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Air-Stable Catalysts for Highly Efficient and Enantioselective Hydrogenation of Aromatic Ketones

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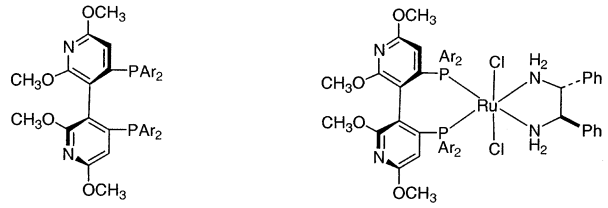
Abstract: A series of chiral *trans*-[$RuCl_2$(dipyridylphosphine)(1,2-diamine)] complexes have been synthesized and characterized by NMR and single-crystal X-ray diffraction studies. These Ru complexes combined with $(CH_3)_3COK$ in 2-propanol formed a very effective catalyst system for the hydrogenation of a diverse range of simple aromatic ketones with high activity (substrate-to-catalyst ratio up to 100 000) and excellent enantioselectivity (up to >99.9%). The catalyst system was also found to be stable in solution even under a normal atmosphere.

The asymmetric hydrogenation of prochiral ketones is one of the most efficient methods of producing enantiomerically enriched secondary alcohols.[1] In contrast to the fruitful results of the asymmetric hydrogenation of functionalized ketones catalyzed by Ru-phosphines complexes,[1,2] only limited examples have been reported for simple ketones because such substrates lack heteroatoms that enable the substrate to anchor strongly to the metal center. Recently, Noyori and co-workers achieved an important breakthrough in this area by using appropriate diphosphine/diamine Ru complexes along with an inorganic base in 2-propanol and obtained the most effective catalyst system for the hydrogenation of ketones.[3,4]

SCHEME 1



Among these catalysts, *trans*-$RuCl_2$[(*S*)-XylBINAP][(*S*)-DAIPEN][5] or its *R*,*R* isomer very often gave the best results.[6] Burk et al. reported that PhanePhos-ruthenium-diamine[7] complexes also showed high activity and enantioselectivity in the asymmetric hydrogenation of a wide range of ketones.[8] To our knowledge, no other diphosphine ligand except PhanePhos has been reported so far to approach the utility of XylBINAP in this reaction.

Recently, we have developed a new class of chiral dipyridylphosphine ligands (Scheme 1) P-Phos (**1a**),[9a,9b] Tol-P-Phos (**1b**),[9c] and Xyl-P-Phos (**1c**).[9d] Their Ru(II) complexes were found to be highly effective catalysts in the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid and β-ketoesters. In addition, it is of high interest to note that the $Ru(C_6H_6)$(P-Phos)Cl_2 catalyst is air-stable even in solution.[9c,9d] Because of the high potential of the practical application of the air-stable catalysts in reactions of industrial interest, we explored the Ru-(P-Phos) catalyzed hydrogenation of aromatic ketones employing Noyori's protocol. In this study, we are delighted to find that a wide variety of aromatic ketones can be hydrogenated quantitatively with excellent enantioselectivities (up to >99.9%) by using a highly air-stable catalyst *trans*-[$RuCl_2${(*R*)-**1c**}{(*R*,*R*)-DPEN}] ((*R*,*RR*)-**2c**, DPEN = 1,2-diphenyl ethylenediamine) combined with $(CH_3)_3COK$ in 2-propanol solution with a substrate-to-catalyst ratio (S/C) up to 100 000 under atmospheric to 400 psi hydrogen pressure. In the meanwhile, unlike the Ru-BINAP catalyst system, which often needs the fancy diamine DAIPEN for the optimum results, the present catalyst system employing much less expensive diamine DPEN gave comparable results to

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(5) XylBINAP = 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl; DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine.

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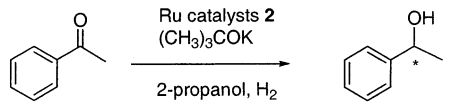
TABLE 1. Asymmetric Hydrogenation of Acetophenone 3a Catalyzed by 2[a]



