ORGANIC LETTERS

2005
Vol. 7, No. 6
1043−1045

Highly Efficient Iridium Catalyst for Asymmetric Transfer Hydrogenation of Aromatic Ketones under Base-Free Conditions

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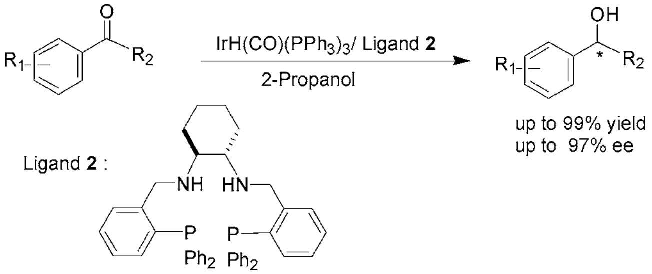
Received December 17, 2004

ABSTRACT



Catalytic systems generated in situ from the chiral PNNP ligands with iridium or rhodium hydride complexes exhibited excellent catalytic activity and good enantioselectivity in the asymmetric transfer hydrogenation of aromatic ketones without added base. The best result was obtained in the $IrH(CO)(PPh_3)_3$–ligand 2 catalytic system with up to 99% yield and 97% ee.

Among the most spectacular recent developments in catalytic asymmetric synthesis, asymmetric transfer hydrogenation is an attractive method for the preparation of optically active alcohols.[1−3] In this reaction, 2-propanol is a conventional hydrogen source having favorable properties: it is stable, easy to handle, nontoxic, and inexpensive.[3c] In most previous studies of asymmetric transfer hydrogenation in 2-propanol, however, a strong base such as KOH, NaOH, or KO^{t}Bu is essential to promote the reduction smoothly. No reaction occurs if the base is absent or its concentration is too low.[2,3] Because the amount of base remarkably affects catalytic activity and the enantioselectivity of the reduction,[2,4] researchers must optimize the reaction conditions by adding the appropriate amount of base. Furthermore, the presence of a base in the reaction is not suitable for hydrogenation of base-sensitive ketones. Recently, Noyori et al. and Morris et al. disclosed useful chiral Ru complexes as catalysts for

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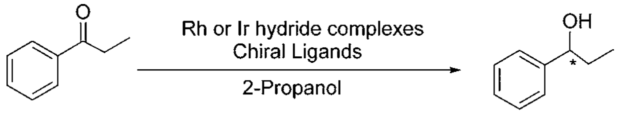
10.1021/ol047412n CCC: $30.25

asymmetric hydrogenation under base-free conditions.[5] And although a few works described the transfer hydrogenation of some ketones in 2-propanol without using any bases,[6] few reports on asymmetric transfer hydrogenation of a variety of aromatic ketones under base-free conditions have appeared.

In earlier studies, we reported the synthesis and catalytic property of the well-designed PNNP-type ligands $C_6P_2N_2$ **1**, $C_6P_2(NH)_2$ **2**, and $Ph_2P_2(NH)_2$ **4**,[4,7−10] which exhibited high enantioselectivity and activity in asymmetric transfer hydrogenation of ketones in the presence of a base. In particular, a Ru cluster complex efficiently catalyzed the reduction of propiophenone in the absence of base.[10] Recently, we found an efficient catalytic system generated from an iridium hydride complex and ligand **2** for enantioselective transfer hydrogenation of a series of aromatic ketones without using any base.

We set out by examining the catalytic activity of the metal hydride complexes combined with various chiral ligands for the asymmetric transfer hydrogenation of propiophenone in 2-propanol (Table 1).[11]

Table 1. Asymmetric Transfer Hydrogenation Catalyzed by Rh and Ir Hydride Complexes−Chiral PNNP Systems without Adding Any Base[a]



entry	metal hydride complexes	ligand	temp (°C)	time (h)	yield (%)[b]	ee (%)[b]
1	$RhH(CO)(PPh_3)_3$	**2b**	75	45	79	65
2	*mer*-$IrH_3(PPh_3)_3$	**2b**	75	24	99	74
3	$IrH(CO)(PPh_3)_3$	**2b**	75	0.5	97	90
4	$IrH(CO)(PPh_3)_3$	**1b**	70	3.5	94	50
5	$IrH(CO)(PPh_3)_3$	**4b**	70	2.5	98	56
6	$IrH(CO)(PPh_3)_3$		70	20	21	

[a] Reaction was carried out with S/C = 200. [b] Determined by GC analysis (chiral column: Chrompack CP-cyclodextrin-β-236-M-19 column).

