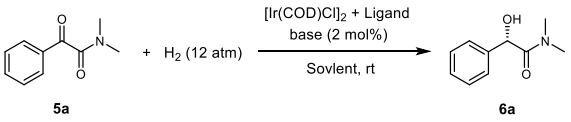


Figure 2. Representative biologically active compounds containing α-hydroxy amide moiety and flavors (FEMA = Flavour Extract Manufacturers Association) (top part); Asymmetric hydrogenation of α-keto amides catalyzed by Ir-SpiroOAP (bottom part).

The hydrogenation of *N*,*N*-dimethyl-2-oxo-2-phenylacetamide (**5a**) was performed in EtOH under 12 atm of H_2 to evaluate the new ligands. As shown in Table 1, all iridium catalysts with ligands **1** displayed high reactivity, the yields are >99%. However, the enantioselectivity of catalysts varied with the substituent and configuration on the oxazoline ring of ligand. When the steric hindrance of the substituent on the oxazoline ring increased from methyl (**1a**) to *tert*-buty (**1d**), the enantioselectivity changed from 88% ee to 97% ee (Table 1, entries 3, 4 and 6–8). The combination of the configurations of the ligand is critical for the enantioselectivity, with (R_a,*R*) being the choice of the configuration of the ligand (entry 4 vs entry 5). A study of solvent showed that the MeOH gives even higher enantioselectivity (98% ee, entry 9). It is delighted to find that the K_2CO_3 is also a suitable base for the reaction, giving excellent yield and enantioselectivity (entry 11). The weaker basicity and low loading of K_2CO_3 endowed this reaction with another advantage, tolerating more functional groups in the substrates

Table 1. Asymmetric hydrogenation of α-keto amide **5a**. Optimization of the reaction conditions.[a]



Entry	Ligand	Solvent	Base	Yield (%)[b]	ee (%)[c]
1	SpiroPAP	EtOH	^{t}BuOK	>99	82
2	SpiroSAP	EtOH	^{t}BuOK	>99	84
3	(R_a)-**1a**	EtOH	^{t}BuOK	>99	88
4	(R_a,*R*)-**1b**	EtOH	^{t}BuOK	>99	92
5	(R_a,*S*)-**1b**	EtOH	^{t}BuOK	>99	68
6	(R_a,*R*)-**1c**	EtOH	^{t}BuOK	>99	93
7	(R_a,*R*)-**1d**	EtOH	^{t}BuOK	>99	97
8	(R_a,*R*)-**1e**	EtOH	^{t}BuOK	>99	90
9	(R_a,*R*)-**1d**	MeOH	^{t}BuOK	>99	98
10[d]	(R_a,*R*)-**1d**	^{i}PrOH	^{t}BuOK	>99	25
11	(R_a,*R*)-**1d**	MeOH	K_2CO_3	>99	98

[a]Reaction conditions: 1.0 mmol scale, 0.17 mol% $[Ir(COD)Cl]_2$, 0.37 mol% ligand, 2 mol% base, 4.0 mL

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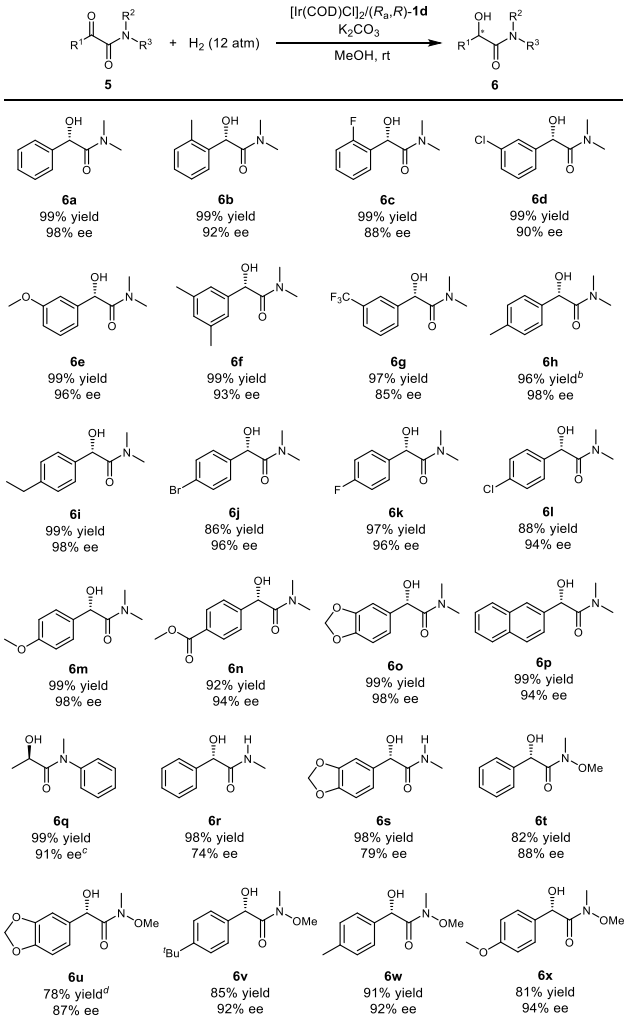
solvent, rt,1-2 h. [b] Isolated yield. [c] Determined by HPLC with chiral OD-H. [d] Reaction time is 22 h.

