

# Practical Synthesis of Optically Active Styrene Oxides via Reductive Transformation of 2-Chloroacetophenones with Chiral Rhodium Catalysts

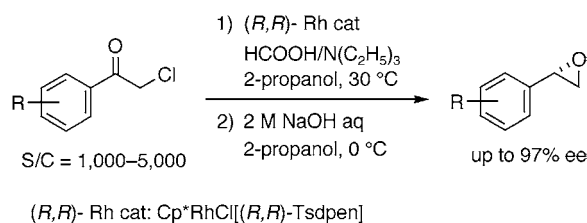
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Received October 17, 2002

## ABSTRACT



A practical method for the synthesis of optically active styrene oxides has been developed via formation of optically active 2-chloro-1-phenylethanols generated by reductive transformation of ring-substituted 2-chloroacetophenones. The optically active alcohols with up to 98% ee are obtainable from the asymmetric reduction of acetophenones with an S/C = 1000–5000 with a formic acid triethylamine mixture containing a well-defined chiral Rh complex, Cp\*RhCl[(*R,R*)-Tsdpen].

Optically active styrene oxides are useful building blocks for the synthesis of various pharmaceuticals such as  $\alpha$ 1-,  $\beta$ 2-, and  $\beta$ 3-adrenergic receptor agonists.<sup>1</sup> To access com-

pounds of this important class, Jacobsen's asymmetric epoxidation of styrenes with (salen)Mn(III) complex<sup>2a,b</sup> and kinetic resolution of racemic epoxides with cobalt–salen complexes<sup>2c</sup> have been well-established as practical synthetic procedures in addition to some microbial approaches.<sup>3</sup> Besides these transformations, chiral styrene oxides are also

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(3) (a) Matsuyama, A.; Kobayashi, Y. EP 0611826A2, 1994. (b) Tanaka, K.; Yasuda, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3275–3282.

**Table 1.** Asymmetric Transfer Hydrogenation of 2-Chloroacetophenone, **2a**, Catalyzed by Chiral Catalysts **1a–c** with a HCOOH/ $N(C_2H_5)_3$  Mixture or 2-Propanol<sup>a</sup>

catalyst	S/C	HCOOH/ $N(C_2H_5)_3$	solvent	time, h	yield, % <sup>b</sup>	ee, % <sup>b</sup>	config <sup>c</sup>
<b>1a</b>	1000	5:2	$CH_3CO_2C_2H_5$	1	99	97	<i>S</i>
<b>1a</b>	5000	5:2	$CH_3CO_2C_2H_5$	2	99	96	<i>S</i>
<b>1a</b>	1000	5:2		1	99	89	<i>S</i>
<b>1a</b>	100	2-propanol	2-propanol	14	94	98	<i>S</i>
<b>1a</b>	1000	2-propanol	2-propanol	16	trace		
<b>1b</b>	1000	1:1	$CH_3CO_2C_2H_5$	24	36	91	<i>S</i>
<b>1c</b>	1000	5:2	$CH_3CO_2C_2H_5$	4	99	71	<i>S</i>

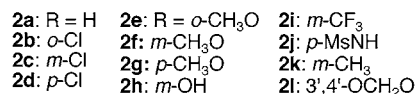
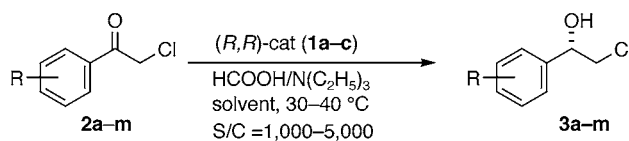
<sup>a</sup> Reaction of **2a** in a 1.0 M solution containing the (*R,R*)-Rh catalyst (**1a**) was conducted with a mixture of HCOOH and  $N(C_2H_5)_3$  at 25 °C. <sup>b</sup> Unless otherwise noted, yields and ee values were determined by HPLC analysis using a Daicel Chiralcel OB or OB-H column. Configuration was determined from the sign of rotation of the isolated product. 2-Formyloxyacetophenone was formed as the main byproduct.

readily accessible with conventional procedures from chiral 1-aryl-2-haloethanols, which are prepared with asymmetric boron reduction<sup>4</sup> or microbial reduction<sup>5</sup> of 2-haloacetophenones. However, none of the currently available chiral catalyst systems can efficiently convert these 2-haloacetophenones to chiral alcohols in a practical manner except for some chiral Rh hydrogenation catalysts that give the product in only moderate ees.<sup>6</sup> We now describe a practical method for the synthesis of optically active styrene oxides via optically active 2-halo-1-phenylethanols. These optically active alcohols are obtainable from the asymmetric reduction of acetophenones with a formic acid triethylamine mixture containing an isolable chiral Rh complex,  $Cp^*RhCl[(R,R)\text{-Tsdpen}]$  (**1a**), where  $Cp^*$  = pentamethylcyclopentadienyl and TsDPEN = (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine), as a catalyst<sup>7</sup> and can be converted to optically active epoxides with excellent yields and ees in either a one- or two-pot procedure.

