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Asymmetric transfer hydrogenation of ketones in 2-propanol catalyzed by arsinooxazoline–ruthenium(II) complex

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Abstract—Chiral arsinooxazoline Ru(II) complex has been found to be an efficient catalyst for asymmetric transfer hydrogenation of aromatic ketones in 2-propanol. Secondary alcohols with up to 94% enantiomeric excess were obtained at a substrate/catalyst mole ratio of 1000:1. Asymmetric kinetic resolution has also been obtained with 1-arylalkanols at room temperature with 99% ee.

Enantioselective reduction of prochiral ketones to produce optically pure secondary alcohols via transfer hydrogenation has achieved rapid progress during the last decade by using organometallic complexes as catalysts.[1–3] The non-hazardous hydrogen donors such as 2-propanol and formate can replace the dangerous dihydrogen in a more easily handled way. Catalytic chiral Ru, Rh, and Ir complexes have shown high reactivity and enantioselectivity for asymmetric transfer hydrogenation of prochiral ketones and imines. Most of the effective chiral ligands provide P, N, or O atoms chelating to metal centers. Since only limited arsine ligands have been used for enantioselective catalytic reactions,[4,5] we would like to explore the use of chiral arsine complexes[6] as catalysts for asymmetric transfer hydrogenation and kinetic resolution via dehydrogenative oxidation.

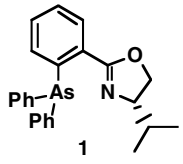

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Figure 1.

The chiral 2-[2-(diphenylarsino)phenyl]-4-isopropyloxazoline[6] (**1**) (Fig. 1) is prepared by the $ZnCl_2$-catalyzed reaction of (*S*)-2-amino-3-methyl-1-butanol and 2-(diphenylarsino)-benzonitrile, which in turn is obtained from Pd-mediated arsination of 2-cyanophenyl triflate. Initial studies of the complex formed in situ from optically active **1** and $RuCl_2(PPh_3)_3$ in asymmetric transfer hydrogenation of acetophenone with 2-propanol (Eq. 1) promoted by catalytic amounts of NaOH, revealed slightly higher activity and enantioselectivity in giving 89% yield with 82% ee of (*R*)-1-phenylethanol than its *P*,*N* analogue **2**, which gives 83% yield and 73% ee in 1 h.[7]

Various metal complexes with **1** were then screened to search for optimal catalysis. At room temperature, acetophenone was reduced slowly into 1-phenylethanol under the catalysis of the complex of **1**–$RhCl_3{\cdot}3H_2O$ in 2-propanol. A lower yield of 27% was obtained after 115 h with moderate enantioselectivity of 35% ee (Table 1, entry 1). When $[RhCl(cod)]_2$, $RhCl(PPh_3)_3$, $IrCl_3{\cdot}3H_2O$, and $[IrCl(cod)]_2$ were used, no enantioselectivity was found (Table 1, entries 2–5) at room or elevated temperature. Complex **1**–$RuCl_2(PPh_3)_3$ exhibited low activity at room temperature with high ee of 83% (Table 1, entry 6). Reaction in refluxing 2-propanol (bp 82 °C) gave faster rate without significant loss of enantioselectivity (82% ee, Table 1, entry 7) with a turnover number of 890. Longer reaction time led to a slightly higher yield but diminished enantioselectivity of 92% yield and 58% ee, respectively (Table 1, entry 8).

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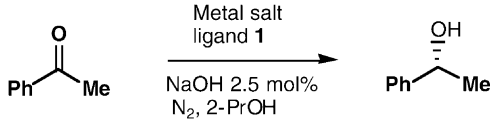
Table 1. Asymmetric transfer hydrogenation of acetophenone catalyzed by arsinooxazoline 1-metal complexes in 2-propanol (Eq. 1)[a]

Entry	Metal salts (mol %)	Lig **1**/M	[$PhCOCH_3$]/M	Temp/°C	Time/h	Yield[b]/%	% Ee
1	$RhCl_3{\cdot}3H_2O$ (0.25)	1.5	0.5	Rt	115	27	35
2	$[RhCl(cod)]_2$ (0.1)	1.5	0.33	82	19	40	0
3	$RhCl(PPh_3)_3$ (0.25)	1.4	0.4	Rt	19	16	0
4	$IrCl_3{\cdot}3H_2O$ (0.25)	1.5	0.5	Rt	18	49	0
5	$[IrCl(cod)]_2$ (0.25)	1.4	0.4	Rt	20	29	0
6	$RuCl_2(PPh_3)_3$ (0.1)	1.4	0.33	Rt	89	17	83
7	$RuCl_2(PPh_3)_3$ (0.1)	1.4	0.33	82	2	89	82
8	$RuCl_2(PPh_3)_3$ (0.1)	1.4	0.33	82	16	92	58
9	$RuCl_2(PPh_3)_3$ (0.1)	1.4	0.33	82	2	87[c]	78[c]
10	$RuCl_2(PPh_3)_3$ (0.01)	1.4	0.33	82	11	38	18
11	$RuCl_3{\cdot}3H_2O$ (0.1)	1.5	0.33	82	4	29	8
12	$[RuCl_2(cod)]_x$ (1.0)	1.4	0.33	82	76	51	22

[a] Complexes were formed in situ in 2-propanol by refluxing for 1 h unless otherwise noted.
[b] Yields and % ee were determined by GC (Chiraldex B-PH). Absolute configurations determined by optical rotations of isolated alcohols were in *R* forms.
[c] 2 equiv of water w.r.t. acetophenone were added.

