The Importance of the N-H Bond in Ru/TsDPEN Complexes for Asymmetric Transfer Hydrogenation of Ketones and Imines.

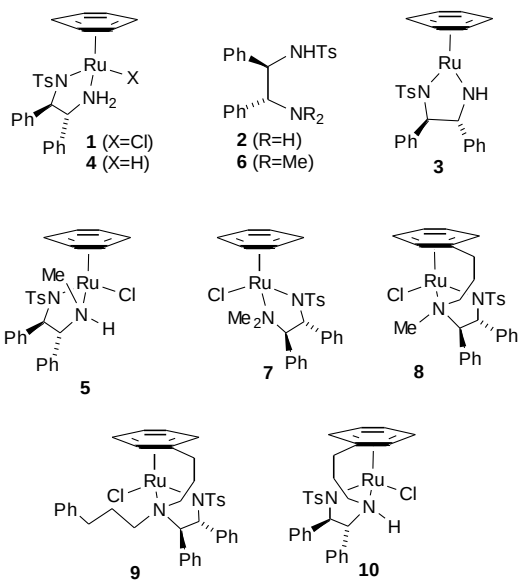
Rina Soni,[a] Fung Kei Cheung,[a] Guy C. Clarkson,[a] Jose E. D. Martins,[a] Mark A. Graham[b] and Martin Wills*[a]

Received (in XXX, XXX) 1st January 2007, Accepted 1st January 2007
First published on the web 1st January 2007
DOI: 10.1039/b000000x

Ru(II) complexes of TsDPEN containing two alkyl groups on the non-tosylated nitrogen atom are poor catalysts for asymmetric transfer hydrogenation of ketones and imines; this observation provides direct evidence for the importance of the *N*-H interaction in the transition state for ketone reduction.

Introduction

Asymmetric transfer hydrogenation (ATH) pre-catalysts of general structure [(arene)Ru(TsDPEN-H)Cl] **1**[1-3] are formed in the reaction between TsDPEN **2** and the ruthenium dimer [(arene)$RuCl_2]_2$**.** During the catalytic cycle, the unsaturated species **3** is formed, and this reacts with a suitable hydrogen donor to form hydride **4**.[4] Hydride **4** transfers two hydrogen atoms to a substrate such as a ketone or an imine to form an alcohol or an amine respectively. For ketone reduction, there is convincing evidence that this transfer takes place via an outer sphere mechanism in which the two hydrogen atoms are transferred through the cyclic six-membered transition state depicted in Figure 1.[5,6a] Reactions conducted in water appear to be further assisted by an additional hydrogen bond from the solvent.[6b] The transition states for the corresponding imine reductions are less well understood,[3c-f,7a] although there is evidence that the iminium salt, formed by protonation, rather than the free imine, is reduced. This may involve an ionic mechanism, as has been proposed for related hydrogenation reactions of imines.[7b,7c]



Definitive evidence for the importance of the *N*-H interaction, however, would require the study of complexes in which this bond is not present; such complexes would be predicted to be poor catalysts for reduction.

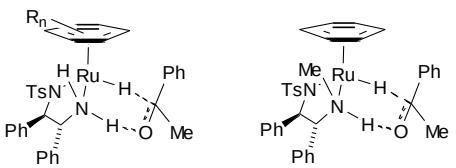


Figure 1. Involvement of *N*-H from TsDPEN in ATH ketone reduction transition state using **1** and **5**

It has been reported that the use of N-methylated and N',N'-dimethylated derivative of TsDPEN are poor catalysts for ATH reactions when a mestylene group is employed as the arene.[2b] If an η^6-benzene ring is used, however,[7a] good results can be obtained with N'-monoalkylated TsDPENs. Complex **5**, which is similar to **1** but formed from TsDPEN derivatives containing one methyl group on the basic amine, is highly active in ATH reactions, and an X-ray structure of the related *N'*-benzyl derivative indicated that the favoured conformation allows the catalytically important *N*-H bond to be correctly positioned to interact with the ketone substrate (also illustrated in Figure 1).

Results and Discussion.

