ORGANIC LETTERS

2007
Vol. 9, No. 13
2565−2567

Asymmetric Hydrogenation of α-Hydroxy Ketones Catalyzed by MsDPEN–Cp*Ir(III) Complex

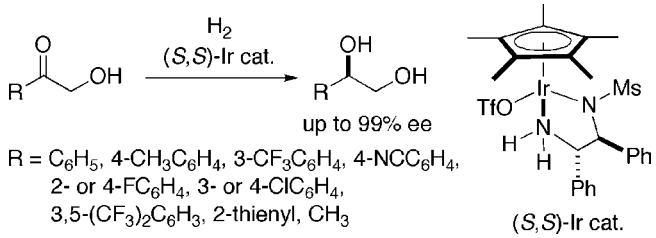
Takeshi Ohkuma,*,† Noriyuki Utsumi,‡ Masahito Watanabe,‡ Kunihiko Tsutsumi,‡ Noriyoshi Arai,† and Kunihiko Murata‡

Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan, and Central Research Laboratory, Technology and Development Division, Kanto Chemical CO., Inc., Soka, Saitama 340-0003, Japan

ohkuma@eng.hokudai.ac.jp

Received April 25, 2007

ABSTRACT



Asymmetric hydrogenation of a series of α-hydroxy aromatic ketones in methanol catalyzed by Cp*Ir(OTf)(MsDPEN) (MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine) affords the 1-aryl-1,2-ethanediols in up to 99% ee. The reaction can be conducted with a substrate-to-catalyst molar ratio as high as 6000 under 10 atm of H_2. 1-Hydroxy-2-propanone is also hydrogenated with high enantioselectivity.

Exploitation of synthetic procedures for useful chiral building blocks is one of the main subjects in the area of organic chemistry. Recently, practical asymmetric syntheses of biologically active compounds using chiral 1-aryl-1,2-ethanediols as key intermediates have been reported.[1] Enantioselective dihydroxylation of styrene derivatives with AD-mix reagents is a representative method to produce this important class of compounds.[1,2] Asymmetric hydrogenation of α-hydroxy aromatic ketones is another reliable procedure for this purpose (Scheme 1).[3−5] However, this asymmetric transformation is still difficult even with modern, well-designed molecular catalysts.[6] For example, RuX_2(BINAP) (polymeric form) (X = Cl, Br)[7,8] and its analogues catalyze the asymmetric hydrogenation of 1-hydroxy-2-alkanones to afford chiral 1,2-diols in high enantiomeric excess (ee).[7−9] However, reaction of α-hydroxyacetophenone (**3a**) with the BINAP−Ru(II) catalyst gave the 1,2-diol **4a** in only 66%

† Hokkaido University.
‡ Kanto Chemical CO., Inc.

(1) (a) Pye, P. J.; Rossen, K.; Weissman, S. A.; Maliakal, A.; Reamer, R. A.; Ball, R.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *Chem.—Eur. J.* **2002**, *8*, 1372−1376. (b) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771−1774. (c) Singh, A. K.; Prasad, J. S.; Delaney, E. J. In *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches, and Solutions*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 335−348.

(2) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771. (b) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785−3786. (c) Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940−3941. (d) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448−451.

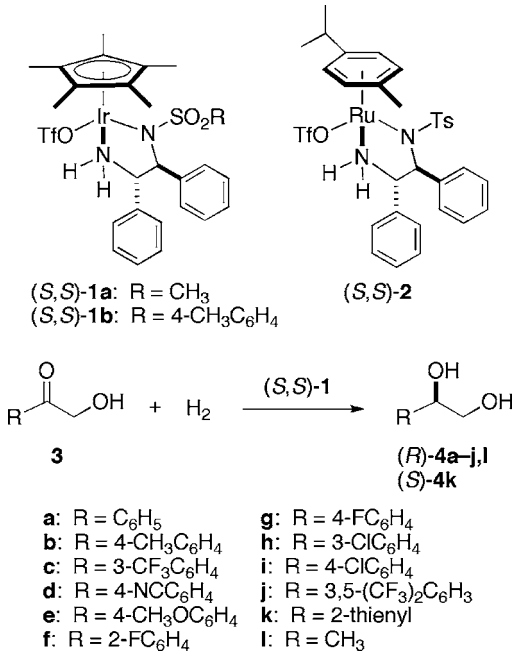
(3) For asymmetric hydrogenation of α-chloro aromatic ketones with chiral arene−Ru(II) complex **2**, see: Ohkuma, T.; Tsutsumi, K.; Utsumi, N.; Arai, N.; Noyori, R.; Murata, K. *Org. Lett.* **2007**, *9*, 255−257. See also: Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Sandoval, C.; Noyori, R. *J. Am. Chem. Soc.* **2006**, *128*, 8724−8725.

