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Graphical abstract:



A robust Ru-PNNP catalyst system for the asymmetric hydrogenation of α,β-unsaturated ketones to allylic alcohol

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Abstract:

A robust and stable Ru-Biphosphinobioxazoline catalyst system is discovered for the highly enantioselective hydrogenation of enones to allylic alcohols. A series of acyclic α,β -unsaturated ketones react well affording the desired products in high yields (up to 98%) and enantioselectivities (up to 98% ee). Simple manipulation process and tolerance of water and air make this catalysis more practical and appealing.

Keywords: ruthenium; biphosphinobioxazoline; hydrogenation; unsaturated ketones, allylic alcohol

Asymmetric hydrogenation has become a very important transformation to obtain chiral compounds both in academic and industry. For substrates with only one single unsaturated C=C, C=O or C=N bond, their asymmetric hydrogenations have been well developed.¹ However, for substrates containing multiple different unsaturated bonds such as heteroaromatic compounds,² unsaturated ketones and imines, asymmetric hydrogenation of them is much more complex and chemoselectivity, regioselectivity and enantioselectivity are involved in these reactions. For example, hydrogenation of α,β -unsaturated ketones will produce saturated ketones with C=C double bond being hydrogenated and allylic alcohols with C=O double bond being hydrogenated. Controlling the chemoselectivity to obtain one single product with high enantioselectivity is a challenge. Recently, asymmetric hydrogenation of α,β -unsaturated ketones to saturated ketones with high enantioselectivity has been realized using Ir-complex of P,N-ligands as catalyst system.³ For asymmetric hydrogenation of α , β -unsaturated ketones to allylic alcohol, both Ir-complex and Ru-complex are effective for this transformation.⁴ Using in situ prepared Ir-complexes of chiral spiro aminophosphine ligands, Zhou and Xie's group reported highly efficient asymmetric hydrogenation of exo-cyclic enones.⁵ Noyori's group⁶ and Ohkuma's group⁷ reported the asymmetric hydrogenation of acyclic enones by using prepared complex of *trans*-RuCl₂(phosphine)₂(1,2-diamine). Under optimized conditions, the corresponding allylic alcohols were obtained with high yield and enantioselectivity. However, the preparation of such complexes and the manipulation of hydrogenation reactions are usually carried out under the protection of inert atmosphere in order to remove oxygen and water, which brings some problems in practical use. Thus, more stable and robust catalyst systems are highly desirable. Considering that allylic alcohols are important intermediates for the synthesis of a variety of biologically active pharmaceuticals and natural products and asymmetric hydrogenation of α,β -unsaturated ketones to allylic alcohols is the most convenient and efficient approach, herein we describe highly enantioselective hydrogenation of acyclic α,β -unsaturated ketones to allylic alcohols, catalyzed by a robust and stable

Ru-Biphosphinobioxazoline catalyst system under mild conditions.

From the easily available *L*-tartaric acid, the C2-symmetric bisphosphinobioxazoline [(S,S)-Phos-Biox] L1 can be prepared with good yield.⁸ It contains diphosphine structure and rigid dioxazoline ring, but without NH structure. This is different from diamine ligand in Noyori's Ru^{II}- diphosphine/diamine complex, in which the NH structure is believed to be very important for the reaction⁹. L1 has been applied in hydrosilylation,^{8,10} allylic alkylation¹¹ and transfer hydrogenation reactions¹². Considering that its special tetradentate PNNP structure may have different effect on the reaction, we investigated the catalytic performance of Ru-L1 combination for the asymmetric hydrogenation of α,β -unsaturated ketones.





	Entry	Solvent	Ligand	Base	Convn. ^b	Ee^{c} (%)
					(%)	
	1	<i>i</i> -PrOH	L1	t-BuOK	>95	62
	2	<i>i</i> -PrOH	L1	NaOH	>95	85
	3	EtOH	L1	NaOH	>95	90
	4	EtOH	L1	LiOH·H ₂ O	>95	90
v	5	EtOH	L1	КОН	>95	90
	6	EtOH	L1	t-BuOK	>95	90
	7	EtOH	L1	Cs_2CO_3	>95	89
	8	EtOH	L1	K_2CO_3	46	90
	9 ^d	EtOH	L1	LiOH·H ₂ O	>95	92
	10 ^e	EtOH	L1	NaOH	>95	89

11 ^f	EtOH	L1	t-BuOK	>95	88
12	EtOH	L2	LiOH·H ₂ O	<5	/
13	EtOH	L3	LiOH·H ₂ O	>95	66
14 ^g	EtOH	L1	LiOH·H ₂ O	>95	90

^a **1a**: 1.0 mmol; $[Ru(cymeme)Cl]_2$: 1.6 mg (0.0025 mmol); **L**: 0.0055 mmol; substrate/catalyst/base: 200/1/10 ~ 40. Unless otherwise stated, reactions were conducted at room

temperature under $H_2(10 \text{ atm})$ in solvent (3 mL) for 4 hours.

^b The conversion was determined by ¹H-NMR and all the reactions gave the product **2a** with >98% chemselectivity.

