Extremely High Enantioselective Redox Reaction of Ketones and Alcohols Catalyzed by $RuCl_2(PPh_3)$(oxazolinylferrocenylphosphine)

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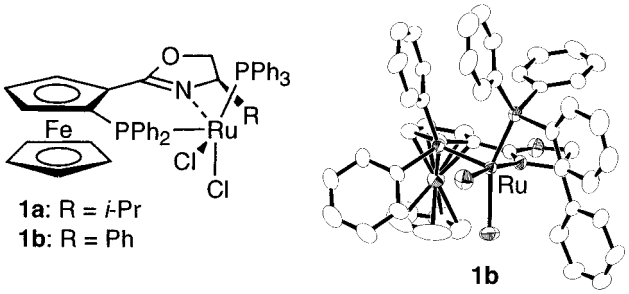
*Summary: The ruthenium complex $RuCl_2(PPh_3)$(oxazolinylferrocenylphosphine), **1**, has been found to be a quite effective catalyst for asymmetric transfer hydrogenation of not only alkyl aryl ketones but also alkyl methyl ketones with ^iPrOH. Asymmetric oxidation of racemic sec-alcohols with acetone via kinetic resolution by using the same catalyst **1** also proceeds with exteremely high enantioselectivity (>99.9% ee).*

Asymmetric hydrogenation,[1] transfer hydrogenation,[2] hydrosilylation,[3,4] and hydroboration[5] of prochiral ketones in the presence of a chiral transition metal complex or a Lewis acid catalyst have been extensively investigated to obtain the homochiral alcohols. However, the extremely high enantioselective reduction of alkyl aryl ketones such as acetophenone with >99% ee was only achieved by using enzymes.[6] Quite recently Noyori et al. have developed the $RuCl_2$(xylbinap)(1,2-diamine)/base system, which was remarkably effective for enantioselective hydrogenation of alkenyl, cyclopropyl, and aryl ketones.[7] Thus, 1-phenylethanol with 99% ee was obtained in a high yield from the asymmetric hydrogenation of acetophenone.

Chart 1



On the other hand, Sammakia et al. previously reported the asymmetric transfer hydrogenation of alkyl aryl ketones using the catalyst prepared in situ from $RuCl_2(PPh_3)_3$ and an oxazolinylferrocenylphosphine at 80 °C for 1 h.[2e] The NMR study of the reaction of $RuCl_2(PPh_3)_3$ and [2-(4′-phenyloxazolin-2′-yl)ferrocenyl]diphenylphosphine showed that the produced catalyst consisted of two diastereomers, **1b** (Chart 1) and another isomer, in an approximately 5:1 ratio.[2e] For example, acetophenone was reduced by using this catalyst with up to 94% ee. Recently, we have succeeded in isolation of the diastereomerically pure ruthenium complex $RuCl_2(PPh_3)$(oxazolinylferrocenylphosphine[8]), **1**, and the mo-

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(1) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675−2676. (b) Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 1086−1087. (c) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1100−1103. (d) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1703−1707.

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(4) (a) Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics* **1995**, *14*, 5486-5688. (b) Nishibayashi, Y.; Segawa, K.; Takada, H.; Ohe, K.; Uemura, S. *Chem. Commun.* **1996**, 847−848. (c) Nishibayashi, Y.; Singh, J. D.; Segawa, K.; Fukuzawa, S.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1375−1376. (d) Nishibayashi, Y.; Singh, J. D.; Segawa, K.; Fukuzawa, S.; Ohe, K.; Uemura, S. *Organometallics* **1996**, *15*, 370−379. (e) Nishibayashi, Y.; Singh, J. D.; Arikawa, Y.; Uemura, S.; Hidai, M. *J. Organomet. Chem.* **1997**, *531*, 13−18.

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(8) The *first* preparation of oxazolinylferrocenylphosphines was *independently* reported by our group[8a,b] and Richards et al.[8c,d] (a) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79−81. (b) Nishibayashi, Y.; Segawa, K.; Arikawa, Y.; Ohe, K.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1997**, *545*−*546*, 381−398, and references therein. (c) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74−75. (d) Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419−1430. Independently, Sammakia et al. reported the diastereoselective lithiation of oxazolinylferrocenes.[8e−g] (e) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10−11. (f) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002−6003. (g) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629−1635.

