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Ru^{II}-SDP-Complex-Catalyzed Asymmetric Hydrogenation of Ketones. Effect of the Alkali Metal Cation in the Reaction

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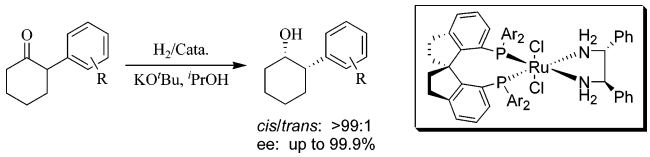

The Ru^{II} complexes of SDP and DPEN combined with *t*-BuOK in 2-propanol formed a very effective catalyst for the hydrogenation of simple aromatic ketones with high activity and enantioselectivity. The racemic α-arylcycloalkanones can also be hydrogenated by this system, providing α-arylcycloalkanols in excellent cis/trans stereoselectivity (>99:1) and enantioselectivity (up to 99.9%) for the cis isomer. In the study of the effect of the alkali metal cation in the hydrogenation of acetophenone using $RuCl_2$(Tol-SDP)(DPEN) and $RuCl_2$(Xyl-SDP)(DPEN) catalysts, we found that *t*-BuONa provided a faster reaction than *t*-BuOK, which indicated that the sterically hindered diphosphine ligands preferred the base with the smaller metal cation.

Introduction

Enantioselective reduction of carbonyl compounds catalyzed by well-defined transition-metal complexes was an effective synthetic tool to produce optically active alcohols.[1] One of the best transition-metal complexes for ketone hydrogenation that has been discovered is the chiral Ru^{II}-diphosphine/1,2-diamine complex, which was developed by Noyori and co-workers.[2] Recently, this catalytic system has been studied intensively. In addition to $RuCl_2$[(*S*)-Xyl-BINAP][(*S*)-DAIPEN] and its enantiomer,[3] $RuCl_2$[(*S*)-Xyl-PhanePhos][(*R*,*R*)-DPEN],[4] $RuCl_2$-[(*R*)-Xyl-P−Phos][(*R*,*R*)-DPEN],[5] $RuCl_2$[(*S*)-Xyl-SDP][(*R*,*R*)-DPEN],[6] and other ruthenium catalytic systems[7] were also reported to have high activity and enantioselectivity in the asymmetric hydrogenation of simple ketones. A combination of desirable features, such as an exceptionally high turnover number (TON), a high turnover frequency (TOF), and excellent enantioselectivity for various simple ketones, makes this catalytic hydrogenation of great practical interest.

After nearly 10 years of development, Ru^{II}-diphosphine/1,2-diamine catalytic systems have been successfully applied in the asymmetric hydrogenation of aromatic, heteroaromatic, α,β-unsaturated ketones,[3−7] and even imines.[8] Furthermore, Noyori reported that the $RuCl_2$-

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(2) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(3) Xyl-BINAP = 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl; DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine. (a) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703. (b) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529. (c) Ohkuma, T.; Koizumi, M.; Ikariya, T.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659. (d) Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett*. **2000**, *2*, 1749. (e) Ohkuma, T.; Koizumi, M.; Muñiz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc*. **2002**, *124*, 6508.

(4) Xyl-PhanePhos = 4,12-bis(di-3,5-xylylphosphino)-4,4′-[2,2]paracyclophane; DPEN = 1,2-diphenylethylenediamine. Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173.

(5) Xyl-P-Phos = 2,2′,6,6′-tetramethoxy-4,4′-bis[di(3,5-dimethylphenyl)phosphino)-3,3′-bipyridine. (a) Wu, J.; Chen, H.; Kwok, W.-H.; Guo, R.-W.; Zhou, Z.-Y.; Yeung, C.-H.; Chan, A. S. C. *J. Org. Chem.* **2002**, *67*, 7908. (b) Wu, J.; Ji, J.-X.; Guo, R. W.; Yeung, C.-H.; Chan, A. S. C. *Chem.—Eur. J.* **2003**, *9*, 2963.

(6) Xyl-SDP = 7,7′-bis[di(3,5-dimethylphenyl)phosphino]-1,1′-spirobiindane. Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404.

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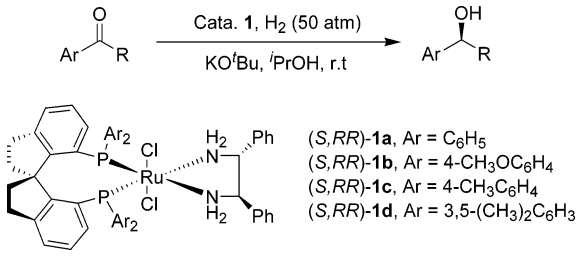
SCHEME 1. Asymmetric Hydrogenation of Ketones with Ru^{II}-SDP/DPEN Complexes



[(*S*)-Tol-BINAP][(*S*)-DPEN] catalyst was also efficient in the asymmetric hydrogenation of racemic α-arylcycloalkanones by a kinetic resolution method, providing the corresponding chiral cyclic alcohols with excellent cis/trans selectivity and enantioselectivity.[9] By using $RuCl_2$-[(*S*)-3,5-Pr^i-MeOBIPHEP][(*R*,*R*)-DPEN][10] as a catalyst, Scalone and Waldmeier performed the asymmetric hydrogenation of 1,4-dibenzyl-3-oxopiperidine to produce (3*S*,4*S*)-1,4-dibenzylpiperidin-3-ol in 96% ee, which was an important intermediate in the synthesis of the NMDA 2B receptor antagonist Ro 67-8867.[7f]

