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ASYMMETRIC HYDROGENATION OF AROMATIC HETEROCYCLIC KETONES CATALYZED BY THE MsDPEN-Cp*Ir(III) COMPLEX[‡]

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[‡]Dedication to Professor Akira Suzuki on the occasion of his 80th 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 H₂. The heterocyclic rings of substrates are left intact.

Asymmetric hydrogenation of ketones is a key technology to synthesize optically active secondary alcohols.¹ 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)^{2,3} and RuXY(diphosphine)(α -picolylamine)⁴ (X = Y = Cl or X = H, Y = η^1 -BH₄), 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)(Tsdpn)(η^6 -*p*-cymene) (TfO[−] = 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.^{5,6} The neutral to slightly acidic reaction conditions prevent decomposition of the substrate. The isoelectronic Ir(III)

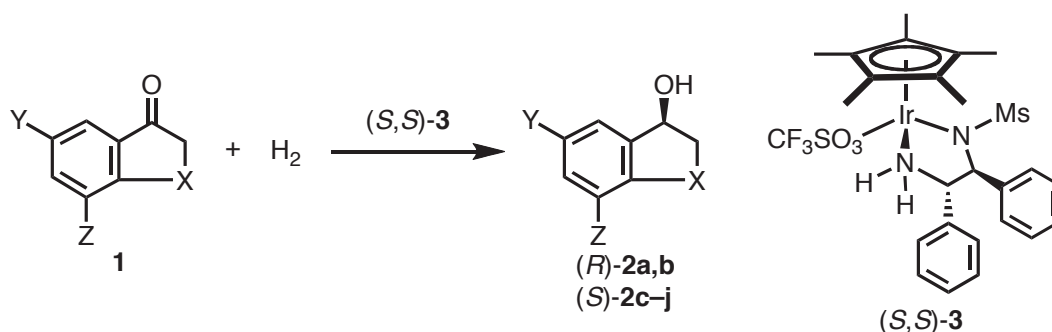
complex, $\text{Cp}^*\text{Ir}(\text{OTf})(\text{Msdpn})$ (**3**) (Cp^* = pentamethylcyclopentadienyl, MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine), has been revealed to be an excellent catalyst for asymmetric hydrogenation of α -hydroxy ketones, which are another class of base-sensitive ketonic substrates.⁷ 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 $\text{Ru}(\text{OTf})(\text{Tsdpen})(\eta^6\text{-}p\text{-cymene})$. 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_3OH at 60 °C under 15 atm of H_2 was completed in 24 h to afford the desired alcohol, (*R*)-**2a**, in 94% ee (Table 1, entry 1).⁸ 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_3O group at the C7 position, **1b**, was also converted to (*R*)-**2b** in high enantioselectivity (entry 2).⁹ When 1-indanone (**1c**) was hydrogenated at 30 °C (S/C = 200, 15 atm H_2 , 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).^{10–12} 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_2 , 60 °C) for 24 h quantitatively gave (*S*)-**2d** in 99% ee (entry 4).^{5,11,13} 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 $\text{Ru}(\text{OTf})(\text{Tsdpen})(\eta^6\text{-}p\text{-cymene})$, but the enantioselective ability is higher than that of the Ru complex (99% vs. 97%).⁵ 4-Chromanones with a CH_3 or Cl substituent at the C6 position, **1e** and **1f**, were also smoothly hydrogenated with **3** in >98% optical yield (entries 5 and 6).^{14,15} 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).¹¹ The desired alcohol (*S*)-**2g** was obtained in >99% ee quantitatively.¹⁶ A cyclic keto sulfone **1h**, which is hardly soluble in CH_3OH , was hydrogenated in a 3:2 mixture of CH_3OH and DMF ([**1h**] = 2.0 M) to give (*S*)-**2h** in 98% ee (entry 8).¹⁷ Hydrogenation of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone (**1i**) afforded **2i** in 96% ee and 90% yield (entry 9).¹⁸ 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_2 , 60 °C, 24 h),^{11,12,19,20} 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 $\text{MsDPEN-Cp}^*\text{Ir(III)}$ complex **3**. The reaction is conducted with an S/C of 200–5000

