RuHCl(diphosphine)(diamine): Catalyst Precursors for the Stereoselective Hydrogenation of Ketones and Imines[1]

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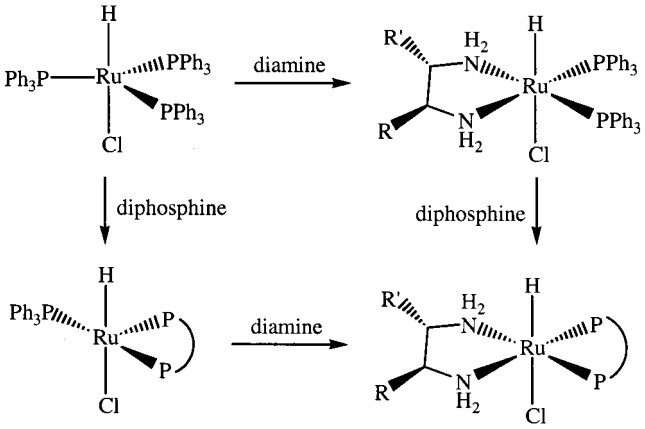
Summary: New chiral complexes RuHCl(diphosphine)(diamine) are readily prepared from RuHCl(PPh$_3$)$_3$. The diamine complexes, in the presence of alkoxide base, catalyze the hydrogenation of a wide variety of ketones and imines at 3 atm H$_2$, 20 °C, including prochiral imines to chiral amines in good to excellent enantiomeric excess.

We have been investigating the ruthenium hydride species generated in mixtures used by Noyori and co-workers that generate very active catalytic species for ketone hydrogenation and asymmetric hydrogenation. These are obtained by mixing dichlororuthenium species containing diamines or chiral diamines, phosphines,[2] or chiral diphosphines[3−6] with a base in 2-propanol under H_2. Recently, we reported that the active catalytic species generated in basic media from the RuCl$_2$(PPh$_3$)$_2$-(cydn)/base system[2] (cydn = R,R-cyclohexyldiamine) is likely to be the dihydride RuH$_2$(PPh$_3$)$_2$(cydn) that is readily prepared from the catalytically inactive monohydride complex RuHCl(PPh$_3$)$_2$(cydn).[7] The latter is readily prepared according to Scheme 1. We also reported that the in-situ generation of RuH$_2$(PPh$_3$)$_2$(cydn) in neat substrates or their solutions in benzene in the presence of H_2 gas could effectively reduce deactivated and sterically congested ketones and some imines to the alcohols and amines, respectively. Here, we report a simple method for the preparation of a series of monohydride complexes, RuHCl(diphosphine)(PPh$_3$), and RuHCl(diphosphine)(diamine) using similar procedures (Scheme 1); diphosphine = R-binap and R,R-1,2-bis-(diphenylphosphinamino)cyclohexane (dppach),[8,9] diamine = cydn and R,R-diphenylethylenediamine (dpen).

Scheme 1



The patents of Noyori and co-workers mention that a range of hydride-containing ruthenium species can be used to generate catalytically active systems for ketone hydrogenation.[10] The present work demonstrates that certain ruthenium complexes generated by the reaction of these monohydride complexes with a base in the presence of hydrogen gas are effective catalysts for the asymmetric hydrogenation not only of ketones but also, for the first time, of imines at room temperature under H_2 gas (1−3 atm), especially when the dppach ligand is employed. The asymmetric hydrogenation of prochiral imines is an emerging technology for the production of chiral amines,[11−18] and the present work provides a facile route to a potentially very wide variety of ruthenium-based catalysts for this purpose.

Refluxing a mixture of RuHCl(PPh$_3$)$_3$ and a diphosphine in tetrahydrofuran under an argon atmosphere produces the substituted complex RuHCl(diphosphine)-(PPh$_3$) (Scheme 1).[19] When an equimolar mixture of a diamine and RuHCl(diphosphine)(PPh$_3$) is stirred in tetrahydrofuran (THF) at room temperature under a

(1) This was presented at the Canadian Society for Chemistry Conference, Calgary, May 2000.

