

## Asymmetric Hydrogenation of Cycloalkanones Catalyzed by BINAP-Ir(I)-Aminophosphine Systems

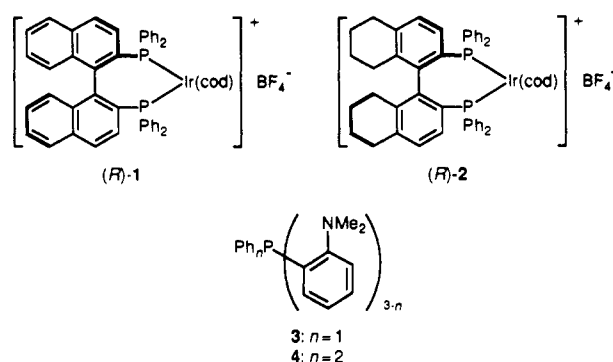
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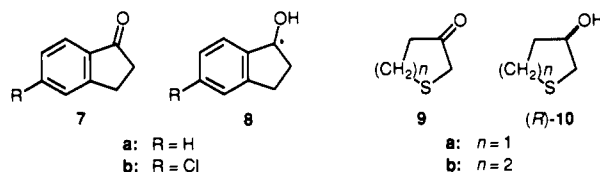
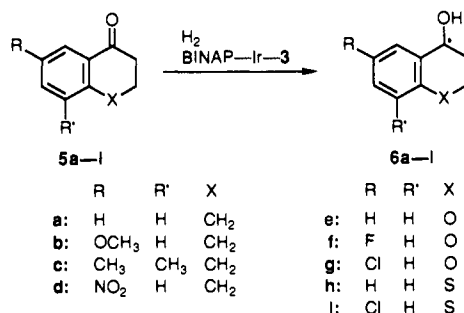
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Although a variety of functionalized ketones can now be readily hydrogenated to optically active secondary alcohols in very high enantiomeric excesses, mainly by use of chiral Ru(II) and Rh(I) catalysts,<sup>1</sup> enantioselective catalytic hydrogenation of ketones without a second ligating functionality is still a difficult but attractive target.<sup>2,3</sup> We describe herein a highly enantioselective hydrogenation of prochiral 1,2-benzocycloalkanones and  $\beta$ -thiacycloalkanones<sup>8</sup> using the new catalytic systems consisting of [Ir(binap)(cod)]BF<sub>4</sub> (**1**)<sup>9</sup> or [Ir(H<sub>8</sub>-binap)(cod)]BF<sub>4</sub> (**2**)<sup>9</sup> and a mixed P,N-donor ligand, bis(*o*-(*N,N*-dimethylamino)phenyl)-phenylphosphine (**3**).<sup>11,15</sup>

Some representative results are given in Table I.<sup>16</sup> In the presence of catalytic amounts of the binap-Ir(I) complex (*R*)-**1** and P,N-ligand **3** (1:2, hereafter abbreviated 1-3 system), hydrogenation of 1-tetralone (**5a**) in a mixture of dioxane and methanol (5:1) at 90 °C under an initial hydrogen pressure of 57 atm was almost complete after 75 h, affording (*R*)-**6a** in 95% ee (entry 1). With the same catalytic system, various five- and



six-membered 1,2-benzocycloalkanones **5b-i** and **7** have been reduced to the corresponding alcohols in 84–95% ees (entries 2–11). It is noteworthy that the enantioselectivities do not change



much when electron-donating or -withdrawing substituents (MeO, Me, NO<sub>2</sub>, F, and Cl) are introduced into the benzene rings of **5a** and **7a** or when the C(4)-atom of **5a** is replaced by oxygen or sulfur. Moreover, ees as high as 100% have been obtained on subsequent recrystallization of the alcoholic products (entries 3, 5–9, and 11). Likewise, hydrogenation of  $\beta$ -thiacycloalkanones **9** proceeded smoothly at 30–90 °C with high ees on use of the combination of the H<sub>8</sub>-binap-Ir(I) complex **2** and ligand **3** (1:1, hereafter abbreviated 2-3 system) (entries 12–14). Parallel

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(15) Recently we reported a chemoselective asymmetric hydrogenation of (*E*)-4-phenyl-3-buten-2-one to the corresponding allylic alcohol in up to 66% ee using [Ir(binap)(cod)]BF<sub>4</sub> (**1**) and (*o*-(*N,N*-dimethylamino)phenyl)-diphenylphosphine (**4**), in which the isolable mixed ligand iridium dihydride complex [Ir(H)<sub>2</sub>((*R*)-binap)(**4**)]BF<sub>4</sub> had been shown to be the catalytically active species: Mashima, K.; Akutagawa, T.; Zhang, X.; Takaya, H.; Taketomi, T.; Kumabayashi, H.; Akutagawa, S. *J. Organomet. Chem.* **1992**, *428*, 213.