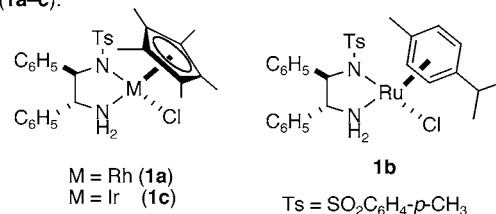
A well-defined chiral Rh complex (*R,R*)-**1a** has proven to effect highly efficient asymmetric transfer hydrogenation of 2-chloroacetophenone (**2a**) with a 5:2 formic acid/triethylamine azeotropic mixture (substrate/catalyst ratio (S/C) = 1000, S/HCOOH = 1/1) in a 0.8 M ethyl acetate solution at room temperature to give (*R*)-2-chlorophenylethanol (**3a**) with 97% ee and in >99% yield after 1 h (Scheme 1).<sup>8</sup> Table 1 lists some examples. The reaction proceeded equally well in various solvents, including acetonitrile, DMF, THF, toluene,  $CH_2Cl_2$ , and acetone,<sup>8</sup> but not in methanol or *t*-BuOH in which a longer reaction time was required or a lower ee was obtained. Although asymmetric reduction of

**2a** with S/C = 100 with 2-propanol as a hydrogen source in the presence of chiral Rh complex **1a** proceeded to give **3a** in 94% yield and with 98% ee after 14 h, an increase in the S/C ratio to 1000 caused a significant decrease in the yield due to the inherent properties of the reversible reaction with 2-propanol. The reaction in a neat formic acid/triethylamine mixture gave unsatisfactory results in terms of enantioselectivity. These results indicate that formic acid with triethylamine is the best choice of hydrogen source in a practical sense.

### Scheme 1



(*R,R*)-cat (**1a–c**):



(4) (a) For a review, see: Wallabaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, 3, 1475–1504. (b) Hett, R.; Senanayake, C. H.; Wald, S. A. *Tetrahedron Lett.* **1998**, 39, 1705–1708. (c) Yaozhong, J.; Yong, Q.; Aiqiao, M.; Zhitang, M. *Tetrahedron: Asymmetry* **1994**, 5, 1211–1214.

(5) (a) Sawa, I.; Konishi, Y.; Maemoto, S.; Hasegawa, J. WO 9201804 A1, 1992. (b) Yasohara, Y.; Sawa, I.; Ueda, M.; Hasegawa, J.; Shimizu, A.; Kataoka, M.; Wada M.; Kawabata, J. JP 11215995, 1999.

(6) Devocelle, M.; Mortreux, A.; Agbossou, F.; Dormoy, J.-P. *Tetrahedron Lett.* **1999**, 40, 4551–4554.

(7) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, 64, 2186–2187.

(8) A mixture of 2-chloroacetophenone **2a** (1 mmol) and catalyst **1a** (0.001 mmol) in a 5:2 mixture of formic acid to triethylamine (0.2 mL) and ethyl acetate (1.0 mL) was stirred at 25 °C for 1 h. The mixture was passed through a  $SiO_2$  column chromatography (eluent: 20%  $CH_3CO_2C_2H_5$  in hexane) to give almost quantitatively 2-chlorophenylethanol **3a**. The ee value was determined by HPLC analysis. See Supporting Information.

A preformed  $Cp^*Rh$  complex, **1a**, is one of the most reactive catalysts for the asymmetric transfer hydrogenation of 2-chloroacetophenones. The reaction of **2a** even with an S/C = 5000 under conditions otherwise identical to those described in Table 1 proceeded rapidly to give almost quantitatively chiral alcohol **3a** with 96% ee and an initial turnover frequency (TOF) exceeding 2500  $h^{-1}$  (0.7  $s^{-1}$ ). The reaction rate and enantioselectivity were far superior to those obtained from the catalyst generated in situ.<sup>9</sup> In contrast to the Rh system, a chiral Ru complex,  $RuCl[(R,R)\text{-Tsdpen}](p\text{-cymene})$  (**1b**),<sup>10</sup> which has a structure isoelectronic with **1a** and effects asymmetric transfer hydrogenation of simple