(4) For asymmetric transfer hydrogenation of α-hydroxyacetophenone, see: (a) Cross, D. J.; Kenny, J. A.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1801−1806. (b) Matharu, D. S.; Morris, D. J.; Kawamoto, A. M.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2005**, *7*, 5489−5491. (c) Matharu, D. S.; Morris, D. J.; Clarkson, G. J.; Wills, M. *Chem. Commun.* **2006**, 3232−3234.

(5) Asymmetric hydrogenation of vinyl bis(boronates) followed by an oxidative treatment with a basic H_2O_2 gave the chiral diol in high ee. See: Morgan, J. B.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15338−15339.

10.1021/ol070964w CCC: $37.00
Published on Web 05/23/2007

Scheme 1



ee.[10] *trans*-$RuCl_2$(XylBINAP)(DAIPEN) with an alkaline base effects asymmetric hydrogenation of α-methoxyacetophenone, affording 2-methoxy-1-phenyl-1-ethanol in 97% ee.[11−14] However, the hydroxy ketone **3a** was not reduced with the catalyst owing to instability of the ketonic substrate under such basic conditions.[15] We report herein for the first time, asymmetric hydrogenation of α-hydroxy aromatic ketones with the newly devised Cp*Ir(OTf)(MsDPEN) (**1a**) (Cp* = pentamethylcyclopentadienyl, TfO^- = trifluoromethanesulfonate, MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine). The hydrogenation proceeded smoothly with a substrate-to-catalyst molar ratio (*S*/*C*) as high as 6000 under 10 atm of H_2, affording a series of 1-aryl-1,2-ethanediols in up to 99% ee. The reaction of 1-hydroxy-2-propanone, an aliphatic α-hydroxy ketone, is also discussed.

Cp*Ir(OTf)[(*S*,*S*)-MsDPEN] [(*S*,*S*)-**1a**] and Cp*Ir(OTf)-[(*S*,*S*)-TsDPEN] [(*S*,*S*)-**1b**][16,17] (TsDPEN = *N*-(toluenesulfonyl)-1,2-diphenylethylenediamine) (Scheme 1) were prepared from commercially available $[Cp^*IrCl_2]_2$ in two steps (see the Supporting Information). The iridium complex reacted with (*S*,*S*)-MsDPEN or (*S*,*S*)-TsDPEN in a basic $H_2O-CH_2Cl_2$ two phase system to give the 16-electron amide complex Cp*Ir[(*S*,*S*)-MsDPEN] or Cp*Ir[(*S*,*S*)-TsDPEN].[16b] Dropwise addition of TfOH in CH_2Cl_2 to the CH_2Cl_2 solution of the amide complex formed (*S*,*S*)-**1a** or (*S*,*S*)-**1b** in good yield.[3]

First, we selected α-hydroxyacetophenone (**3a**)[18] as a typical substrate for the screening of chiral catalysts and reaction conditions (Scheme 1). When hydrogenation of **3a** (1.63 g, 12.0 mmol) using (*S*,*S*)-**1a** (1.5 mg, 2.0 μmol, *S*/*C* = 6000) as a precatalyst in methanol (4.8 mL) under 10 atm of H_2 at 60 °C was conducted for 15 h, (*R*)-1-phenyl-1,2-ethanediol [(*R*)-**4a**] was produced in 96% ee and 97% yield (Table 1). The reactivity was reduced when the reaction was carried out in ethanol or 2-propanol, while a high level of enantioselectivity was preserved. An optimal yield was attained in the reaction at 60 °C. The catalytic species may have a short life at a higher temperature. The hydrogenation proceeded smoothly even under 1 atm of H_2 at an *S*/*C* of

