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## ASYMMETRIC HYDROGENATION OF AROMATIC HETEROCYCLIC KETONES CATALYZED BY THE MsDPEN–Cp\*Ir(III) COMPLEX<sup>‡</sup>

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<sup>‡</sup>Dedication to Professor Akira Suzuki on the occasion of his 80<sup>th</sup> birthday

**Abstract** – Asymmetric hydrogenation of aromatic heterocyclic ketones catalyzed by Cp\*Ir(OTf)(Msdpn) (MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine) affords the heterocyclic alcohols in 93% to >99% ee. The reaction is conducted in a methanolic solution with a substrate-to-catalyst molar ratio of 200–5000 under 15 atm of H<sub>2</sub>. The heterocyclic rings of substrates are left intact.

Asymmetric hydrogenation of ketones is a key technology to synthesize optically active secondary alcohols.<sup>1</sup> Selection of appropriate chiral catalysts according to the structure and chemical features of the ketonic substrates is crucial to achieve high reactivity and enantioselectivity. We have previously exploited RuXY(diphosphine)(1,2-diamine)<sup>2,3</sup> and RuXY(diphosphine)( $\alpha$ -picolyamine)<sup>4</sup> (X = Y = Cl or X = H, Y =  $\eta^1$ -BH<sub>4</sub>), which act as excellent catalysts for asymmetric hydrogenation of simple ketones in basic or slightly basic alcoholic solutions. However, these catalysts cannot be used for the reaction of seriously base-labile 3(2*H*)-benzofuranones, 4-chromanones, and their derivatives. We have recently reported that Ru(OTf)(Tsdpen)( $\eta^6$ -*p*-cymene) (TfO<sup>−</sup> = trifluoromethanesulfonate, TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) without any basic compounds catalyzes hydrogenation of 4-chromanone to give the chiral alcohol in 97% ee quantitatively.<sup>5,6</sup> The neutral to slightly acidic reaction conditions prevent decomposition of the substrate. The isoelectronic Ir(III)

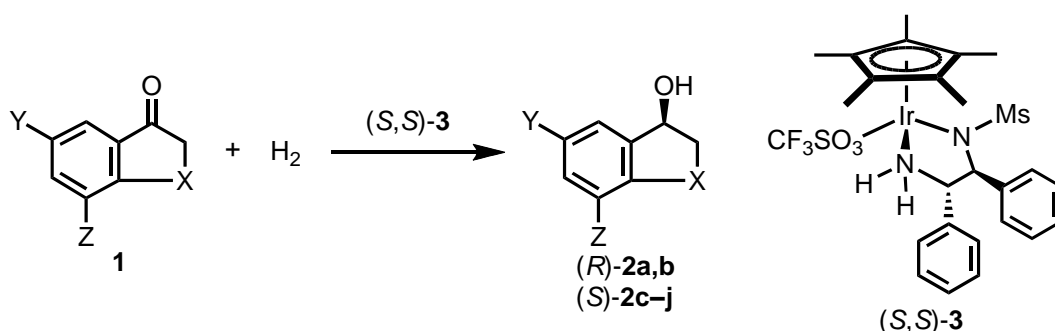
complex, Cp\*Ir(OTf)(Msdpn) (**3**) (Cp\* = pentamethylcyclopentadienyl, MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine), has been revealed to be an excellent catalyst for asymmetric hydrogenation of  $\alpha$ -hydroxy ketones, which are another class of base-sensitive ketonic substrates.<sup>7</sup> We herein describe enantioselective hydrogenation of aromatic heterocyclic ketones catalyzed by the Ir(III) complex **3**. The reaction of 4-chromanone resulted in an optical yield of 99%, even higher than that by Ru(OTf)(Tsdpen)( $\eta^6$ -*p*-cymene). A series of heterocyclic alcohols was obtained with high enantioselectivity.

