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# A Chiral Rhodium Complex for Rapid Asymmetric Transfer Hydrogenation of Imines with High Enantioselectivity

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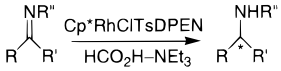
## ABSTRACT




R or R' = alkyl- or aryl-
R" = alkyl- or $ArSO_2$-

**A chiral rhodium complex, (*R*)-Cp*RhCl[(1*S*,2*S*)-*p*-TsNCH($C_6H_5$)CH($C_6H_5$)$NH_2$ ] (1a, (*S*,*S*)-Cp*RhClTsDPEN), generated from [Cp*$RhCl_2$]$_2$ and (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine [(*S*,*S*)-TsDPEN], and its enantiomer 1b were found to provide superior catalysts for the rapid, high-yielding, asymmetric transfer hydrogenation of some heterocyclic imines, using an $HCO_2H$–$Et_3N$ azeotrope as the hydrogen source.**

Catalytic asymmetric reduction of multiple bonds has received much attention in recent years.[1] In particular, asymmetric hydrogenation and hydrosilation of imines (C═N's) have been at the forefront of research, due, in part, to the importance of optically active amines[2−4] as pharmaceuticals and agrochemicals. Among the methods available for reductions, asymmetric transfer hydrogenation has advantages over other processes in operational simplicity that avoids the use of gaseous hydrogen. In recent years $C_2$-symmetric diamine−ruthenium(II) complexes have been advanced for overcoming the relatively low reactivities observed for the transfer hydrogenation of imines.[1e,2e]

In an ongoing project we had need for a reactive, selective catalyst to asymmetrically reduce imines (C═N's) to amines. Prompted by a report extolling rhodium-based catalysts,[5] we found that a commercially available Cp*Rh complex[6] would catalyze the reduction of imines to racemic amines under mild conditions.[7] Herein we report the development of a process that makes use of a chiral Cp*Rh complex[8] that uses

(1) For recent reviews, see: (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051−1069. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Berlin, 1993. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 2. (d) de Graauw, C. F.; Peters, J. A..; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007−1017. (e) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102. (f) Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3101−3120. (g) Tonks, L.; Williams, M. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3637−52. (h) Itsuno, S. *Org. React.* **1998**, *52*, 395−576.

(2) (a) Oppolzer, W.; Wills, M.; Starkeman, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117−4120. (b) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266−6267. (c) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952−8965. (d) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703−11714. (e) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikriya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917. (f) Ahn, K. H.; Ham, C.; Kim, Seung.-K.; Cho, C.-W. *J. Org. Chem.* **1997**, *62*, 7047−7048. (g) Bolm, C.; Felder, M. *Synlett* **1994**, 655−656. (h) Sakai, T.; Yan, F.; Uneyama, K. *Synlett* **1995**, 753−754. (i) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1992**, *3*, 1583−1590. (i) Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421−6429.

(3) (a) Brunner, H.; Becker, R.; Gauder, S. *Organometallics* **1986**, *5*, 739−746. (b) Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784−6785. (c) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1103−1107.

(4) Johansson, A. *Contemp. Org. Synth.* **1995**, *2*, 393−407.

(5) Stinson, S. C. *Chem. Eng. News* **1998**, June 1, 15−23.

(6) The catalyst was pentamethylcyclopentadienylrhodium chloride dimer from Aldrich Chemical Co. (catalog no. 33,837-0).

(7) Mao, Jianmin; Baker, D. C. *Abstracts of Papers*, 217th National Meeting of the American Chemical Society, Anaheim, CA, March 21−25, 1999; American Chemical Society: Washington, DC, 1999, ORGN 279.

(8) Design of a suitable complex was based on the findings of Noyori and co-workers[1e,2e] that an NH moiety in the ligand may promote stabilization of the requisite cyclic transition state through hydrogen bonding to the substrate. This type of metal−ligand bifunctional catalyst may increase the ability of the substrate to bind the active site of the catalyst, thereby increasing reactivity and selectivity.

(9) (a) Wagner, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 50−54. (b) Narita, K.; Sekiya, M. *Chem. Pharm. Bull.* **1977**, *25*, 135−140. (c) Brown, J. M.; Brunner, H.; Leitner, W.; Rose, M. *Tetrahedron: Asymmetry* **1991**, *2*, 331.

