J|A|C|S
COMMUNICATIONS

Published on Web 01/06/2004

A New Class of "Tethered" Ruthenium(II) Catalyst for Asymmetric Transfer Hydrogenation Reactions

Jérôme Hannedouche,[†] Guy J. Clarkson,[‡] and Martin Wills*,[†]

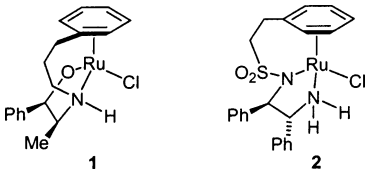
Asymmetric Catalysis Group, and X-ray Crystallography Unit, Department of Chemistry, University of Warwick, Coventry, CV4 7AL

Received October 28, 2003; E-mail: m.wills@warwick.ac.uk

The use of organometallic complexes as catalysts for the asymmetric transfer of hydrogen from a suitable donor (usually 2-propanol or formic acid) has been the subject of ongoing research for some decades.[1] However, it is only in recent years that the level of interest in this area has risen to the extent which now makes it one of intense international activity. This has been the result of the introduction, initially by Noyori,[2] and later developed by others,[3,4] of highly active and enantioselective ruthenium(II)/arene and rhodium(III)/pentamethylcyclopentadienyl complexes of β-amino alcohols and monotosylated 1,2-diamines.

We wished to study ruthenium(II) arene catalysts **1** and **2** in which the amino alcohol or monotosylated diamine, respectively, is covalently bound to the η^6-arene group.[5] Given the correct length of tether, such ligands should allow the chiral ligand component to retain the appropriate conformation for enantiocontrol and benefit from increased stability resulting from attachment to the metal at three points.[6] Furthermore, the "locking" of the aryl group (otherwise free to rotate) permits control over the spatial positions of the substituents on this ring.

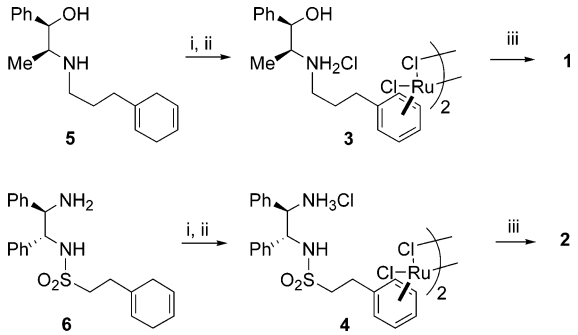
We envisaged that complexes **1** and **2** could be obtained from the corresponding ruthenium(II) dimers **3** and **4** by reaction with a base (such as KOH or HCO_2H/Et_3N), in an intramolecular variation upon the process normally employed for the in-situ preparation of similar transfer hydrogenation catalysts during their application to ketone reduction.



The reaction of **5**·HCl or **6**·HCl[7] with $RuCl_3$ under reflux in ethanol[8] resulted in the formation of the chloro-bridged η^6-arene ruthenium(II) complexes **3** and **4**, respectively (Scheme 1). These complexes were characterized by ^{1}H and ^{13}C NMR. The amine groups in **5** and **6** needed to be protonated prior to formation of the dimers.[9] The attempted reaction with the free amines resulted only in formation of complex product mixtures, possibly because the chelation of ruthenium(III) by the free amine outpaces arene oxidation, and the resulting complexes were not electronically disposed toward reduction of the metal.

Treatment of a quantity of **4** with Et_3N in refluxing 2-propanol[2d] resulted in successful conversion to **2**. An X-ray crystal structure of this material confirmed its tethered structure (Figure 1). The diamine ligand is coordinated to the metal in a manner similar to that observed for the nontethered analogues.[2b,d] Catalyst **2** (0.5 mol %) was employed in the reduction of acetophenone **7a** in HCO_2H/Et_3N and gave a product in >99% yield and 96% ee (*R*) after 18 h at 28 °C (Table 1). The product configuration matched that which would be predicted to be formed from the ligand enantiomer employed, on the basis that the tethering does not alter its mode of action.[10]

Scheme 1 [a]



[a] Conditions: (i) HCl, Et_2O, room temperature; (ii) $RuCl_3$ hydrate, EtOH, reflux, 21 h, 66% (two steps) for **4**, 55% (two steps) for **3**; (iii) in situ during reaction or Et_3N, ^{i}PrOH, reflux, 1 h (preparation of **2**), 57%.

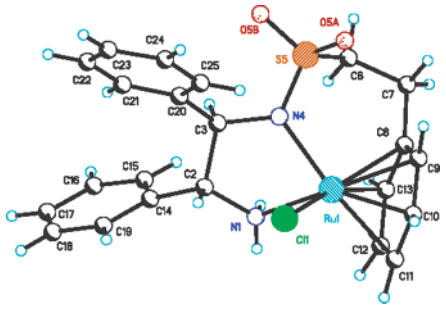


Figure 1. X-ray crystallographic structure of **2**.