Asymmetric hydrogenation of 3(2*H*)-benzofuranone (**1a**) with the Ir complex, (*S,S*)-**3**, at a substrate-to-catalyst molar ratio (S/C) of 500 in CH<sub>3</sub>OH at 60 °C under 15 atm of H<sub>2</sub> was completed in 24 h to afford the desired alcohol, (*R*)-**2a**, in 94% ee (Table 1, entry 1).<sup>8</sup> The heterocyclic ring was left intact. To our knowledge, this is the first example of asymmetric hydrogenation of 3(2*H*)-benzofuranones. The substrate with a CH<sub>3</sub>O group at the C7 position, **1b**, was also converted to (*R*)-**2b** in high enantioselectivity (entry 2).<sup>9</sup> When 1-indanone (**1c**) was hydrogenated at 30 °C (S/C = 200, 15 atm H<sub>2</sub>, 24 h), (*S*)-1-indanol [(*S*)-**2c**] was obtained in 98% ee and 95% yield with some unidentified byproducts, possible due to instability of the substrate (entry 3).<sup>10-12</sup> The reaction conducted at 60 °C was stopped at about 50% conversion. The Ir complex (*S,S*)-**3** exhibited excellent performance in hydrogenation of 4-chromanone (**1d**). Thus, the reaction with an S/C of 5000 (15 atm H<sub>2</sub>, 60 °C) for 24 h quantitatively gave (*S*)-**2d** in 99% ee (entry 4).<sup>5,11,13</sup> The high substrate concentration of 3.5 M is suitable for practical use. The catalytic activity of **3** for hydrogenation of **1d** is comparable to that of an isoelectronic Ru(OTf)(Tsdpen)( $\eta^6$ -*p*-cymene), but the enantioselective ability is higher than that of the Ru complex (99% vs. 97%).<sup>5</sup> 4-Chromanones with a CH<sub>3</sub> or Cl substituent at the C6 position, **1e** and **1f**, were also smoothly hydrogenated with **3** in >98% optical yield (entries 5 and 6).<sup>14,15</sup> The electronic and steric properties of these substituents little affected the reactivity and enantioselectivity. The Ir-catalyzed hydrogenation was applicable to 4-thiochromanone (**1g**) without loss of thiocyclic skeleton (entry 7).<sup>11</sup> The desired alcohol (*S*)-**2g** was obtained in >99% ee quantitatively.<sup>16</sup> A cyclic keto sulfone **1h**, which is hardly soluble in CH<sub>3</sub>OH, was hydrogenated in a 3:2 mixture of CH<sub>3</sub>OH and DMF ([**1h**] = 2.0 M) to give (*S*)-**2h** in 98% ee (entry 8).<sup>17</sup> Hydrogenation of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone (**1i**) afforded **2i** in 96% ee and 90% yield (entry 9).<sup>18</sup> It is noteworthy that hydrogenation of 1-tetralone (**1j**), a carbocyclic aromatic ketone, gave the alcohol **2j** in only 93% ee and 88% yield (entry 10: S/C = 500, 15 atm H<sub>2</sub>, 60 °C, 24 h),<sup>11,12,19,20</sup> suggesting that a heteroatom, especially oxygen, in the aliphatic ring of the substrate plays crucial roles in achieving high reactivity and enantioselectivity (see for example entry 4).

In summary, we have disclosed enantioselective hydrogenation of aromatic heterocyclic ketones catalyzed by the MsDPEN–Cp\*Ir(III) complex **3**. The reaction is conducted with an S/C of 200–5000

under 15 atm of H<sub>2</sub> to give the heterocyclic alcohols in >99% ee in the best cases. The heterocyclic structures are left intact. This is the first example of asymmetric hydrogenation of 3(2*H*)-benzofuranones, 4-thiochromanone 1,1-dioxides, and 1,2,3,4-tetrahydro-4-quinolinones. Thus, this method provides an efficient strategy to synthesize chiral heterocyclic alcohols.

**Table 1.** Asymmetric Hydrogenation of Cyclic Ketones (**1**)<sup>a</sup>



entry	ketone <b>1</b> ([ <b>1</b> ] <sub>0</sub> , M) <sup>b</sup>	S/C <sup>c</sup>	yield, % <sup>d</sup>	ee, % <sup>e</sup>
1	<b>1a</b> : X = O, Y = Z = H (2.0)	500	>99 (97)	94
2	<b>1b</b> : X = O, Y = H, Z = OMe (2.0)	200	>99 (99)	93
3	<b>1c</b> : X = CH <sub>2</sub> , Y = Z = H (3.5) <sup>f</sup>	200	95 (83)	98
4	<b>1d</b> : X = OCH <sub>2</sub> , Y = Z = H (3.5)	5000	>99 (99)	99
5	<b>1e</b> : X = OCH <sub>2</sub> , Y = CH <sub>3</sub> , Z = H (3.5)	3000	98 (98)	98
6	<b>1f</b> : X = OCH <sub>2</sub> , Y = Cl, Z = H (3.5)	3000	>99 (99)	>99
7	<b>1g</b> : X = SCH <sub>2</sub> , Y = Z = H (3.5)	500	>99 (99)	>99
8	<b>1h</b> : X = S(O <sub>2</sub> )CH <sub>2</sub> , Y = Z = H (2.0) <sup>g</sup>	500	>99 (97)	98
9	<b>1i</b> : X = N(Boc)CH <sub>2</sub> , Y = Z = H (2.0)	500	90 (90)	96
10	<b>1j</b> : X = (CH <sub>2</sub> ) <sub>2</sub> , Y = Z = H (3.5)	500	88 (83)	93