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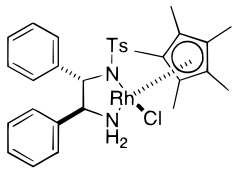
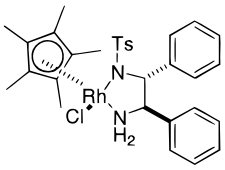
a simple formic acid−triethylamine mixture[9] as the hydrogen source and catalyzes the transfer hydrogenation of the C═N bond to give optically active amines in high yield with, in many cases, exceptionally high enantioselectivity.[10]

The catalyst precursor was synthesized as follows: Organic-soluble pentamethylcyclopentadienylrhodium chloride dimer {[Cp*$RhCl_2$]$_2$}[11] was reacted with (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine [(1*R*,2*R*)-TsDPEN)][12] in dichloromethane in the presence of triethylamine for 20 min at 20 °C to give complex **1b** as red crystals in 91% yield.[13] Complex **1a** was obtained in a similar fashion from (1*S*,2*S*)-TsDPEN.[14]




**1a (*S*,*S*)**




**1b, (*R*,*R*)**

Complex **1b** was characterized by single-crystal X-ray diffraction analysis. The two nitrogen atoms of the chiral ligand coordinate to the Rh center forming a five-membered ring. Noteworthy is the fact that there is an unusually close relationship of the Cl···HN groups (2.66 Å), and there is evidence of considerable intramolecular hydrogen bonding. The $^1$H NMR spectra of **1a** and **1b** showed resonances attributable to single diastereomers (considering the asymmetry at the Rh center). The red crystalline complexes are quite stable, as the product has been used as a catalyst precursor after >3 months' storage in a desiccator at room temperature.

Imine **2c** was selected for development of conditions with catalyst **1a**. The reactions were conducted at a substrate/catalyst (S/C) molar ratio of 200:1 using a 5:2 formic acid−triethylamine azeotrope[9] as the hydrogen source. Use of a preformed, isolated crystalline complex in a suitable solvent along with the substrate, followed by addition of the formic acid−triethylamine azeotrope, was the protocol used in most cases, although a complex formed in situ (same process without isolation of crystalline **1**) gave equivalent results. Experiments revealed that the catalyst is well behaved in a range of solvents, both protic and aprotic; however, the reactions gave slightly better enantioselectivity in polar solvents. The reaction with **2c** proceeded very rapidly and was complete in about 10 min at 20 °C, with an ee value of 99% (see Table 1).[15] The catalyst was still active at −20 °C and, furthermore, did not show a decrease in enantioselectivity at temperatures as high as +40 °C in acetonitrile. The reaction failed when 2-propanol[16] with triethylamine was tried as the hydrogen source. In general, either dichloromethane or acetonitrile was deemed to be the best solvents, with preferred temperatures of ca. 20 °C.

**Table 1.** Asymmetric Transfer Hydrogenation of Imines and Sulfonimides Catalyzed by **1**[a]

| imines[b] | catalyst | S/C[c] | solvent | time (min) | yield (%)[d] | ee (%)[e] | config[f] |
|---|---|---|---|---|---|---|---|
| **2a** | **1a** | 200 | $CH_3CN$ | 10 | 96 | 89 | *R* |
| **2a** | **1b** | 200 | $CH_2Cl_2$ | 10 | 95 | 90 | *S* |
| **2b** | **1a** | 200 | $CH_2Cl_2$ | 10 | 93 | 83 | *R* |
| **2c** | **1a** | 200 | $CH_2Cl_2$ | 10 | 96 | 99 | *R* |
| **2c** | **1a** | 1000 | $CH_2Cl_2$ | 60 | 94 | 93 | *R* |
| **2c** | **1a** | 1000 | $CH_3CN$ | 60 | 93 | 95 | *R* |
| **2d** | **1a** | 200 | $CH_2Cl_2$ | 10 | 94 | 97 | +[g] |
| **2e** | **1a** | 100 | $CH_2Cl_2$ | 180 | 90 | 4.4 | *R* |
| **2f** | **1a** | 100 | $CH_2Cl_2$ | 180 | 89 | 3.2 | *R* |
| **4a** | **1a** | 200 | $CH_2Cl_2$ | 10 | 88 | 8.4 | *S* |
| **4b** | **1a** | 200 | $CH_2Cl_2$ | 10 | 85 | 8.4 | −[h] |
| **6a** | **1b** | 200 | $CH_2Cl_2$ | 20 | 98 | 68 | *R* |
| **6b** | **1b** | 200 | $CH_2Cl_2$ | 30 | 98 | 67 | +[i] |
| **6c** | **1a** | 200 | $CH_2Cl_2$ | 40 | 93 | 68 | *S* |
| **6d** | **1b** | 200 | $CH_2Cl_2$ | 30 | 96 | 81 | *S*[j] |
| **6d** | (*S*,*S*)-Ru-cat.[k] | 100 | $CH_2Cl_2$ | 180 | 96 | 69 | *S*[j] |

