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Asymmetric Hydrogenation of Bicyclic Ketones Catalyzed by BINAP/IPHAN−Ru(II) Complex

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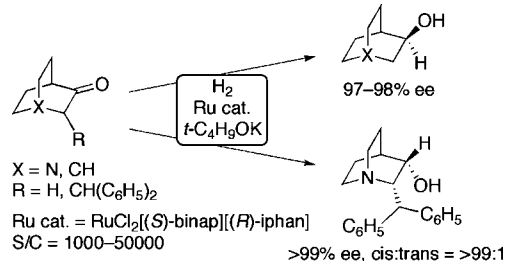
ABSTRACT



Hydrogenation of 3-quinuclidinone and bicyclo[2.2.2]octan-2-one with a combined catalyst system of $RuCl_2$[(*S*)-binap][(*R*)-iphan] and *t*-C_4H_9OK in 2-propanol afforded the chiral alcohols in 97−98% ee. 2-Diphenylmethyl-3-quinuclidinone was hydrogenated with the same catalyst to the cis alcohol with perfect diastereo- and enantioselectivity. The reaction of unsymmetrical ketones with a bicyclo[2.2.1] or -[2.2.2] skeleton gave the corresponding alcohols with high stereoselectivity.

Asymmetric hydrogenation of ketones is one of the most direct and reliable methods to produce synthetically useful chiral secondary alcohols.[1] We have developed highly active and enantioselective Ru catalysts with a chiral diphosphine and a nitrogen-based bidentate ligand for this reaction.[2] Appropriate combination of these two ligands is crucial to achieve high catalyst performance. For instance, a Ru complex bearing XylBINAP and DAIPEN, a chiral 1,2-diamine, catalyzes hydrogenation of a series of acyclic aromatic, heteroaromatic, amino, and α,β-unsaturated ketones in base-containing 2-propanol to afford the corresponding chiral alcohols in >99% ee in the best cases.[2−4] The TolBINAP/chiral 1,4-diamine−Ru complexes show high catalytic activity and enantioselectivity in the hydrogenation of 1-tetralones, a kind of cyclic aromatic ketone.[3,5]

Asymmetric hydrogenation of aliphatic ketones with a bicyclo[2.2.2] or -[2.2.1] skeleton is a challenging subject from the following academic and practical points of view: (1) the

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(1) Resent reviews: (a) Ohkuma, T.; Noyori, R. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 29−113. (b) Ohkuma, T.; Noyori, R. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; Vol. 3, pp 1105−1163.

(2) Reviews: (a) Ohkuma, T. *Proc. Jpn. Acad. Ser. B* **2010**, *86*, 202–219. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.

(3) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. TolBINAP = 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl. XylBINAP = 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl. DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine. (*S*)-IPBAN = (2*S*,3*S*)-2,3-*O*-isopropylidenehexane-1,4-diamine. (*R*)-IPHAN = (2*R*,3*R*,4*R*,5*R*)-3,4-*O*-isopropylidenehexane-2,5-diamine.

(4) (a) 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*, 13529–13530. (b) Ohkuma, T.; Koizumi, M.; Muñiz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508–6509.

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sterically congested framework requires highly active catalytic species, (2) precise discrimination between primary alkyl and secondary alkyl groups is crucial to achieve high enantioselectivity, (3) and the obtained chiral alcohols are key intermediates for the synthesis of biologically active compounds, including solifenacin, an M_3 receptor antagonist.[6] We expected that the BINAP/chiral 1,4-diamine−Ru catalysts would be appropriate for this hydrogenation because the medium-sized diamine-Ru chelate structure has enough space for an approach of the bicyclic ketones to the reaction site. The chiral environment of the Ru catalyst constructed from chiral diphosphine and diamine ligands can be tuned by changing the combination.

