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A Stereochemically Well-Defined Rhodium(III) Catalyst for Asymmetric Transfer Hydrogenation of Ketones

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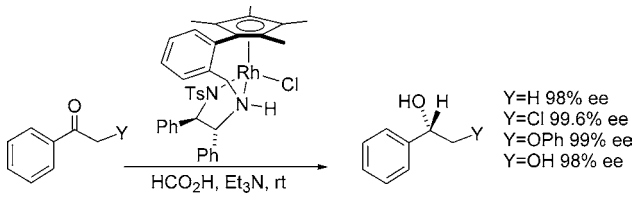
ABSTRACT



A rhodium(III) catalyst for asymmetric transfer hydrogenation of ketones has been designed. The incorporation of a tethering group between the diamino group and the cyclopentadienyl unit provides extra stereochemical rigidity. The catalyst is capable of enantioselective reduction of a range of ketones in excellent ee using formic acid/triethylamine as both the solvent and the reducing agent.

The use of asymmetric transfer hydrogenation (ATH) for the synthesis of enantiomerically enriched alcohols has recently been developed into a practical and versatile tool for synthetic chemistry.[1] The majority of the developments in this area have been concerned with the use of catalysts such as **1**, based on Ru(II), which give excellent enantioselectivities. This class of catalyst, which contains the monotosylated diamine ligand TsDPEN **2**, was first introduced by Noyori[2] and has enjoyed extensive synthetic application.[3] In contrast, the corresponding Rh(III) catalysts such as **3** have a lower profile. These have been applied to ketone[4−6] and imine[7] reductions and are marketed as CATHy catalysts by Avecia.[8] Although less widely reported, they have some advantages over the Ru(II) catalysts, for example, improved selectivity in the reduction of α-chloro ketones.

In recent years, we have reported upon the synthesis and applications of a number of modified Ru(II) catalysts for

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(1) (a) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201.

(2) (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (b) Matsumura, K.; Hashiguchi, Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (d) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119.

(3) (a) Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* **2000**, *41*, 9277. (b) Li, M.; Scott, J.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005. (c) Marshall, J. A.; Ellis, K. *Tetrahedron Lett.* **2004**, *45*, 1351. (d) Lennon, I. C.; Ramsden, J. A. *Org. Proc. Res. Dev.* **2005**, *9*, 110. (e) Watanabe, M.; Murata, K.; Lkariya, T. *J. Org. Chem.* **2002**, *67*, 1712. (f) Yamashita, H.; Ohtani, T.; Morita, S.; Otsubo, K.; Kan, K.; Matsubara, J.; Kitano, K.; Kawano, Y.; Uchida, M.; Tabusa, F. *Heterocycles* **2002**, *56*, 123.

(4) (a) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199. (b) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186. (c) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1201.

(5) (a) Cross, D. J.; Kenny, J. A.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1801. (b) Hamada, T.; Torii, T.; Izawa, K.; Noyori, R.; Ikariya, T. *Org. Lett.* **2002**, *4*, 4373. (c) Hamada, T.; Torii, T.; Izawa, K.; Ikariya, T. *Tetrahedron* **2004**, *60*, 7411. (d) Hamada, T.; Torii, T.; Onishi, T.; Izawa, K.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 7391.

(6) (a) Polborn, K.; Severin, K. *Eur. J. Org. Chem.* **2000**, 1687. (b) Thorpe, T.; Blacker, J.; Brown, S, M.; Bubert, C.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. *Tetrahedron Lett.* **2001**, *42*, 4041. (c) Sterk, D.; Stephan, M. S.; Mohar, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2605. (d) Wu, X.; Vinci, D.; Ikariya, T.; Xiao, J. *Chem. Commun.* **2005**, 4447.

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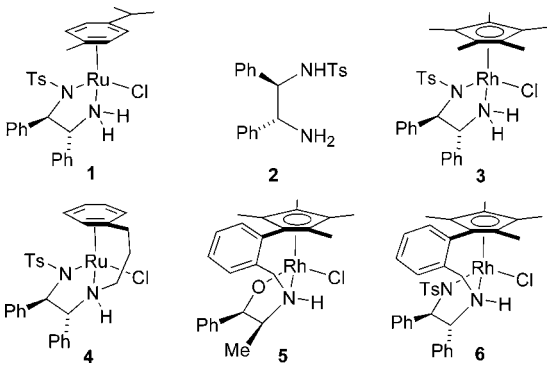