Recently, we have developed a novel class of chiral spiro diphosphine (SDP) ligands and demonstrated that they are highly efficient in the Ru^{II}-diphosphine/1,2-diamine-catalyzed asymmetric hydrogenation of prochiral ketones (Scheme 1).[6] In combination with *t*-BuOK in 2-propanol, $RuCl_2$[(*S*)-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) can catalyze the hydrogenation of a wide range of aromatic, heteroaromatic, and α,β-unsaturated ketones with quantitative yield, excellent enantioselectivity, and very high substrate-to-catalyst ratios. Here we report the results of our detailed studies on this reaction, the new application of SDP ligands in the asymmetric hydrogenation of racemic α-arylcycloalkanones by dynamic kinetic resolution, and the kinetic studies on the effect of the alkali metal cation in the hydrogenation of acetophenone.

Results and Discussion

Asymmetric Hydrogenation of Simple Ketones. The (*S*,*RR*)-**1** catalysts were prepared by reacting SDP ligands with $[(C_6H_6)RuCl_2]_2$ in DMF at 100 °C followed by treatment of the resulting reddish-brown solution with 1 equiv of DPEN at room temperature. The complexes thus obtained were used directly in the catalytic reactions. The hydrogenation of acetophenone was first performed under standard conditions (20−25 °C, 50 atm of H_2, 2-propanol solvent, 2−2.5 M solutions, *t*-BuOK as the base, at S/C = 5000 and S/B = 70) to assess the (*S*,*RR*)-**1** catalysts composed of different SDP and DPEN complexes (Table 1). With the parent SDP ligand, the (*S*,*RR*)-**1a** catalyst provided (*S*)-1-phenylethanol in quantitative yield with 90% ee over 1.5 h (entry 1). By introducing a substituent, such as methyl or methoxy, at the para position of the *P* phenyl of the parent SDP ligand, the (*S*,*RR*)-**1b** and (*S*,*RR*)-**1c** catalysts provided a tiny influence on the enantioselectivity of the product (entries 2 and 3). The enantioselectivity of the reaction was dramatically increased to 99% ee by using the (*S*,*RR*)-**1d** catalyst, showing that the 3,5-dimethyl groups on the *P*-phenyl rings of the SDP ligand significantly benefit the enantioselectivity in the hydrogenation of acetophenone (entry 4). This result further confirmed that the xylyl-substituted ligand provides optimum enantioselectivity and reactivity in the Ru^{II}-diphosphine/1,2-diamine-catalyzed hydrogenation of simple ketones, which was described as a "3,5-dialkyl meta-effect" by Pregosin and co-workers.[11] The **1** catalysts displayed a strong match/mismatch effect between the chiralities of the SDP ligand and diamine DPEN in the hydrogenation of acetophenone. In contrast to the (*S*,*RR*)-**1d** catalyst, the (*S*,*SS*)-**1d** catalyst has mismatched chiralities and gave the lowest reactivity and the lowest enantioselectivity (28% ee, entry 5). However, both catalysts (*S*,*RR*)-**1d** and (*S*,*SS*)-**1d** produced (*S*)-1-phenylethanol, indicating that the configuration of the product was determined by the chirality of the SDP ligand.

TABLE 1. Asymmetric Hydrogenation of Acetopheone[a]

entry	catalyst	S/B	PH_2 (atm)	time (h)	conv. (%)[b]	ee (%)[c]
1	(*S*,*RR*)-**1a**	70	50	1.5	100	90
2	(*S*,*RR*)-**1b**	70	50	3.0	99	89
3	(*S*,*RR*)-**1c**	70	50	2.5	100	92
4	(*S*,*RR*)-**1d**	70	50	1.5	100	99
5	(*S*,*SS*)-**1d**	70	50	48	64	28
6	(*S*,*RR*)-**1d**	60	50	1.5	100	99
7	(*S*,*RR*)-**1d**	80	50	4.0	100	99
8	(*S*,*RR*)-**1d**	100	50	12	100	98
9[d]	(*S*,*RR*)-**1d**	70	50	24	69	98
10[e]	(*S*,*RR*)-**1d**	70	50	1.0	98	99
11	(*S*,*RR*)-**1d**	70	20	12	98	99
12	(*S*,*RR*)-**1d**	70	30	8.0	99	99
13	(*S*,*RR*)-**1d**	70	60	1.5	100	99
14[f]	(*S*,*RR*)-**1d**	100	60	22	100	99
15[g]	(*S*,*RR*)-**1d**	1000	100	72	98	98

[a] Reactions were performed at 20−25 °C using a 2.5 M solution of acetophenone in 2-propanol containing **1a**−**d** (S/C = 5000) and *t*-BuOK (S/B = 60−100) unless otherwise stated. [b] Determined by GC. [c] Determined by chiral GC (Suplco β-DEX 120 column). The absolute configuration was *S*. [d] Performed at 0 °C. [e] Performed at 40 °C. [f] S/C = 10 000. [g] S/C = 100 000, 40 °C.

