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Asymmetric transfer hydrogenation of aromatic ketones catalyzed by the iridium hydride complex under ambient conditions

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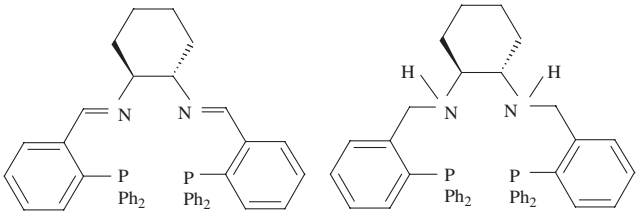
Abstract—The chiral Ir catalytic system generated in situ from iridium hydride complex and chiral diaminodiphosphine ligand was employed in asymmetric transfer hydrogenation of aromatic ketones to give the corresponding optically active alcohols, with up to 99% ee in high yield were obtained even when the substrate-to-catalyst molar ratio reached 10000:1.

Asymmetric transfer hydrogenation of prochiral ketones is one of the most efficient methods for producing enantiomerically enriched secondary alcohols. The reaction is simple and does not require molecular hydrogen.[1,2] Most research works in this area were carried out by using the chirally modified transition metals, such as Ru, Rh, and Ir, as catalyst precursors.[3–12] Although iridium hydride complexes have been used in many other areas,[13–19] they have seldom been used in the asymmetric transfer hydrogenation of ketones.[20,21]

In the field of enantioselective transfer hydrogenation, most effective chiral ligands often contain nitrogen or phosphine atoms.[22–28] Recently, we have synthesized a well-designed chiral diaminodiphosphine ligand *N*,*N*′-bis[*o*-(diphenylphosphino)benzyl]cyclohexane-1,2-diamine (Fig. 1, **II**)[29] to be employed together with Ru and Rh complexes to catalyze asymmetric transfer hydrogenation of ketones. These catalyst systems show high enantioselectivity and activity.[29–31] Herein, we describe a new chiral iridium system generated in situ from iridium hydride complex $[IrHCl_2(COD)]_2$ and the C_2-symmetric chiral ligand $C_6P_2(NH)_2$ for the enantioselective transfer hydrogenation of aromatic ketones (Scheme 1). This catalytic system exhibits excellent activity and enantioselectivity under mild reaction conditions.



I $C_6P_2N_2$ **II** $C_6P_2(NH)_2$

Figure 1.

Using the method reported by Robinson and Shaw,[32] we synthesized $[IrHCl_2(COD)]_2$ by refluxing chloroiridic acid and cycloocta-1,5-diene in absolute ethanol as cream-colored microcrystals. Catalytic experiments were carried out under nitrogen atmosphere using standard schlenk-tube techniques. To an *iso*-PrOH solution of the iridium complex and chiral ligand were added an appropriate amount of ketone and KOH/*iso*-PrOH solutions, respectively, at room temperature. The solution was stirred for several hours, then examined with capillary GLC analysis.

First we studied the effect of chiral ligands **I** and **II** (Fig. 1) combined with $[IrHCl_2(COD)]_2$ on the asymmetric transfer hydrogenation of a diverse range of aromatic ketones. When chiral diiminodiphosphine $C_6P_2N_2$ was used as ligand, the catalytic reaction proceeded slowly with low enantioselectivity (generally, 20–40% conv., 20–40% ee). Nevertheless, the diaminodiphosphine

Keywords: Iridium hydride complex; Chiral ligand; Aromatic ketone; Asymmetric transfer hydrogenation.
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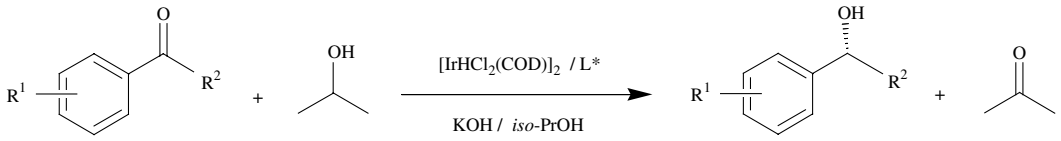
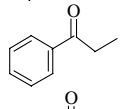
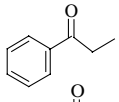
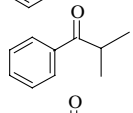
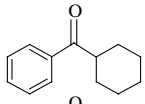
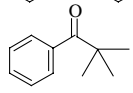
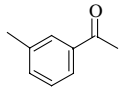
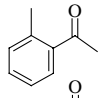
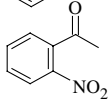
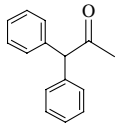


Scheme 1.

$C_6P_2(NH)_2$ has proven to be an excellent ligand and the results are listed in Table 1.

The activity and enantioselectivity are highly dependent on the ring substituent and the steric bulk of the alkyl group. When the size of the alkyl group increased from methyl to cyclohexyl, the enantioselectivity was remarkably improved without deterioration of the activity (entries 1–5). For the asymmetric transfer hydrogenation of propiophenone, the catalyst system showed high activity and enantioselectivity even in the presence of small amount of water (entry 3). The asymmetric transfer hydrogenation of 2,2-dimethylpropiophenone proceeded slowly owing to a bulky *tert*-butyl group (entry 6). The position and electronic property of the ring substituents also influenced hydrogenation results. The introduction of an electron-donating methyl group to the *meta*-position accelerated the reaction (entry 7), but that to the *ortho*-position lowers the rate however improves the enantioselectivity (entry 8). Notably, the asymmetric transfer hydrogenation of ketone with an electron-withdrawing group such as a nitro group to the *ortho*-position led to a high conversion and up to 95% ee. Among all selected ketones, the best result was obtained in the reduction of 1,1-diphenylacetone giving >99% ee and >99% conversion (entry 10).