3a **4a**

entry	catalyst	S/C (M/M)	S/B (M/M)	p_{H_2} (psi)	time (h)	conv (%)[b]	ee (%)[b]
1	(*R*,*RR*)-**2c**	2000	300	14	6	93.4	98.4 (*S*)
2	(*R*,*RR*)-**2c**	2000	300	500	6	100	98.5 (*S*)
3[c]	(*R*,*RR*)-**2c**	2000		300	6		
4	(*R*,*RR*)-**2c**	2000	50	300	12	100	96.9 (*S*)
5	(*R*,*RR*)-**2c**	2000	125	300	12	100	97.6 (*S*)
6	(*R*,*RR*)-**2c**	2000	300	300	12	100	98.3 (*S*)
7	(*R*,*RR*)-**2c**	2000	800	300	2	99.2	99.0 (*S*)
8	(*R*,*RR*)-**2c**	50000	800	500	24	99.8	99.1 (*S*)
9	(*R*,*RR*)-**2c**	100000	800	500	36	99.7	99.1 (*S*)
10[d]	(*R*,*RR*)-**2c**	100000	800	500	18	100	96.6 (*S*)
11	(*S*,*RR*)-**2c**	2000	800	300	2	100	78.0 (*R*)
12	(*R*,*RR*)-**2a**	100000	800	500	36	100	83.3 (*S*)
13	(*R*,*RR*)-**2b**	100000	800	500	36	99.7	84.9 (*S*)
14[e]	(*R*,*RR*)-**2c**	50000	800	500	24	99.8	99.0 (*S*)
15[f]	(*R*,*RR*)-**2c**	50000	800	500	24	100	99.1 (*S*)

[a] Reaction conditions: 100−1000 mg of substrate; substrate concentration = 1.0−2.5 M, 25−28 °C. The substrate and catalyst were added to a stainless steel autoclave under N_2 and the solvents were degassed and dried prior to use unless otherwise stated. [b] The conversions were determined by NMR and by the relative peak sizes in GC. The ee were determined by chiral GC (Chrompack Chirasil-DEX CB columns). The absolute configuration was determined by comparison of the sign of optical rotation or retention time with literature data (ref 6). [c] The reaction was performed without the addition of $(CH_3)_3OK$ and no product was detected. [d] The reaction was performed at 50 °C. [e] The substrate and catalyst were added to the stainless steel autoclave in air. [f] The catalysts solutions in 2-propanol were stirred for 5 h under air before the addition of substrate, $(CH_3)_3OK$, and H_2.

those achieved with the best system XylBINAP-Ru-DAIPEN[6a]

Using a method reported by Doucet et al.,[4b] we first prepared catalysts (**2**) by reacting ligands **1** with $[RuCl_2(C_6H_6)]_2$ in DMF at 100 °C, followed by treatment of the resulting reddish brown solution with 1 equiv of DPEN at room temperature, and the complex was isolated and purified as light brown solid. ^1H, ^{31}P NMR and the single-crystal X-ray diffraction analysis of these complexes showed that they existed as a single conformer in solution.

Preliminary experimental results revealed that rapid, highly enantioselective catalytic hydrogenation of acetophenone **3a** was achieved with complex **2** as catalyst (Table 1). The hydrogenation of acetophenone **3a** with S/C = 2000 under 300 psi hydrogen pressure at 25 °C in 2-propanol containing (*R*,*RR*)-**2c** and $(CH_3)_3COK$ gave 99.2% conversion and 99.0% ee within 2 h (entry 7). Although the enantioselectivity was found to be independent of hydrogen pressure, the rate of reaction was slower at lower pressure (entry 1 vs 2). High reaction temperature gave a higher rate of reaction at the expense of ee (entry 9 vs 10). Consistent with Noyori's findings, the presence of a base was absolutely crucial for high activity in this catalyst system. When **3a** was hydrogenated without the addition of $(CH_3)_3COK$, no desirable product was detected after 6 h (entry 3). The substrate-to-base ratio (S/B) was important as well. An increase of S/B resulted in a somewhat higher enantioselectivity (entries 4−6). The enantioselectivity remained high even when the substrate-to-catalyst ratio was increased to as high as 100 000 (entries 7−9).

Because the selectivity of the Ru-catalyzed hydrogenation relies on the synergistic effects of the chiral diphosphine and diamine ligands, the phosphine and diamine ancillaries must be carefully selected. For example, the mismatching precatalyst (*S*,*RR*)-**2c** (*trans*-[$RuCl_2${(*S*)-**1c**}{(*R*,*R*)-DPEN}]) provided **3b** in only 78% ee under otherwise identical conditions (entry 11 vs 7). Particularly noteworthy was the observation that the use of Xyl-P-Phos (**1c**) as the chiral diphosphine provided far superior ee to those values obtainable with the parent ligand P-Phos (**1a**) or Tol-P-Phos (**1b**) (entry 9 vs 12 and 13).

We previously reported that $Ru(C_6H_6)$(P-Phos)Cl_2 catalyst was rather air-stable even in solution.[9c,9d] In this study, high air-stability of the catalyst system was also demonstrated by performing the experimental procedures in air at S/C = 50 000 prior to the introduction of hydrogen. Complete conversion was observed within 24 h with no diminution of enantioselectivity in comparison with the air-proved system (entry 14 vs 8). The efficiency and enantioselectivity remained unchanged even when the solution of (*R*,*RR*)-**2c** in 2-propanol was exposed to air for 5 h (entry 15).

