

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

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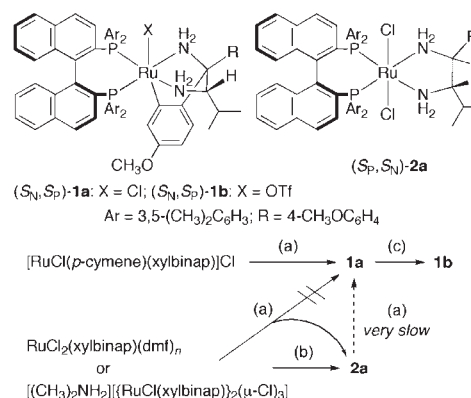
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**S** Supporting Information

**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<sup>-1</sup> 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.<sup>1</sup> 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.<sup>1,2</sup> A series of alkyl aryl ketones, heteroaromatic ketones, unsymmetrical benzophenones, and  $\alpha,\beta$ -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,  $\eta^1$ -BH<sub>4</sub>)<sup>3</sup> with or without an alkaline base are employed for this reaction.<sup>4</sup> 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<sub>N</sub>,S<sub>P</sub>)-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<sup>5</sup> and (S)-DAIPEN (1.1 equiv) with (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NH (1.0 equiv) in refluxed methanol (98% isolated yield; see Figure 1, conditions (a)).<sup>6–8</sup> Interestingly, the known RuCl<sub>2</sub>[(S)-xylbinap][(S)-daipen] [(S<sub>P</sub>,S<sub>N</sub>)-2a]<sup>4a</sup> was exclusively obtained under the same reaction conditions (a) or the aprotic conditions (b), when the neutral complex RuCl<sub>2</sub>[(S)-xylbinap](dmf)<sub>*n*</sub><sup>9</sup> or the dinuclear complex [(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>][{RuCl[(S)-xylbinap]}<sub>2</sub>( $\mu$ -Cl)<sub>3</sub>]<sup>10</sup> was used instead of [RuCl(*p*-cymene){(S)-xylbinap}]Cl. The RuCl<sub>2</sub> 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)]



**Figure 1.** Structures and preparation of chiral Ru(II) complexes. Conditions: (a) DAIPEN (1.1 equiv), (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NH (1.0 equiv), CH<sub>3</sub>OH, 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.

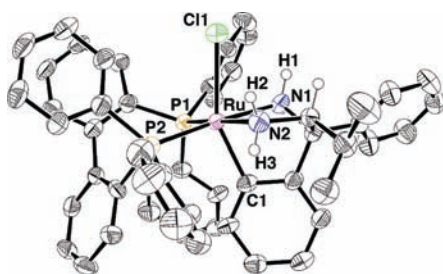
quantitatively gave the triflate complex 1b, leaving the ruthenabicyclic structure intact. RuCl(daipena)(dm-segphos) (1c)<sup>11</sup> was prepared by the same procedure from the corresponding cationic complex.<sup>8</sup> When DPEN was used instead of DAIPEN, the corresponding RuCl<sub>2</sub> complex was obtained exclusively.<sup>3</sup>

Figure 2 shows an ORTEP diagram of the single-crystal X-ray analysis of (S<sub>N</sub>,S<sub>P</sub>)-1c.<sup>8</sup> 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<sub>2</sub>(diphosphine)(diamine) complexes.<sup>12</sup> 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.<sup>12</sup> 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<sub>N</sub>,S<sub>P</sub>)-1a exhibited excellent catalytic activity and enantioselectivity in the hydrogenation of acetophenone (3a) in a *t*-C<sub>4</sub>H<sub>9</sub>OK containing alcoholic solvent (Scheme 1 and Table 1). The order of solvents in the reaction rate was ethanol  $\geq$  2-propanol  $\gg$  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<sub>2</sub> at

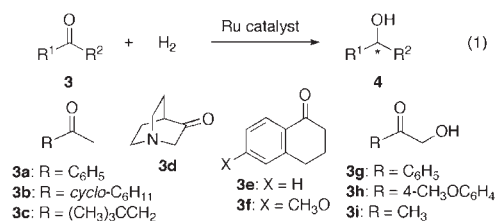
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**Figure 2.** ORTEP drawing of  $(S_N,S_P)$ -1c. All protons except those on the diamine ring and some substituents are omitted for clarity.<sup>8</sup>