(16) The new compounds described herein gave satisfactory analytical and spectroscopic data.

(17) For the coordinating ability of sulfur to Ir species, see, for example: (a) ref 13. (b) Rowe, M. D.; McCaffery, A. J.; Gale, R.; Copey, D. N. *Inorg. Chem.* **1972**, *11*, 3090. (c) Rao, K. M.; Day, C. L.; Jacobson, R. A.; Angelici, R. J. *Inorg. Chem.* **1991**, *30*, 5046.

(18) Volkman, R. A., Pfizer Inc. PCT Int. Appl. WO 88 08,845, 1988; *Chem. Abstr.* **1989**, *110*, 231330p.

(19) [Ir((*S*)-Cy-H<sub>8</sub>-binap)(cod)]BF<sub>4</sub>: deep red crystals, mp 136–138 °C dec; <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  5.69 (d, *J*<sub>HP</sub> = 14.5 Hz) and 23.79 (d).

(20) [Rh((*S*)-H<sub>8</sub>-binap)(cod)]ClO<sub>4</sub>: mp 213 °C dec; <sup>31</sup>P NMR (CDCl<sub>3</sub>)  $\delta$  25.06 (d, *J*<sub>RhP</sub> = 146.3 Hz).

<sup>†</sup> Kyoto University.

<sup>‡</sup> Takasago International Corporation.

(1) (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (b) Takaya, H.; Ohta, T.; Mashima, K. In *Homogeneous Transition Metal Catalyzed Reactions*; Moser, W. R., Slocum, D. W., Eds.; Advances in Chemistry Series 230; American Chemical Society: Washington, DC, 1992; p 124.

(2) Asymmetric hydrogenation of acetophenone catalyzed by a diphosphine-Rh(I) complex has been reported: Bakos, J.; Tóth, I.; Heil, B.; Szalontai, G.; Párkányi, L.; Fülöp, V. *J. Organomet. Chem.* **1989**, *370*, 263, and references therein.

(3) Efficient asymmetric reductions of relatively simple ketones have so far been attained by means of microbial transformations,<sup>4</sup> reduction with hydride reagents,<sup>5</sup> catalytic hydrosilylation,<sup>6</sup> and transfer hydrogenation.<sup>7</sup>

(4) (a) Csuk, R.; Glänzer, B. I. *Chem. Rev.* **1991**, *91*, 49. (b) Jones, J. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, p 183. (c) Holland, H. L.; Manoharan, T. S.; Schweizer, F. *Tetrahedron: Asymmetry* **1991**, *2*, 335.

(5) (a) Nishizawa, M.; Noyori, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, p 159. (b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475.

(6) (a) Brunner, H.; Obermann, Uwe. *Chem. Ber.* **1989**, *122*, 499, and references therein. (b) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500.

(7) (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.

(8)  $\beta$ -Thiacycloalkanones might not be regarded as unfunctionalized ketones. Their chelation to the iridium catalyst, however, seems to be difficult, though such a possibility cannot be ruled out.

(9) Abbreviations: binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; H<sub>8</sub>-binap = 2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl;<sup>10</sup> Cy-binap = 2,2'-bis(dicyclohexylphosphino)-1,1'-binaphthyl;<sup>10</sup> Cy-H<sub>8</sub>-binap = 2,2'-bis(dicyclohexylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl.<sup>10</sup>

(10) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumabayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283.

(11) There have been only a few applications of chiral iridium complexes in asymmetric catalysis,<sup>11,12</sup> although achiral iridium complexes are known to serve as homogeneous catalysts in a wide variety of reactions.<sup>13,14</sup>

(12) (a) Spogliarich, R.; Vidotto, S.; Farnetti, E.; Graziani, M.; Gulati, N. V. *Tetrahedron: Asymmetry* **1992**, *3*, 1001, and references therein. (b) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400. (c) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558.

(13) Serpone, N.; Jamieson, M. A. In *Comprehensive Coordination Chemistry*; Wilkinson, G.; Gillard, R. D.; McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1987; Vol. 4, p 1097.

