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Chiral Ruthenabicyclic Complexes: Precatalysts for Rapid, Enantioselective, and Wide-Scope Hydrogenation of Ketones

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Supporting Information

ABSTRACT: A novel ruthenabicyclic complex with base shows excellent catalytic activity in the asymmetric hydrogenation of ketones. The turnover frequency of the hydrogenation of acetophenone reaches about 35 000 min^{-1} in the best case, affording 1-phenylethanol in >99% ee. Several aliphatic and base-labile ketones are smoothly converted to the corresponding alcohols in high enantioselectivity. The catalytic cycle for this hydrogenation, in which the ruthenabicyclic structure of the catalyst is maintained, is proposed on the basis of the deuteration experiment and spectroscopic analysis data.

Asymmetric hydrogenation of ketones is a key technology for small- to industrial-scale production of optically active compounds, including medicines, agrochemicals, and perfumes.[1] Development of new efficient catalysts for this reaction is a challenging subject from both a scientific and practical viewpoint. Since 1995 we have reported enantioselective hydrogenation of ketones catalyzed by Ru complexes bearing chiral diphosphine and diamine ligands.[1,2] A series of alkyl aryl ketones, heteroaromatic ketones, unsymmetrical benzophenones, and α,β-unsaturated ketones is converted to the chiral alcohols with an excellent enantiomeric excess (ee) of >99% in the best cases, when the catalyst precursors RuXY(xylbinap)(daipen) (X, Y = Cl, Cl or H, η^1-BH_4)[3] with or without an alkaline base are employed for this reaction.[4] We herein report asymmetric hydrogenation of ketones by using novel ruthenabicyclic complexes as precatalysts. The catalyst efficiency, enantioselectivity, and scope of substrates are all superior to those of our previous systems.

The novel ruthenabicyclic complex RuCl[(*S*)-daipena][(*S*)-xylbinap] [(S_N,S_P)-**1a**] (DAIPENA = anion of DAIPEN at the 2-position of an anisyl group) was readily prepared from the cationic complex [RuCl(*p*-cymene){(*S*)-xylbinap}]Cl[5] and (*S*)-DAIPEN (1.1 equiv) with $(C_2H_5)_2NH$ (1.0 equiv) in refluxed methanol (98% isolated yield; see Figure 1, conditions (a)).[6−8] Interestingly, the known $RuCl_2$[(*S*)-xylbinap][(*S*)-daipen] [(S_P, S_N)-**2a**][4a] was exclusively obtained under the same reaction conditions (a) or the aprotic conditions (b), when the neutral complex $RuCl_2$[(*S*)-xylbinap](dmf)$_n$[9] or the dinuclear complex $[(CH_3)_2NH_2][\{RuCl[(S)\text{-xylbinap}]\}_2(\mu\text{-}Cl)_3]$[10] was used instead of [RuCl(*p*-cymene){(*S*)-xylbinap}]Cl. The $RuCl_2$ complex **2a** is not an actual intermediate to **1a**, so that only a trace amount of **1a** was formed from **2a** under the reaction conditions (a). Treatment of **1a** with NaOTf in toluene [conditions (c)] quantitatively gave the triflate complex **1b**, leaving the ruthenabicyclic structure intact. RuCl(daipena)(dm-segphos) (**1c**)[11] was prepared by the same procedure from the corresponding cationic complex.[8] When DPEN was used instead of DAIPEN, the corresponding $RuCl_2$ complex was obtained exclusively.[3]

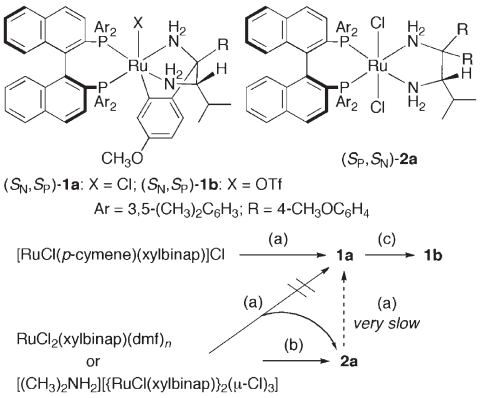


Figure 1. Structures and preparation of chiral Ru(II) complexes. Conditions: (a) DAIPEN (1.1 equiv), $(C_2H_5)_2NH$ (1.0 equiv), CH_3OH, reflux, 3 h; (b) DAIPEN (1.0 equiv), DMF (rt., 6 h) or toluene (80 °C, 2 h); (c) NaOTf (1.1 equiv), toluene, rt, 3 h.