### 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).<sup>13</sup> 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<sub>4</sub>H<sub>9</sub>OK catalyst system was observed. The turnover frequency (TOF) between 2–3 min reached about 35 000 min<sup>-1</sup>. Complete conversion of the hydrogenation under lower pressure of H<sub>2</sub> was achieved without loss of enantioselectivity (entries 6 and 7). Aprotic toluene and CH<sub>2</sub>Cl<sub>2</sub> 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<sub>4</sub>H<sub>9</sub>OK (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<sub>2</sub>Cl<sub>2</sub> as well as in the alcoholic solvent by using DBU as a base (entries 13–15). The 1c/*t*-C<sub>4</sub>H<sub>9</sub>OK system also achieved a high level of reactivity and enantioselectivity, although these were slightly lower than those of the 1a/*t*-C<sub>4</sub>H<sub>9</sub>OK catalyst (entry 16 vs 7). In contrast to the ruthenabicyclic precatalysts 1, the ordinary RuCl<sub>2</sub> 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<sup>-1</sup>; entry 18) was slower than that using 1a (TOF = 6000 min<sup>-1</sup>; entry 3). DBU was useless even in the alcoholic solvent (entry 19 vs 10).

The ruthenabicyclic-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).<sup>14</sup> The enantioselectivity of 85% in the reaction of 3b with 2a was reported.<sup>2</sup> 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<sub>2</sub> affording 3-quinuclidinol (4d)

**Table 1.** Hydrogenation of 3a catalyzed by Ru complexes<sup>a</sup>

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

<sup>a</sup> 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). <sup>b</sup> Ru complexes. <sup>c</sup> Substrate-to-catalyst molar ratio. <sup>d</sup> Determined by chiral GC analysis. (*R*)-4a was obtained. <sup>e</sup> A = EtOH/*i*PrOH (1:1). <sup>f</sup> Not determined.

in high yield and 95% ee (entries 3 and 4).<sup>15</sup> The reaction with 2a resulted in a much less satisfactory result (entry 5). For hydrogenation of 1-tetralone (3e),<sup>16</sup> a cyclic aromatic ketone, RuCl[(*S*)-daipena]-[(*R*)-dm-segphos] [ $(S_N,R_P)$ -1c] with *t*-C<sub>4</sub>H<sub>9</sub>OK acted as an excellent catalyst (entry 6). The corresponding RuCl[(*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).<sup>16</sup> 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).<sup>17</sup> The reaction of 3g with the 2a/*t*-C<sub>4</sub>H<sub>9</sub>OK 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<sub>6</sub>H<sub>5</sub> > CH<sub>2</sub>OH > CH<sub>3</sub>.

ESI mass-spectroscopic (MS) analysis of  $(S_N,S_P)$ -1a in CH<sub>2</sub>Cl<sub>2</sub> and methanol showed prominent signals centered at *m/z* 1184.4 ([M]<sup>+</sup>) and 1149 ([M – Cl]<sup>+</sup>), respectively. The <sup>31</sup>P{<sup>1</sup>H} NMR spectrum in benzene-*d*<sub>6</sub> and methanol-*d*<sub>4</sub>/CD<sub>2</sub>Cl<sub>2</sub> (2:1) showed AB quartet signals at δ 53.3, 61.1 (*J*<sub>P–P</sub> = 38.2 Hz) and δ 19.7, 36.7 (*J*<sub>P–P</sub> = 32.9 Hz), respectively. The [M – Cl]<sup>+</sup> signals remained pronounced in the MS analysis of a reaction mixture of hydrogenation of 3a in methanol. The <sup>1</sup>H NMR measurement of 1a in the methanol-*d*<sub>4</sub>/CD<sub>2</sub>Cl<sub>2</sub> mixture under 1 atm of H<sub>2</sub> at –50 °C showed a broad signal at δ –0.35, which suggested the formation of the Ru( $\eta^2$ -H<sub>2</sub>) species.<sup>18</sup>

The <sup>31</sup>P{<sup>1</sup>H} NMR signals of  $(S_N,S_P)$ -1a in benzene-*d*<sub>6</sub> (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<sup>a</sup>