**Table 2.** Asymmetric Transfer Hydrogenation of the Ring-Substituted 2-Chloroacetophenones,  $\text{RC}_6\text{H}_4\text{COCH}_2\text{Cl}$ , (**2b–m**) Catalyzed by Chiral Rh Complex **1a** with a  $\text{HCOOH}/\text{N}(\text{C}_2\text{H}_5)_3$  Mixture<sup>a</sup>

product alcohol	R	yield, % <sup>b</sup>	ee, %	config <sup>c</sup>
<b>3a</b>	H	99	97	<i>S</i>
<b>3b</b>	<i>o</i> -Cl	81	88	<i>S</i>
<b>3c</b>	<i>m</i> -Cl	93	95	<i>S</i>
<b>3d</b>	<i>p</i> -Cl	90	92	<i>S</i>
<b>3e</b>	<i>o</i> -CH <sub>3</sub> O	90	95	<i>S</i>
<b>3f</b>	<i>m</i> -CH <sub>3</sub> O	90	95	<i>S</i>
<b>3g</b>	<i>p</i> -CH <sub>3</sub> O	94	94	<i>S</i>
<b>3h</b>	<i>m</i> -OH	93	95	<i>S</i>
<b>3i</b>	<i>m</i> -CF <sub>3</sub>	80	96	<i>S</i>
<b>3j</b>	<i>p</i> -MsNH	80	97	<i>S</i>
<b>3k</b>	<i>m</i> -CH <sub>3</sub>	92	96	<i>S</i>
<b>3l</b>	3',4'-OCH <sub>2</sub> O	93	98	<i>S</i>

<sup>a</sup> Reaction of **2a** in a 1.0 M solution containing the (*R,R*)-Rh catalyst (**1a**) was conducted with a mixture of  $\text{HCOOH}$  and  $\text{N}(\text{C}_2\text{H}_5)_3$  at 25 °C. <sup>b</sup> Isolated yields. <sup>c</sup> The ee values were determined by HPLC analysis using a Daicel Chiralcel OB or OB-H column. Configuration was determined from the sign of rotation of the isolated product. 2-Formyloxyacetophenone was formed as the main byproduct.

acetophenones, exhibited no remarkable activity for the reaction of **2a** with  $\text{S/C} = 1000$ , giving 2-formyloxyacetophenone as a main product under the conditions described above. However, a decrease in the volume of the azeotropic mixture to 1 equiv of the ketone **2a** (**2a**: $\text{HCOOH} = 1:1$ ) in ethyl acetate containing 0.1 mol % chiral Ru catalyst caused an increase in the desired product **3a** to 36% yield and 91% ee (Table 1).<sup>11</sup> Despite the structural similarity between the  $\text{Cp}^*\text{Rh}(\text{III})$  and the ( $\eta^6$ -arene) $\text{Ru}(\text{II})$  complexes, the remarkable difference in the reactivity toward 2-chloroacetophenones may be attributed to the electronic properties of the central metals. An analogous Ir complex,  $\text{Cp}^*\text{IrCl}[(\text{R,R})\text{-Tsdpen}]$  (**1c**),<sup>7</sup> exhibited reasonably high reactivity but poor enantioselectivity.

A variety of ring-substituted 2-chloroacetophenones (**2b–l**) can be transformed with **1a** to the corresponding optically active secondary alcohols with high enantiomeric purities as shown in Table 2. In general, 2-chloroacetophenones are

(9) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061. Cross, D. J.; Kenny, J. A.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1801–1806. The reduction of **2a** with a binary Rh catalyst from 0.25 mol % [ $\text{Cp}^*\text{RhCl}_2$ ]<sub>2</sub> and 0.5 mol % (*R,R*)-TsDPEN gave an 85% yield and 75% ee.

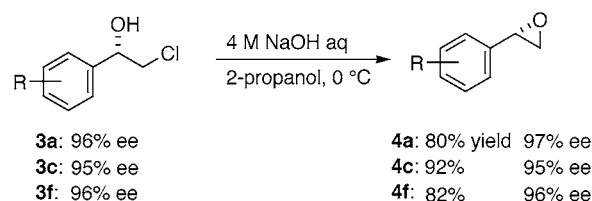
(10) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522. (c) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288. (d) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288–290. (e) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739. (f) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102.