The substrate-to-base ratio (S/B) was important in the hydrogenation of ketones. An increase of the S/B ratio resulted in very little change of the enantioselectivity but strongly decreased the reaction rate. An S/B of 70 was found to be suitable for fast reaction, quantitative conversion, and high enantioselectivity. When an S/B of 100 was used, the hydrogenation was completed over 12 h, and the enantiomeric excess of the product was slightly decreased to 98% ee (entry 8). At a higher temperature (40 °C), the reaction proceeded at a higher rate without loss of enantioselectivity (entry 10). However, at 0 °C, the substrate could not be completely converted in 24 h (entry 9). In another study of hydrogen pressure, we found that the enantiomeric excess of the product was independent of the hydrogen pressure but the reaction rate became slower at a lower hydrogen pressure (entries 11 and 12). It was delightful to find that hydrogenation

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(9) Tol-BINAP = 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl. Ohkuma, T.; Li, J.; Noyori, R. *Synlett* **2004**, 1383.

(10) 3,5-^{i}Pr-MeOBIPHEP = 6,6′-dimethoxy-2,2′-bis [bis(3,5-diisopropylphenyl)-phosphino]biphenyl.

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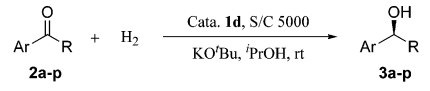
SCHEME 2. Asymmetric Hydrogenation of Aromatic Ketones with Catalyst (*S*,*RR*)-1d



2a-p 3a-p

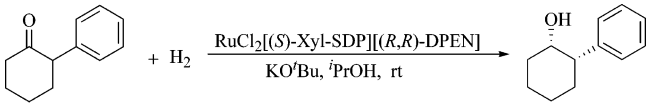
a Ar = C_6H_5	R = CH_3 99% ee	**i** Ar = *p*-$CH_3OC_6H_4$	R = CH_3 98% ee
b Ar = C_6H_5	R = C_2H_5 99.5% ee	**j** Ar = *p*-ClC_6H_4	R = CH_3 99% ee
c Ar = C_6H_5	R = $PhCH_2$ 98% ee	**k** Ar = *p*-BrC_6H_4	R = CH_3 99% ee
d Ar = *o*-ClC_6H_4	R = CH_3 98% ee	**l** Ar = 2-naphthyl	R = CH_3 99.2% ee
e Ar = *o*-BrC_6H_4	R = CH_3 99.2% ee	**m** Ar = ferrocenyl	R = CH_3 98% ee
f Ar = *m*-BrC_6H_4	R = CH_3 99.2% ee	**n** Ar = 2-furyl	R = CH_3 98% ee
g Ar = *m*-$CF_3C_6H_4$	R = CH_3 99% ee	**o** Ar = 2-thienyl	R = CH_3 98% ee
h Ar = *p*-$CH_3C_6H_4$	R = CH_3 99.2% ee	**p** Ar = *t*rans-PhCH=CH	R = CH_3 96% ee

can be performed at an extremely low catalyst loading. The enantioselectivity remained at 98% ee even at a substrate-to-catalyst ratio (S/C) of 100 000 (entry 15).

Asymmetric hydrogenation was extended to other ketones under optimized conditions. As shown in Scheme 2, the (*S*,*RR*)-**1d** catalyst exhibited excellent enantioselectivities and reactivities for the hydrogenation of various aromatic, heteroaromatic, and α,β-unsaturated ketones.[6] Variation of the structure of the alkyl groups on the ketones causes obvious changes in reactivity but not in enantioselectivity. The phenyl ethyl ketone gave the best enantioselectivity, and the phenyl benzyl ketone gave the slowest reaction rate (**2a**: R = CH_3, 1.5 h, 99% ee; **2b**: R = C_2H_5, 3.5 h, 99.5% ee; **2c**: R = $PhCH_2$, 46 h, 98% ee). However, a change of the substituent on the aromatic ring of substrates resulted in little difference in the reactivity and enantioselectivity. Heteroaromatic and α,β-unsaturated ketones can also be hydrogenated smoothly, and the corresponding alcohols were produced in high enantioselectivities. It deserves commendation that the hydrogenation of acetylferrocene with (*S*,*RR*)-**1d** yielded (*S*)-1-ferrocenylethanol in 98% ee at an S/C of 5000. When the S/C was increased to 10 000, the ee value of the product was still 97%. Enantiomerically enriched 1-ferrocenylethanol is a crucial starting material in the synthesis of many chiral ferrocene compounds such as ferrocenylethylamines and ferrocenylphosphines.[12]

Asymmetric Hydrogenation of Racemic α-Arylcycloketones. Asymmetric hydrogenation of α-arylcycloketones is of importance in organic synthesis, which produced the *cis*-α-arylcyclo alcohols, a very useful class of building blocks for the synthesis of biologically active compounds and chiral drugs. For example, chiral *cis*-2-phenylpiperidin-3-ol can be converted to hNK_1 antagonist L-733060,[13] and chiral *cis*-1-aryl-2-hydroxy-1,2,3,4-tetrahydronaphthalene is an intermediate for the synthesis of benzazepine dopamine D1 antagonist Sch 39 166.[14] In the asymmetric hydrogenation of racemic α-arylcycloketones, a highly efficient catalyst can convert only one of the two enantiomers of the substrate (kinetic resolution). If combined with a racemization of α-arylcycloketone in the presence of a suitable base, then the asymmetric hydrogenation will provide 100% theoretical yield of the corresponding *cis*-α-arylcyclo alcohol.[15]