As expected, most of these metal hydride catalytic systems efficiently catalyzed the reaction without addition of any base. In particular, the catalyst system generated from $IrH(CO)(PPh_3)_3$ exhibited high catalytic activity and good enantioselectivity (entry 3). Noticeably, not all metal hydride complexes efficiently catalyzed the reaction under base-free conditions; Ru hydride complexes such as $RuHCl(CO)(PPh_3)_3$ could not promote the reaction smoothly in the absence of bases. This indicated that Rh- and Ir-catalyzed hydrogen transfer occurred via a monohydride and Ru-catalyzed hydrogen transfer via a dihydride.[3a,6c] In addition, chiral ligands also played an important role in the reaction. Without addition of any chiral ligands, the complex $IrH(CO)(PPh_3)_3$ could not catalyze the reaction smoothly and only a low conversion was obtained (entry 6). Various other chiral ligands (Figure 1) together with $IrHCO(PPh_3)_3$ in situ were employed to catalyze the reduction of propiophenone. The reduction with a binary system, $IrH(CO)(PPh_3)_3$ and the diamine ligand **3**, proceeded very slowly and then stopped, leading to the reduction product in low yield (<10%) and low enantioselectivity (<5%). The similar PNNP ligand diiminodiphosphines **1** and another PNNP ligand **4** were effective for the reduction of ketones, but the enantioselectivity of chiral alcohol remarkably decreased (entries 4 and 5). These results indicated that the structure of the PNNP tetradentate ligands was a crucial factor for ligand acceleration, and the NH functions in the ligand **2** and its structure are responsible for the good enantioselectivity.[4]

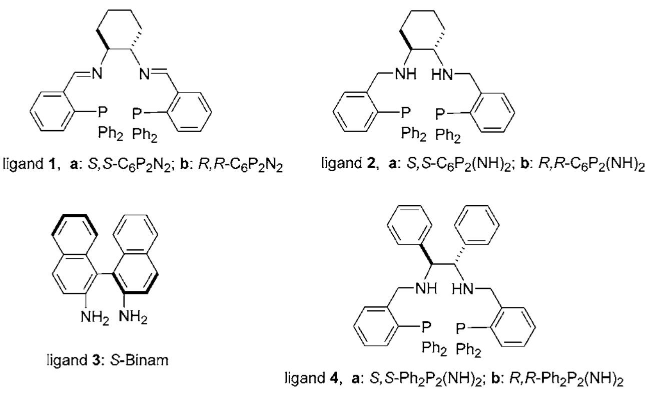


Figure 1. Chiral ligands used in asymmetric transfer hydrogenation.

As shown in Table 2, the chiral $IrH(CO)(PPh_3)_3$−PNNP system catalyzed the asymmetric reduction of various ketones to the secondary alcohols with a high chemical yield and good enantioselectivity under base-free conditions.

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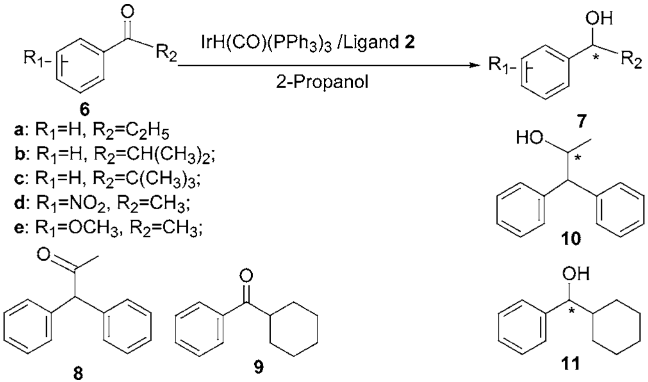
(11) **Typical Procedure for Asymmetric Transfer Hydrogenation.** To a mixture of the metal−hydride complex (0.0025 mmol) and the chiral ligand (0.0026 mmol) was added 2-propanol (5 cm^3). The mixture was stirred at 70 °C for 30 min. To this solution was added the substrate (0.5 mmol), and the mixture was then stirred at the expected temperature. Samples were taken out of the reaction solution after the given time, passed through a column of silica, and analyzed by GC.