under 15 atm of H₂ 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**)^a



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

^a Unless otherwise stated, reactions were conducted at 60 °C under 15 atm of H₂ 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. ^b Initial concentration of **1**. ^c Substrate/catalyst molar ratio. ^d Determined by ¹H NMR analysis. Isolated yield is given in parenthesis. ^e Determined by chiral HPLC analysis. ^f Reaction at 30 °C. ^g 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, CHCl₃) [lit., $[\alpha]_{\text{D}}^{25}$ +47 (*c* 1.70, CHCl₃), 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]. ¹H NMR (400 MHz, CDCl₃) δ 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). ¹³C NMR (100 MHz, CDCl₃) δ 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_R* of (*R*)-**2b**, 19.9 min; *t_R* of (*S*)-**2b**, 24.2 min. $[\alpha]_{\text{D}}^{25}$ –43.2 (*c* 1.00, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 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). ¹³C NMR (100 MHz, CDCl₃) δ 56.0, 72.8, 79.7, 113.1, 117.2, 121.8, 129.3, 145.1, 148.9. The absolute configuration was estimated by ¹H-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 μ 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 H₂ gas (15 atm), and the solution was stirred vigorously at 60 °C for 24 h. The ¹H-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: Et₂O) 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_R* of (*R*)-**2d**, 30.3 min; *t_R* of (*S*)-**2d**, 25.5 min. $[\alpha]_D^{25} -71.3$ (*c* 0.50, EtOH) [lit.,⁵ $[\alpha]_D^{25} -77$ (*c* 0.5, EtOH), 95% ee, (*S*)-isomer]. ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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_R* of (*R*)-**2e**, 27.2 min; *t_R* of (*S*)-**2e**, 22.1 min. $[\alpha]_D^{25} -38.7$ (*c* 1.44, CHCl₃) [lit.,⁵ $[\alpha]_D^{25} -38$ (*c* 1.0, CHCl₃), 98% ee, (*S*)-isomer]. ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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_R* of (*R*)-**2f**, 33.1 min; *t_R* of (*S*)-**2f**, 34.8 min. $[\alpha]_D^{25} -26.3$ (*c* 1.00, CHCl₃) [lit.,⁵ $[\alpha]_D^{25} -24$ (*c* 1.0, CHCl₃), 98% ee, (*S*)-isomer]. ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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_R* of (*R*)-**2g**, 27.4 min; *t_R* of (*S*)-**2g**, 21.0 min. $[\alpha]_D^{25} -136$ (*c* 1.00, CHCl₃) [lit., $[\alpha]_D^{22} -136$ (*c* 1.00, CHCl₃), 97% ee, (*S*)-isomer, C. V. Ursini, G. H. M. Dias, and J. A. R. Rodrigues, *J. Organomet. Chem.*, 2005, **690**, 3176]. ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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_R* of (*R*)-**2h**, 34.3 min; *t_R* of (*S*)-**2h**, 37.8 min. $[\alpha]_D^{25} +5.1$ (*c* 1.00, CHCl₃). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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 ¹H-NMR analysis after

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

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_3). ^1H NMR (400 MHz, CDCl_3) δ 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), ^{13}C NMR (100 MHz, CDCl_3) δ 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 ^1H -NMR analysis after conversion to the (*R*)- and (*S*)-MTPA esters as described in the literature.⁹
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_3) [lit.,¹⁹ $[\alpha]_D^{23} -33.5$ (c 1.01, CHCl_3), 99% ee, (*R*)-isomer]. ^1H NMR (400 MHz, CDCl_3) δ 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), ^{13}C NMR (100 MHz, CDCl_3) δ 18.7, 29.2, 32.2, 68.1, 126.1, 127.5, 128.6, 129.0, 137.1, 138.7.