Figure 2 shows an ORTEP diagram of the single-crystal X-ray analysis of (S_N,S_P)-**1c**.[8] The unique ruthenabicyclo[2.2.1] skeleton causes the significantly distorted octahedral structure (C(1)−Ru−Cl(1) angle: 153°). The Cl(1)−Ru bond length of 2.64 Å is longer than that of the related *trans*-$RuCl_2$(diphosphine)(diamine) complexes.[12] The very small Cl(1)−Ru−N(1)−H(1) torsion angle of about 1.5° means the Cl(1)−Ru and N(1)−H(1) bonds are arranged almost in parallel.[12] The Cl(1)−H(1) distance of 2.65 Å is much shorter than the expected van der Waals separation length of 3.0 Å.

The ruthenabicyclic complex (S_N,S_P)-**1a** exhibited excellent catalytic activity and enantioselectivity in the hydrogenation of acetophenone (**3a**) in a *t*-C_4H_9OK containing alcoholic solvent (Scheme 1 and Table 1). The order of solvents in the reaction rate was ethanol ≥ 2-propanol ≫ methanol (entries 1−3). Interestingly, a 1:1 ethanol/2-propanol mixed solvent gave the highest reactivity. Thus, the hydrogenation with a substrate-to-catalyst molar ratio (S/C) of 10 000 under 50 atm of H_2 at

Received: March 14, 2011
Published: June 16, 2011

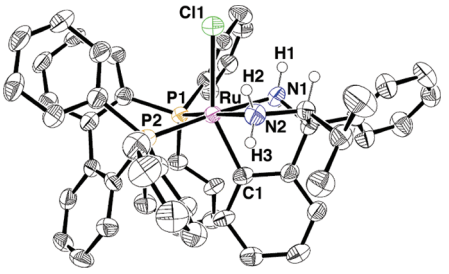
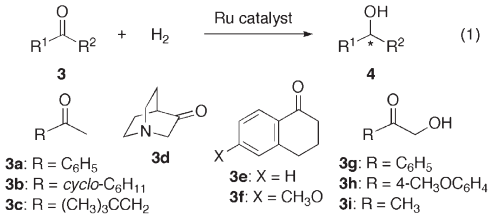


Figure 2. ORTEP drawing of (S_N,S_P)-**1c**. All protons except those on the diamine ring and some substitutents are omitted for clarity.[8]

Scheme 1. Asymmetric Hydrogenation of Ketones



11−35 °C was completed in 1 min to afford (*R*)-1-phenylethanol [(*R*)-**4a**] in >99% ee (entry 4).[13] The time−conversion relationship of this reaction with an S/C of 100 000 was measured as 2 min, 39.7%; 3 min, 74.3%; and 6 min, 100% (entry 5). No distinct incubation period like that seen in the reaction with the **2a**/*t*-C_4H_9OK catalyst system was observed. The turnover frequency (TOF) between 2−3 min reached about 35 000 min^{-1}. Complete conversion of the hydrogenation under lower pressure of H_2 was achieved without loss of enantioselectivity (entries 6 and 7). Aprotic toluene and CH_2Cl_2 were also usable solvents, although the reactivity was lower than that in the alcoholic solvents (entries 8 and 9). Addition of a base for activation of the precatalyst **1a** was required in this reaction system. DBU, an organic base, was useful for the hydrogenation in the ethanol/2-propanol mixture instead of *t*-C_4H_9OK (entry 10), but it was not sufficiently basic for the reaction in the aprotic solvents (entries 11 and 12). It was noteworthy that the corresponding triflate complex **1b** showed high reactivity in toluene and CH_2Cl_2 as well as in the alcoholic solvent by using DBU as a base (entries 13−15). The **1c**/*t*-C_4H_9OK system also achieved a high level of reactivity and enantioselectivity, although these were slightly lower than those of the **1a**/*t*-C_4H_9OK catalyst (entry 16 vs 7). In contrast to the ruthenabicyclic precatalysts **1**, the ordinary $RuCl_2$ complex **2a** showed relatively low activity and enantioselectivity in methanol (entry 17 vs 1). The most appropriate solvent was 2-propanol, but the reaction rate (TOF = 950 min^{-1}; entry 18) was slower than that using **1a** (TOF = 6000 min^{-1}; entry 3). DBU was useless even in the alcoholic solvent (entry 19 vs 10).