<sup>a</sup> Unless otherwise stated, reactions were conducted at 60 °C under 15 atm of H<sub>2</sub> using 1.0–20.0 mmol of **1** in MeOH containing 2.0–15.0 μmol of (*S,S*)-**3** in a glass autoclave. Reaction time was 24 h. <sup>b</sup> Initial concentration of **1**. <sup>c</sup> Substrate/catalyst molar ratio. <sup>d</sup> Determined by <sup>1</sup>H NMR analysis. Isolated yield is given in parenthesis. <sup>e</sup> Determined by chiral HPLC analysis. <sup>f</sup> Reaction at 30 °C. <sup>g</sup> Reaction in a 3:2 mixture of MeOH and DMF.

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8. (*R*)-2,3-Dihydro-3-benzofuranol (*R*)-**2a**: HPLC analytical conditions: column, CHIRALCEL OJ-H (4.6 mm i.d. x 250 mm); eluent, *n*-hexane/2-propanol = 99/1; flow rate, 1.5 mL/min; temp, 35 °C; detection, UV 220 nm; retention time ( $t_R$ ) of (*R*)-**2a**, 34.4 min;  $t_R$  of (*S*)-**2a**, 31.9 min.  $[\alpha]_D^{25}$  –61.6

- (*c* 1.68, CHCl<sub>3</sub>) [lit., [ $\alpha$ ]<sub>D</sub><sup>25</sup> +47 (*c* 1.70, CHCl<sub>3</sub>), 73% ee, (*S*)-isomer, D. R. Boyd, N. D. Sharma, R. Boyle, J. F. Malone, J. Chima, and H. Dalton, *Tetrahedron: Asymmetry*, 1993, 4, 1307]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.88 (d, 1H, *J* = 7.3 Hz), 4.45 (dd, 1H, *J* = 2.7, 11.0 Hz), 4.54 (dd, 1H, *J* = 6.4, 11.0 Hz), 5.36 (m, 1H), 6.88–6.97 (m, 2H), 7.28 (m, 1H), 7.43 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  72.2, 79.1, 110.6, 121.0, 125.4, 128.2, 130.8, 160.2.
9. (*R*)-7-Methoxy-2,3-dihydro-3-benzofuranol (*R*)-**2b**: HPLC analytical conditions: column, CHIRALCEL OJ-H; eluent, *n*-hexane/2-propanol = 9/1; flow rate, 1.0 mL/min; temp, 35 °C; detection, UV 220 nm; *t*<sub>R</sub> of (*R*)-**2b**, 19.9 min; *t*<sub>R</sub> of (*S*)-**2b**, 24.2 min. [ $\alpha$ ]<sub>D</sub><sup>25</sup> –43.2 (*c* 1.00, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.97 (br d, 1H, *J* = 7.3 Hz), 3.89 (s, 3H), 4.51 (dd, 1H, *J* = 2.3, 10.5 Hz), 4.59 (dd, 1H, *J* = 6.4, 10.5 Hz), 5.38 (m, 1H), 6.86 (m, 1H), 6.91 (t, 1H, *J* = 7.8 Hz), 7.04 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  56.0, 72.8, 79.7, 113.1, 117.2, 121.8, 129.3, 145.1, 148.9. The absolute configuration was estimated by <sup>1</sup>H-NMR analysis after conversion to the (*R*)- and (*S*)-MTPA esters as described in the literature, see: I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, 113, 4092.
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13. Procedure for asymmetric hydrogenation of 4-chromanone (**1d**) with (*S,S*)-**3**: 4-Chromanone (**1d**) (2.97 g, 20.0 mmol) and (*S,S*)-**3** (3.10 mg, 4.0  $\mu$ mol) were placed in a 100-mL glass autoclave. The atmosphere was replaced with Ar gas, and MeOH (3.3 mL) was added to this mixture. Hydrogen was initially introduced into the autoclave at a pressure of 10 atm, before being reduced to 1 atm. This procedure was repeated five times. Then the autoclave was pressurized with H<sub>2</sub> gas (15 atm), and the solution was stirred vigorously at 60 °C for 24 h. The <sup>1</sup>H-NMR and chiral HPLC analysis