We recently reported asymmetric hydrogenation of 3-quinuclidinone (**1a**) catalyzed by an (*S*,*S*)-XylSkewphos/α-picolylamine−Ru complex.[7] The high catalytic activity achieved complete conversion in the reaction with a substrate-to-catalyst molar ratio (S/C) of 100 000 (15 atm H_2, 30−40 °C, 4 h) to give (*R*)-3-quinuclidinol [(*R*)-**2a**] in 88% ee. A patent described that 97% ee of **2a** was obtained in the reaction by using the (*R*)-DM-SEGPHOS/(*S*)-DM-DAIPEN−Ru catalyst, but the reactivity was insufficient for practical use (S/C = 1000, 30 atm of H_2, rt, 16 h, 97.5% conversion).[8] Therefore, we aimed to develop a Ru catalyst with both high activity and enantioselectivity for the hydrogenation of bicyclic ketones.

We selected **1a** as a typical substrate for optimization of the catalyst structure due to the synthetic importance of product **2a** (Table 1).[6] When **1a** (1.63 g, 13 mmol) was hydrogenated with $RuCl_2$[(*R*)-binap][(*S*)-ipban] [(*R*,*S*)-**3a**][3] (S/C = 10 000) in *t*-C_4H_9OK containing 2-propanol under 20 atm of H_2, (*S*)-3-quinuclidinol [(*S*)-**2a**] was obtained in 92% ee quantitatively (entry 1). The reaction with the diastereomeric (*S*,*S*)-**3a** gave (*R*)-**2a** in 88% ee (entry 2). The enantioselection was primarily dependent on the configuration of BINAP, and the (*R*)-BINAP/(*S*)-diamine combination was preferable to the *R*/*R* diastereomer. The use of (*S*)-BINAP/(*R*)-IPHAN−Ru complex (*S*,*R*)-**3b**[3] resulted in an excellent ee of 97% (entry 3). Introduction of two methyl groups at the α-carbons of the amino groups with an *R* configuration appeared to fix the diamine−Ru chelate ring appropriately. The high catalytic activity of the (*S*,*R*)-**3b**−*t*-C_4H_9OK system achieved complete conversion in the reaction with an S/C of 50 000 under 50 atm of H_2 without loss of enantioselectivity (entry 4). The (*S*)-TolBINAP/(*R*)-IPHAN−Ru complex [(*S*,*R*)-**3c**] exhibited catalyst efficiency comparable to that of (*S*,*R*)-**3b** (entry 5). The acetonide moiety of the 1,4-diamine was also important for attaining high catalyst performance. Thus, the ee value of **2a** in the reaction with the (*S*)-BINAP/(2*R*,5*R*)-2,5-hexanediamine−Ru complex [(*S*,*R*)-**3d**] decreased to 95%, and high pressure conditions (80 atm) were required for completion of the hydrogenation with an S/C of 20 000 (entries 6 and 7). High enantioselectivity was gained by using a combination of

Scheme 1

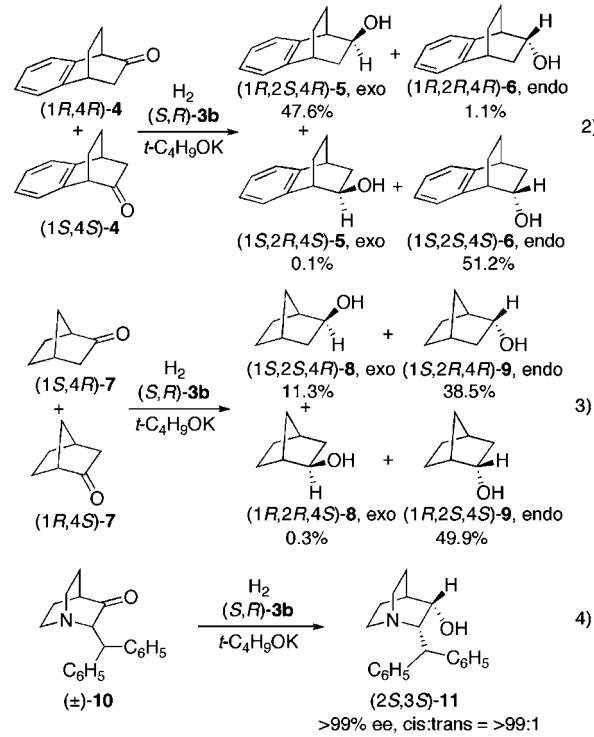
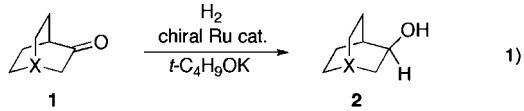
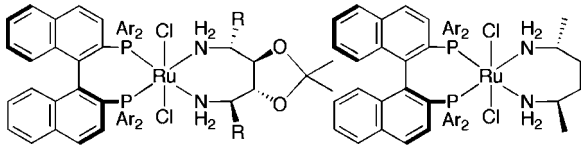


