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BINAP/1,4-Diamine–Ruthenium(II) Complexes for Efficient Asymmetric Hydrogenation of 1-Tetralones and Analogues

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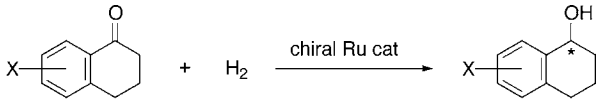
ABSTRACT



X = H, 5-, 6-, or 7-CH_3O, 7-F, 5,7-$(CH_3)_2$, 4,4-$(CH_3)_2$ 92–99% ee
chiral Ru cat = *trans*-$RuCl_2$(binap)(1,4-diamine)

A combined system of a $RuCl_2$(binap)(1,4-diamine) complex and *t*-C_4H_9OK in *i*-C_3H_7OH catalyzes enantioselective hydrogenation of various 1-tetralone derivatives and some methylated 2-cyclohexenones. Hydrogenation of 2-methyl-1-tetralone under dynamic kinetic resolution gives the cis alcohol with high ee.

Chiral diphosphine/1,2-diamine−RuX_2 complexes (X = anionic ligand) combined with[1−5] or without[6] an alkaline base in *i*-C_3H_7OH effect rapid, enantioselective hydrogenation of simple, unfunctionalized aryl,[3,6] heteroaryl,[4] alkenyl,[3b−d,g,4−6] and certain aliphatic ketones.[3d]

Our recent mechanistic study revealed that *acetophenone*, the simplest aromatic ketone, is reduced with an 18e *trans*-RuH_2(binap)(1,2-diamine) intermediate via a six-membered pericyclic transition state.[7] Because the ketone enantiofaces are differentiated on the chiral molecular surface of the saturated RuH_2 complex, suitable combination of the catalyst and substrate is necessary for high efficiency. The enantioselectivity and reaction rate are affected by subtle changes in electronic and steric parameters of the Ru complexes and ketones. No universal chiral catalysts exist because of the structural diversity of ketonic substrates. Thus, hydrogenation of 1-tetralones **1** has remained very slow and poorly

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(2) 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. DPEN = 1,2-diphenylethylenediamine.
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Table 1. Asymmetric Hydrogenation of 1-Tetralone (**1a**)[a]

Ru catalyst no.	conditions: S/C[b]	solvent[c]	H_2 [atm]	time [h]	(*R*)-**2a**: yield [%][d]	ee [%][d]
(*S*,*R*)-**3a**	11 000	A	9	3	99.9	90
(*S*,*R*)-**3b**	1 000[e]	A	8	1.2	98	89
(*S*,*R*)-**3c**	3 000	A	9	8	72	99
(*S*,*R*)-**3c**	3 000	B	9	8	99.6	99
(*S*,*R*)-**3c**	11 000[f]	B	50	17	99.8	98

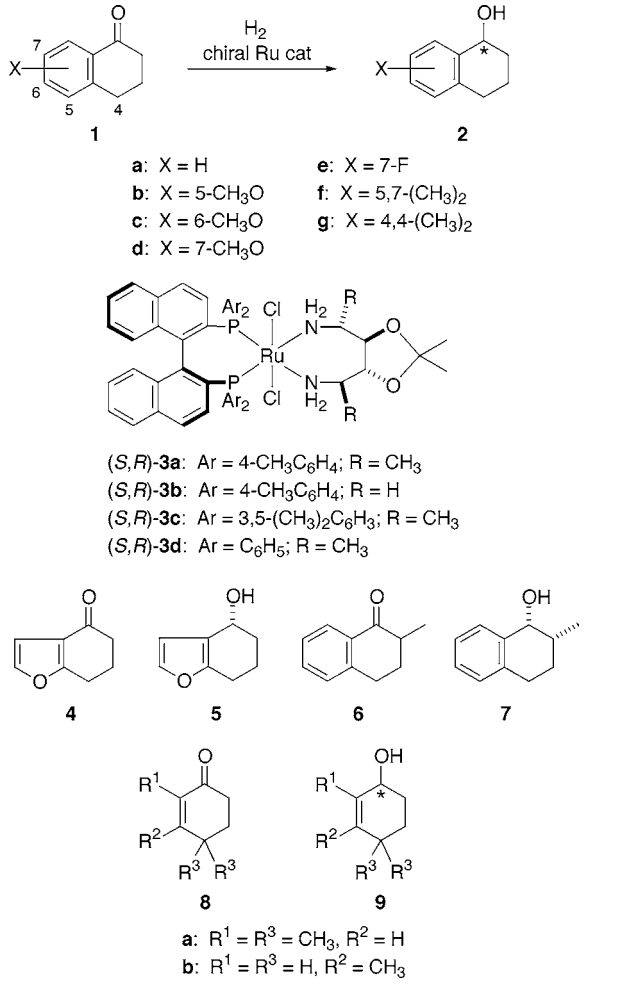
[a] Unless otherwise stated, reactions were conducted using 3.0 mmol of **1a** (1.0 M) in solvent containing an (*S*,*R*) Ru catalyst and *t*-C_4H_9OK (8−20 mM) at 25 °C. [b] Substrate/catalyst molar ratio. [c] Solvent: A = *i*-C_3H_7OH; B = 3:1 *i*-C_3H_7OH−*t*-C_4H_9OH. [d] Determined by chiral GC analysis. [e] [*t*-C_4H_9OK] = 100 mM. [f] Reaction using 11.5 mmol of **1a**.

