α-Amino acidate-Ru(II) Catalysts for Asymmetric Transfer Hydrogenation: First Utilization of α-Amino Acids as an Efficient Ligand

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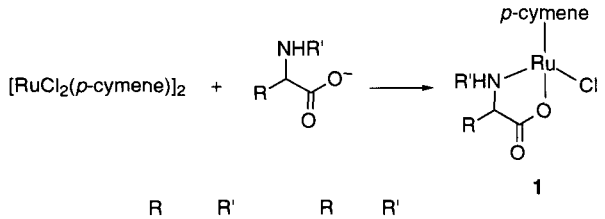
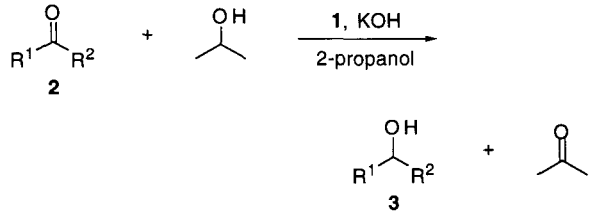
Ruthenium complexes, prepared by mixing potassium salt of α-amino acids and $[RuCl_2(arene)]_2$, acted as catalysts for asymmetric transfer hydrogenation of ketones from 2-propanol in the presence of KOH, and enantiomeric excesses of the products reached 92%.

α-Amino acids are chiral materials of the most easily available natural compounds. Although they have frequently been used for synthesis of optically active compounds as starting materials, their applications as ligands for asymmetric catalysis are limited, and derivatizations of α-amino acids are needed for this purpose.[1] We now wish to describe the utilization of α-amino acids as a ligand in the asymmetric transfer hydrogenation of ketones from alcohols.



	R	R'		R	R'
a:	$-(CH_2)_3-$		**e**:	^{t}Bu	H
b:	Me	H	**f**:	Ph	H
c:	^{i}Pr	H	**g**:	$PhCH_2$	H
d:	^{s}Bu	H	**h**:	$PhCH_2$	Et

α-Amino acidate–Ru complexes were known to be prepared from the reaction of α-amino acidate anion with $[RuCl_2(C_6H_6)]_2$,[2] and same procedure was applied to preparation of the catalyst **1a–h**.[3,4] These catalysts were subjected to the reaction of acetophenone with 2-propanol in the presence of potassium hydroxide to give 1-phenylethanol.



The typical reaction was performed as follows. Into an 80 mL Schlenk tube containing ruthenium complex **1a** (23 mg, 5.0 x 10^{-2} mmol) under argon atmosphere was added a mixture of a solution of acetophenone (600 mg, 5.0 mmol) in 2-propanol (49.5 mL) and a solution of potassium hydroxide in 2-propanol (0.10 mol dm^{-3}, 0.50 mL, 5.0 x 10^{-2} mmol), which were degassed by five freeze-thaw cycles. The resulting mixture was stirred for 24 h at room temperature. This solution was neutralized by adding 1.0 mol dm^{-3} hydrochloric acid, and the solvent was removed under reduced pressure. To the residue were added water and ethyl acetate, and then separated organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (silica gel 200, hexane : ethyl acetate = 4 : 1) gave the desired product 1-phenylethanol (440 mg) in 72% yield and in 81% *ee* (Daicel Chiralcel OD-H or OJ-R). Some other representative results are listed in Table 1.

Table 1. Asymmetric transfer hydrogenation of ketones by α-amino acidate–Ru complexes[a]

substrate **2**				product **3**		
	R^1	R^2	catalyst	yield[b]/%	*ee* [c]/%	config.[d]
2a	Me	Ph	**1a**	72	81	*R*
2a	Me	Ph	**1b**	95	5	*R*
2a	Me	Ph	**1c**	79	56	*R*
2a	Me	Ph	**1d**	72	63	*R*
2a	Me	Ph	**1e**	60	50	*R*
2a	Me	Ph	**1f**	98	37	*S*
2a	Me	Ph	**1g**	74	28	*R*
2a	Me	Ph	**1h**	11	3	*S*
2b	Et	Ph	**1a**	30	87	*R*
2c	^{i}Pr	Ph	**1a**	27[e]	77	*R*
2d	Me	*m*-$MeOC_6H_4$	**1a**	74[e]	68	*R*
2e	Me	*p*-$MeOC_6H_4$	**1a**	37[e]	62	*R*
2f	Me	*m*-ClC_6H_4	**1a**	76	76	*R*
2g	Me	*p*-ClC_6H_4	**1a**	81	61	*R*
2h	Me	1-naphthyl	**1a**	64[e]	82	*R*
2i	Me	2-naphthyl	**1a**	63[e]	58	*R*
2j	1-indanone		**1a**	6	43	*R*
2k	1-tetralone		**1a**	8	92	*R*
2k	1-tetralone[f]		**1a**	37	90	*R*

[a]The reaction was carried out at room temperature using a 0.1 mol dm^{-3} solution of substrate in 2-propanol for 24 h. Substrate : Ru : KOH = 1 : 0.01 : 0.01. [b]Determined by GLC (0.3 x 300 cm of 5% PEG-HT on Uniport HP (80/100)). [c]Determined by HPLC analysis using a Daicel Chiralcel OD-H or OJ-R column.[6] [d]Determined from the sign of optical rotation value of the isolated product. [e]Isolated yield. [f]At 80°C for 5 h.