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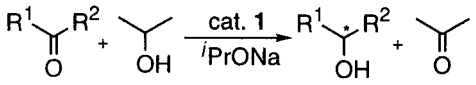
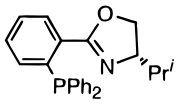
Scheme 1. Transfer Hydrogenation



lecular structures of **1a** and **1b** have been determined by X-ray analysis.[9,10] Complexes **1a** and **1b** have been found to be effective for the asymmetric hydrosilylation of ketones and an imine.[9] As an extension of our study on catalysis of complex **1**, we have now investigated the asymmetric transfer hydrogenation of ketones with ^{i}PrOH and the asymmetric oxidation of racemic *sec*-alcohols with acetone via kinetic resolution. Interestingly, optically active *sec*-alcohols with extremely high enantioselectivities have been obtained from these two reactions using complexes **1a** and **1b** as the catalyst. Preliminary results about these reactions will be described here.

Treatment of acetophenone (1 mmol) in the presence of a catalytic amount of **1a**[9,10] (0.5 mol %) and ^{i}PrONa (2.0 mol %) in anhydrous ^{i}PrOH (50 mL) at room temperature for 2 h afforded 1-phenylethanol in 94% GLC yield with >99.6% ee (*R*) (Scheme 1; R^1 = Ph; R^2 = CH_3). It was revealed that no racemization of the resultant chiral alcohol occurred during the reaction. However, unnecessarily long exposure of the reaction mixture to the Ru catalyst should be avoided to prevent the racemization. The reaction proceeded even at 0 °C, although a longer reaction time (72 h) was necessary. Almost the same result (>99.7% ee) was also obtained in the case of **1b**, bearing a phenyl-substituted oxazoline. In contrast, the Ru complex $RuCl_2(PPh_3)$(**2**),[2c,9] having an (oxazolinylphenyl)phosphine without the planar chirality of ferrocene, showed lower catalytic activity (43% conversion for 24 h) and selectivity (55% ee) under the same reaction conditions.



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A variety of simple alkyl aryl ketones can be transformed to the corresponding secondary alcohols with very high enantioselectivities. Typical results are shown in Table 1. The bulkiness of the alkyl group and the substituent of the phenyl ring affected both the rate and stereoselectivity. At elevated temperatures, the reactions of propiophenone and butyrophenone catalyzed by **1b** proceeded to give the corresponding alcohols in high conversions with high enantioselectivities (Table 1; runs 3 and 4), although **1a** did not work effectively. Use of *para*- and *ortho*-fluoro-substituted acetophenones slightly decreased the stereoselectivity (Table 1; runs 6 and 14). However, other substituted acetophenones did not influence the reactivity and enantioselectivity. A heteroaromatic methyl ketone, acetylfuran, was also reduced with high enantioselectivity, but the ee value of the produced alcohol was slightly decreased with increase of the reaction time (Table 1; runs 17 and 18). Overall, the

Table 1. Asymmetric Transfer Hydrogenation of Ketones Catalyzed by 1[a]

run	ketone	time (h)	conversion[b] (%)	ee (%)[c] /(config.)
1	R = CH_3	2	94	**>99.6 (*R*)**
2[d]	R = CH_3	2	95	**>99.7 (*R*)**
3[d]	R = Et	8[e]	99	**>99.7 (*R*)**
4[d]	R = *n*-Bu	4[f]	99	98.7 (*R*)
5	X = CH_3	4	98	**>99.3 (*R*)**
6	X = F	2	99	97.3 (*R*)
7	X = Cl	2	99	98.7 (*R*)
8	X = Br	18	99	**>99.3 (*R*)**
9	X = CH_3	1	98	**>99.9 (*R*)**
10	X = F	3	98	**>99.6 (*R*)**
11	X = Cl	2	99	**>99.7 (*R*)**
12	X = Br	1	77	**>99.7 (*R*)**
13	X = CH_3	1	99	**>99.9 (*R*)**
14	X = F	1	92	96.6 (*R*)
15	X = Cl	1	99	**>99.7 (*R*)**
16	Me, Me	5	99	**>99.9 (*R*)**
17		1	33	98 (*R*)
18		2	66	95 (*R*)
19	R = *t*-Bu	16[e]	81	**>99 (*S*)**
20	R = *c*-hexyl	24	68	52 (*S*)
21[d]	R = *c*-hexyl	10	31	66 (*S*)
22	R = *n*-hexyl	1	99	26 (*S*)
23		1	19	**>99 (*S*)**
24		3[e]	78	**98 (*S*)**