TABLE 2. Asymmetric Hydrogenation of Racemic 2-Phenylcyclohexanones[a]



4a 5a

entry	S/B	PH_2 (atm)	time (h)	conv. (%)[b]	cis/trans[b]	ee (%)[c]
1	10	50	2.0	100	>99:1	99
2	5	50	1.2	100	>99:1	99
3	2.5	50	1.2	100	>99:1	99
4	1.6	50	1.2	100	>99:1	99
5[d]	10	50	0.5	100	>99:1	98
6	10	20	12	100	>99:1	96
7	10	100	1.2	100	>99:1	99

[a] Reactions were performed at 20−25 °C for 0.8 M solutions of 2-phenylcyclohexanone in 2-propanol containing (*S*,*RR*)-**1d** (S/C = 2000). [b] Determined by GC. [c] Determined by chiral GC (Suplco β-DEX 225 column). The absolute configuration was (1*S*,2*S*). [d] At 50 °C.

The simple substrates for the study of the asymmetric hydrogenation of α-arylcycloketones are 2-arylcyclohexones, which were easily synthesized by coupling aryl Grinard reagents with 2-chlorocyclohexanone.[16] The asymmetric hydrogenation of 2-phenylcyclohexanone (**4a**) was tested first with the $RuCl_2$[(*S*)-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**) (S/C = 2000) catalyst in 2-propanol in the presence of *t*-BuOK (S/B = 10) under 50 atm of H_2 at room temperature to provide (1*S*,2*S*)-*cis*-2-phenylcyclohexanol (**5a**) in quantitative yield with 99% ee over 2 h (Table 1, entry 1). Increasing the amount of base resulted in a higher reaction rate and no obvious influence on the enantioselectivity (entries 2−4). A high reaction temperature gave a higher reaction rate with little expense of enantiomeric excess of the product (entry 5 vs 1). Hydrogen pressure also provided a manifest effect on both the reaction rate and the enantioselectivity. At a lower hydrogen pressure, such as 20 atm, the reaction was completed over 12 h and provided a lower enantioselectivity (96% ee, entry 6). The reason for the lower enantioselectivity was that the hydride-transfer reaction of the ketone took place at lower hydrogen pressures.[8b,17] To check this point, we carried out a reaction under N_2, instead of H_2, and found that 2-phenylcyclohexanone (**4a**) was indeed converted to *cis*-2-phenylcyclohexanol (**5a**) in 11% conversion with 5% ee in 4 h, indicating the existence of a hydride-transfer reaction.

Under the optimized conditions, a series of 2-arylcyclohexanones was hydrogenated by $RuCl_2$[(*S*)-Xyl-SDP]-[(*R*,*R*)-DPEN] (**1d**) with excellent cis/trans stereoselectivities and enantioselectivities. The results summarized in Table 3 showed the following: (1) The hydrogenations

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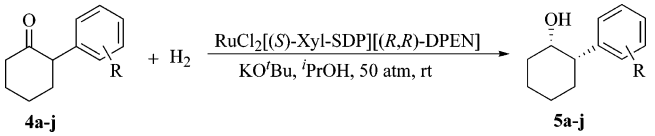
TABLE 3. Asymmetric Hydrogenation of Racemic 2-Arylcyclohexanone[a]



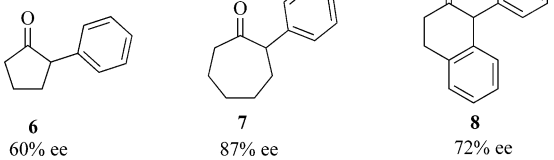
4a-j 5a-j

entry	substrate	time (h)	cis/trans[b]	ee (%)[c]	$[\alpha]_D^{20}$[d]
1	R = H (**4a**)	2.0	>99:1	99	+97 (*c* 1.06)
2	R = 4-Me (**4b**)	1.8	>99:1	99.5	+78 (*c* 0.95)
3[e]	R = 4-MeO (**4c**)	6.0	100:0	97	+89 (*c* 1.04)
4	R = 4-Cl (**4d**)	1.8	>99:1	99	+77 (*c* 1.00)
5	R = 4-CF_3 (**4e**)	0.8	100:0	98	+96 (*c* 1.10)
6	R = 3-Me (**4f**)	2.0	>99:1	98	+100 (*c* 0.99)
7	R = 3-MeO (**4g**)	2.0	100:0	99.9	+92 (*c* 1.03)
8	R = 3-Cl (**4h**)	2.0	>99:1	98	+86 (*c* 0.98)
9	R = 3,5-diMe (**4i**)	2.0	>99:1	94	+90 (*c* 1.12)
10	R = 2-Me (**4j**)	8.0	>99:1	89	+102 (*c* 1.14)