In order to eliminate the possibility of involvement of a *N*-H bond in the transition state, TsDPEN derivatives with two alkyl substituents on the basic nitrogen are required. The reaction of [(benzene)$RuCl_2]_2$ with the *N'N'*-dimethyl-TsDPEN **6**[8] gave [(benzene)Ru(**6**-H)Cl] **7**, which proved to be sufficiently stable to isolate and characterise by X-ray crystallography (Figure 2).[9] The use of a benzene ring in **7** is important; complexes containing substituted arene rings proved to be less stable. This instability has been observed by others in attempts to prepare derivatives of complex **7**.[10]

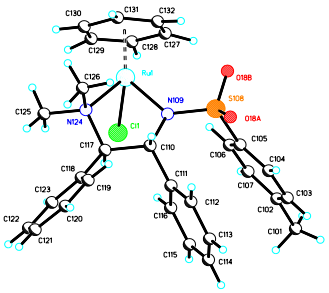
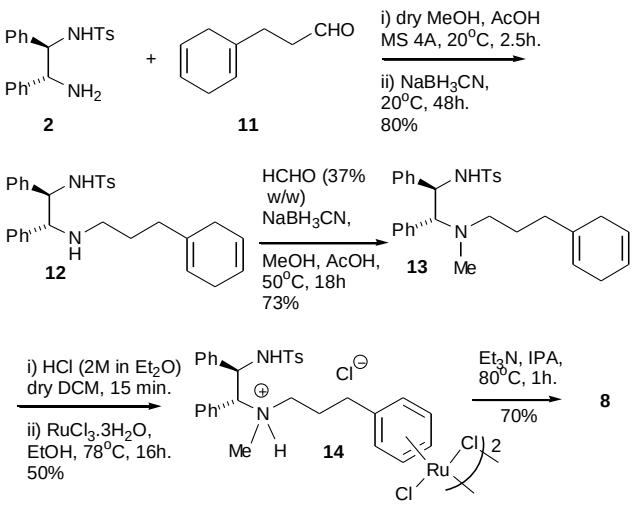


Figure 2. X-ray crystallographic structure of (*R*,*R*)-**7**.



Scheme 1. Synthesis of catalyst (*R*,*R*)-**8**.

We also prepared samples of the *N'*-alkylated derivatives **8** and **9** of the tethered catalyst **10**.[11,12] Complex **8** was prepared via the reaction of **2** and aldehyde **11** to give **12**, which was subjected to a second reductive amination with formaldehyde to form N'-methyl derivative **13**. The dimer **14**, formed by complexation of **13**, was converted into monomer **8** using Et_3N in IPA (Scheme 1). An X-ray crystallographic analysis of **8** (Figure 3)[13] confirmed its structure. Although the pattern of bond connectivity in **7** and **8** were those predicted, both complexes formed the opposite diastereoisomer with respect to the configuration at the Ru atom compared to other TsDPEN-derived complexes.[4,7a,11] Complex **9** was prepared in an analogous manner to **8** (see Supporting Information).

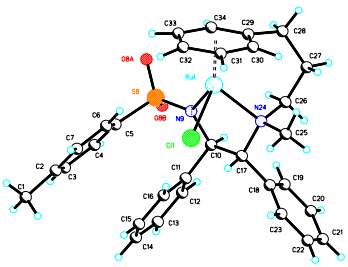
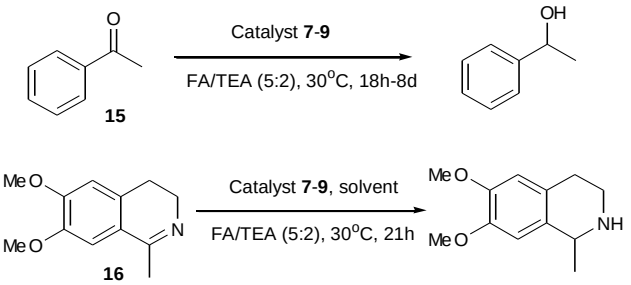


Figure 3. X-ray crystallographic structure of (*R*,*R*)-**8**.



Scheme 2. Reduction reactions used to test catalyst activity.

Complexes **7-9** were employed in ATH reductions of acetophenone **15** and cyclic imine **16** (Scheme 2) using formic acid/triethylamine (5:2) (FA/TEA) as the reducing agent. Each proved to be sluggish relative to the complexes which contain an *N*-H bond. Using 1 mol% of catalyst (*R*,*R*)-**7**, acetophenone **15** was reduced in only 1.7% conversion after 6 days (alcohol of 46% ee (*R*) was formed), whilst the reduction of **16** gave a better conversion of 91% after 5 days (18% ee (*S*)). In the case of imine reduction, the addition of a cosolvent slowed the reaction further. Figures 4 and 5 illustrate conversion/time graphs for reduction of **15** and **16** respectively, using catalysts **8** and **10** (see supporting information). For acetophenone, N'-methylation resulted in significant loss of catalytic activity. The non methylated catalyst (*R*,*R*)-**10** gave an alcohol of 96.5% ee (*R*)[11] in 100% conversion after 3h, whilst (*S*,*S*)-**8** gave the same product in 73% ee (*R*) in just 6% conversion after 18h (example for [ketone]=2M). Complex (*R*,*R*)-**9** gave a product of 36% ee (*R*) in 17% yield after 4 days ([ketone]=2M).