For this reaction, the use of an equimolar amount of potassium hydroxide to a ruthenium complex was effective. Using two equiv. of KOH decreased the yield and the enantiomeric excess, while no reaction occurred without KOH.

KOH is considered to approach complex **1** for generation of catalytically active species, which may be the similar structure in Noyori's report.[5] On the other hand, an excess amount of KOH could take away α-amino acidate ligand from ruthenium center to result low catalytic activity and selectivity.

Proline complex **1a** showed the best stereoselectivity among the α-amino acidate–Ru complexes used, and bulkiness of substituent on α-amino acidate moieties influenced the catalytic activity and the stereoselectivity. Five-membered ring in proline is considered to make rigid asymmetric circumstance on ruthenium center, and therefore better selectivities were obtained by **1a**. Further substituents on nitrogen atom of α-amino acids made the reaction slow and less selective. Various arene ligands were also investigated, and the complex bearing *p*-cymene gave the best selectivity.

This reaction was basically reversible, and the reaction under a condition at higher concentration of acetophenone (1.0 M) afforded a low yield of 1-phenylethanol (49% after 24 h) with an almost same stereoselectivity (79% *ee*)

Several ketones were allowed for this transfer hydrogenation. Some representative results are listed in Table 1. The reactivity was sometimes not high, but moderate to good enantiomeric excesses were obtained. For example, propiophenone and 1-tetralone were reduced to 1-phenylpropanol and 1-tetralol in 87 and 92% *ee*, respectively.

Asymmetric catalytic reductions of ketones by transfer hydrogenation is now paid much attentions from a viewpoint of synthesis in laboratory because of mild conditions and easy operation.[7] By Noyori's group highly efficient transfer hydrogenation of ketones was reported recently, in which catalysts were prepared from ruthenium precursors and chiral aminoalcohols.[8] Even though the results were excellent, aminoalcohols used are very expensive or scarcely available. We also examined the catalytic activity of prolinol–Ru complex, in which prolinol was prepared by reduction of proline, and realized that the enantiomeric excess of the product, 1-phenylethanol, was 37% (*R*). We now figure out that α-amino acids are usable as effective ligands for this reaction, which are common and cheap chiral sources. Mechanistic aspects and further applications of this reaction are underway.

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3 Typical procedure for the preparation of α-amino acidate–Ru complexes. A solution of potassium (*S*)-2-pyrolidine-carboxylate in water (2.5 mL, 0.50 mmol), which was prepared by mixing L-(-)-proline (0.23 g, 2.0 mmol) and potassium hydroxide (0.11 g, 2.0 mmol) in water (10 mL), was dropwisely added to a solution of $[RuCl_2(p\text{-cymene})]_2$ (0.15 g, 0.25 mmol) in CH_2Cl_2 (2.5 mL). After stirring for 1 h, solvent was removed in vacuo to give orange solid. This solid was used for catalytic reaction without further purification. ^1H NMR ($CDCl_3$) δ 1.28 (d, 3H, J = 7 Hz, $CH(CH_3)(CH_3)$), 1.33 (d, 3H, J = 7 Hz, $CH(CH_3)(CH_3)$), 1.7-2.0 (m, 4H), 2.23 (s, 3H, CH_3), 2.93 (heptet, 1H, $CH(CH_3)(CH_3)$), 3.07 (ddd, 1H, J = 16.5, 11, and 5.5 Hz), 3.91 (dt, 1H, J = 11 and 6.5 Hz), 4.36 (br q, 1H, J = 8 Hz), 5.25 (d, 1H, J = 6 Hz), 5.41 (d, 1H, J = 6 Hz), 5.47 (d, 1H, J = 6 Hz), 5.53 (d, 1H, J = 6 Hz).

4 Stereochemistry of α-amino acids used was as below; **1a**: (*S*)-proline; **1b**: (*S*)-alanine; **1c**: (*S*)-valine; **1d**: (*S*)-isoleucine; **1e**: (*S*)-*tert*-leucine; **1f**: (*R*)-phenylglycine; **1g**: (*S*)-phenylalanine; **1h**: (*S*)-*N*-ethylphenylalanine.

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6 Conditions of determining enantiomeric excesses (column, eluent, flow rate (mL/min.), detection uv (nm)); **3a**: Daicel Chiralcel OD-H, hexane / 2-propanol = 19, 0.30, 254; **3b**: Daicel Chiralcel OD-H, hexane / 2-propanol = 99, 0.30, 254; **3c**: Daicel Chiralcel OD-H, hexane / 2-propanol = 19, 0.50, 254; **3d**: Daicel Chiralcel OD-H, hexane / 2-propanol = 9, 0.50, 254; **3e**: Daicel Chiralcel OD-H, hexane / 2-propanol = 99, 0.50, 220; **3f**: Daicel Chiralcel OD-H, hexane / 2-propanol = 199, 0.30, 254; **3g**: Daicel Chiralcel OD-H, hexane / 2-propanol = 99, 0.50, 254; **3h**: Daicel Chiralcel OD-H, hexane / 2-propanol = 9, 0.50, 254; **3i**: Daicel Chiralcel OJ-R, methanol / H_2O = 1.5, 0.30, 254; **3j**: Daicel Chiralcel OD-H, hexane / 2-propanol = 49, 0.50, 254; **3k**: Daicel Chiralcel OD-H, hexane / 2-propanol = 249, 0.30, 220

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