- indicate that (*S*)-4-chromanol [(*S*)-**2d**] was obtained in 99% ee and >99% yield. Silica gel chromatography (silica gel 60N (Kanto Chemical), eluent: Et<sub>2</sub>O) of the crude product gave pure (*S*)-4-chromanol [(*S*)-**2d**] in 99% ee and 99% isolated yield (2.98 g, colorless crystals). The HPLC analytical conditions were the same as those described in note 8; *t<sub>R</sub>* of (*R*)-**2d**, 30.3 min; *t<sub>R</sub>* of (*S*)-**2d**, 25.5 min.  $[\alpha]_{\text{D}}^{25} -71.3$  (*c* 0.50, EtOH) [lit.,<sup>5</sup>  $[\alpha]_{\text{D}}^{25} -77$  (*c* 0.5, EtOH), 95% ee, (*S*)-isomer]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.86 (br s, 1H), 2.00–2.17 (m, 2H), 4.26–4.31 (m, 2H), 4.79 (dd, 1H, *J* = 3.7, 4.1 Hz), 6.84–6.94 (m, 2H), 7.19–7.32 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 30.8, 61.9, 63.2, 117.1, 120.6, 124.3, 129.6, 129.7, 154.6.
14. (*S*)-6-Methyl-4-chromanol (*S*)-**2e**: HPLC analytical conditions were the same as those described in note 8; *t<sub>R</sub>* of (*R*)-**2e**, 27.2 min; *t<sub>R</sub>* of (*S*)-**2e**, 22.1 min.  $[\alpha]_{\text{D}}^{25} -38.7$  (*c* 1.44, CHCl<sub>3</sub>) [lit.,<sup>5</sup>  $[\alpha]_{\text{D}}^{25} -38$  (*c* 1.0, CHCl<sub>3</sub>), 98% ee, (*S*)-isomer]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.81 (br s, 1H), 1.98–2.15 (m, 2H), 2.28 (s, 3H), 4.22–4.25 (m, 2H), 4.75 (dd, 1H, *J* = 3.7, 4.1 Hz), 6.75 (d, 1H, *J* = 8.2 Hz), 7.01 (dd, 1H, *J* = 1.8, 8.2 Hz), 7.11 (d, 1H, *J* = 1.8 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 20.5, 31.0, 61.9, 63.3, 116.8, 123.9, 129.79, 129.83, 130.4, 152.3.
15. (*S*)-6-Chloro-4-chromanol (*S*)-**2f**: HPLC analytical conditions were the same as those described in note 8; *t<sub>R</sub>* of (*R*)-**2f**, 33.1 min; *t<sub>R</sub>* of (*S*)-**2f**, 34.8 min.  $[\alpha]_{\text{D}}^{25} -26.3$  (*c* 1.00, CHCl<sub>3</sub>) [lit.,<sup>5</sup>  $[\alpha]_{\text{D}}^{25} -24$  (*c* 1.0, CHCl<sub>3</sub>), 98% ee, (*S*)-isomer]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.89 (br s, 1H), 1.99–2.16 (m, 2H), 4.23–4.29 (m, 2H), 4.76 (dd, 1H, *J* = 4.1, 4.6 Hz), 6.78 (d, 1H, *J* = 9.2 Hz), 7.15 (dd, 1H, *J* = 2.7, 9.2 Hz), 7.30 (d, 1H, *J* = 2.7 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 30.6, 62.2, 63.1, 118.5, 125.2, 125.6, 129.1, 129.6, 153.2.
16. (*S*)-4-Thiochromanol (*S*)-**2g**: HPLC analytical conditions: column, CHIRALCEL OD (4.6 mm i.d. x 250 mm); eluent, *n*-hexane/2-propanol = 98/2; flow rate, 1.0 mL/min; temp, 35 °C; detection, UV 220 nm; *t<sub>R</sub>* of (*R*)-**2g**, 27.4 min; *t<sub>R</sub>* of (*S*)-**2g**, 21.0 min.  $[\alpha]_{\text{D}}^{25} -136$  (*c* 1.00, CHCl<sub>3</sub>) [lit.,  $[\alpha]_{\text{D}}^{22} -136$  (*c* 1.00, CHCl<sub>3</sub>), 97% ee, (*S*)-isomer, C. V. Ursini, G. H. M. Dias, and J. A. R. Rodrigues, [J. Organomet. Chem., 2005, 690, 3176](#)]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.84 (br s, 1H), 2.05 (m, 1H), 2.35 (m, 1H), 2.86 (ddd, 1H, *J* = 3.7, 5.5, 12.4 Hz), 3.32 (dt, 1H, *J* = 12.4, 2.8 Hz), 4.81 (m, 1H), 7.05–7.18 (m, 3H), 7.31 (d, 1H, *J* = 6.9 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 21.5, 30.0, 66.5, 124.3, 126.7, 128.4, 130.3, 133.2, 134.6.
17. (*S*)-4-Thiochromanol 1,1-dioxide (*S*)-**2h**: HPLC analytical conditions were the same as those described in note 9; *t<sub>R</sub>* of (*R*)-**2h**, 34.3 min; *t<sub>R</sub>* of (*S*)-**2h**, 37.8 min.  $[\alpha]_{\text{D}}^{25} +5.1$  (*c* 1.00, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.30 (d, 1H, *J* = 5.5 Hz), 2.55 (m, 1H), 2.75 (m, 1H), 3.30 (ddd, 1H, *J* = 3.2, 7.8, 14.2 Hz), 3.72 (ddd, 1H, *J* = 3.2, 11.0, 14.2 Hz), 4.93 (dd, 1H, *J* = 5.5, 9.2 Hz), 7.51–7.61 (m, 3H), 7.90 (d, 1H, *J* = 8.2 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 29.4, 46.5, 65.7, 123.6, 129.1, 129.7, 133.0, 137.7, 137.8. The absolute configuration was estimated by <sup>1</sup>H-NMR analysis after