Although we were unable to isolate crystals of complex **1** from treatment of **3** with base, we felt that **1** could be formed in situ under the reaction conditions employed in transfer hydrogenation when an amino alcohol is the ligand (^{i}PrOH, KOH). In the event, the addition of 0.25 mol % of **3** (i.e., 0.5 mol % with respect to **1** and Ru) to a 0.1 M solution of **7a** followed by 5 mol % of KOH resulted in reduction to the corresponding alcohol in 96% yield and 66% ee after 1 h (Table 1). Although modest, the ee obtained in this reaction represents an improvement on that of 58% ee (86% yield) reported for the analogous nontethered catalyst derived from the combination of (*1R*,*2S*)-ephedrine and $[Ru(benzene)Cl_2]_2$.[3h] This suggests that there is potential for improvement through modification of the arene in the catalyst.

Complex **3** gave a product of similar enantiopurity when used at a S/C (with respect to Ru) of 1000. A series of further ketones **7**−**10** were reduced in similar yields and ee's (Table 1). As

[†] Asymmetric Catalysis Group.
[‡] X-ray Crystallography Unit.

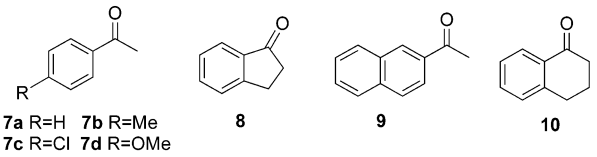
10.1021/ja0392768 CCC: $27.50

Table 1. Asymmetric Transfer Hydrogenation of Aromatic Ketones **7**−**10** Catalyzed by Ruthenium(II) Dimer **3**, **4**, or Complex **2**[a]

catalyst	ketone	time/h	% yield[b]	% ee (*R*/*S*)[c]
2	**7a**	18	>99	96[d] (*R*)
3	**7a**	1	96	66[d] (*R*)
3 (S/C 1000)	**7a**	7	83	67[d] (*R*)
3	**7b**	1	88	57[d] (*R*)
3	**7c**	0.5	98	54[d] (*R*)
3	**7d**	1	71	52[d] (*R*)
3	**8**	1	44	66[f] (*R*)
3	**9**	1	97	58[f] (*R*)
4	**7a**	21	>99	96[d] (*R*)
4 (S/C 1000)[e]	**7a**	45	>99	93[d] (*R*)
4	**7c**	12	>99	92[d] (*R*)
4	**7d**	44	98	90[d] (*R*)
4	**8**	14	>99	84[f] (*R*)
4	**9**	17	>99	90[f] (*R*)
4	**10**	18	>99	98[f] (*R*)

[a] Reaction at 28 °C in a 0.1 M solution of ketone in propan-2-ol, 5 mol % KOH, and S/C = 200 (for **3**) or at 28 °C with a 2 M solution of ketone in a formic acid/triethylamine azeotrope mixture and S/C = 200 (for **2** and **4**) unless otherwise specified. [b] Determined by GC or ^{1}H NMR. [c] Assigned by the sign of optical rotation. [d] Determined by GC analysis using a Beta DEX 120 capillary column. [e] Reaction with a 10 M solution of ketone (12 mmol) in a formic acid/triethylamine (2:1) (1.2 mL) and S/C = 1000. After 12 h, 0.2 mL of formic acid/triethylamine (2:1) was added. [f] Determined by HPLC analysis using a Daicel chiralcel OD column.

expected, however, attempts to use **3** in formic acid/triethylamine resulted in failure; no amino alcohol ligand has, to our knowledge, been successfully employed in this medium for Ru(II)-catalyzed transfer hydrogenation reactions.



We also wished to see if the in-situ strategy could be used for the generation of **2**. This would be desirable as it avoids the requirement to isolate **2**. We were pleased to find that the addition of 0.25 mol % of **4** (0.5 mol % with respect to ruthenium) to a 5:2 (molar) formic acid/triethylamine solution, followed by acetophenone **7a**, resulted in reduction to the product 1-phenylethanol in >99 % yield and 96% ee (*R*) after a reaction time of 21 h at 28 °C (Table 1). This result was identical to that obtained with the purified complex **2**. The significantly improved result as compared to that obtained with **3** may reflect to some extent the lack of reversibility under the formic acid conditions. As in the case of **3**, further tests demonstrated that **4** could be employed at a S/C of 1000 (Table 1). At the 0.5 mol % level of **2** (0.25 mol % of **4**), a further series of ketones were reduced to alcohols in high yield and enantioselectivity (Table 1).