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(9) The Supporting Information describes an improvement on the synthesis[8] of R,R-dppach. The solvent for all NMR experiments here and in ref 7 is C_6D_6. Yield: 4.13 g, 98%. ^{1}H NMR: 0.82−2.76 ppm (m, 12 H), 7.03−7.45 ppm (m, 20 H). ^{31}P{^{1}H} NMR: 34.4 ppm (s).

(10) Emura, M.; Toyoda, T.; Seido, N.; Noyori, R.; Ikariya, T.; Ohkuma, T. U.S. Patent 5,856,590, Jan 855, 1999, assigned to Takasago Int. Corp.
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(15) Tani, K.; Onouchi, J.-I.; Yamagata, T.; Kataoka, Y. *Chem. Lett.* **1995**, 955−956.
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(17) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917.
(18) Zhang, X. M. *Enantiomer* **1999**, *4*, 541−555.

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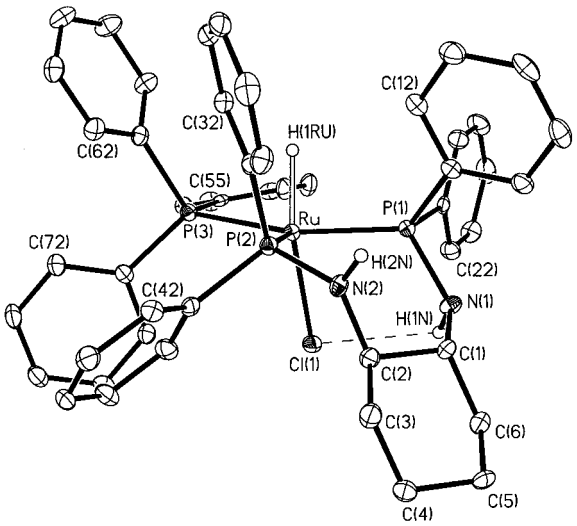


Figure 1. Structure and atomic numbering of **2**.

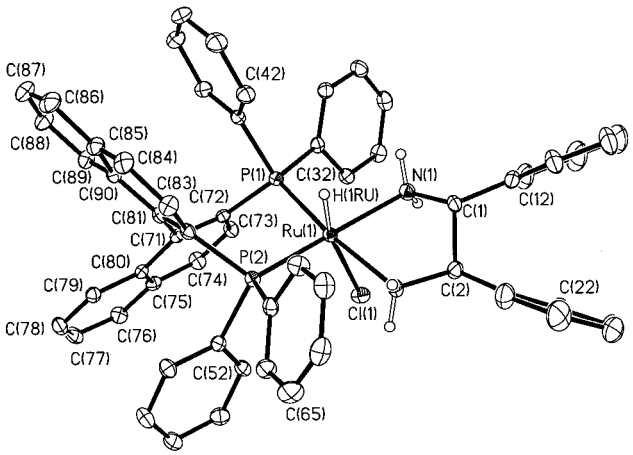


Figure 2. Structure and atomic numbering of **4**.

nitrogen atmosphere, the substituted amino complex RuHCl(diphosphine)(diamine) is formed quantitatively.[20] In addition, RuHCl(R-binap)(cydn) can also be generated by refluxing $RuHCl(PPh_3)_2$(cydn) with 1 equiv of R-binap in toluene under argon. The doublet of triplets and the ABX patterns in the ^1H and $^{31}P\{^1H\}$ NMR spectra, respectively, of RuHCl(R-binap)(PPh_3), **1**, and RuHCl(R,R-dppach)(PPh_3), **2**, are consistent with distorted square pyramidal geometries for these complexes. The X-ray structure of **2** is shown in Figure 1. The phosphine ligands are meridional, with the triphenylphosphine ligand, P(3), being approximately trans to one of the phosphorus atom, P(1), of the dppach ligand, while the other, P(2), occupies the apical position of the square pyramid. The hydride ligand is trans to the chloride (H(1Ru)−Ru−Cl(1) = 158.7(12)°), which in turn is weakly hydrogen bonded (H···Cl = 2.74(3) Å) to hydrogen, H(1N), of the dppach ligand. Various attempts at obtaining X-ray quality crystals of **1** were unsuccessful. However, its structure is expected to be similar to that of **2** on the basis of their similar infrared and ^1H and $^{31}P\{^1H\}$ NMR spectra.