The ruthenabicycle-catalyst system was applied to the asymmetric hydrogenation of ketones, which are difficult substrates to reduce with high reactivity and enantioselectivity by using the precatalysts **2** (Scheme 1, Table 2). Hydrogenation of aliphatic ketones **3b** and **3c** with **1a** gave the chiral alcohols in 90% ee and 77% ee, respectively (entries 1 and 2).[14] The enantioselectivity of 85% in the reaction of **3b** with **2a** was reported.[2] A rigid bicyclic ketone 3-quinuclidinone (**3d**) was hydrogenated by using **1a** with an S/C of 50 000−100 000 under 30 atm of H_2 affording 3-quinuclidinol (**4d**)

Table 1. Hydrogenation of 3a catalyzed by Ru complexes[a]

entry	Ru[b]	S/C[c]	base	solvent	H_2, atm	time, h	% yield[d]	% ee[d]
1	**1a**	10000	*t*BuOK	MeOH	50	0.75	>99	99
2	**1a**	100000	*t*BuOK	EtOH	50	0.22	>99	>99
3	**1a**	100000	*t*BuOK	*i*PrOH	50	0.42	>99	>99
4	**1a**	10000	*t*BuOK	**A**[e]	50	0.017	>99	>99
5	**1a**	100000	*t*BuOK	**A**[e]	50	0.10	>99	>99
6	**1a**	100000	*t*BuOK	**A**[e]	7	0.25	>99	>99
7	**1a**	10000	*t*BuOK	**A**[e]	1	24	>99	>99
8	**1a**	2000	*t*BuOK	toluene	10	2.5	>99	>99
9	**1a**	2000	*t*BuOK	CH_2Cl_2	10	2.5	>99	>99
10	**1a**	10000	DBU	**A**[e]	10	0.13	>99	>99
11	**1a**	1000	DBU	toluene	10	5	1.2	nd[f]
12	**1a**	1000	DBU	CH_2Cl_2	10	5	8	96
13	**1b**	10000	DBU	**A**[e]	10	0.083	>99	>99
14	**1b**	4000	DBU	toluene	10	2	>99	>99
15	**1b**	4000	DBU	CH_2Cl_2	10	3	>99	>99
16	**1c**	10000	*t*BuOK	**A**[e]	1	24	98	98
17	**2a**	10000	*t*BuOK	MeOH	50	9	89	94
18	**2a**	100000	*t*BuOK	*i*PrOH	50	4	>99	98
19	**2a**	1000	DBU	*i*PrOH	10	5	9	98

[a] Unless otherwise stated, reactions were conducted at 11−35 °C using a 1.0−3.3 M solution of **3a** containing (S_N,S_P)-**1** or (S_P,S_N)-**2a**, and a base (1.7−33 mM). [b] Ru complexes. [c] Substrate-to-catalyst molar ratio. [d] Determined by chiral GC analysis. (*R*)-**4a** was obtained. [e] A = EtOH/*i*PrOH (1:1). [f] Not determined.