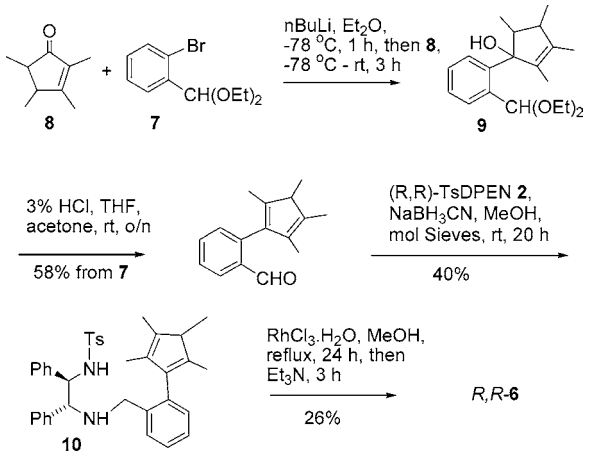
ATH which contain a tethering group between the chiral ligand component and the η^6-arene ring.[9] Tethered complex **4**, for example, reduces ketones more rapidly than the untethered **1**. In addition, certain substrates can be reduced in much improved yield and enantioselectivity.[5]

In view of the promising results obtained using complex **4**, we thought that a tethered version of the Rh(III) catalyst **3** would be a valuable material for study. We have already reported the synthesis and use of the tethered amino alcohol/Rh(III) catalyst **5**; however, this proved to be unstable under the reduction conditions used.[10] In contrast, catalysts containing TsDPEN **2** have generally proved to be significantly more stable than those containing amino alcohols, and are therefore much more useful catalysts. Furthermore, and in contrast to Ru(II) and Rh(III) complexes of amino alcohol ligands, the TsDPEN **2** complexes are stable to the preferred formic acid/triethylamine (FA/TEA) solvent system. The use of FA/TEA significantly reduces the possibility of any significant erosion in ee due to reversibility, which is often a problem in the 2-propanol/KOH (IPA) solvent system. Our target catalyst in this project was **6**, which represents a Rh(III) analogue of **4**.

After some investigations, we were able to establish a successful approach to the synthesis of **6** through the route illustrated in Scheme 1. Pivotal to this approach was the lithium/bromine exchange reaction of **7** followed by addition of cyclopentenone **8** to give the tertiary alcohol **9**.[10] Deprotection of the acetal in **9** was followed by reductive amination with TsDPEN **2** to furnish **10** in 40% yield.

Intermediate **10** had a very complex ^{1}H NMR spectrum, due to the mixture of isomers of the cyclopentadiene component. Upon treatment of **10** with 1 equiv of $RhCl_3$ and base, the stable complex **6** was formed which, after purification by flash chromatography and recrystallization, was isolated as a single diastereisomer. In contrast to **10**, the ^{1}H NMR of **6** was very clean and clearly indicated the

Scheme 1



formation of one isomer, the relative configuration of which was confirmed by X-ray crystallography (Figure 1). The

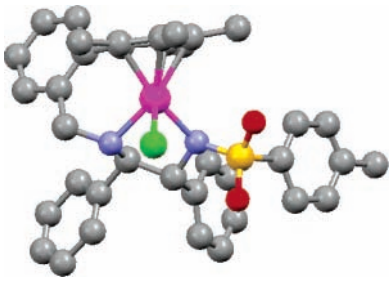


Figure 1. X-ray crystallographic structure of *RR*-**6**.

major diastereoisomer matches that reported for closely related (i.e., untethered) complexes containing TsDPEN **2** as a ligand.[4,6a]

Catalyst **6** proved to be a very effective catalyst for ATH of ketones and demonstrated improved activity over **3** (Scheme 2, Table 1). In our investigations, we chose to focus

Scheme 2

our studies on the use of the FA/TEA solvent system. In the reduction of acetophenone, for example, it was possible to achieve full reduction in this medium at room temperature to give a product in 98% ee (*R*). Although the reaction time was long, this represents the first report, to our knowledge, of the reduction of acetophenone using a Rh(III)/TsDPEN-type catalyst in FA/TEA; most literature reports describe the use of the IPA system.[4,6,8] In contrast, more reactive ketones,

(7) (a) Mao, J.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841.
(8) (a) Blacker, J.; Martin, J. Scale-up studies in Asymmetric Transfer Hydrogenation. In *Asymmetric Catalysis on an Industrial Scale: Challenges, Approaches and Solutions*; Blaser, H. U., Schmidt, E., Eds.; Wiley: New York, 2004; pp 201−216. (b) Sun, X.; Manos, G.; Blacker, J.; Martin, J.; Gavriilidis, A. *Org. Proc. Res. Dev.* **2004**, *8*, 909.
(9) (a) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318. (b) Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986.
(10) Cross, D. J.; Houson, I.; Kawamoto, A. M.; Wills, M. *Tetrahedron Lett.* **2004**, *45*, 843.