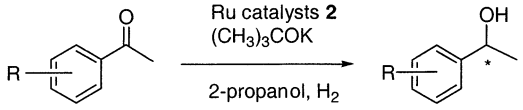
In addition to the marked activity and enantioselectivity observed for the new catalyst system in the hydrogenation of acetophenone **3a**, similarly excellent results were obtained in the hydrogenation of a variety of ring-substituted aromatic ketones (Table 2). Introduction of a methyl, methoxy, or trifluoromethyl substituent to the meta (**3e**, **3f**) or para (**3h**, **3i**, **3k**) position of acetophenone had almost no effect on the enantioselectivity of the reaction (entries 6, 7, 9, 10, and 12). A substrate possessing an electron-withdrawing group on ortho position of **3a** (**3d**, entry 5) was more reactive than those with an electron-donating substituent (**3b**, **3c**, entries 1 and 2). The ortho-, meta-, and para-brominated acetophenones (**3d**, **3g**, **3j**) all displayed excellent enantioselectivities (>99.5% ee) with the use of (*R*,*RR*)-**2c** as catalyst. The hydrogenation of **3d** gave over 99.9% ee irrespective of the use of P-Phos, Tol-P-Phos, or Xyl-P-Phos as the chiral ligand in the catalyst.

In conclusion, Ru complex (*R*,*RR*)-**2c** or its isomer combined with $(CH_3)_3COK$ in 2-propanol gave a very effective catalyst system for highly enantioselective hydrogenation of a diverse range of simple aromatic ketones. The combination of desirable features, such as fast rate of reaction, broad substrate scope, excellent enantioselectivity, high substrate-to-catalyst ratio, employment of less expensive diamine, and high air-stability of catalysts in solution makes the present catalyst system of high practical interest. The studies on the hydrogenation of heteroaromatic, alkenyl, cyclopropyl, and amino ketones by using this catalyst system are in progress.

Experimental Section

General and Materials. All manipulations with air-sensitive reagents were carried out under a dry nitrogen atmosphere using standard Schlenk techniques or in a nitrogen atmosphere glovebox unless otherwise stated. The ketones were stirred over CaH_2 to remove acidic impurities and distilled prior to use. DMF

TABLE 2. Asymmetric Hydrogenation of Substituted Acetophenone Catalyzed by 2[a]



3b-3k **4b-4k**

entry	ketone	R	catalyst	S/C (M/M)	p_{H_2} (psi)	time (h)	conv (%)	ee (%)[b]
1	**3b**	*o*-CH_3	(*R*,*RR*)-**2c**	4000	300	24	100	97.7 (*S*)
2	**3c**	*o*-OCH_3	(*R*,*RR*)-**2c**	4000	300	30	99.6	93.3 (*S*)
3	**3d**	*o*-Br	(*R*,*RR*)-**2a**	4000	300	7	90.7	>99.9 (*S*)
4	**3d**	*o*-Br	(*R*,*RR*)-**2b**	4000	300	7	100	>99.9 (*S*)
5	**3d**	*o*-Br	(*R*,*RR*)-**2c**	10000	400	18	100	>99.9 (*S*)
6	**3e**	*m*-CH_3	(*R*,*RR*)-**2c**	12000	300	50	100	97.7 (*S*)
7	**3f**	*m*-OCH_3	(*R*,*RR*)-**2c**	4000	300	6	100	98.8 (*S*)
8	**3g**	*m*-Br	(*R*,*RR*)-**2c**	4000	300	6	100	99.5 (*S*)
9	**3h**	*p*-CH_3	(*R*,*RR*)-**2c**	20000	300	14	99.1	98.8 (*S*)
10	**3i**	*p*-OCH_3	(*R*,*RR*)-**2c**	20000	300	10	99.6	98.7 (*S*)
11	**3j**	*p*-Br	(*R*,*RR*)-**2c**	50000	300	20	100	>99.9 (*S*)
12	**3k**	*p*-CF_3	(*R*,*RR*)-**2c**	12000	300	24	100	97.7 (*S*)

[a] Reaction conditions: 100−1000 mg of substrate; substrate concentration = 1.0−2.5 M; 25−28 °C; S/B (M/M) = 50−800. [b] The conversions were determined by NMR and by the relative peak sizes in GC. The ee values were determined by chiral GC (Chrompack Chirasil-DEX CB columns). The absolute configuration was determined by comparison of the sign of optical rotation or retention time with literature data (ref 6).