Table 1. Asymmetric Hydrogenation of α-Hydroxyacetophenone (**3a**)[a]

	conditions				(*R*)-**4a**	
catalyst no.	*S*/*C*[b]	solvent	temp °C	H_2 atm	yield %[c]	ee %[d]
(*S*,*S*)-**1a**	6000	CH_3OH	60	10	97 (94)	96
(*S*,*S*)-**1a**	6000	C_2H_5OH	60	10	36	96
(*S*,*S*)-**1a**	6000	*i*-C_3H_7OH	60	10	67	95
(*S*,*S*)-**1a**	6000	CH_3OH	50	10	50	97
(*S*,*S*)-**1a**	6000	CH_3OH	70	10	65	96
(*S*,*S*)-**1a**	200[e]	CH_3OH	60	1	97 (94)	96
(*S*,*S*)-**1b**	6000	CH_3OH	60	10	12	85
(*S*,*S*)-**2**	6000	CH_3OH	60	10	<1	

[a] Unless otherwise stated, reactions were conducted using 12 mmol of **3a** (2.0 M) in solvent containing **1** or **2** (2.0 μmol, 0.33 mM) in a silanized glass autoclave. Reaction time was 15 h. [b] Substrate/catalyst molar ratio. [c] Determined by ^1H NMR analysis. Isolated yield is stated in parentheses. [d] Determined by chiral HPLC analysis (DAICEL CHIRALCEL OB). [e] Reaction using 0.80 mmol of **3a** (0.067 M) with **1a** (4.0 μmol, 0.33 mM).

(6) (a) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 199−246. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1−110. (c) Ohkuma, T.; Noyori, R. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 29−113. (d) Ohkuma, T.; Noyori, R. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 1105−1163.

(7) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629−631.

(8) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(9) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264−267.

(10) Ohkuma, T. Ph.D. Thesis, Nagoya University, 1991.

(11) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529−13530.

(12) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73.

(13) For asymmetric hydrogenation of arylglyoxal dialkylacetals, see: Arai, N.; Ooka, H.; Azuma, K.; Yabuuchi, T.; Kurono, N.; Inoue, T.; Ohkuma, T. *Org. Lett.* **2007**, *9*, 939−941.

(14) For asymmetric hydrogenation of amino ketones catalyzed by chiral Ru complexes, see: Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510−6511.

(15) See for example: Edmonds, J. S.; Morita, M.; Turner, P.; Skelton, B. W.; White, A. H. *Steroids* **2006**, *71*, 34−41.

(16) For asymmetric transfer hydrogenation of ketones catalyzed by TsDPEN−Cp*Ir complexes, see: (a) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199−1200. (b) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1201−1202. (c) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186−2187.

(17) Reaction of $[Cp^*Ir(TsDPEN)]^+$ with H_2 gave the IrH species. See: Heiden, Z. M.; Rauchfuss, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 13048−13049.

(18) Martin, R. *Handbook of Hydroxyacetophenones*; Springer: Berlin, Heidelberg, New York, 2005.

200 without loss of enantioselectivity. The catalyst feature was significantly affected by the *N*-sulfonate substituents. When the reaction was conducted with Cp*Ir(OTf)[(*S*,*S*)-TsDPEN] [(*S*,*S*)-**1b**] (*S*/*C* = 6000, 10 atm H_2, 60 °C, 15 h), (*R*)-**4a** was obtained in only 12% yield and 85% ee (Table 1). It is worth noting that Ru(OTf)(TsDPEN)(η^6-*p*-cymene) (**2**), which is an efficient catalyst for asymmetric hydrogenation of α-chloro aromatic ketones,[3] was virtually inert for the reaction of the electronically related α-hydroxy ketones.

The catalyst system was applied to the asymmetric hydrogenation of a series of α-hydroxy ketones **3**, and the results are shown in Table 2. Hydrogenation of the 4′-CH_3-substituted ketone **3b** in the presence of (*S*,*S*)-**1a** with an *S*/*C* of 1000 at 60 °C under 10 atm of H_2 afforded the chiral diol (*R*)-**4b** in 94% ee quantitatively. An excellent optical yield of 97% was achieved in the reaction of 3′-CF_3-substituted ketone **3c**. The reactivity was markedly influenced by the electronic properties of the substrates. Thus, a hydroxy ketone **3e** bearing an electron-donating CH_3O group at the 4′ position was not converted at all under the standard reaction conditions, while the hydrogenation of **3d** substituted by an electron-attracting CN group at the 4′ position proceeded smoothly. Complete conversion was achieved with a high level of enantioselectivity in the hydrogenation of 4′-F- and 4′-Cl-substituted ketones, **3g** and **3i**, at an *S*/*C* of 3000 under otherwise identical conditions. Reaction of 3′-Cl-substituted ketone **3h** afforded the chiral alcohol **4h** in 95% ee, while the fluorinated ketone **3f** at the 2′ position was reduced with moderate enantioselectivity. Disubstituted ketone **3j** with a CF_3 group at the 3′ and 5′ positions was hydrogenated in the presence of (*S*,*S*)-**1a** to yield (*R*)-**4j** in 96% ee. The antipode of the product, that is, (*S*)-**4j**, is a key intermediate for the synthesis of substance P inhibitors.[1a] 2-Thienyl ketone **3k** was converted to the chiral alcohol **4k** with nearly perfect enantioselectivity, leaving the heteroaromatic ring intact.[19] Interestingly, (*S*,*S*)-**1a** efficiently catalyzed the hydrogenation of 1-hydroxy-2-propanone (**3l**), the simplest aliphatic α-hydroxy ketone, producing (*R*)-1,2-propanediol [(*R*)-**4l**] in 80% ee (Table 2).[7−9] Again, the chiral arene−Ru complex **2**[3] showed poor activity and enantioselectivity for this reaction.