The ^1H, ^{31}P, and $^{31}P\{^1H\}$ spectra of RuHCl(R-binap)(cydn), **3**, RuHCl(R-binap)(dpen), **4**, RuHCl(R,R-dppach)(cydn), **5**, and RuHCl(R,R-dppach)(dpen), **6**, are consistent with an octahedral coordination geometry for these complexes, with the hydride ligand trans to the chloride. This is confirmed by the single-crystal X-ray structure of **4** (Figure 2). The complex crystallizes as RuHCl(R-binap)(dpen)·THF. The Ru−H bond length is 1.55(3) Å. The Ru(1)−N(1) and Ru(1)−N(2) bond lengths are 2.164(2) and 2.198(2) Å, respectively, which are comparable to those previously reported for $RuCl_2$(binap)(dpen).[4]

The solid state infrared spectra of **3**, **4**, **5**, and **6** show ν(RuH) bands at 1968, 1974, 1989, and 1969 cm^{-1}, respectively. There are also ν(NH) bands between 3340 and 3140 cm^{-1}.

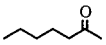
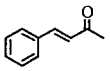
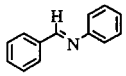
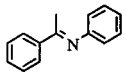
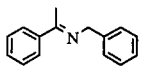
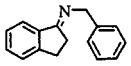
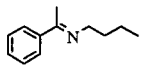
In the presence of catalytic amounts of potassium isopropoxide under H_2 gas (3 atm) at 20 °C, complexes **3** and **4** efficiently catalyze the hydrogenation of various ketones (neat or dissolved in benzene) to the alcohols (Table 1).[21] In the absence of a base, no hydrogenation was observed, indicating that an in-situ-generated species that has lost chloride, possibly a dihydride similar to $RuH_2(PPh_3)_2$(cydn)[7] or a related compound, is likely to be the true catalyst. The high activity of the catalyst generated from **3** is illustrated by the hydrogenation of the various dialkyl ketones listed in Table 1, including deactivated and sterically congested pinacolone (entry 4). The enantiometric excess (ee) for the dialkyl alcohol products range from 40 to 50%. The phenethyl alcohol and 4-phenyl-3-buten-2-ol, derived from acetophenone and benzalacetone (Table 1; entries 5 and 6), were obtained in ee of 88 and 64%, respectively, by use of **3**, numbers similar to those reported by Noyori et al., using the $RuCl_2$(R-binap)(diamine)/KO^{t}Bu system in 2-propanol.[4] The reduction of benzalacetone using **3** and **4**

(19) **1.** Identified in solution by K. S. Macfarlane and B. R. James (personal communication). Yield: 1.48 g, 89%. ^1H NMR: −21.69 ppm (dt, 1H, RuH, $^2J_{HP}$ = 36.1, 22.5 Hz), 6.22−8.38 ppm (m, 47H). $^{31}P(^1H)$: 34.3 ppm (dd, $^2J_{PP}$ = 307, 20.0 Hz), 43.8 ppm (dd, $^2J_{PP}$ = 307, 38.0 Hz), 90.0 ppm (dd, $^2J_{PP}$ = 38.0, 20.0 Hz). IR (Nujol): 2067 cm^{-1} (RuH). **2.** Yield: 1.34 g, 93%. ^1H NMR: −16.40 ppm (dt, 1H, RuH, $^2J_{HP}$ = 34.2, 22.1 Hz), 0.61−4.26 ppm (m, 12H), 6.80−7.92 ppm (m, 35H). $^{31}P(^1H)$: 35.5 ppm (dd, $^2J_{PP}$ = 253, 33.0 Hz), 99.4 ppm (dd, $^2J_{PP}$ = 253, 47.2 Hz), 122.5 ppm (dd, $^2J_{PP}$ = 33.0, 47.2 Hz). IR (Nujol): 2025 cm^{-1} (RuH), 3369 cm^{-1} (NH). Anal. Calcd: C, 65.34; H, 5.48; N, 3.17. Found: C, 65.69; H, 5.71; N, 3.19.