in high yield and 95% ee (entries 3 and 4).[15] The reaction with **2a** resulted in a much less satisfactory result (entry 5). For hydrogenation of 1-tetralone (**3e**),[16] a cyclic aromatic ketone, RuCl[(*S*)-daipena]-[(*R*)-dm-segphos] [(S_N,R_P)-**1c**] with *t*-C_4H_9OK acted as an excellent catalyst (entry 6). The corresponding $RuCl_2$[(*R*)-dm-segphos][(*S*)-daipen] [(R_P,S_N)-**2b**] gave only medium yield with lower stereoselectivity (entry 7). 6-Methoxy-1-tetralone (**3f**) was quantitatively converted to **4f** in 98% ee by using (S_N,R_P)-**1c** (entry 8).[16] Hydrogenation of 2-hydroxyacetophenone (**3g**) and the 4′-methoxy ketone **3h** was catalyzed by the (S_N,S_P)-**1a**/DBU system to give (*S*)-**4g** and **4h** in high ees (entries 9 and 10).[17] The reaction of **3g** with the **2a**/*t*-C_4H_9OK system gave only trace amounts of **4g** with many unidentified compounds due to the significant instability of **3g** to base. Acetol (**3i**), an aliphatic hydroxy ketone, was reduced with (S_N,S_P)-**1a** to afford (*R*)-**4i** in 95% ee (entry 11). The finding that the enantiomeric sense was opposite that of the reaction of **3g** with the same catalyst suggests that the priority order of groups in the enantioface-recognition is C_6H_5 > CH_2OH > CH_3.

ESI mass-spectroscopic (MS) analysis of (S_N,S_P)-**1a** in CH_2Cl_2 and methanol showed prominent signals centered at *m*/*z* 1184.4 ($[M]^+$) and 1149 ($[M - Cl]^+$), respectively. The $^{31}P\{^1H\}$ NMR spectrum in benzene-d_6 and methanol-d_4/CD_2Cl_2 (2:1) showed AB quartet signals at δ 53.3, 61.1 (J_{P-P} = 38.2 Hz) and δ 19.7, 36.7 (J_{P-P} = 32.9 Hz), respectively. The $[M - Cl]^+$ signals remained pronounced in the MS analysis of a reaction mixture of hydrogenation of **3a** in methanol. The ^1H NMR measurement of **1a** in the methanol-d_4/CD_2Cl_2 mixture under 1 atm of H_2 at −50 °C showed a broad signal at δ −0.35, which suggested the formation of the Ru(η^2-H_2) species.[18]

The $^{31}P\{^1H\}$ NMR signals of (S_N,S_P)-**1a** in benzene-d_6 (δ 53.3 and 61.1) were converted to the peaks at δ 55.9 and 59.9

Table 2. Hydrogenation of Ketones 3 Catalyzed by Ru Complexes[a]

entry	3	Ru[b]	S/C[c]	base	solvent[d]	time, h	% yield[e]	% ee[f]
1	**b**	(S_N,S_P)-**1a**	4000	*t*BuOK	P	5	96	90 (*R*)
2	**c**	(S_N,S_P)-**1a**	10000	*t*BuOK	P	5	>99	77 (*R*)
3[g]	**d**	(S_N,S_P)-**1a**	50000	*t*BuOK	P	6	>99	95 (*S*)
4[g]	**d**	(S_N,S_P)-**1a**	100000	*t*BuOK	P	6	92	95 (*S*)
5[g]	**d**	(S_P,S_N)-**2a**	20000	*t*BuOK	P	6	50	86 (*S*)
6	**e**	(S_N,R_P)-**1c**	2000	*t*BuOK	A	14	>99	97 (*S*)
7	**e**	(R_P,S_N)-**2b**	1000	*t*BuOK	P	15	42	90 (*S*)
8	**f**	(S_N,R_P)-**1c**	1000	*t*BuOK	A	21	>99	98 (*S*)
9	**g**	(S_N,S_P)-**1a**	2000	DBU	M	5	>99	95 (*S*)
10	**h**	(S_N,S_P)-**1a**	2000	DBU	E	5	>99	97 (*S*)
11[h]	**i**	(S_N,S_P)-**1a**	1500	DBU	M	5	95	95 (*R*)