[a] Reactions were performed at 20−25 °C under 50 atm of H_2 using a 0.8 M solution of 2-arylcyclohexanone in 2-propanol containing (*S*,*RR*)-**1d** (S/C = 2000) and *t*-BuOK (S/B = 10). All conversions were >99% as judged by GC. [b] Determined by GC. [c] Determined by chiral GC (Suplco *β*-DEX 225 column). The absolute configurations of entries 1, 3, and 5 were (1*S*,2*S*). [d] For the pure cis isomer, measured in MeOH. [e] A mixed solvent of 2-propanol/toluene (5:1) was used to dissolve the substrate.

of all of the substrates gave almost quantitative cis isomers; (2) The introduction of either an electron-donating or -withdrawing group at the para or meta position of the phenyl ring in 2-arylcyclohexanone had little influence on the enantioselectivity (entry 2−8); (3) The substitutions at the ortho or 3,5-position of the phenyl ring in 2-arylcyclohexanone caused a notable decrease of the enantioselectivity (entries 9 and 10). The highest enantioselectivity (99.9% ee) was achieved in the hydrogenation of 2-(3-methoxyphenyl)cyclohexanone (**4g**) (entry 7).

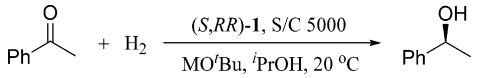
The scope of the substrate was extended to other α-arylcycloketones, such as 2-phenylcyclopentanone (**6**), 2-phenylcycloheptanone (**7**), and 1-phenyl-2-tetralone (**8**). Under the optimized reaction conditions, these cycloketones were hydrogenated to the corresponding chiral *cis*-2-arylcycloalkanols over 24 h in high cis/trans ratios (>99:1) and moderate to good enantioselectivities (60−87% ee). The reason for the lower reactivity and enantioselectivity achieved in the hydrogenation of α-phenylcyclopentanone (**6**) might be attributable to the relatively rigid five-membered ring of substrate that decreases the rate of the racemization. The hydrogenation of compound **8**, a benzo analogue of α-phenylcyclohexanone, is a similar situation. For seven-membered-ring substrate α-phenylcycloheptanone, the racemization is comparably easier and gave a better enantioselectivity.



6 60% ee **7** 87% ee **8** 72% ee

Effect of the Alkali Metal Cation in the Hydrogenation of Ketones. It is necessary to use a base in the asymmetric hydrogenations of the simple ketones with a Ru^{II}-diphosphine/1,2-diamine catalyst. The most popular base that was utilized in this reaction was *t*-BuOK.[3−7] We also used *t*-BuOK as a base in the hydrogenations of simple ketones and α-arylcycloketones

SCHEME 3. Asymmetric Hydrogenation of Acetophenone



with Ru^{II}-SDP/DPEN catalysts. By accident, *t*-BuONa was taken for the hydrogenation of acetophenone catalyzed by $RuCl_2$[(*S*)-Xyl-SDP][(*R*,*R*)-DPEN] (**1d**), and we found that the reaction rate of the hydrogenation was higher than that when using *t*-BuOK. This is different from the result reported by Hartmann and Chen.[18] They found that the alkali metal cations influence the activity in the order $K^+ > Na^+ \approx Rb^+ > Li^+$ in the $RuCl_2$[(*S*)-BINAP][(*S*,*S*)-DPEN]-catalyzed hydrogenation of acetophenone. To understand this unexpected finding, we studied the alkali metal cation influence on the reaction rate systematically in the hydrogenation of acetophenone by the kinetic method. The experiments were carried out in a 120-mL stainless-steel autoclave equipped with a sampling tube under the following conditions: 20 °C, [acetophenone] = 1.6 M, PH_2 (initial) = 50 atm using (*S*,*RR*)-**1** (S/C = 5,000) as the catalyst and *t*-BuOM (M = K, Na, Li, S/B = 80) as the base (Scheme 3). For the kinetic analyses, samples were taken by means of a sampling tube at regular time intervals. The conversions of acetophenone were determined by gas chromatography. Time−conversion curves are plotted in Figures 1−4.

From Figure 1, we can see that the reaction rates of hydrogenation using the (*S*,*RR*)-**1a** catalyst are $K^+ > Na^+ > Li^+$ (Figure 1). Whereas in the hydrogenation using the (*S*,*RR*)-**1b** catalyst, which has a methoxy group in the para position of the *P*-phenyl rings in the ligand, the reaction rates became $K^+ \approx Na^+ > Li^+$ (Figure 2). However, the (*S*,*RR*)-**1c** and (*S*,*RR*)-**1d** ligands, which have 4-methyl or 3,5-dimethyl groups on the *P*-phenyl rings, changed the reaction rates to $Na^+ > K^+ > Li^+$ (Figures 3 and 4). These results showed that the choice of the alkali metal cation in the hydrogenation of a ketone using Ru^{II}-diphosphine/1,2-diamine as the catalyst was not always the K^+ cation. Sometimes the use of Na^+ gave

(18) Hartmann, R.; Chen, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3581.