^c Enantiomer ratios were determined by HPLC using a Chiralcel OD-H column. The *R* enantiomer of product was formed in excess.

^dReaction was carried out at 0 °C;

^e Ethanol (2.5 mL) and water (0.5 mL) were used as solvent;

^f The reaction was manipulated in glove box using anhydrous ethanol.

^g **1a**: 5.0 mmol, S/C: 1000/1.

(*E*)-chalcone (**1a**) is chosen as a standard substrate. The reaction was performed without protection and the solvents were reagent pure grade and used as received without manipulation. Under such conditions, hydrogenation of **1a** with the catalyst prepared in situ from [Ru(cymene)Cl₂]₂ and **L1** in *i*-PrOH at room temperature under 10 atm of H₂ with *t*-C₄H₉OK gave complete conversion in 4 hours, affording (*R*)-1,3-diphenyl-2-propen-1-ol ((*R*)-**2a**) in 62% ee (Table 1, entry 1). No saturated ketone 1,3-diphenyl-1-propanone (**3**) and alcohol, 1,3-diphenyl-1-propanol (**4**) was detected with ¹H-NMR. Without base or hydrogen, no product was detected, which indicated that base was necessary and transfer hydrogenation did not occur. When NaOH was used as the base under the same conditions, higher enantioselectivity of 85% was achieved (entry 2), which indicated that base have great influence on the reaction in *i*-PrOH. However, when ethanol was used as the solvent, the reactions with LiOH, NaOH, KOH, *t*-C₄H₉OK and Cs₂CO₃ as the base all gave full conversion and similar

enantioselectivities of 89-90% (entries 3-7). The reaction only with the weak base K_2CO_3 gave 46% conversion, still with 90% ee (entry 8). When the reaction was carried out at 0 °C, 92% ee was obtained, slightly higher than that at 25 °C (entry 9). Full conversion and 89% ee were obtained when 0.5 mL of water was added to the reaction, which showed the reaction and the catalyst is not sensitive to water (entry 10). For comparison, a reaction was tried in glove box in anhydrous ethanol and full conversion and slightly lower enantioselectivity (88% ee) was obtained (entry 11). All these results indicated that Ru-[(*S*,*S*)-Phos-Biox] system is rather stable and robust for the asymmetric hydrogenation of α , β -unsaturated ketones to allylic alcohols. When P,N-ligand L2 with the similar half part structure of L1 was used, no product can be detected (entry 12). Although L3 has the similar PNNP structure as L1, the reaction with L3 as ligand gave the product with full conversion, but lower enantioselectivity (entry 13). When the reaction was performed on a 5.0 mmol scale of 1a with a catalyst loading of 0.1 mol%, conversion (>95%) and enantioselectivity (90% *ee*) were maintained under the same conditions (entry 14).

R ¹		Ru(cymene)Cl ₂] ₂ / L1 EtOH, H ₂ (10 bar), 6 h, LiOH•H ₂ O	OH R ¹ R ² 2	L1 O N N PPh ₂ Ph ₂	P P
Entry	Substrate			Yield of 2	<i>ee</i> (%) ^c
				(%) ^b	Config. ^d
1		0 	1a , R = H	2a , 98	90 (<i>R</i>)
2		Ph	1b , R = 2-Cl	2b , 94	96 (<i>R</i>)
3			1c , R = 3-Cl	2c , 96	92 (<i>R</i>)
4			1d , R = 4-Cl	2d , 95	93 (<i>R</i>)
5			1e , R = 2-CF ₃	2e , 89	97 (<i>R</i>)
6			1f , $R = 4-CF_3$	2f , 94	94 (<i>R</i>)
7			1g, R = 4-CH ₃	2g , 92	88 (R)

Table 2: Hydrogenation of α , β -unsaturated ketones using Ru-L1 catalyst system.^a



^a All reactions were carried out in ethanol (5 mL) for 6 h at room temperature under 10 bar of H₂. Substrates (1.0 mmol) was used and the catalyst was prepared in situ from 0.25 mol % of $[Ru(cymene)Cl]_2$ and 0.55 mol% L1 in ethanol (3 mL) without protection, unless otherwise specified.

^b The yields are based on enones and refer to the amount of isolated product.

^c Determined by HPLC analysis, see supporting information.

^d The absolute configurations were assigned by comparison of the optical rotations with literature values or assuming analogous reaction pathways.

^e S/C/B: 100/1/5; A mixture of enol and saturated alcohol were obtained and unseparated using

chromatography. ¹H-NMR was used to determine the conversion (>95%) and the ratio of them (88/12).

