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trans-RuH(η^1-BH_4)(binap)(1,2-diamine): A Catalyst for Asymmetric Hydrogenation of Simple Ketones under Base-Free Conditions

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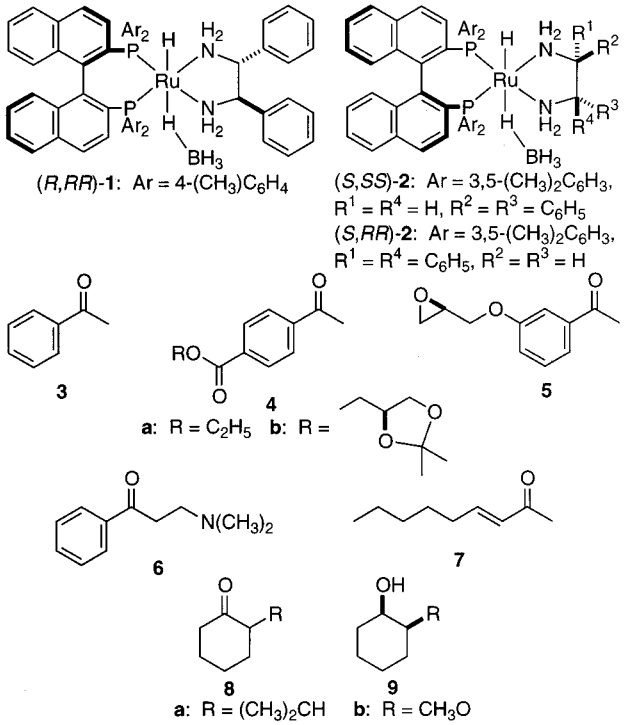
Chiral $RuCl_2$(diphosphine)(1,2-diamine) complexes[1] catalyze rapid, highly productive asymmetric hydrogenation of simple ketones in 2-propanol containing an alkaline base such as KOH, KO-*i*-C_3H_7, or KO-*t*-C_4H_9.[2] A range of chiral alcohols is accessible in high enantiomeric purity from aromatic, heteroaromatic, and olefinic ketones by this method. Since the discovery of this procedure in 1995,[3] and more recently, as its high practicality became recognized,[2] we have been encouraged to develop a robust (pre)catalyst that promotes the enantioselective reaction under base-free conditions.[4] Here we disclose useful chiral Ru complexes that meet this demand. The asymmetric hydrogenation using a newly devised RuH(η^1-BH_4)(binap)(1,2-diamine) complex proceeds without any base, with a high substrate/catalyst molar ratio (S/C), up to 100 000, and with a 3−4 M substrate concentration in 2-propanol.



The requisite chiral catalyst can be synthesized in a straightforward fashion. $RuCl_2$[(*R*)-tolbinap][(*R*,*R*)-dpen][1,5] and 25 mol equiv of $NaBH_4$ were dissolved in a 1:1 benzene−ethanol mixture, and the solution was stirred at 65 °C for 5 min and at 25 °C for 30 min and then evaporated. Extraction of the residue with benzene followed by concentration gave RuH(η^1-BH_4)[(*R*)-tolbinap][(*R*,*R*)-dpen] [(*R*,*RR*)-**1**] as a yellow solid in a quantitative yield, dec 164 °C. Recrystallization from a THF−hexane mixture gave (*R*,*RR*)-**1**·THF·*n*-C_6H_{14}. Single-crystal X-ray analysis (Figure 1) revealed that the BH_4 anion is bound to the Ru center in an η^1 fashion[6] and is located trans to the hydride. The (*R*)-TolBINAP and (*R*,*R*)-DPEN ligands are accommodated in the same Ru plane and have a λ conformation. The Ru−H bond length, 1.52(5) Å, is very short,[7] whereas the Ru−HBH_3 length, 1.74(7) Å, is rather long. The BH_4 ligand is further supported in the complex through BH···HN hydrogen bonds (1.8 and 2.0 Å). A benzene-d_6 solution of (*R*,*RR*)-**1** gave $^{31}P\{^1H\}$ NMR signals at 71.2 and 75.2 ppm (AB quartet, J_{P-P} = 41.4 Hz), and an ^1H signal for Ru−H at δ −13.60 (triplet, J_{H-P} = 22.4 Hz). The BH_4 moiety gave a broad signal at δ −0.79 in toluene-d_8 at room temperature, suggesting its fluxional behavior. Its IR spectrum in toluene showed a characteristic Ru−H stretching band[6b] at 1862 (s) cm^{-1} and B−H stretching bands at 2317 (s) cm^{-1} as well as BH_3 deformation frequencies at 1092 (s) and 1080 (s) cm^{-1}. In the same manner, various RuH(η^1-BH_4) complexes including (*S*,*SS*)-**2** and (*S*,*RR*)-**2** were synthesized from the corresponding $RuCl_2$ precursors. The new Ru−hydride complexes are relatively stable. They can be quickly weighed in open air and stored for a long time in an argon-sealed bottle below −30 °C, although preparation directly prior to use is preferable.