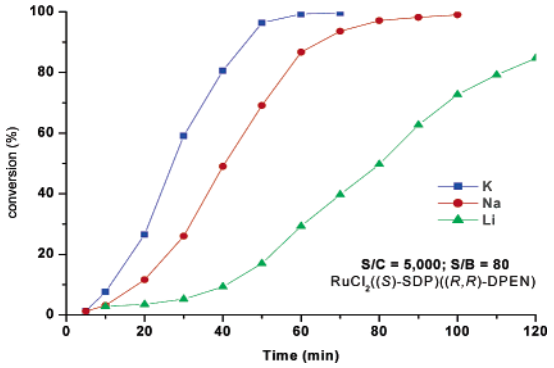


FIGURE 1. Hydrogenation of acetophenone catalyzed by (*S*,*RR*)-**1a**.

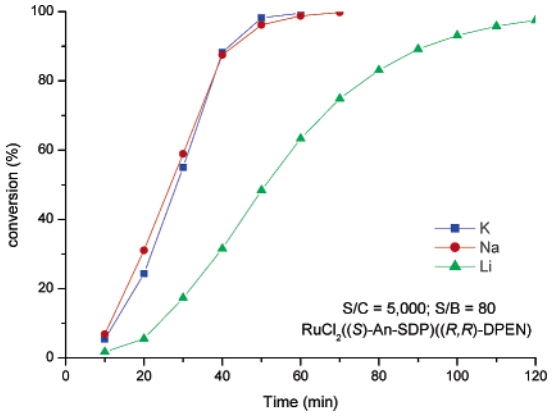


FIGURE 2. Hydrogenation of acetophenone catalyzed by (*S*,*RR*)-**1b**.

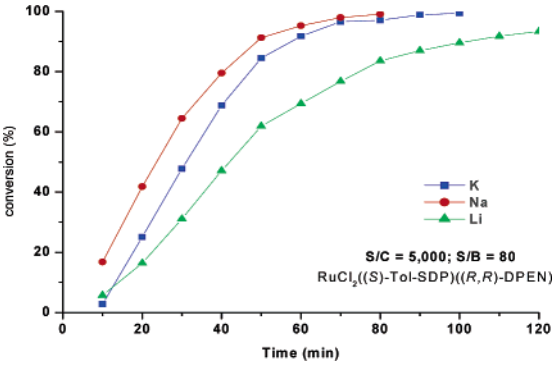


FIGURE 3. Hydrogenation of acetophenone catalyzed by (*S*,*RR*)-**1c**.

a faster reaction, especially in the case of a catalyst having relatively larger steric *P* aryls in the diphosphine ligand.

We further studied the effect of the alkali metal cation in hydrogenations of acetophenone catalyzed by Noyori catalysts $RuCl_2$[(*R*)-BINAP][(*R*,*R*)-DPEN] ((*R*,*RR*)-**9a**), $RuCl_2$[(*R*)-Tol-BINAP][(*R*,*R*)-DPEN] ((*R*,*RR*)-**9b**), and $RuCl_2$[(*R*)-Xyl-BINAP][(*R*,*R*)-DPEN] ((*R*,*RR*)-**9c**) to confirm this trend. Under the same conditions, the reaction rate of hydrogenation with the (*R*,*RR*)-**9a** catalyst decreased in the order $K^+ > Na^+ > Li^+$, which is the same as the result reported by Chen.[18] In the hydrogenation with the (*R*,*RR*)-**9b** catalyst, the reaction rates are $K^+ >$

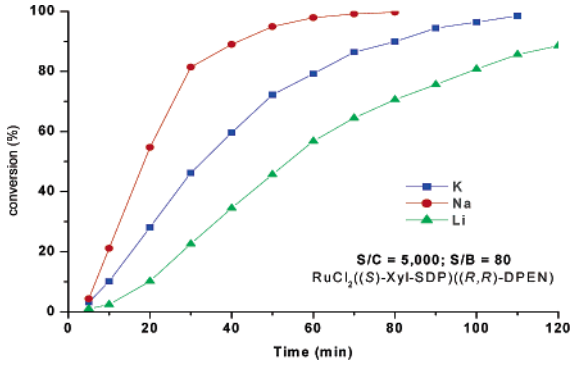


FIGURE 4. Hydrogenation of acetophenone catalyzed by (*S*,*RR*)-**1d**.

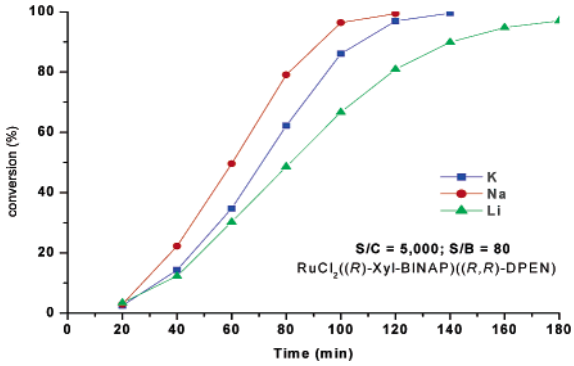


FIGURE 5. Hydrogenation of acetophenone catalyzed by (*R*,*RR*)-**9c**.

$Na^+ > Li^+$.[19] However, in the hydrogenation using the (*R*,*RR*)-**9c** catalyst, which has 3,5-dimethyl groups on the *P* phenyl of the BINAP ligand, the reaction rates changed to $Na^+ > K^+ > Li^+$ (Figure 5), which are similar to those in the hydrogenations using the (*S*,*RR*)-**1c** and (*S*,*RR*)-**1d** catalysts. The results that were obtained by using Ru^{II}-BINAP/DPEN further showed that the sterically hindered catalyst preferred *t*-BuONa.