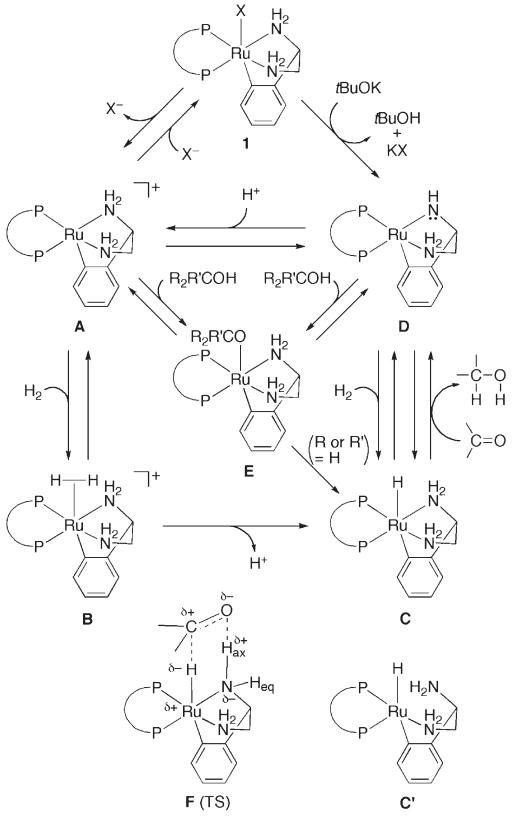
[a] Unless otherwise stated, reactions were conducted under 10 atm of H_2 at 5−30 °C using **3** (0.5−2.0 M) in solvent containing a Ru complex and a base (5−100 mM). [b] Ru complexes. [c] Substrate-to-catalyst molar ratio. [d] A = EtOH/*i*PrOH (1:1). E = ethanol. M = methanol. P = 2-propanol. [e] Determined by GC or HPLC analysis. [f] Determined by chiral GC or HPLC analysis.[8] Absolute configurations of **4** are indicated in the parentheses. [g] Under 30 atm of H_2. [h] Under 15 atm of H_2.

when 2 equiv of *t*-C_4H_9OK were added. The observed ^1H NMR signals of the *t*-C_4H_9O moiety (δ 1.24) and presence of the four amino-protons suggested formation of the RuO-*t*-C_4H_9 complex.[8] This complex was reacted with methanol (6 equiv) to afford the $RuOCH_3$ complex, which showed the NMR signal of the CH_3O moiety (δ 3.16).[8] This signal was broadened with the addition of a large excess amount of methanol. The MS analysis of this mixture revealed formation of the Ru cationic species (m/z 1149). When the RuO-*t*-C_4H_9 complex was mixed with H_2 (1 atm) or **4a** (3 equiv), two RuH species showing hydride peaks at δ −6.50 and −13. 55 were afforded.[8] The latter species did not show signals of the coordinated benzylic amino protons. This mixture acted as the catalyst for hydrogenation of **3a** to give (*R*)-**4a** in >99% ee under the regular conditions. The NMR peaks at δ −6.50 disappeared by the addition of **3a**, but the other peaks at δ −13.55 remained.

Treatment of the RuO-*t*-C_4H_9 complex with 2-propanol-d_8 afforded the two kinds of RuD species and the RuO-*i*-C_3D_7 complex, in which the most reactive one benzylic amino proton was deuterated in >95%. Three other amino protons were deuterated in <50%. No ortho aryl deuterium incorporation was detected in the recovered **1a** after deuteration (10 atm) of acetone in methanol quenched with HCl (methanol solution), suggesting the Ru−aryl bond of **1a** was maintained through the reaction.[8]

Scheme 2 illustrates a plausible mechanism for the hydrogenation of ketones with ruthenabicyclic complexes **1** based on the spectroscopic analysis. The X^- (X = Cl or OTf) readily liberates from **1** to give the cationic species **A** in an alcoholic medium. Hydrogen reversibly interacts with **A** to form the molecular hydrogen species **B**. The base (*t*-C_4H_9OK or DBU)-induced heterolysis of hydrogen forms the active RuH complex **C**, which is the rate-determining step. The monoamino RuH complex **C**′, which shows feeble activity, is formed as a minor compound. The ketonic substrate is smoothly reduced by **C** to form an alcoholic product and the amide−Ru complex **D**. The complex **D** is in rapid equilibrium with **A** and the alkoxide complexes **E**. In the presence of excess amounts of the polar