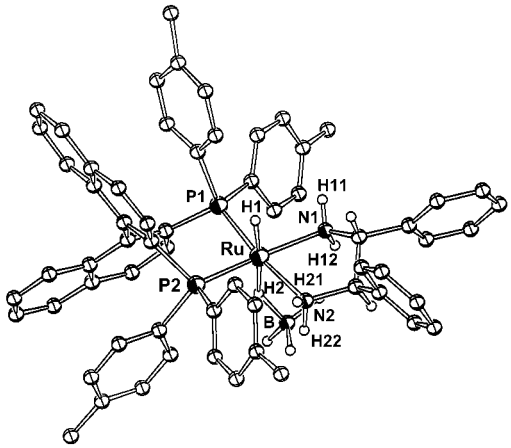


Figure 1. ORTEP drawing of (*R*,*RR*)-**1**. Selected distances (Å) and bond angles (deg): Ru−H1 1.52(5), Ru−H2 1.74(7), Ru−P1 2.219(3), Ru−P2 2.233(3), Ru−N1 2.140(8), Ru−N2 2.163(8), B−H2 1.32(7); H1−Ru−H2 172(3), P1−Ru−P2 91.9(1), N1−Ru−N2 76.9(3). Only the ruthenium- and borohydrides, and amino and methine protons of DPEN are shown.

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Table 1. Asymmetric Hydrogenation of Ketones Catalyzed by *trans*-RuH(η^1-BH_4)(binap)(dpen)[a]

				alcohol		
ketone	Ru cat	S/C[b]	time, h	% yield[c]	% ee[d]	config[e]
3[f]	(*R*,*RR*)-**1**	100000	6[g]	99.9	82	*S*
3[f]	(*S*,*SS*)-**2**	100000	7[h]	100	99	*R*
3	(*S*,*SS*)-**2**	2000	12[i]	99.9	97	*R*
3	(*S*,*SS*)-**2**	4000	12	99.9	99	*R*
4a	(*S*,*SS*)-**2**	4000	15	100	99	*R*
4b	(*S*,*SS*)-**2**	2000	16	100	97[j]	*R*[k]
5	(*S*,*SS*)-**2**	2000	14	99	99[j]	*R*[k]
6	(*S*,*SS*)-**2**	4000	12	100	97	*R*
7	(*S*,*SS*)-**2**	4000	16	95	99	*R*

[a] Unless otherwise stated, reactions were conducted at 8 atm of H_2 at 23−25 °C using a 1.0−2.0 M ketone solution in 2-propanol containing a Ru catalyst. [b] Substrate/catalyst molar ratio. [c] GC or ^{1}H NMR analysis.[d] Chiral GC or HPLC analysis. [e] Determined by the sign of rotation. [f] Reaction using 102 g of **3** in 100 mL of 2-propanol (3.4 M). [g] Reaction temperature was increased to 38 °C by the heat of reaction. [h] At 45 °C.[i] At 1 atm of H_2. [j] Diastereomeric excess. [k] See Supporting Information.

These complexes showed an excellent catalytic efficiency without addition of any base. When a 3.4 M solution of acetophenone (**3**) (102 g) in 2-propanol (106 mL) containing (*S*,*SS*)-**2** (9.0 mg, S/C = 100 000) was stirred under 8 atm of H_2 at 45 °C for 7 h in a 1-L stainless steel autoclave, (*R*)-1-phenylethanol was obtained quantitatively in 99% ee.[8] Addition of 0.014 M KO-*t*-C_4H_9 increased the catalytic activity by an order of magnitude, completing the hydrogenation of **3** in 45 min under otherwise identical conditions (*R* in 99% ee). The standard $RuCl_2$/0.014 M KO-*t*-C_4H_9-combined system[2] required 2.5 h for the completion.