It should be emphasized that the hydrogenations, upon employing the same catalyst, had the same level of enantioselectivity regardless of which base was used. In addition, the relative reaction rates did not change when the S/B ratio varied from 80 to 250 in the above investigations. These results are in accord with the metal−ligand bifunctional mechanism reported by Noyori.[2] In this catalytic cycle, the ketone was hydrogenated by a six-membered transition state, and the alkali metal cation was not involved in it.

More importantly, it was found that the enantioselectivity was much lower at the beginning of all of the reactions and increased quickly as the reactions proceeded. The changes in the ee value versus the conversion of the substrate for the hydrogenation of acetophenone using the (*S*,*RR*)-**1d** catalyst in the presence of *t*-BuOK were plotted in Figure 6. The reason for the low enantioselectivity in the beginning was that under the reaction conditions (2-propanol and *t*-BuOM) Ru^{II}-diphosphine/1,2-diamine not only catalyzed Noyori's hydrogenation

(19) Sandoval, C. A.; Ohkuma, T.; Muňiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490.
(20) Abdur-Rashid, K.; Faatz, M.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7473 and refs 17−19.

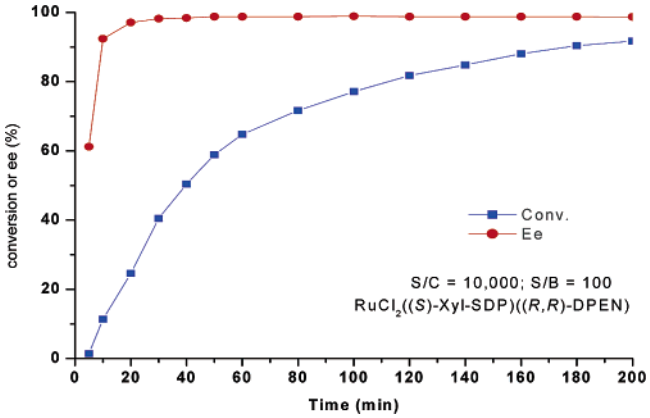


FIGURE 6. Relationship of the ee of the product and the conversion of the substrate in the hydrogenation of acetophenone catalyzed by (*S*,*RR*)-**1d**.

of the ketone but also catalyzed the hydride-transfer reaction, which has a low enantioselectivity.[17] In the first stage, the hydride transfer reaction occurred until the solution was saturated with hydrogen. Along with the acceleration of highly enantioselective hydrogenation, the ee value of the product increased rapidly and reached its the highest level in about 20 min and was maintained to the end of the reaction.

The mechanism of the $RuCl_2$(BINAP)(diamine)-catalyzed asymmetric hydrogenation of ketones has been extensively investigated.[20] In the reaction, the use of *t*-BuOK as a base is necessary to generate the active catalyst by dehydrochlorination of the catalyst precursor. Chen reported that the K^+ ion might be involved in the steps of addition and cleavage of H_2 in the catalytic cycle.[18] Morris and co-workers suggested that the role of potassium ions in $RuCl_2$-diphosphine/1,2-diamine systems was to precipitate chloride during the activation of the catalyst.[17a] Our findings on the effect of alkali metal cations can be explained by a combination of the basicity of *t*-BuOM and the steric hindrance that the M^+ alkali metal cation has to overcome during its interaction with the precatalyst to generate the active catalyst (Scheme 4). In the hydrogenation using catalyst **1a**, which has no substituents on the *P*-phenyl rings, all three alkali metal cations can easily approach the chlorine atom in the precatalyst, and the basicity of *t*-BuOM is the principal factor in determining the reaction rate. Because a stronger basicity benefits the deprotonation of the NH_2 group on DPEN in the generation of an active catalyst, the reaction rates of the hydrogenations are *t*-BuOK > *t*-BuONa > *t*-BuOLi. For the hydrogenation with catalyst **1b**, the stronger basicity of *t*-BuOK was balanced by the steric hindrance that the K^+ cation suffered from the *p*-methoxy group on the *P*-phenyl rings of the catalyst, and the reaction rates are *t*-BuOK ≈ *t*-BuONa > *t*-BuOLi. However, in the cases of catalysts **1c** and **1d**, the steric hindrance of substituents on the *P*-phenyl rings constantly increased and prevented the relatively larger K^+ cation from approaching the chlorine atom in the precatalyst. Consequently, the reaction rates of hydrogenation became *t*-BuONa > *t*-BuOK > *t*-BuOLi. The experiments with the series of BINAP catalyst **9** can also be explained by similar analysis.