[a] All reactions of ketone (1.0 mmol) were carried out in the presence of **1a** (0.5 mol %) and ^{i}PrONa (2 mol %) in ^{i}PrOH (50 mL) at rt. [b] Determined by GLC. [c] Determined by GLC with chiral capillary column. [d] The complex **1b** was used in place of **1a**. [e] At 50 °C. [f] At 70 °C.

chiral efficiency is extremely high (>99% ee) in the asymmetric transfer hydrogenation of alkyl aryl ketones with ^{i}PrOH catalyzed by **1a** and **1b**. This is almost the same as Noyori's system recently developed.[7]

We postulate that the active species in the reduction is a ruthenium(II) dihydride.[11,12] To account for the stereoselectivity of the reduction of alkyl aryl ketones, we propose a transition state model shown in Figure 1. Thus, acetophenone (R′ = CH_3) would approach the complex in such a way to minimize steric interactions among the phenyl group of the ketone, the phenyl groups of two phosphines, and the substituent of the oxazoline ring. The reaction through this transition state results in the formation of the (*R*)-alcohol as observed.

Asymmetric transfer hydrogenation of alkyl methyl ketones, which are difficult to transform into the corresponding alcohols with high enantioselectivity,[1c,13]

(9) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1998**, *17*, 3420−3422.

(10) Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1999**, *572*, 163−168.

(11) (a) Chowdhury, R. L.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1063−1064. (b) Aranyos, A.; Csjernyik, G.; Szabo, K. J.; Bäckvall, J.-E. *Chem. Commun.* **1999**, 351−352.

(12) The NMR spectrum of a reaction mixture of **1** and ^{i}PrONa in C_6D_6/^{i}PrOH solution suggested the formation of two ruthenium dihydride complexes.

(13) For a short review: Fehring, V.; Selke, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1827−1830.

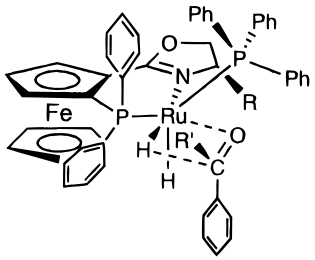
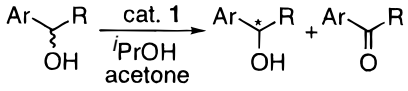


Figure 1.

Scheme 2. Oxidation (Kinetic Resolution)



was also investigated. In the case of *tert*-butyl methyl ketone, the best enantioselectivity of >99% ee was achieved with a high yield of the product (Table 1, run 19). Unfortunately, cyclohexyl methyl ketone and 2-octanone were converted into the corresponding alcohols with 66% ee and 26% ee, respectively (Table 1, runs 20−22). In contrast, 2,2-dimethylcyclohexanone was reduced at room temperature in only 19% yield with >99% ee, but at 50 °C in 78% yield with 98% ee (Table 1, runs 23 and 24). To the best of our knowledge, this is the first example of extremely high enantioselective reduction of dialkyl ketones with >99% ee by using a purely chemical method. The effective enantioselective reduction of dialkyl ketones was previously reported by using a Rh(I)−PennPhos[14] catalyst; however, *tert*-butyl methyl ketone was reduced to the corresponding alcohol with up to 94% ee.[1c]