As shown in Table 1, this method also demonstrated excellent performance in hydrogenation of some base-sensitive ketones. The keto benzoate **4a** and its hydrogenation product undergo ready transesterification under our earlier conditions using KO-*t*-C_4H_9 in 2-propanol. The new base-free procedure effected hydrogenation of 2.0 M **4a** in 2-propanol containing (*S*,*SS*)-**2** (S/C = 4000) to give only the ethyl (*R*)-4-(1-hydroxyethyl)benzoate in 99% ee in 100% yield, and without contamination of the isopropyl ester.[9] This feature is most beneficial in the reaction of some precious keto esters. In the presence of (*S*,*SS*)-**2**, the *R* keto ester **4b** was hydrogenated in 2-propanol to the (*R*,*R*)-hydroxy ester with 97% de quantitatively, and without transesterification.

Hydrogenation of the keto (*R*)-glycidyl ether **5** with (*S*,*SS*)-**2** gave the *R*,*R* alcohol with 99% de in 99% yield, leaving the base-labile epoxy ring.[10] Highly base-sensitive β-amino ketone **6** can be hydrogenated without any special precautions. Thus, the reaction using a 1.0 M 2-propanol solution of **6** and (*S*,*SS*)-**2** gave the *R* amino alcohol in 97% ee in 100% yield, which is convertible to the antidepressant (*R*)-fluoxetine.[11] No trace of 1-phenyl-1-propanol was detected.[12] 3-Nonen-2-one (**7**) is a highly base-sensitive acyclic ketone, prone to polymerize in the presence of an alkaline base.[4] However, hydrogenation of **7** using (*S*,*SS*)-**2** as catalyst occurred easily, resulting in the *R* allylic alcohol in 99% ee and in 95% yield. The substrate concentration, 2.0 M in 2-propanol, is much higher than the 0.1 M used in the earlier method.[4]

The original procedure is useful for stereoselective hydrogenation of α-substituted ketones[12−14] via dynamic kinetic resolution.[15] However, because of the basic conditions, it is unsuitable for access to the configurationally labile ketones. Now the kinetic resolution of such ketones is possible due to a very small degree of racemization, if any. When racemic 2-isopropylcyclohexanone [(±)-**8a**] was hydrogenated with (*S*,*RR*)-**2** (S/C = 2000), the *R* enantiomer was consumed 28 times faster than was the *S* isomer. Thus, after 53% conversion, unreacted (*S*)-**8a** in 91% ee was recovered, together with (1*R*,2*R*)-**9a**, in 85% ee. More importantly, enantiomers of 2-methoxycyclohexanone (**8b**) can be discriminated by a factor of 38. Thus, hydrogenation of the racemate with (*S*,*SS*)-**2** afforded, at 53% conversion, (*R*)-**8b** (94% ee, 42% isolated yield), and (1*R*,2*S*)-**9b** (91% ee, 50% isolated yield). No trans alcohol was detected. The chiral α-alkoxy ketone (*S*)-**8b** is a key intermediate for the synthesis of the potent antibacterial sanfetrinem.[14,16]

This alkaline base-free procedure using the new chiral Ru complexes substantially expands the scope of asymmetric hydrogenation of ketones. In the presence of an alkaline base, these complexes are more reactive than the standard $RuCl_2$ complexes.[2,17]

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Supporting Information Available: Preparative methods and properties of **1** and **2**, procedure for asymmetric hydrogenation of ketones (PDF) and an X-ray crystallographic file (CIF) of complex **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Although this problem was partly solved by utilizing K_2CO_3, the reaction became much slower than that with the strong base.[2]
(5) TolBINAP = 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl. XylBINAP = 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl. DPEN = 1,2-diphenylethylenediamine.
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(7) Survey of more than 20 crystal structures of RuH(phosphine) complexes recorded in the Cambridge Crystallographic Data Base indicates that the Ru−H bond length is normally about 1.6 Å, with some exceptions.
(8) Use of a *glass* reaction vessel should be avoided to obtain a high catalytic activity in hydrogenation with an S/C >5000. Reaction temperature of 45 °C was necessary to achieve a turnover number as high as 100 000 in hydrogenation of **3** catalyzed by **2**. **1** is more reactive, achieving a high catalytic activity without heating.
(9) Hydrogenation of **4a** with *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen] and KO-*t*-C_4H_9 in 2-propanol ([**4a**] = 2.0 M, **4a**:Ru:base = 2000:1:8, 8 atm, 25 °C, 12 h) gave a 36:64 mixture of the hydroxy ethyl ester and the isopropyl ester (both *R* in 99% ee, 100% yield). DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine.
(10) Hydrogenation of **5** with a $RuCl_2$/KO-*t*-C_4H_9 catalyst gave the desired alcohol in only 59% yield accompanied by various byproducts.
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(17) RuHCl(binap)(dpen) acts as an excellent catalyst in the presence of a strong base. See: Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2001**, *20*, 1047−1049.

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