Under the optimized reaction conditions, a variety of α-keto amides were hydrogenated to α-hydroxy amides and the results are summarized in Table 2. The tertiary α-keto amide substrates showed high yield and high enantioselectivity in the hydrogenation reaction (Table 2, **6a** – **6q**). The catalyst (R_a,*R*)-**1d** exhibited high activity, its TON reaches 10,000 (**6h**). The functional groups on the benzene ring of substrates, such as halogen, trifluoromethyl, ether, and ester were tolerated in the reaction. The electronic property of the substituents on the benzene ring of substrates has a little influence on the enantioselectivity of reaction, with electron-withdrawing group at *ortho*- and *meta*-position giving slightly lower ee (**6c**, **6d** and **6g**). It was delighted to find that the substrate with an acetyl group

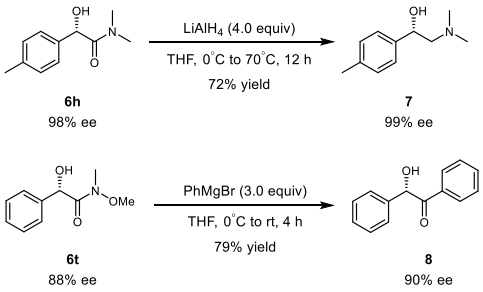
Table 2 The asymmetric hydrogenation of α-keto amides catalyzed by Ir-(R_a,*R*)-**1d** [a]



[a] Reaction conditions: 1.0 mmol scale, 0.17 mol% $[Ir(COD)Cl]_2$, 0.37 mol% (R_a,*R*)-**1d**, 0.02 mmol K_2CO_3, 4.0 mL MeOH, rt,1-6 h, isolated yield. [b] TON = 10,000. 100% conv., 15 h. [c] Ligand (R_a,*S*)-**1b** used. [d] Reaction time is 24 h.

(R^1 = Me) underwent the hydrogenation smoothly, providing the desired product **6q** in 99% yield with 91% ee. The secondary α-keto amide substrates can also be hydrogenated to α-hydroxy amides in high yield, however, with lower enantioselectivity (**6r** (74% ee) and **6s** (79% ee), respectively). As we expected, the α-keto Weinreb amides are suitable substrates for the asymmetric hydrogenation catalyzed by Ir-SpiroOAP, affording the desired products with 78−91% yield and 87−94% ee (**6t**–**6x**).

The hydrogenation products, optical α-hydroxy amides, can be readily converted to β-amino alcohols, α-hydroxy ketones and other useful compounds. For example, the reduction of α-hydroxy amide **6h** with $LiAiH_4$ produced β-amino alcohol **7** (72% yield, 99% ee), which is an intermediate for the synthesis of 1,2-amino ether ligands[14]. The addition of PhMgBr to **6t** afforded α-hydroxy ketone **8** (79% yield, 90% ee), which is a widely used flavor (Scheme 2).



Scheme 2 Transformations of the hydrogenation products

In summary, a new type of chiral tridentate spiro PNN ligands SpiroOAP have been synthesized through four steps. The iridium catalysts coordinated with ligands SpiroOAP showed high activity and enantioselectivity for the asymmetric hydrogenation of α- keto amides. By using catalysts Ir-SpiroOAP, a variety of chiral α-hydroxy amides have been synthesized with excellent enantioselectivity (up to 98% ee) and turnover numbers (up to 10,000). Further investigations on the applications of the new ligands to other asymmetric reactions are underway in our group.

Experimental Section

The catalyst precursor $[Ir(COD)Cl]_2$ (1.2 mg), Ligand **1d** (3.1 mg), and anhydrous MeOH (1 mL) were added under Ar atmosphere to a hydrogenation vessel (20 mL). The vessel was then placed in an autoclave and purged with hydrogen by pressurizing to 12 atm. The mixture was stirred for 10 min to give a clear yellow solution. After releasing the pressure, α-keto amide (1.0 mmol), K_2CO_3 (2.8 mg) and MeOH (3 mL) were added through the

injection port. The autoclave was then pressurized to 12 atm of H_2 and the reaction mixture was stirred at room temperature until no obvious hydrogen pressure drop was observed. After releasing the hydrogen pressure, the solvent was removed, and the residue was purified with column chromatography on silica gel. The enantiomeric excess of product was determined by HPLC on a chiral stationary phase.

Acknowledgements

We thank the National Natural Science Foundation of China (Nos. 21532003, 21790330 and 21871152) and the "111" project (B06005) of the Ministry of Education of China for financial support.

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10.1002/adsc.201900251

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