In the case of imine reduction, N'-alkylated tethered complexes were less active than the parent catalysts, however reactions did generally proceed to >95% within 20h, even in the presence of a cosolvent. In the example shown in Figure 5, the amine product was of 22% ee (*S*) at the end of the reaction using catalyst (*R*,*R*)-**8** and 34.5% ee (*S*) with catalyst (*R*,*R*)-**10**. Although not illustrated, complex (*R*,*R*)-**9** gave an amine product of 7% ee (*S*) in 95% conversion after 24h under the same conditions. The relative rate of reduction of an imine using **8** was not as sharply different to that observed using catalyst **10** containing the '*N*-H' bond, as it was for a ketone.

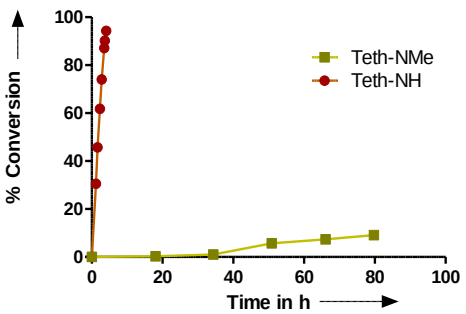


Figure 4. Time course of acetophenone **15** reduction using tethered catalysts **10** (*N*-H) and **8** (*N*-Me). FA/TEA=5:2, [Ketone]=0.86 M, S/C=100, 25 °C, S/C = 100. Followed by ^{1}H-NMR (400 MHz).

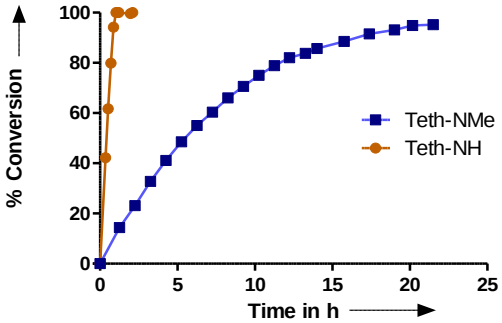


Figure 5. Time course of imine **16** reduction using tethered catalysts **10** (*N*-H) and **8** (*N*-Me). MeCN cosolvent, FA/TEA=5:2, [Imine]=0.45 M, S/C=100, 25 °C, S/C = 100. Followed by ^{1}H-NMR (400 MHz).

The low reactivity of the N'-alkylated catalysts relative to the non-alkylated ones could be due to a number of reasons[12,14] including (i) catalyst decomposition, (ii) slow formation of the Ru-H species or (iii) slow transfer of the hydride from the Ru-H species to the substrate. We followed reduction reactions of **15** and **16** and attempted to observe a Ru-H peak in the reaction.[12] Ikariya and Koike have obtained evidence that the assistance of the *N*-H bond in **1** is required for the formation of [(p-cymene)Ru(TsNCH$_2$CH$_2$NH$_2$)OCHO] from the hydride [(p-cymene)Ru(TsNCH$_2$CH$_2$NH$_2$)H] by insertion into carbon dioxide; no formation of the Ru-formate complex was observed in an attempt to add carbon dioxide to [(p-cymene)Ru(TsNCH$_2$CH$_2$NMe$_2$)H].[10] It was not possible to establish whether the same N-H bond interaction with Ru-bound formate was required for the decarboxylation to form a hydride. A similar formate precursor to a rhodium hydride complex has also been reported.[14]

In the case of catalyst **7**, derived from *N'N'*-dimethylTsDPEN **6**, no strong Ru-H peak could be observed during the attempted reduction of either ketone or imine. This suggests that either **7**, or its hydride derivative, may be undergoing decomposition,[10] which may explain, in part, its lower reactivity. In one case (see supporting information) where a RuH peak was observed (reduction of **16** using 3 mol% **7**) and measured by NMR, this decreased over the course of the reaction and was <0.2 mol% by the time full imine reduction was achieved (ca 180h). The results obtained with catalyst **8** were more encouraging. Clear evidence of a Ru-H peak was observed at ca. δ -5.3 which persisted throughout the reduction of both ketone and imine. At 3 mol% catalyst it was possible to establish that the level of the Ru-H species increased gradually and eventually remained constant at a maximum value (Figure 6); ca. 5h was required for 90% imine reduction. This would suggest that, although hydride formation is slow, the rate-limiting step is likely to be the transfer of the hydride to the imine substrate.