[a] Reactions were conducted in a solution using a 5:2 formic acid−triethylamine azeotrope as hydrogen source at 20 °C. Products that were known compounds gave, at a minimum, $^1$H NMR data consistent with those reported in the literature for either one enantiomer or the racemic compound; **7d**, a new compound, gave an acceptable NMR spectrum and elemental analysis. [b] Compounds **2a**−**2f** were prepared by the Bischler−Napieralski reaction as described by Craig, P. N.; Nabenhauer, F. P.; Williams, P. M.; Macko, E.; Jones, J. *J. Am. Chem. Soc.* **1952**, *74*, 1316−1317. Compounds **4a** and **4b** were prepared as an *E*/*Z* mixture of 13:1 (**4a**) and 25:1 (**4b**) by the procedure in ref 2c. Compounds **6a**−**6c** were prepared by the procedure in Abramovich, R. A; Smith, E. M.; Humber, M.; Purtschert, B.; Srinivasan, P. C.; Singer, G. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2589−2594. [c] Substrate:catalyst molar ratio. [d] Isolated yield. [e] Determined by HPLC analysis (Chiralcel OD column) on products after a preliminary cleanup on silica gel. [f] Determined from the sign of the optical rotation of isolated, but not purified, products. [g] (*R*) configuration presumed, based on (+) optical rotation. [h] (*S*) configuration presumed, based on (−) optical rotation. [i] (*R*) configuration presumed, based on (+) optical rotation. [j] Reference 20. [k] RuCl(*S*,*S*)-TsDPEN(*p*-cymene) in ref 2e.

The scope of the asymmetric reduction is shown with the different substrates in Table 1. As indicated, the reduction of both achiral imines and sulfonimides proceeds rapidly and in excellent yields under the general conditions outlined in

(10) After our work had been carried out, the catalyst described herein has been advanced for the transfer hydrogenation of carbonyl compounds. See: Mashina, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199−1200, 1201−1202. Kunikiko, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186−2187. We find that **1** is more successful in reducing imines than ketones as evidenced by higher yields of products with generally excellent enantioselectivity.

(11) Kang, J. W.; Moseley, K.; Maitlis, P. M. *J. Am. Chem. Soc.* **1969**, *91*, 5970−5977.

(12) ter Halle, R.; Breheret, A.; Schulz, E.; Pinel, C.; Lemaire, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2101−2108.

(13) Complex **1b**: red crystals; mp 221−224 °C (dec); $^1$H NMR (250 MHz, $CDCl_3$, 25 °C, TMS) $\delta$ 1.86 (s, 15H; $CH_3$ in Cp*), 2.22 (s, 3H; $CH_3$ in *p*-Ts), 3.32 (m, 1H; N*H*H), 3.71 (m, 1H; *H*$CNH_2$), 3.97 (d, $J$ = 11 Hz, 1H; *H*CN-*p*-Ts), 4.03 (m, 1H; NH*H*), 6.64−7.61 (m, 14H; ArH); $^{13}$CNMR (62.9 MHz, $CDCl_3$, 25 °C) $\delta$ 9.65 ($CH_3$ in Cp*); 21.2 ($CH_3$ in *p*-Ts), 69.4 ($CNH_2$), 71.8 (CN-*p*-Ts), 93.9, 94.0, 126.4, 126.7, 127.0, 127.7, 126.2, 128.4, 128.6, 139.2, 139.3, 139.7, 140.6. Anal. Calcd for $C_{31}H_{36}ClN_2O_2RhS$: C, 58.26; H, 5.68; Cl, 5.55; N, 4.38; S, 5.02; Found: C, 58.18; H, 5.67; Cl, 5.69; N, 4.29; S, 4.92.