Table 1. Asymmetric Hydrogenation of Ketones with Bicyclo[2.2.2] Skeletons **1**[a]





(*S*,*R*)-**3a**: Ar = C_6H_5; R = H
(*S*,*R*)-**3b**: Ar = C_6H_5; R = CH_3
(*S*,*R*)-**3c**: Ar = 4-$CH_3C_6H_4$; R = CH_3
(*S*,*R*)-**3d**: Ar = C_6H_5
(*S*,*R*)-**3e**: Ar = 4-$CH_3C_6H_4$

entry	ketone **1**	Ru cat. **3**	S/C[b]	H_2 (atm)	time (h)	% ee of **2**[c]
1	**1a**	(*R*,*S*)-**3a**	10000	20	5	92 (*S*)
2	**1a**	(*S*,*S*)-**3a**	10000	20	5	88 (*R*)
3	**1a**	(*S*,*R*)-**3b**	10000	20	5	97 (*R*)[d]
4[e]	**1a**	(*S*,*R*)-**3b**	50000	50	24	97 (*R*)[d]
5[e]	**1a**	(*S*,*R*)-**3c**	50000	50	24	97 (*R*)[d]
6	**1a**	(*S*,*R*)-**3d**	10000	20	5	95 (*R*)
7[f]	**1a**	(*S*,*R*)-**3d**	20000	80	16	95 (*R*)[d]
8	**1a**	(*R*,*S*)-**3e**	10000	20	5	97 (*S*)
9[g]	**1b**	(*S*,*R*)-**3b**	1000	20	2	98 (*S*)[h]

[a] Unless otherwise stated, reactions were conducted at 25 °C using 13 mmol of **1** in 2-propanol (2.7 mL) containing **3** and *t*-C_4H_9OK (20 mM). Complete conversion was observed in all cases. [b] Substrate/catalyst molar ratio. [c] Determined by chiral HPLC analysis after conversion to the benzoate. [d] The isolated yield was 99%. [e] **1a** (18.8 g, 150 mmol) and 2-propanol (49 mL) were used. [f] **1a** (3.3 g, 26 mmol) and 2-propanol (8.4 mL) were used. [g] **1b** (168 mg, 1.35 mmol) and a 3:1 2-propanol−*t*-C_4H_9OH (6.4 mL) mixture were used. [h] The isolated yield was 90%.

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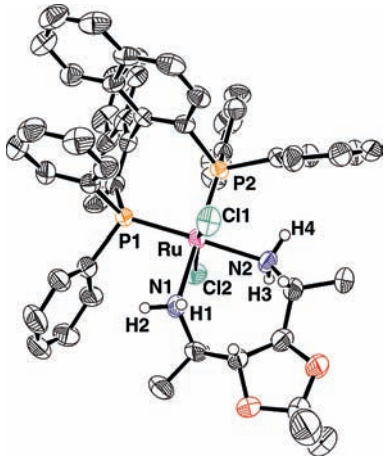

Figure 1. ORTEP drawing of (*S*,*R*)-**3b**. All protons except those on the diamine ring are omitted for clarity.

TolBINAP and the simple-shaped diamine (entry 8). It is noteworthy that hydrogenation of bicyclo[2.2.2]octan-2-one (**1b**) with (*S*,*R*)-**3b** afforded (*S*)-**2b** [same sense as (*R*)-**2a**] in 98% ee (entry 9), suggesting that the nitrogen atom in the ketone **1a** did not affect the enantioselection.