Scheme 2. Proposed Catalytic Cycle for Asymmetric Hydrogenation of Ketones Catalyzed by the Chiral Ruthenabicyclic Complexes[a]



[a] X = Cl or OTf. R = alkyl, aryl, H. R′ = CH_3, H. P—P = XylBINAP. NH_2—NH_2 = DAIPENA.

alcohol, **A** is the most preferable species. The amide complex **D** reacts with hydrogen (partly with a primary or secondary alcohol) to furnish the RuH species **C**.

When the hydrogenation is carried out in a less polar aprotic solvent, such as toluene and CH_2Cl_2, **1a** (X = Cl) does not ionize and requires strong base *t*-C_4H_9OK to remove Cl^- in the manner of Dcb, providing the amide complex **D** (see Table 1, entries 8, 9, 11, and 12). Hydrogen reacts with **D** to give **C** and less reactive **C**′, and then **C** reduces ketone to return to **D**. **1b** (X = OTf) reversibly loses $^-$OTf to form **A** under the aprotic conditions and transforms to the amide complex **D** through **B** and **C**. DBU is sufficiently basic for this process (see Table 1, entries 14 and 15). Then **D** returns to **C** by reaction with hydrogen in the aprotic media. The alcoholic products formed in this reaction may promote the same pathway that occurs in the alcohol.

The benzylic amino axial-proton (H_{ax}) of the RuH complex **C** is the most reactive among the four amino protons, because the H−Ru−N−H_{ax} torsion angle is expected to be the smallest based on the structure of **1c** (Figure 2).[2,18] The ketonic substrate is reduced by **C** through the six-membered pericyclic transition state (TS) **F** (metal−ligand cooperative TS), in which the $H^{\delta-}$−$Ru^{\delta+}$−$N^{\delta-}$−$H_{ax}{}^{\delta+}$ quadrupole of the catalyst fits with the $C^{\delta+}$=$O^{\delta-}$ dipole of the substrate.[2,12] The key issue is that **C** has a ruthenabicyclic structure, in contrast to the previous $RuCl_2$-(diphosphine)(1,2-diamine)/*t*-C_4H_9OK catalyst systems in which the corresponding *trans*-RuH_2 complexes are the expected active species.[18,19] The difference of the *trans* influence between

arene-carbon and H to the Ru−H could be a primary reason for the marked difference in reactivity between the two catalyst systems.

In conclusion, the newly devised ruthenabicyclic complexes RuX(daipena)(xylbinap) (X = Cl, OTf) with base (t-C_4H_9OK, DBU) exhibit remarkably high catalytic activity in the hydrogenation of ketones. A turnover frequency of about 35 000 min^{-1} is achieved in the best case. The enantioselectivity and scope for the substrates are even superior to those of the previous $RuCl_2$(xylbinap)(daipen)/t-C_4H_9OK system, which is one of the most efficient catalysts. The catalytic cycle for this hydrogenation, in which the ruthenabicyclic structure of the catalyst is maintained, is proposed on the basis of the deuteration experiment and spectroscopic analysis data.

■ ASSOCIATED CONTENT

Supporting Information. Preparative methods and properties of chiral ruthenabicyclic complexes **1**, procedures for asymmetric hydrogenation of ketones **3**, NMR, GC, and HPLC behavior, $[\alpha]_D$ values of products, and the X-ray structure of (S_N,S_P)-**1c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 21350048). We thank Dr. Kimiko Hasegawa at the Rigaku Corporation for her help in analyzing the X-ray diffraction data. We thank also Messrs. Yoshihiro Yaguchi and Akihiro Kawaraya, Mrs. Kyoko Zaizen, and the ruthenabicyclic catalysts (RUCY) research members at the Takasago International Corporation for measurement of NMR and mass spectra, and experimental assistance.

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