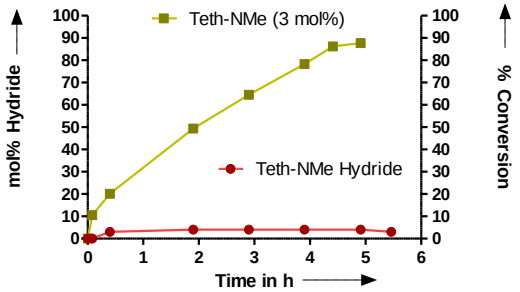


Figure 6. Time course of RuH peak of catalyst **8** (red line) during reduction of imine **16** (conversion shown by green line), FA/TEA=5:2, [Imine]=0.50 M, 30 °C. Followed by ^{1}H-NMR (700 MHz).

Conclusions

Taken together, these results suggest that, in [(arene)Ru(TsDPEN-H)H] catalysts, the presence of the *N*-H bond is (i) beneficial, but not essential, for formation of the ruthenium hydride species,[10] (ii) essential for the transfer of hydrogen to ketones in the reduction step and (iii) beneficial but not essential for the transfer of hydrogen to imines. Whilst it is difficult to factor in the clearly important effect of the extra steric hindrance created by a second alkyl group on the basic nitrogen atom in **8**, this and the slower hydride formation may be responsible for the lower rate of imine reduction observed with **8** compared to **10**. If this is the case, then our observations suggest that the mechanism of reduction of imines[3f] may not rely on the directing effect of the *N*-H bond in the catalyst to the same extent.[3,7a,14] The extra alkyl groups in **7**-**9** also reduce the enantioselectivities of reduction reactions which are catalysed by Ru(II)/TsDPEN complexes.

Experimental section

General experimental details, and procedures for synthesis of complex precursors and of complex **9**, Tables, Graphical data, X-ray crystallographic data and NMR spectra may be found in the Electronic Supporting Information.

Preparation of N-[(1R,2R)-2-(dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide benzeneruthenium chloride ***7***. A mixture of *N*-[(1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **6** (0.250 g, 0.635 mmol), benzeneruthenium(II)chloride dimer (0.318 g, 0.635 mmol, 1.0 eq) and triethylamine (0.353 mL, 2.54 mmol, 4.0 eq) in IPA (25 mL) was heated at 80 °C for 1 h under an inert atmosphere. The reaction mixture was cooled to room temperature and concentrated to give a residue. The residue was filtered and washed with water to leave a solid. The solid was purified by flash column chromatography on Florisil. The complex was eluted in Hexane:EtOAc:MeOH (5:4:1) to give compound **7** as a light brown solid (0.145 g, 0.242 mmol, 38%). m.p.146-148 °C with decomposition; $[\alpha]_D^{20}$ = +1687 (*c* = 0.0048 in $CHCl_3$); ν_{max} = 2921, 1452, 1437, 1252, 1129, 1086, 942, 809, 699, 663 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.37 (2H, d, *J* = 8.0 Hz, o-CH of -SO$_2$C$_6$H$_4$CH$_3$),

7.15-7.11 (2H, m, ArH), 6.98-6.92 (4H, m, ArH), 6.80 (2H, d, ^3J = 8.0 Hz, m-CH of -$SO_2C_6H_4CH_3$), 6.60-6.54 (4H, m, ArH), 5.79 (6H, s, C_6H_6), 4.90 (1H, d, *J* = 11.7 Hz, C*H*N$(CH_3)_2$), 4.58 (1H, d, *J* = 11.7 Hz, C*H*NHTs), 3.20 (3H, s, N$(CH_3)_2$), 2.89 (3H, s, N$(CH_3)_2$), 2.20 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 142.27, 139.65, 139.19, 130.11, 129.65, 128.56, 128.10, 126.80, 126.33, 125,46, 84.46, 76.88, 66.38, 52.24, 50.15, 21.17; *m/z* ESI-MS $[M\text{-}Cl]^+$ 573.0; HRMS found 573.1147 ($C_{29}H_{31}ClN_2O_2RuS$ -Cl requires 573.1147, error = 0.7 ppm).