**Table I.** Asymmetric Hydrogenation of Cyclic Ketones Catalyzed by [Ir(binap)(cod)]BF<sub>4</sub> (1)–3 and [Ir(H<sub>8</sub>-binap)(cod)]BF<sub>4</sub> (2)–3 Systems<sup>a</sup>

entry	substrate	catalyst <sup>b</sup>	conditions			product			
			solvent <sup>c</sup>	time, h	% conv <sup>d</sup>	% yield <sup>e</sup>	% ee <sup>f</sup>	config <sup>g</sup>	
1	<b>5a</b>	( <i>R</i> )-1-3	A	75	97	<b>6a</b>	88	95	( <i>R</i> )-(-)
2	<b>5b</b>	( <i>R</i> )-1-3	A	69	91	<b>6b</b>	74	95	(-)
3	<b>5c</b>	( <i>R</i> )-1-3	A	60	95	<b>6c</b>	78	95 (100)	(-)
4	<b>5d</b>	( <i>R</i> )-1-3	A	68	73	<b>6d</b>	64	94 <sup>h</sup>	(-)
5	<b>5e</b>	( <i>R</i> )-1-3	B	64	>99	<b>6e</b>	89	93 (>99)	( <i>R</i> )-(+)
6	<b>5f</b>	( <i>R</i> )-1-3	B	68	82	<b>6f</b>	77	92 (100)	(+)
7	<b>5g</b>	( <i>S</i> )-1-3	B	68	>99	<b>6g</b>	91	84 (96)	(-)
8	<b>5h</b>	( <i>S</i> )-1-3	B	40	91	<b>6h</b>	87	84 (100)	( <i>S</i> )-(-)
9	<b>5i</b>	( <i>R</i> )-1-3	B	68	94	<b>6i</b>	91	87 (100)	(+)
10	<b>7a</b>	( <i>S</i> )-1-3	B	22	90	<b>8a</b>	72	86	( <i>S</i> )-(+)
11	<b>7b</b>	( <i>R</i> )-1-3	B	40	93	<b>8b</b>	81	84 (100)	(-)
12	<b>9a</b>	( <i>R</i> )-2-3	A	63	38 <sup>i</sup>	<b>10a</b>	30	82 <sup>j</sup>	( <i>R</i> )-(+)
13	<b>9a</b>	( <i>R</i> )-2-3	A	13	97	<b>10a</b>	87	75 <sup>j</sup>	( <i>R</i> )-(+)
14	<b>9b</b>	( <i>S</i> )-2-3	A	13	100	<b>10b</b>	94	70 <sup>j</sup>	( <i>S</i> )-(-)

<sup>a</sup> Hydrogenation was carried out in an autoclave under an initial hydrogen pressure of 50–57 atm at 90 °C unless otherwise stated. <sup>b</sup> Substrate/[Ir] = 190–230 mol/mol. <sup>c</sup> 3/[Ir] ratios were 2 for entries 1–11 and 1 for entries 12–14. <sup>d</sup> A, dioxane–MeOH (5:1); B, THF–MeOH (5:1). Solvent/substrate ratio was 5 mL/g for entries 2–11 and 5 mL/mL for entries 1 and 12–14. <sup>e</sup> As given by GLC analysis. <sup>f</sup> Isolated yield obtained on column chromatography. <sup>g</sup> Determined by HPLC analysis with a DAICEL CHIRALCEL OD or OJ column unless otherwise indicated. Values in parentheses were obtained after one or two recrystallizations of the alcoholic products from acetone–, chloroform–, or toluene–hexane. <sup>h</sup> Determined by the signs of optical rotation, which were given in parentheses, where possible. <sup>i</sup> Determined by <sup>19</sup>F NMR analysis of the (*R*)-MTPA ester. <sup>j</sup> Reaction was performed at 30 °C. <sup>k</sup> Measured by HPLC analysis of the (*R*)-MTPA ester with a DAICEL CHIRALCEL OJ column.

experiments showed that matching between the catalyst and substrate is important. Complex **1** gave higher conversions and ees for hydrogenation of ketones **5a–f,i** and **7**, while complex **2** was more suitable for that of **9**. Comparable results (83–84% ee), however, have been obtained for the reduction of **5g,h** with the 1–3 and 2–3 catalytic systems.