Although the **1**–$RuCl_2(PPh_3)_3$ catalyst was found to be readily poisoned in air, small amounts of water were compatible.[8] With the addition of 2 equiv of water, no significant difference in reaction rate and enantioselectivity were observed (Table 1, entry 9).

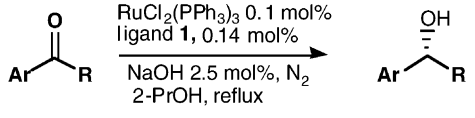


(1)

Lower loading of 0.01 mol % equiv of **1**–$RuCl_2(PPh_3)_3$ catalyst to substrate resulted in significant lower enantioselectivity of 18% ee (Table 1, entry 10). Longer reaction time was required and likely caused the erosion of enantiomeric excess due to competitive backward reaction.

Other ruthenium salts such as $RuCl_3$ or polymeric $[RuCl_2(cod)]_x$ gave much lower reactivity and enantioselectivity than $RuCl_2(PPh_3)_3$ (Table 1, entries 11 and 12; 8% and 22% ee, respectively). Therefore, the presence of PPh_3 ligand is essential for high catalytic reactivity and enantioselectivity.[9]

$RuCl_2(PPh_3)_3$–**1** complex in acetonitrile did not catalyze any reduction of acetophenone when either HCOOH/Et_3N or HCOONa was used as the hydrogen source.



(2)

The results of catalytic transfer hydrogenation in 2-propanol with $RuCl_2(PPh_3)_3$–**1** complex for a series of aromatic ketones are listed in Table 2. The reaction of phenyl ethyl ketone (Table 2, entries 2 and 3) showed slower rate but higher enantioselectivity than that of acetophenone (Table 2, entry 1). Up to 94% ee could be achieved. Other ketones, including a more hindered 2-chlorophenyl methyl ketone, gave similar yields and ee as acetophenone (Table 2, entries 4–9).

Table 2. Asymmetric transfer hydrogenation of ketones catalyzed by **1**–$RuCl_2(PPh_3)_3$ in 2-propanol[a]

Entry	Ar	R	Time/h	Yield[b]/%	% Ee[b]
1	Ph	CH_3	1	88	82
2	Ph	CH_2CH_3	0.5	26	94
3			4	68	90
4	2-Cl–C_6H_4	CH_3	0.5	86	84
5			1	97	79
6	4-Cl–C_6H_4	CH_3	1	86	80
7	3-Cl–C_6H_4	CH_3	1	90	85
8	4-Br–C_6H_4	CH_3	2	68	82
9	4-F–C_6H_4	CH_3	0.5	65	78

[a] Substrate/ligand **1**/$RuCl_2(PPh_3)_3$/NaOH = 1000/1.4/1/25; [substrate] = 0.4 M.
[b] Yields and % ee were determined by GC (Chiraldex B-PH). Absolute configurations determined by optical rotations of isolated alcohols were all in *R* forms.

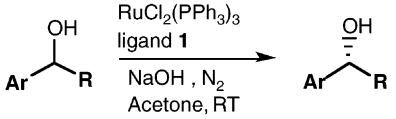
Successful kinetic resolution via dehydrogenative oxidation of 1-arylalkanols catalyzed by $RuCl_2(PPh_3)_3$–**1** complex in alkaline acetone at room temperature was achieved (Eq. 3).[10,11] Fast rates and high enantioselectivity of over 98% ee at over 50% conversion were obtained with unhindered aryl alcohols (Table 3, entries 1–3). 1-(4-Chlorophenyl)ethanol (Table 3, entry 5) reacted more slowly than 1-phenylethanol. Presumably, the electron withdrawing chlorine substituent decreases

Table 3. Room temperature catalyzed kinetic resolution of alkanols[a]

Entry	Ar	R	Time/h	% Conv.[b]	% Ee[b]
1	Ph	CH_3	1	52	73
2	Ph	CH_3	2	58	99
3	Ph	CH_3	3	60	>99.5
4	Ph	Et	3	64	>99.5
5	4-Cl–C_6H_4	CH_3	8	74	98
6	2-Cl–C_6H_4	CH_3	9	0	0

[a] Substrate/ligand **1**/$RuCl_2(PPh_3)_3$/NaOH = 500/1.0/1.4/1/12.5; [substrate] = 0.25 M.
[b] Conversion and % ee were absolute configuration (all *R*) were determined by GC (Chiraldex B-PH).

the rate of beta-hydride elimination step during the catalysis. The sterically more hindered 1-(2-chlorophenyl)ethanol did not react even at elevated temperature.



(3)

In summary, we have discovered that a new chiral *N*,*As*-ligand–$RuCl_2(PPh_3)_3$ complex can catalyze the transfer hydrogenation in alkaline 2-propanol and the kinetic resolution of 1-phenylalkanols in alkaline acetone. Further studies of asymmetric catalysis of chiral arsinooxazoline complexes are in progress.

Typical procedure for the transfer hydrogenation: $RuCl_2(PPh_3)_3$ (9.6 mg, 0.010 mmol) and *As*,*N*-ligand **1** (5.9 mg, 0.014 mmol) (*Caution*: toxic) were mixed in N_2-purged 2-propanol (10 mL) and heated to reflux for 1 h. After cooled to rt, 1/10 of the resulting yellow solution (1.0 mL) was transferred into a degassed solution of ketone (1 mmol) in 2-propanol (0.5 mL) and stirred for 30 min. Then degassed 2-propanol (1.0 mL) containing of NaOH (1.0 mg, 0.025 mmol) was added and the resulting solution was heated to reflux. Aliquots were taken and pass through a small silica gel column eluting with EtOAc before analysis by GC–MS using a Chiraldex B-PH column. The absolute configuration was determined by the sign of rotation of the isolated product.

Acknowledgements

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