enantioselective. We here report that replacement of conventional 1,2-diamine ligands by certain chiral 1,4-diamines can solve this difficult problem.[8] A chiral $RuCl_2$(binap)(1,4-diamine)/*t*-C_4H_9OK combined system promotes hydrogenation of ketones **1** with a substrate to catalyst molar ratio (S/C) as high as 55 000 to afford chiral 1-tetralols **2** in up to 99% ee and high yield.[9]

(2*R*,3*R*,4*R*,5*R*)-3,4-*O*-Isopropylidenehexane-2,5-diamine [(*R*)-IPHAN], a chiral 1,4-diamine, was synthesized from natural (2*R*,3*R*,4*R*,5*R*)-mannitol. Treatment of the known (2*S*,3*S*,4*S*,5*S*)-3,4-*O*-isopropylidenehexane-2,5-diol bismethanesulfonate[10] with NaN_3 in DMF (4 equiv, 50 °C) followed by hydrogenation on 5% Pd/C in methanol (25 °C, 1 atm H_2) gave (*R*)-IPHAN in 59% yield (see Supporting Information). (2*S*,3*S*)-2,3-*O*-Isopropylidenebutane-1,4-diamine [(*S*)-IPBAN] is obtainable from diethyl (*R*,*R*)-tartrate according to the literature.[11] *trans*-$RuCl_2$[(*S*)-tolbinap][(*R*)-iphan] [(*S*,*R*)-**3a**] was prepared in 50% isolated yield by reaction of oligomeric $RuCl_2$[(*S*)-tolbinap](dmf)$_n$[12] and 1.1 equiv of (*R*)-IPHAN in DMF (25 °C, 15 h). The $^{31}P\{^1H\}$ NMR spectrum showing a singlet at 44.3 ppm indicated a *trans*-$RuCl_2$ geometry.[3c] Other diphosphine/1,4-diamine−Ru complexes (*S*,*R*)-**3b**−**d** were synthesized by similar procedures.

First, the reactivity and stereoselectivity of the chiral Ru complexes **3** were tested by using parent 1-tetralone (**1a**) as substrate (Table 1). The (*S*)-XylBINAP/(*R*)-IPHAN−Ru complex [(*S*,*R*)-**3c**] was found to exhibit the highest enantioselectivity in reaction of **1a**. Thus when **1a** was hydrogenated with (*S*,*R*)-**3c** in a 3:1 mixture of *i*-C_3H_7OH and *t*-C_4H_9OH under 50 atm of H_2 (S/C = 11 000, [**1a**] = 1.0 M, [*t*-C_4H_9OK] = 20 mM, 25 °C, 17 h), (*R*)-**2a** was obtained in 98% ee and 99.8% yield. The reaction proceeded even at 9 atm. The less congested Ru complexes (*S*,*R*)-**3a** and (*S*,*R*)-**3b** hydrogenated **1a** faster but less stereoselectively, giving (*R*)-**2a** in ca. 90% ee and quantitative yield. (*S*)-TolBINAP/(*S*)-IPBAN-based Ru complex, a diastereomer of (*S*,*R*)-**3b**, exhibited a comparable activity in the hydrogenation of **1a** to form (*R*)-**2a** in 85% ee, where the absolute configuration of the 1,4-diamine was relatively unimportant. However, the combination of (*S*)-TolBINAP and simple 1,4-butanediamine led to a low reactivity (11% yield, *R* in 52% ee, S/C = 1000, 9 atm, 25 °C, 2 h), suggesting that the acetonide ring on the diamine backbone contributes to the stability of the catalytic species. 1-Tetralone (**1a**) is not a simple analogue of acetophenone. Although acetophenone was best hydrogenated with $RuCl_2$[(*S*)-xylbinap][(*S*)-daipen]$_2$ (ketone/Ru/*t*-C_4H_9OK = 1000:1:20, 9 atm H_2, 25 °C, 14 h), giving (*R*)-1-phenylethanol in 99% ee and 100% yield,[3d] reaction of the structurally rigid, cyclic ketone **1a** with the same complex and the same reaction conditions afforded (*R*)-**2a** in only 30% ee and 15% yield. On the other hand, (*S*,*R*)-**3c**, the best catalyst for **1a** (Table 1), smoothly hydrogenated acetophe-

