Asymmetric Transfer Hydrogenation Catalyzed by Diamine - Iridium(I) Complexes

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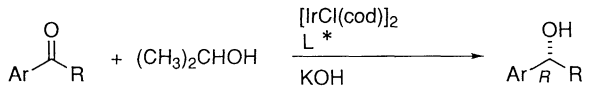
Asymmetric transfer hydrogenation of a range of aromatic ketones in 2-propanol was carried out by using the iridium(I) complexes, prepared from $[IrCl(cod)]_2$ and a variety of chiral diamine ligands derived from α-amino acids. Good catalytic activity and enantioselectivity were observed in the presence of KOH at room temperature.

Although great success of chiral phosphine–Ru complexes in the asymmetric hydrogenation of the functionalized ketones stimulated their application to other types of substrates, such as simple ketones,[1] imines[2] and olefines,[3] these complexes were not able to achieve superior enantioselectivity and catalytic activity, except for our recent report.[4] On the other hand, asymmetric transfer hydrogenation of simple ketones in 2-propanol, catalyzed by transition metal complexes with chiral bidentate ligands, has been reported in high enantioselectivity and catalytic efficiency.

Pfaltz found that the reduction of alkyl aryl ketones catalyzed by a tetrahydrobioxazole–Ir(I) (substrate/catalyst (S/C) mole ratio = 200) complexes with 2-propanol proceeded smoothly at reflux temperature to afford optical active alcohols.[5] Certain chirality modified Ir(I) and Rh(I) complexes promoted asymmetric reduction at high S/C ratios in refluxing 2-propanol.[6] Recently, Gamez reported that Rh(I) (S/C = 20) complexes with chiral 1,2-diphenylethylenediamine derivatives reduced the functionalized ketones with high enantioselectivity at room temperature.[7] The enantioselectivity of the reaction using Ru(II) complexes with chiral nitrogen ligands, such as 1,2-diphenylethylenediamine derivatives and β-amino alcohol derivatives, was very high.[8,9] However, the catalytic performance of the complexes with amine ligands should be improved for practical use.

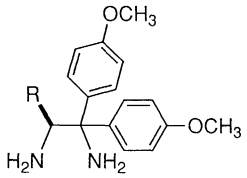
Here, we report the asymmetric transfer hydrogenation of alkyl aryl ketones using novel chiral iridium(I) complexes prepared from $[IrCl(cod)]_2$ and chiral 1,1-di(*p*-anisyl)ethylenediamine derivatives with 2-propanol at room temperature (Scheme 1).



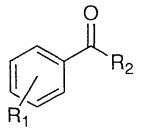
L * = **1a**, **1b**, and **1c**

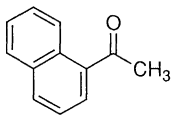
Scheme 1.

The iridium(I) catalysts in the solution were prepared *in situ* from $[IrCl(cod)]_2$ and chiral 1,1-di(*p*-anisyl)ethylenediamine derivatives (**1a** - **c**) (Ir atom:**1a** - **c** mole ratio = 1:2) at 80 °C for 20 min under argon, which were used for reduction without further purification. After the introduction of acetophenone (**2a**) to the catalyst solution at 0.13 M concentration (S/C = 500), the reduction was conducted in the presence of KOH (5 equiv to Ir atom) at room temperature for 12 h. The results are summarized in Table1.



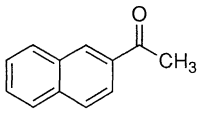
1a : R = $(CH_3)_2CH$–
1b : R = $(CH_3)_3C$–
1c : R = $C_6H_5CH_2$–





2 k

2a : R_1 = H, R_2 = CH_3
2b : R_1 = H, R_2 = C_2H_5
2c : R_1 = H, R_2 = $CH(CH_3)_2$
2d : R_1 = H, R_2 = $C(CH_3)_3$
2e : R_1 = H, R_2 = *cyclo*-C_5H_9
2 f : R_1 = H, R_2 = $(CH_2)_5CH_3$
2g : R_1 = CH_3, R_2 = CH_3
2h : R_1 = OCH_3, R_2 = CH_3
2 i : R_1 = NO_2, R_2 = CH_3
2 j : R_1 = Cl, R_2 = CH_3



2 l

Table 1. Asymmetric transfer hydrogenation of acetophenone (**2a**) in 2-propanol catalyzed by chiral Ir(I) complexes [a]

		alcohol		
run	ligand	yield,[b] %	ee,[c] %	confg.[c]
1	**1a**	68	63	*R*
2	**1b**	96	53	*R*
3	**1c**	74	78	*R*

[a] The reaction was carried out at room temperature for 12 h using a 0.13 M solution of acetophenone in 2-propanol. Ketone:$[IrCl(cod)]_2$:ligand:KOH = 500:1:4:10. [b] Determined by capillary GLC analysis using a PEG G-300 column. [c] Determined by capillary GLC analysis using a chiral Chrompack CP- cyclodextrin-β-236-M-19 column.