and 2-propanol were freshly distilled over CaH_2 before use. Optically pure P-Phos (**1a**), Tol-P-Phos (**1b**), and Xyl-P-Phos (**1c**) were synthesized according to our previously reported procedures.[9a−d]

***trans*-[RuCl$_2${(*R*)-P-Phos}{(*R*,*R*)-DPEN}] [(*R*,*RR*)-2a].** $[RuCl_2(C_6H_6)]_2$ (18.2 mg, 0.036 mmol) and (*R*)-P-Phos (50 mg, 0.078 mmol) were placed in a 25-mL round-bottom Schlenk flask. After the air in the flask was replaced by N_2, dried and degassed DMF (2 mL) was added. The mixture was stirred under N_2 at 100 °C for 1 h to form a reddish brown solution. After the solution was cooled to room temperature, (*R*,*R*)-DPEN (18.4 mg, 0.078 mmol) was added and the mixture was stirred for 4 h. The solvent was evaporated under high vacuum. The residue was dissolved in CH_2Cl_2 (1 mL) and the turbidity was removed by filtration. The filtrate was concentrated to about 0.5 mL, then hexane (2 mL) was added and a brown precipitate was obtained. The supernatant was removed and the resulting solid was dried under reduced pressure to give (*R*,*RR*)-**2a** (41.5 mg, 56% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.19−3.21 (m, 2H), 3.30−3.33 (m, 2H), 3.39 (s, 6H), 3.79 (s, 6H), 4.27−4.29 (m, 2H), 6.64−6.66 (m, 2H), 6.82−7.82 (m, 30H); ^{31}P NMR ($CDCl_3$, 202 MHz) δ 46.0 (s).

***trans*-[RuCl$_2${(*R*)-Tol-P-Phos}{(*R*,*R*)-DPEN}] [(*R*,*RR*)-2b].** (*R*,*RR*)-**2b** was synthesized in 58% yield according to the same procedure as in the preparation of (*R*,*RR*)-**2a**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.18 (s, 6H), 2.29 (s, 6H), 3.24−3.25 (m, 2H), 3.31−3.32 (m, 2H), 3.41(s, 6H), 3.79 (s, 6H), 4.28−4.30 (m, 2H), 6.57−6.58 (m, 2H), 6.85−7.68 (m, 26H); ^{31}P NMR ($CDCl_3$, 202 MHz) δ 45.1 (s).

***trans*-[RuCl$_2${(*R*)-Xyl-P-Phos}{(*R*,*R*)-DPEN}] [(*R*,*RR*)-2c].** (*R*,*RR*)-**2c** was synthesized in 63% yield according to the same procedure as in the preparation of (*R*,*RR*)-**2a**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.14 (s, 12H), 2.21 (s, 12H), 3.16−3.24 (m, 2H), 3.29−3.32 (m, 2H), 3.33 (s, 6H), 3.85 (s, 6H), 4.23−4.25 (m, 2H), 6.77−6.79 (m, 2H), 6.80−7.48 (m, 22H); ^{31}P NMR ($CDCl_3$, 202 MHz) δ 44.4 (s).

A Typical Procedure for the Ru(II)-Catalyzed Asymmetric Hydrogenation of Aromatic Ketone. A solution of 2.19×10^{-3} mol·L^{-1} (*R*,*RR*)-**2c** in 2-propanol (97 μL, 2.13×10^{-4} mmol), acetophenone (50 μL, 0.425 mmol), 2-propanol (251 μL), and a 0.02 mol·L^{-1} $(CH_3)_3COK$ solution in *t*-BuOH (26.5 μL, 5.3×10^{-4} mmol) were added to a 50-mL autoclave under a nitrogen atmosphere. Hydrogen was initially introduced into the autoclave at a pressure of 300 psi before being reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated three times, the vessel was pressurized to 300 psi. The reaction mixture was stirred at room temperature for 2 h before releasing the H_2. The conversion and enantiomeric excess of (*S*)-1-phenylethanol (**4a**) were determined by NMR and chiral GC analysis to be 99.2% and 99.0%, respectively (column, Chirasil-DEX CB; 50 m × 0.25 mm or 25 m × 0.25 mm, CHROMPACK, carrier gas, N_2).

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Supporting Information Available: Crystallographic procedures, ORTEP drawing, and selective bond distances and angles of (*R*,*RR*)-**2b** (PDF) and X-ray data for (*R*,*RR*)-**2b**, including tables of coordinates for non-hydrogen atoms, selected bond lengths and angles, anisotropic thermal parameters, and coordination of hydrogen atoms (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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