conversion to the (*R*)- and (*S*)-MTPA esters as described in the literature.<sup>9</sup>

18. (*S*)-1-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydro-4-quinolinol (*S*)-**2i**: HPLC analytical conditions were the same as those described in note 8;  $t_R$  of (*R*)-**2i**, 21.6 min;  $t_R$  of (*S*)-**2i**, 18.6 min.  $[\alpha]_D^{25} -27.7$  (*c* 1.04, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.53 (s, 9H), 1.85 (br s, 1H), 1.98–2.11 (m, 2H), 3.59 (ddd, 1H,  $J = 3.7, 9.6, 13.3$  Hz), 4.05 (ddd, 1H,  $J = 4.6, 6.0, 13.3$  Hz), 4.77 (t, 1H,  $J = 4.6$  Hz), 7.07 (m, 1H), 7.25 (m, 1H), 7.38 (m, 1H), 7.78 (m, 1H), <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  28.3, 31.9, 40.4, 65.9, 81.2, 123.4, 123.6, 127.9, 128.2, 130.5, 137.8, 153.6. The absolute configuration was estimated by <sup>1</sup>H-NMR analysis after conversion to the (*R*)- and (*S*)-MTPA esters as described in the literature.<sup>9</sup>
19. For asymmetric hydrogenation of 1-tetralones catalyzed by BINAP/chiral 1,4-diamine–Ru(II) complexes, see: T. Ohkuma, T. Hattori, H. Ooka, T. Inoue, and R. Noyori, *Org. Lett.*, 2004, **6**, 2681.
20. (*S*)-1-Tetralol (*S*)-**2j**: HPLC analytical conditions were the same as those described in note 8;  $t_R$  of (*R*)-**2j**, 14.6 min;  $t_R$  of (*S*)-**2j**, 13.3 min.  $[\alpha]_D^{25} +31.1$  (*c* 1.05, CHCl<sub>3</sub>) [lit.,<sup>19</sup>  $[\alpha]_D^{23} -33.5$  (*c* 1.01, CHCl<sub>3</sub>), 99% ee, (*R*)-isomer]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.65 (br s, 1H), 1.76–2.02 (m, 4H), 2.71–2.86 (m, 2H), 4.79 (dd, 1H,  $J = 3.7, 5.5$  Hz), 7.11 (m, 1H), 7.18–7.22 (m, 2H), 7.43 (m, 1H), <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  18.7, 29.2, 32.2, 68.1, 126.1, 127.5, 128.6, 129.0, 137.1, 138.7.