Table 1. Asymmetric transfer hydrogenation of various ketones catalyzed by $[IrHCl_2(COD)]_2$/(*R*,*R*)-$C_6P_2(NH)_2$[a]

Entry	Substrate	Time, h	Alcohol		
			% Yield[b]	% ee	Config.[c]
1		7.5	92	79	*S*
2		2	93	93	*S*
3[d]		2	95	93	*S*
4		2.5	99	99	*S*
5		2	98	98	*R*
6		1	23	93	*R*
7		2	96	84	*S*
8		4	55	93	*S*
9		5	92	95	*S*
10		4	>99	>99	*R*

[a] The reactions were carried out in the presence of $[IrHCl_2(COD)]_2$/(*R*,*R*)-$C_6P_2(NH)_2$ (0.005 mmol) using a 0.1 M solution of ketone (0.5 mmol) in *iso*-PrOH (5 mL) at room temperature; The catalyst was made in situ by stirring a solution of $[IrHCl_2(COD)]_2$ and chiral ligand (*R*,*R*)-$C_6P_2(NH)_2$ in *iso*-PrOH; [ketone]:[Ir]:[KOH] = 100:1:4.

[b] Yield and enantiomeric excesses were determined by GC analysis using a Chirasil-DEX CB column or G-TA column.

[c] The configurations were determined by comparison of the retention times of the enantiomers on the GC traces with literature values.

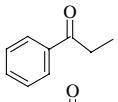
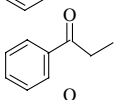
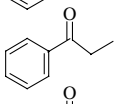
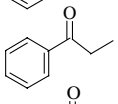
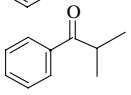
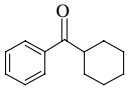
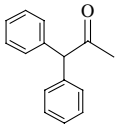
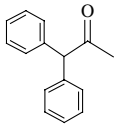
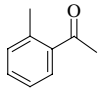
[d] Added 0.1 mL H_2O.

As Table 1 shows, high conversions and optical yields can be achieved with the $[IrHCl_2(COD)]_2$/(*R*,*R*)-$C_6P_2(NH)_2$ catalyst system. Next, we have expanded the substrate-to-catalyst ratio to observe the effect on catalytic efficiency.

As shown in Table 2, increasing the substrate-to-catalyst ratio does not damage the optical yield of the product in most cases. Remarkably, the transfer hydrogenation of 1,1-diphenylacetone (entry 8) could achieve up to 99% ee even when the substrate concentration was increased from 0.1 to 0.5 M and the substrate-to-catalyst ratio reached 10000:1. When propiophenone was used as substrate, the reactions proceeded slowly at room temperature, however it can be reduced to 1-phenyl-1-propanol almost completely in only 5 h at 45 °C (entry 2). Performing the reaction in air, slowed down the reaction but did not affect enantioselectivity of the product (entry 3). When we increased the amount of water in the reaction system, the high optical yield remained intact (entry 4).

In conclusion, the $[IrHCl_2(COD)]_2/C_6P_2(NH)_2$ systems demonstrate remarkable catalytic reactivity and enantioselectivity in the asymmetric transfer hydrogenation under ambient conditions. In a certain case, optically active alcohols with up to 99% ee in high yield could be obtained even when the substrate-to-catalyst molar ratio reached 10000:1. Amazingly, the reaction was not affected in the air or with the addition of water. This may imply industrial applications and the recycling of the catalysts.

Table 2. Asymmetric transfer hydrogenation of ketones under high substrate-to-catalyst ratio[a]

Entry	Substrate	Ligand	S/C/KOH	Time, h	Alcohol		
					% Yield[b]	% ee	Config.[c]
1		*R*,*R*	7500:1:50	14	91	92	*S*
2[d]		*R*,*R*	4000:1:40	5	90	92	*S*
3[e]		*R*,*R*	4000:1:40	72	67	93	*S*
4[f]		*R*,*R*	4000:1:40	19.5	37	93	*S*
5		*R*,*R*	4000:1:40	52.5	98	93	*S*
6		*S*,*S*	2000:1:20	24.5	96	99	*S*
7[g]		*S*,*S*	4000:1:40	17	90	>99	*S*
8[h]		*S*,*S*	10000:1:120	63	89	>99	*S*
9		*R*,*R*	2000:1:20	6	12	89	*S*

[a] The reactions were carried out in the presence of $[IrHCl_2(COD)]_2$/(*R*,*R*)- or (*S*,*S*)-$C_6P_2(NH)_2$ using a 0.1 M solution of ketones in *iso*-PrOH at room temperature. The catalysts were made in situ by stirring a solution of $[IrHCl_2(COD)]_2$ and chiral ligand in *iso*-PrOH.
[b] Yield and enantiomeric excesses were determined by GC analysis using a Chirasil-DEX CB column or G-TA column.
[c] The configurations were determined by comparison of the retention times of the enantiomers on the GC traces with literature values.
[d] Carried out under 45 °C.
[e] Carried out in the air.
[f] Added 2 mL H_2O into the reaction.
[g] Separated yield; Obtained 18.9 g white crystals as 1,1-diphenyl-2-propanol.
[h] 0.5 M solution of substrate in *iso*-PrOH.

Acknowledgements

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