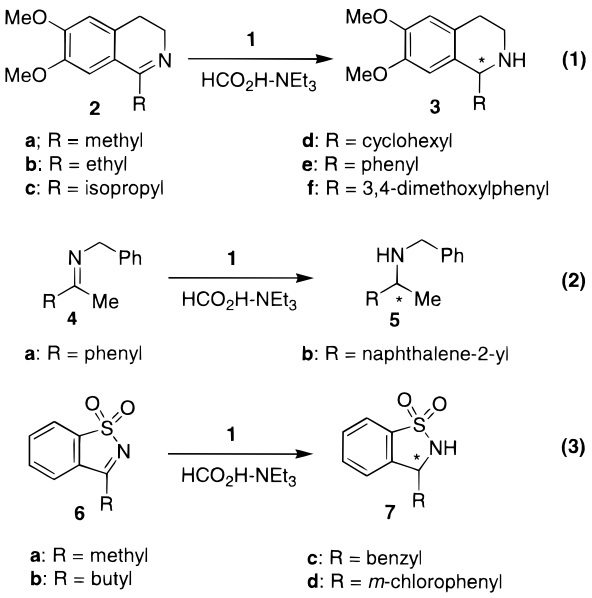
(14) Oda, T.; Irie, R.; Katsuki, T.; Okawa, H. *Synlett* **1992**, 641−643.

(15) It is pointed out that the reductions with **1a** or **1b** proceeded at considerably faster rates than those using the Ru-based catalysts for identical reactions, e.g., **2a** and **6d**. Comparisons are as follows: for **2a**, 10 min for **1a** or **1b** at 20 °C vs 3 h at 28 °C or more for the Ru catalysts;[2e] for **6d**, see Table 1, last two entries.

(16) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562−7563.

the previous paragraph. At a substrate:catalyst ratio of 1000:1, the reactions proceeded more slowly with a slight loss of enantioselectivity. It is noted that the catalyst exhibited excellent enantioselectivity with a number of cyclic imines (Scheme 1, eq 1) and respectable enantioselectivity was

**Scheme 1**




maintained as the alkyl R group on the imino carbon increased in steric bulk. The method was found particularly useful in reductions to produce 1-alkyl-substituted tetrahydroisoquinolines, such as the naturally occurring alkaloid salsolidine ((*S*)-**3a**).[17] In contrast, however, were the results of reductions where R is an aryl group, as shown in examples **2e** and **2f**, where the second aromatic system apparently interferes with selective catalyst binding, resulting in low enantioselectivity. Similar results, where the enantioselectivities were disappointingly low, were observed for a set of acyclic *N*-benzyl-substituted imines derived from acetophenone and 2-acetonaphthone [1-(naphthalen-2-yl)ethanone] (Scheme 1, eq 2).

(17) Battersby, A. R.; Edwards, T. P. *J. Chem. Soc.* **1960**, 1214−1221.

The investigations were extended to include the reduction of certain cyclic sulfonimides that have been widely used in asymmetric reactions[2a,f,18] and have become of intense interest as precursors for sultams that are potent inhibitors of HIV reverse transcriptase.[19] The catalyst was found to be very active in reducing the C═N bond, in high yield and good enantioselectivity, as demonstrated by the four examples chosen, **6a**−**d** (Scheme 1, eq 3). Most interesting was the fact that compounds **6a**−**c**, which have 3-*C*-alkyl groups, as well as **4a** and **4b**, reduced to give products of opposite absolute stereochemistry from those in examples **2a**−**f**, where (*S*,*S*)-**1a** gives (*R*) products and (*R*,*R*)-**1b** gives (*S*) products. Such behavior has also been reported for **6c**[2f] with Ru-based catalysts. Furthermore, we observed that the 3-*C*-(*m*-chlorophenyl) analogue **6d**, which has a 3-*C*-aryl moiety, reduced analogously to **2a**−**2f**, but in a sense opposite to that obtained with the Ru-based catalyst (see last two entries in Table 1).[20] While the reason for these results is not clear, one can take comfort in the fact that the reductions proceed rapidly and with good-to-excellent enantioselectivity (Table 1). Enantiomerically pure products are obtained via simple crystallization of the products that have been purified by silica gel chromatography.

Thus these rhodium-based catalysts function as rapid, efficient hydrogen-transfer agents for the reduction of several types of C═N groups, often with high enantioselectivity.

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**Supporting Information Available:** Experimental details for compounds prepared and crystallographic data for **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Wills, M.; Oppolzer, W.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015−5018. (b) Oppolzer, W.; Rodriguez, I.; Starkeman, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019−5022.

(19) Baker, D. C., and co-workers, unpublished work. Details on the synthesis and structural identification of **7d** will be reported in the full paper.

(20) The absolute configuration was confirmed by single-crystal X-ray diffraction carried out on the *N*-Me derivative of **7d**.