Table 2. Asymmetric Transfer Hydrogenation of Aromatic Ketones Catalyzed by $IrH(CO)(PPh_3)_3$−Ligand **2** in Situ in the Absence of Bases[a]



entry	ligand	ketone	temp (°C)	time (h)	yield (%)[c]	ee (%)[c]
1	**2b**	**6a**	75	0.5	97	90[f]
2	**2b**	**6a**[b]	82	2	98	84[f]
3	**2b**	**6b**	75	6	90	93[f]
4	**2a**	**6c**	75	4	99	80[e]
5	**2b**	***o*-6d**	70	1	99	92[f]
6	**2b**	***m*-6e**	75	1	91	70[f]
7	**2a**	**8**	75	8.5	99	97[d]
8	**2b**	**9**	75	3	96	94[d]

[a] Unless otherwise stated, the reaction was carried out with S/C = 200. [b] S/C = 2000. [c] Determined by GC analysis. [d] Chiral column: CP-chiralsil-Dex CB column. [e] Chiral column: Chiraldex G-TA column. [f] Chiral column: Chrompack CP-cyclodextrin-β-236-M-19 column.

For propiophenone, even when the molar ratio of substrate to catalyst is up to 2000, the activity of the catalytic system is still very high with a good enantioselectivity (entry 2). In addition, for reduction of the congested ketones such as isobutyrophenone and 2,2-dimethyl-propiophenone, which are difficult to reduce because of the bulkiness of the alkyl substituents,[1g,4,10,12] the chiral Ir−PNNP catalytic system still exhibited high activity and good to excellent enantioselectivity (entries 3 and 4). Notably, the enantioselectivity was improved with an increase of the bulkiness of the alkyl substituents (entries 1, 3, 4, 7, and 8). The introduction of an electron-withdrawing group such as nitro was helpful to obtain high enantioselectivity (entry 5), while the introduction of an electron-donating substituent such as methoxyl tended to lower the enantioselectivity while maintaining satisfactory activity (entry 6).

Some possible mechanisms for transfer hydrogenation in the presence of a base were described in the literature.[3,13] For transition metals, a metal hydride complex is considered to be the key active intermediate for transfer hydrogenation. The role of an alkaline base is believed to facilitate the formation of a metal alkoxide, which then β-eliminates, forming a reducing metal hydride species (hydridic route),[3] or to generate a 16e metal complex as a true catalyst of the reaction, which then forms an 18e metal hydride intermediate (metal−ligand bifunctional catalysis).[13] The use of bases is helpful to form the metal hydride complexes. Thus, chiral metal hydride complexes are expected to be good catalysts for asymmetric transfer hydrogenation in the absence of added base.[6e,f] On the other hand, chiral PNNP tetradentate ligand **2** is also an important factor for this catalytic system to promote the reaction smoothly under base-free conditions.

In conclusion, we have discovered a good catalyst system generated in situ from $IrH(CO)(PPh_3)_3$ and the chiral PNNP ligand **2** for the asymmetric transfer hydrogenation of aromatic ketones. High conversion and good to excellent enantioselectivity were obtained in the catalytic reaction without adding any base. Future work will concentrate on finding the structure of the real catalyst and improving the enantioselectivity of the catalytic system.

Acknowledgment. We thank the National Natural Science Foundation of China (20373056), the Fujian Provincial Science and Technology Commission (2002F016), and Xiamen Science and Technology Commission (3502Z200-21044) for financial support.

Supporting Information Available: Experimental procedure for the synthesis and IR spectra of Ru, Rh, and Ir hydride complexes, typical procedures for asymmetric transfer hydrogenation of prochiral ketones, and GC analytical data for chiral aromatic alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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