Interestingly, asymmetric oxidation of racemic *sec*-alcohols with acetone by using the same catalyst **1** led to the kinetic resolution of the alcohols with extremely high enantioselectivity. Treatment of racemic 1-phenylethanol (1 mmol) in the presence of a catalytic amount of **1a** (0.5 mol %) and ^{i}PrONa (2.0 mol %) in anhydrous acetone (10 mL) at room temperature for 4 h afforded a mixture of 1-phenylethanol (48% GLC yield with 98.8% ee) and acetophenone (52% GLC yield) (Scheme 2; Ar = Ph; R = CH_3). The absolute configuration of the unreacted 1-phenylethanol is opposite that obtained from the transfer hydrogenation of acetophenone (vide supra). The efficiency of the kinetic resolution, the k_f/k_s value,[15] was estimated to be >110. Use of **1b** in place of **1a** resulted in a slightly lower selectivity. In contrast, the catalyst prepared in situ from $RuCl_2(PPh_3)_3$ and [2-(4′-phenyloxazolin-2′-yl)ferrocenyl]diphenylphosphine, which has been found to be effective for the asymmetric transfer hydrogenation,[2e] showed lower catalytic activity (30% conversion for 100 h) and selectivity (39% ee) under the same reaction conditions.

Table 2. Kinetic Resolution of Racemic *sec*-Alcohols Catalyzed by 1[a]

run	alcohol		time (h)	unreacted alcohol		
				recov-[b] ery (%)	ee (%)[c] /(config.)	k_f/k_s[d]
1		X = H	4	48	98.8 (*S*)	>110
2[e]		X = H	1.5	42	97.8 (*S*)	>25
3[e]	X, OH	X = H	2	39	**>99.7 (*S*)**	>27
4		X = Me	1	49	**>99.9 (*S*)**	>368
5		X = F	2	27	**>99.1 (*S*)**	>10
6		X = Cl	1	45	**>99.8 (*S*)**	>66
7		X = Br	2	49	**>99.8 (*S*)**	>368
8	X, OH	X = Me	2	41	**>99.8 (*S*)**	>35
9	X, OH	X = Me	18	43	**>99.8 (*S*)**	>46
10	O, OH		5	47	96 (*S*)	>46

[a] All reactions of racemic alcohol (1.0 mmol) were carried out in the presence of **1a** (0.5 mol %) and ^{i}PrONa (2 mol %) in acetone (10 mL) at rt. [b] Determined by GLC. [c] Determined by GLC with chiral capillary column. [d] The ratio was estimated based on the final conversion and enantiomeric purity of the recovered alcohol unless otherwise specified. [e] Complex **1b** was used in place of **1a**.

Although the enantioselective oxidation of racemic *sec*-alcohols with acetone by using a Ru(II)−diamido catalyst via kinetic resolution was already reported, the enantioselectivity of 1-phenylethanol was up to 94% ee, and the k_f/k_s value was estimated to be >100.[16]

Asymmetric oxidation of several other *sec*-alcohols also proceeded with high stereoselectively. Typical results are shown in Table 2. The reactions of racemic 1-phenylethanol derivatives led to the kinetic resolution of the slow-reacting (*S*)-alcohols with >99% ee (Table 2, runs 4−9). Optically active 2′-furyl-1-ethanol was obtained in 47% GLC yield with 96% ee (Table 2, run 10).

In conclusion, we have developed the extremely high enantioselective ruthenium-catalyzed transfer hydrogenation of not only *alkyl aryl ketones* but also *alkyl methyl ketones* with ^{i}PrOH by using **1**. In addition, we have succeeded in asymmetric oxidation of racemic *sec*-alcohols with acetone via kinetic resolution by employing the same catalyst **1**. In several cases, the enantioselectivies of the alcohols obtained exceed >99.9% ee. Our methods reported here are very useful to obtain alcohols of extremely high enantiomeric purity.

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Supporting Information Available: Detailed experimental procedures and typical GLC charts of resultant chiral alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) PennPhos = *P*,*P*′-1,2-phenylenebis(*endo*-2,5-dialkyl-7-phosphabicyclo[2.2.1]heptanes.

(15) The efficiency of the kinetic resolution is characterized by k_f/k_s, the selectivity factor = (rate of fast-reacting enantiomer)/(rate of slow-reacting enantiomer). For a review, see: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56, and references therein.

(16) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288−290.