(20) **3.** Yield: 236 mg, 93%. ^1H NMR: −17.1 ppm (vt, 1H, RuH, $^2J_{HP}$ = 25.4 Hz), 0.26−3.85 ppm (m, 14H), 6.29−8.63 ppm (m, 32H). $^{31}P\{^1H\}$: 73.0 ppm (d), 65.1 ppm (d), $^2J_{PP}$ = 45 Hz. IR (Nujol): 1968 cm^{-1} (RuH), 3339, 3276, 3238, 3139 cm^{-1} (NH). **4.** Yield: 261 mg, 92%. ^1H NMR: −16.9 ppm (vt, 1H, RuH, $^2J_{HP}$ = 25.2 Hz), 0.08−4.24 ppm (m, 6H), 6.34−8.72 ppm (m, 42H). $^{31}P\{^1H\}$: 73.0 ppm (d), 65.1 ppm (d), $^2J_{PP}$ = 45 Hz. IR (Nujol): 1974 cm^{-1} (RuH), 3339, 3281, 3239, 3139 cm^{-1} (NH). Anal. Calcd: C, 71.63; H, 5.08; N, 2.88. Found: C, 71.24; H, 5.51; N, 2.73. **5.** Yield: 236 mg, 95%. ^1H NMR: −17.6 ppm (vt, 1H, RuH, $^2J_{HP}$ = 28.8 Hz), 0.11−4.98 ppm (m, 26H), 6.98−8.09 ppm (m, 20H). $^{31}P\{^1H\}$: 104.3 ppm (d), 106.0 ppm (d), $^2J_{PP}$ = 59.4 Hz. IR (Nujol): 1989 cm^{-1} (RuH), 3381, 3362, 3348, 3341, 3330, 3282, 3251, 3215, and 3137 cm^{-1} (NH). Anal. Calcd: C, 58.89; H, 6.45; N, 7.63. Found: C, 59.03; H, 6.53; N, 7.35. **6.** Yield: 274 mg, 97%. ^1H NMR: −17.4 ppm (vt, 1H, RuH, $^2J_{HP}$ = 28.9 Hz), 0.81−4.98 ppm (m, 20H), 6.30−8.18 ppm (m, 30H). $^{31}P\{^1H\}$: 102.3 ppm (d), 106.1 ppm (d), $^2J_{PP}$ = 59.5 Hz. IR (Nujol): 1969 cm^{-1} (RuH), 3339, 3281, and 3243 cm^{-1} (NH).

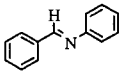
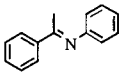
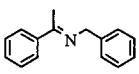
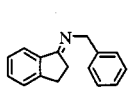
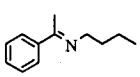
(21) **Catalysis Procedure.** A typical catalytic run using **5** for the hydrogenation of phenyl(1-phenylethylidene)amine is described here. Phenyl(1-phenyl-ethylidene)amine (2.0 g) was added under a flow of hydrogen gas to a Schlenk flask containing **5** (5 mg) and KO^{i}Pr (5 mg) in benzene (1.0 mL). The flask was cooled to liquid nitrogen temperature, filled with H_2 gas, closed, and allowed to gradually warm to room temperature. The mixture was vigorously stirred for 24 h. A ^1H NMR spectrum of the reaction mixture indicated complete conversion of the imine to the amine. Hexanes (10 mL) were added to the mixture, which was then eluted (hexanes) through a short column (10 cm) of silica gel in order to remove the spent catalyst and KO^{i}Pr. Evaporation of the hexanes under reduced pressure resulted in pure phenyl(1-phenyl-ethyl)amine. Yield: 1.98 g, 98%.