In order to obtain an insight into the functions played by the benzene ring of ketones **5** and **7** as well as the sulfur atom in **9**, we have performed reduction of cyclopentanone (90 °C, 17 h, 26% conversion) catalyzed by the 2–3 system. The hydrogenation was much slower in this case than in the reduction of **7a** (18 h, 49% conversion, 72% ee) and **9a** (entry 13) under similar conditions, indicating that the benzene ring and S-atom<sup>17</sup> contribute much to satisfactory conversions. Further, comparison of the hydrogenation of tetrahydrofuran-3-one (90 °C, 17 h, 84% conversion, 12% ee) by the 2–3 system with that of **9a** suggests that the S-atom β to the carbonyl in **9a** also has significant influence upon the enantioselectivity. 2-Isothiochroman-4-one, in which the β-S-atom is opposite the benzene ring across the plane bisecting the cyclohexanone ring through the carbonyl group, was hydrogenated to 2-isothiochroman-4-ol in only 5 and 34% ee by the (*S*)-1–3 and (*S*)-2–3 systems, respectively.

Extensive screening of other binap–metal complexes, auxiliary ligands, and solvents has been carried out for the hydrogenation of **5a** and, especially, **9a**, since the product (*S*)-**10a** acts as an important building block in the synthesis of β-lactam antibacterials.<sup>18</sup> Use of [Ir((*S*)-Cy-binap)(cod)]BF<sub>4</sub><sup>15</sup> or [Ir((*S*)-Cy-H<sub>8</sub>-binap)(cod)]BF<sub>4</sub><sup>19</sup> containing the more basic diphosphines Cy-binap<sup>9,10</sup> and Cy-H<sub>8</sub>-binap<sup>9,10</sup> in tandem with **3** gave rise to substantial decreases in ees of **10a** (37 and 13%, respectively). A wide variety of known binap–Rh(I) and binap–Ru(II) complexes<sup>1</sup> as well as [Rh((*S*)-H<sub>8</sub>-binap)(cod)]ClO<sub>4</sub><sup>20</sup> have also been tested as catalysts for hydrogenation of **5a** and/or **9a**, but either no reduction or reduction with little or no enantioselectivities (0–15%) occurred.

Dramatic effects of auxiliary ligands on the efficiencies of this hydrogenation have been observed. For example, in the absence of an auxiliary ligand or in the presence of the analogous P,N-ligand **4** or the P,O-ligand tris(2,4,6-trimethoxyphenyl)phosphine, the catalytic activities and/or enantioselectivities of complexes

**1** and **2** for the hydrogenation of **7a** and/or **9a** were found to be much lower than those of the 1–3 and 2–3 systems under similar conditions. Reduction of **9a** was even completely suppressed on addition of 2 equiv of PPh<sub>3</sub> to (*R*)-**2**, though the 2–3 system (1:2 or 1:3) exhibited activities and enantioselectivities similar to those of the 2–3 system (1:1). These results suggest that in the catalytic cycles the P,N-ligand **3** is acting transiently as a multidentate ligand, but one or both of the N-donors can readily swing away from the metal to open up a coordination site or sites and allow binding of the ketone.<sup>14d,e,15,21</sup> Such coordination and dissociation of the amine arms can be expected to promote subsequent elementary processes such as insertion and reductive elimination and also might contribute to high enantioselectivities.

In addition, systematic studies revealed that both catalytic activities and enantioselectivities of the binap–Ir(I) catalysts are remarkably dependent on the solvent system employed.<sup>22</sup> The highest ees, coupled with satisfactory conversions, were attained when the hydrogenations of **5a** and **9a** were performed in dioxane–methanol (5:1) or THF–methanol (5:1), which have rarely been used in asymmetric catalysis.

In most of the successful asymmetric hydrogenations of functionalized ketones previously reported, chelation of the carbonyl group that undergoes hydrogenation and a second functionality located α, β, or γ to the carbonyl has been considered to be crucial. With the present substrates, however, such bidentate coordination seems to be difficult, though transient benzene ring– or sulfur–iridium<sup>17</sup> interactions prior to coordination of the carbonyl group may be required for high catalytic efficiency.

In conclusion, we have, by using the new binap–Ir(I)–aminophosphine catalytic systems, explored a highly enantioselective hydrogenation of a series of relatively simple cycloalkanones which had remained unsuccessful with conventional chiral phosphine–metal catalysts.

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**Supplementary Material Available:** Experimental details (4 pages). Ordering information is given on any current masthead page.

(21) Park, S.; Johnson, M. P.; Roundhill, D. M. *Organometallics* 1989, 8, 1700.

(22) For the solvent sensitivity of the catalytic activities of iridium–phosphine complexes in hydrogenation of olefins and ketones, see refs 14a–c.