Comparing the three diamine ligands, **1c** gave the high reactivity and enantioselectivity, but **1a** and **1b** gave the high reactivity and low enantioselectivity. Without **1a** - **c** under otherwise identical conditions, the alcoholic product was obtainable in < 2% yield. Changing the ligand/iridium ratio (L/Ir = 0.5~4) affected the reaction rate, but not enantioselectivity. A suitable ligand/iridium ratio was 2. Time course of asymmetric transfer hydrogenation of the 0.07 M solution is indicated in Table 2.

The enantioselectivity of the product in an early stage (0.5 h) was lower than that in a late stage (12 h). However, the

Table 2. Time course of asymmetric transfer hydrogenation of the 0.07 M solution [a]

run	time, h	alcohol yield,[b] %	alcohol e.e.,[c] %	alcohol confg.[c]
1	0.5	1	65	*R*
2	4	27	72	*R*
3	6	42	75	*R*
4	12	94	81	*R*
5	16	97	76	*R*
6	24	99	73	*R*

[a] The reaction was carried out at room temperature using a 0.07 M solution of acetophenone in 2-propanol. Ketone:$[IrCl(cod)]_2$:ligand(**1c**):KOH = 500:1:4:10. [b] Determined by capillary GLC analysis using a PEG G-300 column. [c] Determined by capillary GLC analysis using a chiral Chrompack CP- cyclodextrin-β-236-M-19 column.

enantioselectivity of overall reactions reached about 80%ee for 12 h. In this manner, the prolonged reaction time deteriorated the enantiomeric purity of the product because of the reverse reaction.[8]

With complex prepared from $[IrCl(cod)]_2$ and **1c**, a variety of alkyl aryl ketones were transformed to the corresponding secondary alcohols with high enantioselectivities, as shown in Table 3. The reactivity and enantioselectivity were delicately affected by the bulkiness and electronic properties of the alkyl and aryl groups. Although the reactivity gradually decreased by increasing bulkiness of alkyl groups (ethyl (**2b**) < *iso*-propyl (**2c**) < *tert*-butyl (**2d**) < *cyclo*-pentyl (**2e**)), the enantioselectivity was not influenced by the bulkiness of alkyl groups, except for only one example : *n*-heptanophenone (**2f**). Also, when propiophenone (**2b**) and isobutyrophenone (**2c**) were reduced, each of the products obtained a 93%ee, which was the best enantioselectivity in these experiments. On the other hand, the bulkiness of the aryl group seriously affected the reactivity. When the stereochemically congested 1'- (**2k**) and 2'-acetonaphtone (**2l**) were reduced, the reactivity of **2k** was very low.

The reactivities were repressed by introduction of the electron-donating groups, such as methyl and methoxy groups, and were accelerated by introduction of the electron-withdrowing groups, such as chloro and nitro groups, to acetophenone at meta- or para- position. For example, the reactivity of 4-methoxyacetophenone (*p*-**2h**) was very low, but enantioselectivity was high. Also, the reactivity of 3-nitroacetophenone (*m*-**2j**) was very high, but the enantioselectivity was the lowest in these experiments (21%ee). In the case of 4-chloroacetophenone (*p*-**2i**), both the reactivity and enantioselectivity were very high.

The enantioselectivity of asymmetric transfer hydrogenation catalyzed by diamine–iridium(I) complexes is comparable to it of the reaction catalyzed by rhodium(I) and ruthenium(II) complexes.[1,2] The performance of an overall asymmetric transfer hydrogenation is very high. This reaction is of the degree as the best transfer hydrogenation methods currently available.[8,9] This result will provide a useful index for further designing efficient catalyst systems.

Table 3. Asymmetric transfer hydrogenation of aromatic ketones in 2-propanol catalyzed by diamine-Ir(I) complex[a]

run	ketone	time, h	alcohol yield,[b] %	alcohol ee,[c] %	alcohol config.[d]
1	**2b**	12	96	93	*R*
2	**2c**	20	79	93[e]	*R*
3	**2d**	90	82	83	*R*
4	**2e**	105	96	83[e]	*(+)*
5	**2f**	30	97	89	*(+)*
6	*p* - **2g**	24	93	77	*R*
7	*m* - **2h**	16	96	71	*R*
8	*p* - **2h**	90	5	75[f]	*R*
9	*p* - **2i**	8	96	80	*R*
10	*m* - **2j**	1	93	21[e]	*R*
11	**2k**	64	90	79[f]	*R*
12	**2l**	18	97	76[f]	*R*

[a] The reaction was carried out at room temperature using a 0.07 M solution of ketone in 2-propanol. Ketone:$[IrCl(cod)]_2$:ligand(**1c**):KOH = 500:1:4:10. [b] Determined by capillary GLC analysis using a PEG G-300 column. [c] Determined by capillary GLC analysis using a chiral Chrompack CP-cyclodextrin-β-236-M-19 column. [d] Determined from the sign of rotation of the isolated product. [e] Chiralpak AS column. [f] Chiralpak OB column.

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