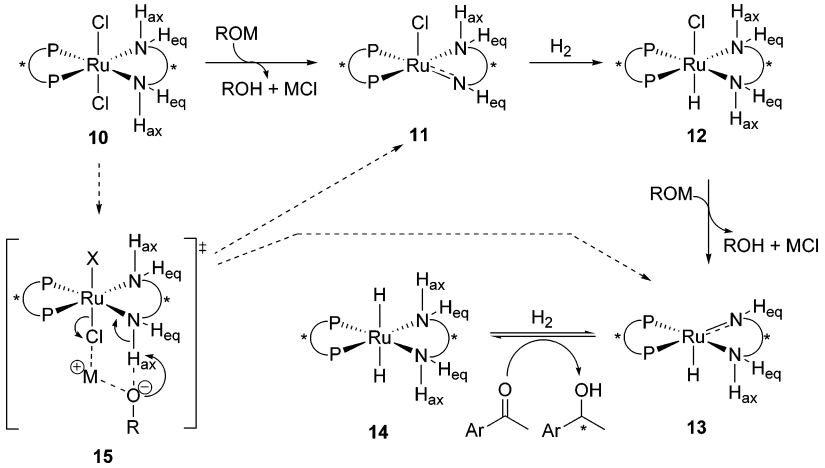
Conclusions

The chiral $RuCl_2$(Xyl-SDP)(DPEN) **1d** complex was demonstrated to be a very effective catalyst for the highly enantioselective hydrogenation of simple ketones and α-arylcyclohexanones. In the asymmetric hydrogenation of acetophenone with Ru^{II}-diphosphine/diamine catalysts, we observed a different reaction rate when a base with a different alkali metal cation was used. The change in reaction rate can be explained by the combination of the basicity of *t*-BuOM and the size of the M^+ alkali metal cation. Generally, diphosphine ligands without the substituents on the *P*-phenyl ring prefer the *t*-BuOK base, and the diphosphine ligands, having sterically hindered groups on *P*-phenyl rings, favor the *t*-BuONa base. This trend can also be influenced by the backbone of the chiral diphosphine ligand.

Experimental Section

General Procedure for Asymmetric Hydrogenation of Aromatic Ketones: **Hydrogenation of Acetophenone at S/C = 5000.** The catalyst (0.002 mmol) was placed in a 20-mL hydrogenation vessel. The vessel was purged with hydrogen by pressurizing to 10 atm and releasing the pressure. This procedure was repeated three times. Anhydrous *i*-PrOH (3.0 mL) was introduced with a syringe, and the vessel was purged

SCHEME 4. Proposed Mechanism of Asymmetric Hydrogenation of Aromatic Ketones with Ru(P−P)(N−N) Catalysts



with hydrogen and pressurized to 20 atm for 5 min. After releasing the pressure, acetophenone (1.2 g, 10 mmol) and a solution of *t*-BuOK in *i*-PrOH (0.2 mmol/mL, 0.7 mL, 0.14 mmol) were added. The vessel was purged with hydrogen and pressurized to 50 atm. After stirring at room temperature for several hours, the reaction was stopped. The reaction mixture was filtered through a short silica gel column, and the filtrate was diluted with acetone and analyzed by GC to determine the conversion and enantioselectivity.

General Procedure for Asymmetric Hydrogenation of 2-Arylcycloalkanones: Hydrogenation of 2-Arylcycloalkanone at S/C = 2000, S/B = 10, at Room Temperature under 50 atm of Hydrogen. The $RuCl_2$[(*S*)-Xyl-SDP][(*R*,*R*)-DPEN] catalyst (**1d**) (2.2 mg, 0.002 mmol) was placed in a 20-mL hydrogenation vessel. The vessel was purged with hydrogen by pressurizing to 10 atm and releasing the pressure. This procedure was repeated three times. Anhydrous *i*-PrOH (1.0 mL) was introduced with a syringe, and the vessel was purged with hydrogen and pressurized to 20 atm for 5 min. After releasing the pressure, 2-arylcycloalkanone (4 mmol in 2.5 mL *i*-PrOH) and a solution of *t*-BuOK in *i*-PrOH (1 mmol/mL, 0.4 mL, 0.4 mmol) were added. The vessel was purged with hydrogen and pressurized to 50 atm. After stirring at room temperature for several hours, the reaction was stopped. The reaction mixture was filtered through a short silica gel column, and the filtrate was diluted with acetone and analyzed by GC to determine the conversion, cis/trans selectivity, and enantioselectivity.

General Procedure for the Kinetic Study on the Effect of the Alkali Metal Cation in the Hydrogenation of Acetophenone. A 120-mL stainless-steel hydrogenation vessel was charged with 0.008 mmol of **1** or **9**, hydrogen was introduced into the vessel three times to replace the argon, and 15.4 mL of *i*-PrOH was introduced under a hydrogen atmosphere. Then the vessel was closed and stirred for 5 min to ensure that catalyst **1** or **9** was completely dissolved. The vessel was opened, and acetophenone (4.8 g, 40 mmol) and *t*-BuOM (4.8 mmol) in *i*-PrOH (4.8 mL) were introduced into the vessel. The vessel was reclosed and pressurized to 50 atm. The reaction was vigorously stirred at 20 °C, and the samples were withdrawn by means of the sampling tube at regular time intervals. The conversions of acetophenone were determined by GC (HP-1 column 25 m × 0.25 mm × 0.25 μm; N_2 1 mL/min, 80 °C then 1 °C/min to 160 °C) with t_R(subs) = 8.69 min and t_R(prod) = 8.96 min.

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Supporting Information Available: Preparations and properties of compounds **4**, **6**, **7**, and **8**, procedures for the asymmetric hydrogenation of 2-arylcycloalkanones, and chiral separation conditions for compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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