Table 2. Asymmetric Hydrogenation of α-Hydroxy Ketones[a]

ketone		conditions			alcohol		
no.	catalyst	S/C[b]	H_2 atm	time h	yield %[c]	ee %[d]	config[e]
3a[f]	(*S*,*S*)-**1a**	6000	10	15	97 (94)	96	*R*
3b	(*S*,*S*)-**1a**	1000	10	15	>99 (89)	94	*R*
3c	(*S*,*S*)-**1a**	1000	10	15	>99 (94)	97	*R*
3d	(*S*,*S*)-**1a**	1000	10	15	>99 (94)	94	*R*
3e	(*S*,*S*)-**1a**	1000	10	15	<1		
3f	(*S*,*S*)-**1a**	1000	10	15	>99 (89)	74	*R*[g]
3g[h]	(*S*,*S*)-**1a**	3000	10	15	>99 (93)	96	*R*
3h	(*S*,*S*)-**1a**	1000	10	15	89 (80)	95	*R*
3i[h]	(*S*,*S*)-**1a**	3000	10	15	>99 (91)	96	*R*
3j	(*S*,*S*)-**1a**	1000	10	15	>99 (91)	96	*R*
3k	(*S*,*S*)-**1a**	1000	10	15	>99 (97)	99	*S*[g]
3l	(*S*,*S*)-**1a**	1000	10	15	97 (90)	80[i]	*R*
3l	(*S*,*S*)-**2**	1000	10	15	35	10[i]	*R*

[a] Unless otherwise stated, reactions were conducted using 2.0 mmol of ketone (0.33 M) in methanol containing **1a** or **2** (2.0 μmol, 0.33 mM) at 60 °C in a silanized glass autoclave. [b] Substrate/catalyst molar ratio. [c] Determined by ^{1}H NMR analysis. Isolated yield is stated in parentheses. [d] Determined by chiral HPLC analysis. [e] Determined by the sign of rotation. [f] Reaction with 12.0 mmol of **3a** (2.0 M). [g] See Supporting Information. [h] Reaction with 6.0 mmol of **3** (1.0 M). [i] Determined by chiral GC analysis after conversion to the acetone cyclic acetal.

In summary, we have described the first example of highly enantioselective hydrogenation of α-hydroxy aromatic ketones catalyzed by the newly devised MsDPEN−Cp*Ir(III) triflate **1a**. The closely related catalysts, TsDPEN−Cp*Ir(III) triflate **1b** and arene/TsDPEN−Ru(II) triflate **2**, as well as several other known catalysts, are not effective for this transformation. A series of 1-aryl-1,2-ethanediols and the heteroaryl analogues are quantitatively obtained in up to 99% ee by hydrogenation with the Ir catalyst **1a**. A simple 1,2-propanediol is also available in high stereoselectivity. Thus, this method provides a new, efficient pathway to produce synthetically useful chiral 1,2-diols.

Acknowledgment. This work was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (Grant No. 18350046).

Supporting Information Available: Preparative methods and properties of chiral Ir complexes **1**, procedures for asymmetric hydrogenation of α-hydroxy ketones, NMR and HPLC behavior of products, $[\alpha]_D$ values and absolute-configuration determination. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070964W

(19) Due to the group priority in nomenclature, (*R*)-**4a**−**j**,**l** and (*S*)-**4k** have the same *β* configuration in Scheme 1.