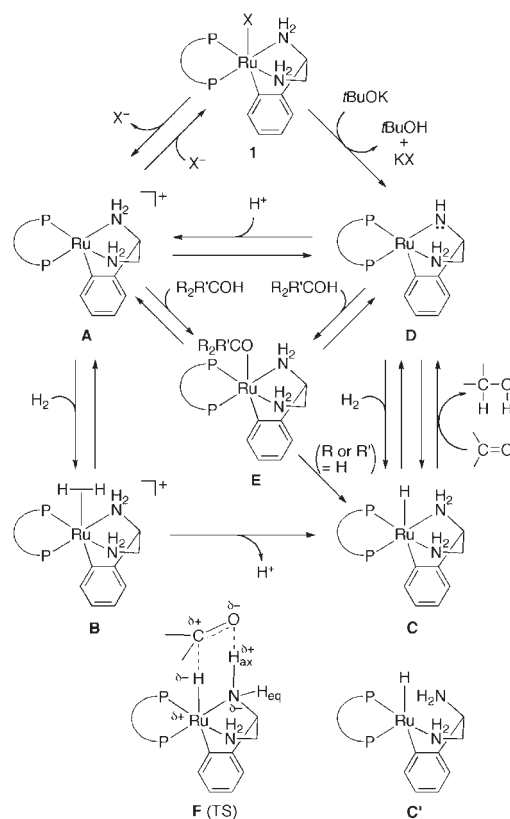
entry	<b>3</b>	Ru <sup>b</sup>	S/C <sup>c</sup>	base	solvent <sup>d</sup>	time, h	% yield <sup>e</sup>	% ee <sup>f</sup>
1	<b>b</b>	(S <sub>N</sub> ,S <sub>P</sub> )- <b>1a</b>	4000	<i>t</i> BuOK	P	5	96	90 ( <i>R</i> )
2	<b>c</b>	(S <sub>N</sub> ,S <sub>P</sub> )- <b>1a</b>	10000	<i>t</i> BuOK	P	5	>99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

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

when 2 equiv of *t*-C<sub>4</sub>H<sub>9</sub>OK were added. The observed <sup>1</sup>H NMR signals of the *t*-C<sub>4</sub>H<sub>9</sub>O moiety ( $\delta$  1.24) and presence of the four amino-protons suggested formation of the RuO-*t*-C<sub>4</sub>H<sub>9</sub> complex.<sup>8</sup> This complex was reacted with methanol (6 equiv) to afford the RuOCH<sub>3</sub> complex, which showed the NMR signal of the CH<sub>3</sub>O moiety ( $\delta$  3.16).<sup>8</sup> 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<sub>4</sub>H<sub>9</sub> complex was mixed with H<sub>2</sub> (1 atm) or **4a** (3 equiv), two RuH species showing hydride peaks at  $\delta$  -6.50 and -13.55 were afforded.<sup>8</sup> 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  $\delta$  -6.50 disappeared by the addition of **3a**, but the other peaks at  $\delta$  -13.55 remained.

Treatment of the RuO-*t*-C<sub>4</sub>H<sub>9</sub> complex with 2-propanol-*d*<sub>8</sub> afforded the two kinds of RuD species and the RuO-*i*-C<sub>3</sub>D<sub>7</sub> 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.<sup>8</sup>

Scheme 2 illustrates a plausible mechanism for the hydrogenation of ketones with ruthenabicyclic complexes **1** based on the spectroscopic analysis. The X<sup>-</sup> (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<sub>4</sub>H<sub>9</sub>OK 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<sup>a</sup>

<sup>a</sup> X = Cl or OTf. R = alkyl, aryl, H. R' = CH<sub>3</sub>, H. P—P = XylBINAP. NH<sub>2</sub>—NH<sub>2</sub> = 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<sub>2</sub>Cl<sub>2</sub>, **1a** (X = Cl) does not ionize and requires strong base *t*-C<sub>4</sub>H<sub>9</sub>OK to remove Cl<sup>-</sup> 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 <sup>-</sup>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<sub>ax</sub>) of the RuH complex **C** is the most reactive among the four amino protons, because the H—Ru—N—H<sub>ax</sub> torsion angle is expected to be the smallest based on the structure of **1c** (Figure 2).<sup>2,18</sup> The ketonic substrate is reduced by **C** through the six-membered pericyclic transition state (TS) **F** (metal–ligand cooperative TS), in which the H<sup>δ-</sup>—Ru<sup>δ+</sup>—N<sup>δ-</sup>—H<sub>ax</sub><sup>δ+</sup> quadrupole of the catalyst fits with the C<sup>δ+</sup>=O<sup>δ-</sup> dipole of the substrate.<sup>2,12</sup> The key issue is that **C** has a ruthenabicyclic structure, in contrast to the previous RuCl<sub>2</sub>-(diphosphine)(1,2-diamine)/*t*-C<sub>4</sub>H<sub>9</sub>OK catalyst systems in which the corresponding *trans*-RuH<sub>2</sub> complexes are the expected active species.<sup>18,19</sup> 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<sub>4</sub>H<sub>9</sub>OK, DBU) exhibit remarkably high catalytic activity in the hydrogenation of ketones. A turnover frequency of about 35 000 min<sup>-1</sup> is achieved in the best case. The enantioselectivity and scope for the substrates are even superior to those of the previous RuCl<sub>2</sub>(xylbinap)(daipen)/*t*-C<sub>4</sub>H<sub>9</sub>OK 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

**S 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<sub>N</sub>,S<sub>P</sub>)-**1c** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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