(11) (a) Bayston, D. J.; Travers, C. B.; Polywka, M. E. C. *Tetrahedron: Asymmetry* **1998**, *9*, 2015–2018. The asymmetric transfer hydrogenation of 2-chloroacetophenone catalyzed by polymer supported  $\text{Ru}-(\text{S,S})\text{-TsDPEN}$  with formic acid as a hydrogen source in DMF proceeded to give 1-aryl-2-chloro ethanol in 95% ee and with a  $\text{S/C}$  of 100. (b) Kenny, J. A.; Palmer, M. J.; Smith, A. R. C.; Walsgrove, T.; Wills, M. *Synlett* **1999**, *10*, 1615–1617.

more favorable substrates for transfer hydrogenation than the parent acetophenone due to thermodynamic reasons.<sup>12</sup> In fact, the reduction of the simple acetophenone with **1a** ( $\text{S/C} = 1000$ ) under the same conditions gave 1-phenylethanol in only 6% with 91% ee after 24 h.<sup>10a</sup> Noticeably, the rate and enantioselectivity are not seriously affected by the electronic properties of the ring substituent (Table 2). The enantiomeric excesses of the product alcohols were generally very high (up to 97% ee). The electron-donating methoxy group on the phenyl group (**2e–g**) exerted no significant effect on either reactivity or enantioselectivity. An *o*-chloro group in acetophenone slightly decreases the enantioselectivity possibly due to steric reasons.

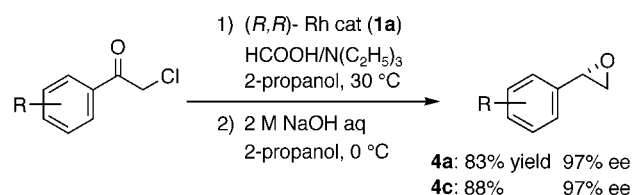
2-Chloro-1-phenylethanol and the ring-substituted 2-chloro-1-phenylethanols (**3a**, **3c**, **3f**) were readily convertible with conventional procedures to optically active styrene oxides (**4a**, **4c**, **4f**, respectively) with excellent ees as shown in Scheme 2. Treatment of (*R*)-**3a** (96% ee) with 4 M aqueous

**Scheme 2**



$\text{NaOH}$  in 2-propanol afforded (*R*)-styrene oxide **4a** (97% ee) in an 80% isolated yield without loss of enantiomeric purity. In particular, *m*-chlorostyrene oxide (*R*)-**4b**, which is obtained from the reduction product (*R*)-**3b** (92% yield and 95% ee), is a key intermediate for the preparation of several  $\beta$ -3-adrenergic receptor agonist compounds. This reductive transformation of 2-chloroacetophenones to the optically active epoxides is more appealing when the one-pot synthetic procedure was applied. As shown in Scheme 3, sequential

**Scheme 3**



asymmetric reduction of **2a** or **2b** with a mixture of formic acid and triethylamine in 2-propanol containing catalyst **1a** ( $\text{S/C} = 1000$ ) for 2 h and the treatment of its reaction mixture with 2 M  $\text{NaOH}$  aqueous solution at 0 °C gave optically

(12) Adkins, H.; Eloffson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc.* **1949**, *71*, 3622–3829.

active styrene oxide **4a** or **4b**, respectively, in 80–90% isolated yield with 96–98% ee in a single reactor.<sup>13</sup>

This asymmetric reduction of 2-chloroacetophenone with a chiral Rh catalyst is characterized by a rapid and carbonyl group-selective transformation because of the coordinatively

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(13) **One-Pot Procedure for Synthesis of 4a.** A mixture of 2-chloroacetophenone **2a** (5 mmol) and catalyst **1a** (0.005 mmol) in a 5:2 mixture of formic acid to triethylamine (1.0 mL) and 2-propanol (6.0 mL) was stirred at 25 °C for 2 h. The reaction mixture was then treated with 2 M NaOH aqueous solution (10.0 mL) at 0 °C for 1 h. After the usual workup procedure, (*R*)-styrene oxide **4a** with 96.8% ee was obtained in 83% yield. The ee value was determined by HPLC analysis. In a large-scale experiment, the reaction of 4.73 g of **2a** with **1a** (S/C = 5000) gave the corresponding optically active styrene oxide with 94% ee in a 93% total isolated yield (3.54 g). Even commercially available reagents and solvents without special purification could be used in this reaction.

(14) (a) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119–1121. (b) Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* **2000**, *41*, 9277–9280. (c) Koike, T.; Murata, K.; Ikariya, T. *Org. Lett.* **2000**, *2*, 3833–3836. (d) Watanabe, M.; Murata, K.; Ikariya, T., *J. Org. Chem.* **2002**, *67*, 1712–1715.

saturated nature of the diamine-based Cp\*Rh(III) hydride complexes.<sup>7,10,14</sup> The neighboring chloro group at the  $\alpha$  position of the carbonyl group is possibly free from the metal center, leading to excellent reactivity and enantioselectivity. This epoxide synthetic process in either a one- or two-pot procedure is particularly useful for the large-scale production of optically active styrene oxides.<sup>13</sup>

**Acknowledgment.** This work was financially supported by a grant-in-aid from the Ministry of Education, Science, Sports and Culture of Japan (Nos. 12305057, 14078209).

**Supporting Information Available:** Experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL020213O