The catalyst system was also effective for hydrogenation of unsymmetrical ketones. When a racemic bicyclo[2.2.2] ketone **4** was hydrogenated with (*S*,*R*)-**3b** (S/C = 1000, [*t*-C_4H_9OK] = 20 mM, 20 atm H_2), the exo alcohol (1*R*,2*S*,4*R*)-**5** in 48% yield and 99% ee, and the endo isomer (1*S*,2*S*,4*S*)-**6** in 52% yield and 96% ee were obtained (Scheme 1, eq 2). These results indicated that both enantiomers of **4** were reduced with high stereoselectivity. The stereoselective manner was highly dependent on the substrate structure. The hydrogenation of racemic 2-norbornanone (**7**) with a bicyclic[2.2.1] skeleton in the presence of (*S*,*R*)-**3b** gave an 11.6:88.4 mixture of *exo*-**8** (95% ee) and *endo*-**9** (13% ee), showing that the stereoselectivity of (1*R*,4*S*)-**7** was high, but the diastereomeric face selection of (1*S*,4*R*)-**7** was insufficient by this catalyst (Scheme 1, eq 3).

The (*S*,*R*)-**3b**−*t*-C_4H_9OK catalyst system was fairly effective for hydrogenation of racemic 2-diphenylmethyl-3-quinuclidinone (**10**) through dynamic kinetic resolution (Scheme 1, eq 4).[9,10] The reaction with an S/C of 5000 ([*t*-C_4H_9OK] = 20 mM) in a 6:1 2-propanol−$CH_3CON(CH_3)_2$ under 10 atm of H_2 for 20 h quantitatively gave the (2*S*,3*S*)-**11** (cis/trans = >99:1) in >99% ee. Interestingly, the sense of enantioselection was the opposite of that in the reaction of **1a**. The obtained alcohol is a useful intermediate for the synthesis of a series of human NK_1 antagonists.[11]

Our recent mechanistic studies on the BINAP/diamine−Ru-catalyzed hydrogenation of ketones revealed that the *trans*-RuH_2(binap)(diamine) is the active species with a structure closely related to that of the precatalyst, the *trans*-$RuCl_2$ complex (see the Supporting Information).[12,13] Figure 1 shows the distorted octahedral structure of the (*S*)-BINAP/(*R*)-IPHAN−$RuCl_2$ complex, (*S*,*R*)-**3b**, determined by a single-crystal X-ray analysis. The torsion angle of Cl(1)−Ru−N(1)−H(1) (6°) was much smaller than that of Cl(1)−Ru−N(1)−H(2) (110°), indicating that two amino protons H(1) and H(2) are discriminated to be axial (H_{ax}) and equatorial (H_{eq}), respectively, by the skewed (*R*)-IPHAN−Ru chelate ring.[12,13] On the basis of the (*S*,*R*)-**3b** structure, molecular models of *trans*-RuH_2[(*S*)-binap][(*R*)-iphan] and diastereomeric transition states (TSs) $\mathbf{TS_A}$ and $\mathbf{TS_B}$ in the hydrogenation of **1** are schematically illustrated in Figure 2. The hydrogenation of ketones proceeds through the six-membered TS, $\mathbf{TS_A}$ or $\mathbf{TS_B}$, in which the $H^{\delta-}-Ru^{\delta+}-N^{\delta-}-H_{ax}{}^{\delta+}$ quadrupole of the Ru complex interacts with the $C^{\delta+}=O^{\delta-}$ dipole of the ketone.[12,13] $\mathbf{TS_A}$ is