We anticipated that the stability of **2** would benefit from the "three-point" ligand attachment to the metal. Some evidence for the longevity of **2** was obtained in a preliminary study. Specifically, following a 24 h acetophenone reduction (400 mg of ketone, S/C = 200), a further portion of acetophenone (400 mg) and fresh formic acid/triethylamine (1.5 mL) was added to the reaction. After a further 73 h, full reduction was again observed, without erosion of ee. This process was repeated again, and full reduction was once more observed after 176 h. This suggests that **2** remains intact and active for some significant time after the initial reduction reaction. Some important control reactions were also carried out: No reduction was observed using a combination of $RuCl_3$ (0.5 mol %) and the oxidized version of either **5** or **6** (0.5 mol %)[11] under the same conditions. This eliminates the possibility that the reaction is catalyzed by a nontethered component in the reaction.

In conclusion, we have developed an effective method for the synthesis of dimers **3** and **4**, which act as precursors of tethered-ligand complexes **1** and **2**, respectively. These "one-component" catalysts form the basis for controlled and selective modification toward the development of "fine-tuned" catalysts for the reduction of an extended range of substrates. Studies are currently underway to define the scope and mechanisms of these reagents, and further results will be reported in due course.

Acknowledgment. We thank the EPSRC for financial support of this project. We also acknowledge the use of the EPSRC Chemical Database Service at Daresbury.[12] We thank J. C. Bickerton of the Warwick MS service and Prof. D. Games and Dr. B. Stein of the EPSRC MS service for analyses of certain compounds.

Supporting Information Available: Experimental procedures, characterization data, NMR spectra, chiral chromatography analysis of reduction products, and data of single-crystal X-ray analysis of **2** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.

(2) (a) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.-I.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (c) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (d) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285. (e) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186. (f) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818. Hamada, T.; Torii, T.; Izawa, K.; Noyori, R.; Ikariya, T. *Org. Lett.* **2002**, *4*, 4373.

(3) (a) Nordin, S. J. M.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem.-Eur. J.* **2001**, *7*, 1431. (b) Everaere, K.; Mortreux, A.; Bulliard, M.; Brussee, J.; van der Gen, A.; Nowogrocki, G.; Carpentier, J. F. *Eur. J. Org. Chem.* **2001**, 275. (c) Hennig, M.; Puntener, K.; Scalone, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1849. (d) Blacker, A. J.; Mellor, B. J. (Avecia/Zeneca), WO 98/42643 A1, 1998. (e) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291. (f) Langer, T.; Helmchen, G. *Tetrahedron Lett.* **1996**, *37*, 1381. (g) Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 215. (h) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J.-W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. E.; van Leeuwen, P. W. N. M. *Chem.-Eur. J.* **2000**, *6*, 2818. (i) Faller, J. W.; Lavoie, A. R. *Organometallics* **2002**, *21*, 2010. (j) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199.

(4) (a) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226. (b) Hannedouche, J.; Kenny, J. A.; Walsgrove, T.; Wills, M. *Synlett* **2002**, 263. (c) Palmer, M. J.; Kenny, J A.; Walsgrove, T.; Kawamoto, A. M.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 416.

(5) Strictly, compounds **1** and **2** are catalyst precursors. The true catalytic species are formed by HCl elimination.

(6) Related complexes with potential for forming a tether have been reported since the start of this project: (a) Soleimannejad, J.; Sisson, A.; White, C. *Inorg. Chim. Acta* **2003**, *352*, 121. (b) Wendicke, S. B.; Burri, E. Scopelliti, R.; Severin, K. *Organometallics* **2003**, *22*, 1894.

(7) Compounds **5** and **6** were synthesised respectively via the reductive coupling of 3-(cyclohexa-1,4-dienyl)propanal with (*1R*,*2S*) norephedrine and the reaction of (*R*,*R*)-1,2-diphenylethylenediamine and 2-(cyclohexa-1,4-dienyl)ethanesulfonyl chloride. See Supporting Information.

(8) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233.

(9) Miyaki, Y.; Onishi, T.; Kurosawa, H. *Inorg. Chim. Acta* **2000**, *300*−*302*, 369.

(10) A direct comparison with nontethered ligand performance is hampered by the fact that the reported work (ref 2b) employed a η^6-mesitylene rather than unsubstituted benzene. In this study, a product of 98% ee was obtained from acetophenone.

(11) The oxidized versions of **5** and **6** were synthesized in a similar manner using (3-bromo-propyl)benzene and 2-(phenyl)ethanesulfonyl chloride, respectively.

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

JA0392768