Scheme 1



(8) Asymmetric hydrogenation of **1a**, giving **2a** in 95% ee and 88% yield, was achieved with a BINAP−Ir complex with an achiral amino phosphine under harsh conditions and with a rather high catalyst loading (50−57 atm, 90 °C, 75 h, S/C = 190−230). Zhang, H.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318−3319.

(9) Transfer hydrogenation of **1a** catalyzed by a chiral Ru complex in a formic acid−$(C_2H_5)_3N$ mixture gave **2a** in 99% ee and quantitatively but only with S/C = 200. Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522.

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Table 2. Asymmetric Hydrogenation of Cyclic Ketones[a]

		conditions			alcohol		
ketone no.	Ru catalyst no.	S/C[b]	base [mM]	time [h]	no.	yield [%][c]	ee [%][c]
1a[d]	(*S*,*R*)-**3c**	3 000	10	8	(*R*)-**2a**	99.6	99
1b	(*S*,*R*)-**3a**	10 000	20	2	(*R*)-**2b**	100	98
1b[e]	(*S*,*R*)-**3a**	55 000	20	14	(*R*)-**2b**	100	98
1c	(*S*,*R*)-**3a**	1 000	50	13	(*R*)-**2c**	98	92
1d[d]	(*S*,*R*)-**3c**	3 300	20	8	(*R*)-**2d**	100	99[f]
1e[d]	(*S*,*R*)-**3c**	3 000	20	8	(*R*)-**2e**	100	98[f]
1f	(*S*,*R*)-**3d**	3 300	30	2	(*R*)-**2f**	99.9	95[f]
1g	(*S*,*R*)-**3a**	12 000	20	18	(*R*)-**2g**	99.9	93
4	(*S*,*R*)-**3a**	12 000	20	14	(*R*)-**5**	98	96
6	(*S*,*R*)-**3d**	10 000	16	16	(*R*,*R*)-**7**	97[g]	87
8a	(*S*,*R*)-**3a**	10 000	20	7	(*R*)-**9a**	99.5	96
8b	(*R*,*S*)-**3b**	1 000	20	8	(*S*)-**9b**	100[h]	80

[a] Unless otherwise stated, reactions were conducted using 3.0 mmol of ketone (0.5−1.0 M) in *i*-C_3H_7OH containing a chiral Ru catalyst and *t*-C_4H_9OK at 25 °C under 9 atm of H_2. [b] Substrate/catalyst molar ratio. [c] Determined by chiral GC analysis. [d] In a 3:1 *i*-C_3H_7OH−*t*-C_4H_9OH mixture. [e] Reaction using 11.3 g (63.9 mmol) of **1b**. [f] Determined after conversion to the acetate. [g] *cis*:*trans* = 98.6:1.4. [h] Contaminated by 2% of 3-methylcyclohexanol.

none to give the *R* alcohol in 77% ee. Most notably, the reaction of acetophenone and **1a** using (*S*,*R*)-**3b** under the same conditions (Table 1) displayed an opposite sense of asymmetric induction, giving (*S*)-1-phenylethanol in 81% ee and (*R*)-**2a** and 89% ee, respectively.