Under the optimized reaction conditions, a series of α,β -unsaturated ketones were hydrogenated to demonstrate the scope and limitations of the Ru-L1 catalyst system. The results are summarized in Table 2. The hydrogenation results of aryl substituted enones (entries 1-16) revealed that changing the substitution pattern of the olefinic moiety and ketonic moiety has no obvious effect on conversion but has important effect on enantioselectivity. All the reactions gave full conversion after 6 h under a H_2 pressure of 10 bar and products were allylic alcohols with >98% chemselectivity. The hydrogenation of enones 1b-f indicated that electron-withdrawing group at benzene ring of olefinic moiety has positive effect on the enantioselectivity, leading to higher ee (Table 2, entries 2-6, 92-97% ee) than that of 1a (entry 1, 90% ee). In addition, the position of the substituent has influence on the enantioselectivity. Substrates 1b-d with Cl-group at orth-, meta- and para-position of benzene ring were hydrogenated with 96, 92 and 93% ee, respectively. CF3-group is more electron deficient than Cl-group, so the substrate 1e and 1f with CF₃-group at orth- and para-position of benzene ring were hydrogenated with 97% and 94% ee (entries 5-6). Hydrogenation of substrate 1g and 1h with electron-donating group CH₃ and CH₃O at para-position of benzene ring gave the products 2g and 2h with the similar enantioselectivity as 2a (entries 7 and 8, 90% ee for both). 2-Furyl and 2-thienyl substituted enones 1i and 1j, were also good substrates for this reaction, affording the corresponding allylic alcohol 2i and 2j in 82% (entry 9) and 84% ee (entry 10), respectively. Substrate 1k with 1-Naphthyl on the olefinic moiety was hydrogenated smoothly to the desired allylic alcohol with 91% ee (entry 11). When electro-withdrawing Cl-group was located at the benzene ring of the ketonic moiety (substrate 11), slightly higher ee of 92% (entry 12) was obtained compared with H-group (entry 1). F-group has no effect on the reaction (entry 13) and 89% ee was achieved (entry 13). When substrate **1n** with electron-donating CH₃O-groups at the para-position of benzene ring of the ketonic moiety was hydrogenated, complete conversion was obtained, albeit with a lower enantioselectivity (entry 14, 86% ee).

The reaction of **1o** with both olefinic moiety and ketonic moiety having Cl-group at the para-position of benzene ring gave the product **2o** with 94% ee in high yield (entry 15). Hydrogenation of substrate **1p** with orth-CF₃-group at the benzene ring of the olefinic moiety and para-Cl-group located at the benzene ring of the ketonic moiety gave the product **2p** with the highest enantioselectivity of 98% and high yield (entry 16).

For the enone 1q with alkyl substituent methyl-group at the ketonic moiety, the Ru-L1 catalyst system is also effective, giving the product 2q in high yield, but with much lower ee (28%, entry 17) compared with 2a, which indicated that the aromatic ring of the ketonic moiety may have important effect on the enantioselectivity. When alkyl substituent *i*-propyl is located at olefinic moiety, hydrogenation of such enone 1r gave uncompleted conversion under the same conditions. Increasing the catalyst loading from 0.5 to 1.0 mol%, full conversion was achieved and a mixture of unsaturated (*E*)-4-methyl-1-phenyl-2-penten-1-ol (88%, 95% ee) and saturated (*E*)-4-methyl-1-phenyl-2-penten-1-ol (88%, 95% ee) and saturated (*E*)-4-methyl-1-phenyl-2-penten-1 (12%, 76% ee) were obtained (entry 18). For the cyclic 3,5,5-trimethylcyclohex2-enone, the Ru-L1 gave no conversion (entry 19). From the above results, it permitted us to conclude that aryl substituted enones are good substrates for chemo- and enantioselective hydrogenation with Ru-L1 catalyst system.

For the mechanism of this reaction, with *trans*-RuCl₂(phosphine)₂(1,2-diamine) complex containing N-H structure as the catalyst, a metal-ligand bifunctional catalysis process through a pericyclic six-membered transition state is proposed⁷. With Ru-L1 catalyst system without N-H structure, the reaction may proceed through a classic [2+2] mechanism and N-H effect is not approved here.

In conclusion, we discovered a stable and robust Ru-PNNP catalyst system for the highly enantioselective hydrogenation of α , β -unsaturated ketones to allylic alcohols. This Ru-PNNP catalyst system can tolerate water and air, which provides a practical approach for the synthesis of allylic alcohols with high yield and enantioselectivity under mild conditions.

Experimental section

General Procedure for Hydrogenation: $[Ru(cymene)Cl]_2$ (1.6 mg, 0.0025 mmol), ligand L1 (3.7 mg, 0.0055 mmol) and LiOH·H₂O (6.3 mg, 0.15 mmol) were placed in a 5 mL vial equipped with a stirrer bar. To the mixture was added ethanol (3 mL) and then stirred without any protection for 2 minutes. Then substrate 1 (1.0 mmol) and ethanol (2 mL) was added and then the vial was put into a steel autoclave. The autoclave was then closed, purged three times with hydrogen (less than the pressure needed) and finally pressurized to the value needed. The reaction mixture was stirred for the indicated period of time, and then the hydrogen gas slowly released. The conversion of the substrate was determined by ¹H NMR spectroscopy of the crude reaction mixture, and the product was purified by chromatography using a petrolic ether/ethyl acetate mixture (10:1-5:1). Enantiomeric ratios were determined with HPLC using a Chiralcel column. The HPLC conditions and the spectral data of all compounds are provided in the Supporting Information.

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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