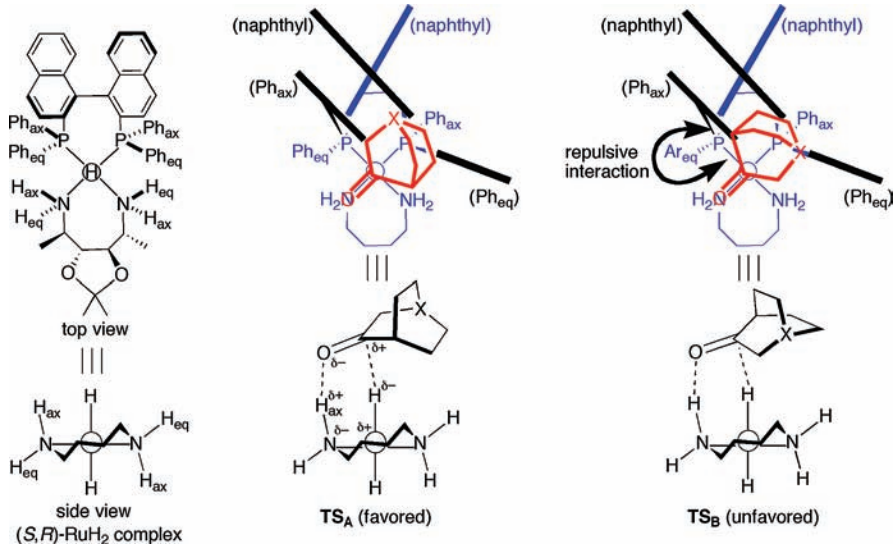

Figure 2. Molecular models of the (*S*,*R*)-RuH_2 complex (O = Ru) derived from **3b** and diastereomeric transition states (TSs) in the hydrogenation of **1** (X = N or CH). The structures are simplified for clarity.

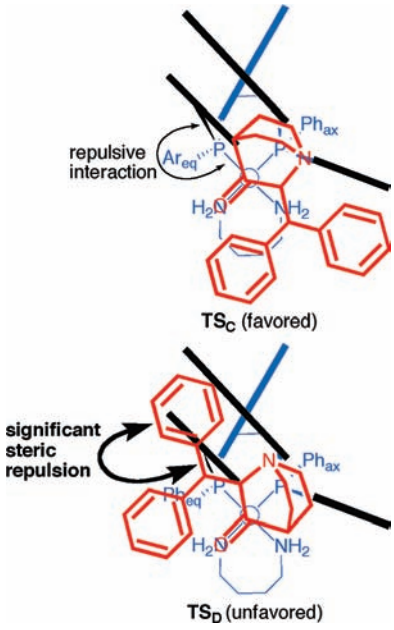

Figure 3. Molecular models of diastereomeric TSs in the hydrogenation of **10** with (*S*,*R*)-**3b**.

favored over $\mathbf{TS_B}$, resulting in (*R*)-**1a** or (*S*)-**1b** selectively, because repulsive interaction between an axial *P*-phenyl ring (Ph_{ax}) of BINAP and a bridged alkyl moiety of **1** in $\mathbf{TS_B}$ exists. This interpretation is consistent with the results that **1a** (X = N) and **1b** (X = CH) were hydrogenated with the same degree and sense of enantioselectivity.

The mode of enantioselection in hydrogenation of **10** is explained by using two TS models, $\mathbf{TS_C}$ and $\mathbf{TS_D}$ (Figure 3). The steric repulsion between the $(C_6H_5)_2CH$ group of **10** and the Ph_{ax} of BINAP in $\mathbf{TS_D}$ is large enough to cancel the repulsive interaction caused by the bridged alkyls of **10** and the BINAP's Ph_{ax} in $\mathbf{TS_C}$. The $(C_6H_5)_2CH$ group connected at the configurationally interconvertible α-carbon locates anti to the nucleophilic RuH_2 complex. Therefore, (2*S*,3*S*)-**11** was obtained with perfect diastereo- and enantioselectivity.[10]

In summary, the BINAP/IPHAN−Ru complex **3b** with *t*-C_4H_9OK catalyzes asymmetric hydrogenation of bicyclo[2.2.2] ketones **1** to afford the chiral alcohols **2** in 97−98% ee. The high catalytic activity achieves a turnover as high as 50 000. Unsymmetrical bicyclo[2.2.1] and -[2.2.2] ketones **4** and **7** are also hydrogenated with high stereoselectivity. A 2-substituted bicyclic ketone **10** is converted to the cis alcohol in perfect diastereo- and enantioselectivity. The mode of enantioselection is interpreted by using molecular models based on the X-ray structure of **3b**.

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

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