Table 1. Catalytic Hydrogenation of Neat Ketones and Imines Using 3/KO^{i}Pr and 4/KO^{i}Pr and H_2 Gas (3 atm), 20 °C (solid substrates were dissolved in benzene)[a]

Substrate	Complex	S:C ratio	% Conversion	Time (hr)	e.e.(%)
	3	4000	100	<12	40
	3	5000	100	<12	52
	3	3600	100	<12	46
	3	5000	87	48	50
	3, 4	5000	100	<12	88, 73
	3, 4	5000	100	<12	64, 60
	3, 4	500	100	<4	...
	3, 4	500	100, 90	36, 72	71, 70
	3, 4	500	100	36, 24	60, 50
	3, 4	500	100	24	nd
	3, 4	500	12, 17	60	60

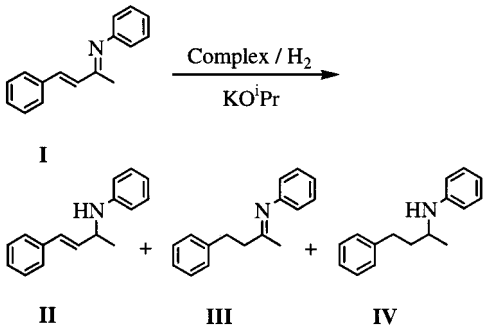
[a] nd = not determined; S:C = substrate to catalyst.

Table 2. Catalytic Hydrogenation of Neat Imines Using 5/KO^{i}Pr and 6/KO^{i}Pr and H_2 Gas (3 atm), 20 °C (solid substrates were dissolved in benzene)

Substrate	Complex	S:C ratio	% Conversion	Time (hr)
	5, 6	3000	100	<4
	5, 6	3000	100	<24
	5, 6	2500	100	30, 24
	5, 6	3000	100	<24
	5, 6	1500	91, 60	60

in the presence of potassium isopropoxide under hydrogen results in 100 and 96% of the allyl alcohol, respectively, which is also consistent with the reported C=O versus C=C bond selectivities using the Noyori system.[3] This hydrogenation process is also very effective for various activated acyclic imines (neat or in benzene), producing the amines in fairly good yields and moderate ee (Table 1). The high activity and turnovers using these comparatively mild conditions (20 °C and 3 atm H_2 gas) for imine hydrogenation are unprecedented. The hydrogenation of the imines using the dppach complexes **5** and **6** (Table 2) was even more facile than for the binap analogues. A comparison of the results in Tables 1 and 2 indicates that the turnover rate increases by almost an order of magnitude for the phosphinamino complexes, relative to the binap analogues. An ee of 92% was obtained for *N*-butyl-1-phenylethylamine that was produced from the hydrogenation of neat *N*-(1-phenylethylidene)butylamine using complex **5** and KO^{i}Pr under hydrogen (Table 2, entry 5). Current research toward the optimization of this process is underway, since this is a simple procedure for the facile production of chiral secondary amines.

Scheme 2



Initial experiments indicate that the dppach complex **6** appears to be more selective for the hydrogenation of the C=N over the C=C bond of the α,β-unsaturated imine **I** (Scheme 2) compared to the binap analogue **4**.

Thus, the hydrogenation of **I** using **4**/KO^{i}Pr (S:C = 500:1) resulted in 20% of both the allyl (**II**) and saturated (**IV**) amines and 60% of **III** after 24 h at 20 °C, with no further change in the composition of the mixture after 48 h. On the other hand, hydrogenation of **I** using **6**/KO^{i}Pr under similar conditions resulted in only the allyl (48%) and saturated (52%) amines after 2 h. Thus, our on-going work to optimize this process could lead to a simple and mild procedure for the production of valuable chiral allylamines.

The coordinated diamine ligands are necessary for complexes **3**−**6** to function as hydrogenation catalysts in the presence of KO^{i}Pr. For example, with a S:C ratio of 2000:1, only 5% conversion of neat acetophenone was obtained after 24 h using **1**/KO^{i}Pr (20 °C and 3 atm H_2). Complexes **1** and **2** were totally ineffective for the hydrogenation of ketimines under similar conditions.

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Supporting Information Available: Text giving synthetic methods and complete X-ray crystallographic tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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