A series of 1-tetralone derivatives **1** was hydrogenated with high enantioselectivity as shown in Table 2. Here, one must carefully choose the precatalyst **3** depending on the substitution pattern. In most cases, *i*-C_3H_7OH served as the best solvent, while a 3:1 mixture of *i*-C_3H_7OH and *t*-C_4H_9OH gave higher yield for the reaction catalyzed by **3c** with an S/C ratio of >3000. Hydrogenation of 5-methoxy-1-tetralone (**1b**) with (*S*,*R*)-**3a** and *t*-C_4H_9OK proceeded smoothly with an S/C of 55 000 (*i*-C_3H_7OH, 9 atm, 14 h) to give (*R*)-**2b** in 98% ee.[13] With the same catalyst, the 6-methoxy ketone **1c** was hydrogenated slowly, as a result of the electron-donating para substituent, to give (*R*)-**2c** in 92% ee. The 7-methoxy- and 7-fluoro-1-tetralone, **1d** and **1e**, were hydrogenated with (*S*,*R*)-**3c** in excellent enantioselectivity (>99:1). Electronic properties of the C(7) substituents did not affect the rate and enantioselectivity. The 5,7- and 4,4-dimethyl ketones, **1f** and **1g**, were quantitatively hydrogenated with (*S*,*R*)-**3d** and (*S*,*R*)-**3a**, respectively, in good enantioselectivity. Thus, we recommend the Ru complex **3c** for hydrogenation of unsubstituted and 7-substituted 1-tetralones and the complex **3a** for reaction of the 4-, 5-, and 6-substituted derivatives. The complex **3d** is the best for reaction of **1f**. None of these tetralones were efficiently hydrogenated with the conventional BINAP/1,2-diamine complexes. The resulting chiral 1-tetralols **2** are useful intermediates for the synthesis of bioactive compounds such as potent hypnotic and antimycotic agents and empomil inhibitors.[14] Hydrogenation of 4,5,6,7-tetrahydrobenzofuran-4-one (**4**) with (*S*,*R*)-**3a** gave (*R*)-**5** in 96% ee quantitatively without saturation of the furan ring (Table 2).[4] Attempted hydrogenation of highly base-sensitive 1-chromanone and 1-indanone resulted in complex mixtures.[15]

Hydrogenation of racemic 2-methyl-1-tetralone [(±)-**6**] with (*S*,*R*)-**3d** under the basic, protic conditions ([**6**] = 1.0 M in *i*-C_3H_7OH, [*t*-C_4H_9OK] = 15 mM, ketone/Ru/base = 10 000:1:100, 25 °C, 9 atm) proceeded via dynamic kinetic resolution[16,17] to afford (1*R*,2*R*)-**7** in 87% ee and 97% yield (*cis*:*trans* = 98.6:1.4).

Certain alkylated 2-cyclohexenones behave similarly to 1-tetralones. For example, 2,4,4-trimethyl-2-cyclohexenone (**8a**) was hydrogenated with (*S*,*R*)-**3a** (S/C = 10 000, 9 atm, 25 °C, 7 h) to give the chiral allylic alcohol (*R*)-**9a** in 96% ee,[18] leaving the olefinic bond intact. Reaction of the simpler 3-methyl-2-cyclohexenone (**8b**) with (*R*,*S*)-**3b** gave (S)-**9b** in 80% ee[19] and 98% yield, accompanied by 2% of a fully saturated alcohol.

The chiral BINAP/1,4-diamine−Ru catalysts enable the enantioselective hydrogenation of a series of 1-tetralones and analogues with a low catalyst loading (S/C = 1000−55 000). The reason for the high efficiency of the 1,4-diamine ligands remains unclear. It might be ascribed to the increased flexibility of the resulting seven-membered Ru chelate ring, in comparison to the five-membered ring formed with 1,2-diamines, or the structural change in reactive Ru hydride species. It should be emphasized that the newly devised catalysts are not substitutes for the previously found BINAP/1,2-diamine−Ru catalysts. Because these have different characteristics, both are used complementarily, depending on the ketone structures.

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Supporting Information Available: Preparative methods and properties of a chiral 1,4-diamine, IPHAN, and Ru complexes **3**. Procedures of hydrogenation of the cyclic ketones, GC behavior of alcoholic products, and $[\alpha]_D$ values and absolute configuration determination procedure for chiral alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A single recrystallization from a 1:3 mixture of methanol and hexane at −30 °C gave pure (*R*)-**2b** in 81%.

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(18) Use of (*S*)-TolBINAP/(*R*,*R*)-DPEN−Ru catalyst gave the *R* alcohol in 94% ee.[5b]

(19) An (*R*)-BINAP/(*R*,*R*)-DPEN−Ru complex gave only 47% ee.[5b]