Table 1. Asymmetric Transfer Hydrogenation of Aromatic Ketones Catalyzed by Rhodium Catalyst **6a**

ketone		t (h)	% conv	ee (%) (R/S)
X	Y			
H	H	10	100	98 R
p-Cl	H	9	99	95 R
m-Cl	H	8	100	96 R
o-Cl	H	28	100	77 R
p-CF_3	H	7	100	96 R
m-CF_3	H	8	100	96 R
o-CF_3	H	24	33	17 R
p-(MeO)	H	30	96	97 R
m-(MeO)	H	30	93	97 R
o-(MeO)	H	48	93	90 R
1-naphthyl	H	8	35	80 R
2-naphthyl	H	10	100	95 R
tetralone		9	100	99.9 R
H	Cl[b,c]	2	100	99.6 S
H	OH	5[c]	100	99 S
H	OPh	3	100	98 S

[a] Reaction at 25 °C in a 2 M solution of ketone in a formic acid/triethylamine (5:2) azeotrope mixture and S/C = 200 unless otherwise specified. [b] EtOAc cosolvent added. [c] 0.1 mol % of catalyst used.

such as α-chloroacetophenone[5] and *p*-fluoroacetophenone,[8] have been reduced by **3** in the FA/TEA system.

A further series of ketones were reduced to the alcohols using catalyst **6** (Table 1). In most cases, the products were obtained in high conversions and excellent ee. α-Tetralone proved to be an excellent substrate and gave a product in 99.9% ee, as measured by chiral HPLC against a racemic sample. This represents one of the highest reported enantioselectivities for this substrate using any reduction method, and an improvement upon nontethered systems. In two reports involving the use of the Rh(III) complexes of N-tosylated cyclohexyl-1,2-diamine, tetralone reduction products of 95% ee (53% conversion after 24 h) and 97% ee (79% yield after 48 h) have been reported to be formed, both with the IPA system.[4] Tetralone can be reduced in an ee of 97% (95% yield) using a Rh(III) catalyst related to **3** but containing *cis*-aminoindanol as ligand, again in the IPA solvent system. [8a]

Substitution of the aromatic ring in the ketones did not have a detrimental effect on the selectivity of the reduction unless the substituent was in the *ortho* position, in which case the enantioselectivity dropped sharply. It is assumed that this is due to an undesirable steric clash.

One of the strengths of the Rh(III)/TsDPEN complexes over the corresponding Ru(II) versions is their ability to reduce α-chloro ketones with both high activity and in high ee. For example, complex **3** gives a product of α-chloroacetophenone reduction in 99% yield and 97% ee after 1 h, whereas the Ru(II) complex **1** completes this reduction in only 36% yield and 91% ee after 24 h (FA/TEA system).[5b,c] Complex **6** was highly competent at this reduction and furnished the reduction product in 99.6% ee (as determined by chiral HPLC) after 2 h at room temperature. The addition of some ethyl acetate cosolvent proved beneficial to this application (see the Supporting Information). The reductions of α-hydroxy- and α-phenoxyacetophenones also proved highly enantioselective; products of 99% and 98% ee were formed in quantitative yield.

The reduction of acetophenone was also carried out in the IPA system (0.5 mol % catalyst loading). After 2 h at room temperature, the reaction was 30% complete and the ee 98%. After an 18 h reaction time, the conversion had reached 74% and the ee was 97%. Although the ee was competitive with the result from the FA/TEA system, the conversions were not, and there was some evidence of deterioration in the ee due to the reversibility of the reaction.

In conclusion, it has been demonstrated that the introduction of a tether into an ATH catalyst brings significant benefits to its performance in reduction reactions. The reasons for the dramatic improvement in catalyst performance and enantioselectivity are not clear. One possibility is that the tether introduces a further element of stereochemical rigidity to the catalysts. Alternatively, the preorganized structures may benefit from a steric or electronic modification which optimizes the selectivity. We are currently investigating the scope and mechanism of this catalyst.

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Supporting Information Available: Experimental procedures, characterization data, NMR spectra, chiral chromatography analysis of reduction products, and data of single-crystal X-ray analysis of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Fletcher, D. A.; McMeeking; R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.