*Preparation of {N-[(1R,2R)-2-((3-cyclohexa-1,4-dienyl)propyl)(methyl)ammonium chloride)-1,2-diphenylethyl]-4-methylbenzenesulfonamide} ruthenium chloride dimer **14**.*

To a solution of *N*-[(1*R*,2*R*)-2-((3-cyclohexa-1,4-dienyl)propyl)(methyl)amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **13** (0.355 g, 0.710 mmol) in DCM (10 mL) was added a 2M solution of HCl in diethyl ether (0.89 mL, 1.77 mmol) and the mixture was stirred at 22 °C for 30 min under an inert atmosphere. The solvents were removed under reduced pressure to give a residue. This was dissolved in ethanol (20 mL) and ruthenium trichloride trihydrate (0.139 g, 0.532 mmol) was added. The resulting mixture was heated at 78 °C for 16 h. The reaction mixture was cooled, solid separated out, filtered and washed with ethanol to give compound **14** as green solid (0.250 g, 0.177 mmol, 50%) which was used directly in the next step, m.p > 300 °C; m/z ESI-MS $[M\text{-}Cl]^+$ 599.1 (monomer formed by dimer cleavage and loss of HCl *in-situ*); ^{1}H NMR (300 MHz, d6-DMSO, TMS): δ 9.30-8.50 (2H, 4 x brs, NH), 7.60-6.80 (30H, m, ArH), 6.08-6.00 (4H, m, $\eta^6C_6H_5$), 5.95-5.80 (6H, m, $\eta^6C_6H_5$), 5.15-5.05 (2H, m, CH), 4.95-4.80 (2H, m, CH), 2.90-2.00 (12H, m, CH_2), 2.40 (12H, brs, CH_3).

*Preparation of {N-[(1R,2R)-2-((3-cyclohexa-1,4-dienyl)propyl)(methyl)amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide} ruthenium chloride monomer **8**.*

A mixture of {*N*-[(1*R*,2*R*)-2-((3-cyclohexa-1,4-dienyl)propyl)(methyl)ammonium chloride)-1,2-diphenylethyl]-4-methylbenzenesulfonamide} ruthenium chloride dimer **14** (0.275 g, 0.195 mmol) and triethylamine (0.162 mL, 1.168 mmol, 6.0 eq) in IPA (15 mL) was heated at 80 °C for 1 h under an inert atmosphere. The reaction mixture was cooled to room temperature and concentrated to give a residue. This was filtered and washed with water. The solid was purified by flash column chromatography on Florisil. The complex was eluted in Hexane: EtOAc:MeOH (5:4:1) to give compound **8** as a light brown solid (0.175 g, 0.275 mmol, 70%). m.p. 184-186 °C with decomposition; $[\alpha]_D^{24}$ = +1394 (*c* = 0.0052 in $CHCl_3$); ν_{max} 3435, 2973, 2924, 1600, 1454, 1267, 1129, 1085, 1045, 940, 841, 699, 664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.44 (br s, 1H, ArH), 7.28 (d, *J* = 7.6 Hz, 2H, ArH), 7.22 (br s, 1H, ArH), 7.11 (t, *J* = 6.9 Hz, 1H, ArH), 6.97 (br s, 1H, ArH), 6.89 (br d, *J* = 5.2 Hz, 2H, ArH), 6.73 (2H, d, *J* = 7.6 Hz, m-CH of -$SO_2C_6H_4CH_3$), 6.62-6.58 (m, 2H, ArH), 6.53-6.49 (m, 2H, ArH), 6.44 (1H, t, *J* = 4.9 Hz, p-CH of $\eta^6C_6H_5$), 6.29 (1H, d, *J* = 4.4 Hz, o-CH of $\eta^6C_6H_5$), 5.74 (1H, t, *J* = 5.3 Hz, m-CH of $\eta^6C_6H_5$), 5.46 (1H, t, *J* = 5.2 Hz, m-CH of $\eta^6C_6H_5$), 5.31 (1H, d, *J* = 5.6 Hz, o-CH of $\eta^6C_6H_5$), 4.87 (1H, d, *J* = 11.8 Hz, CHNH$(CH_2)_3$-), 4.70 (1H, d, *J* = 11.8 Hz, CHNHTs), 3.34-3.28 (1H, m, $NHCH_2$), 2.93 (1H, br d, *J* = 13.2 Hz, $NHCH_2$), 2.83 (3H, s, NCH_3), 2.77 (1H, br d, *J* = 9.2 Hz, -$CH_2CH_2CH_2$), 2.43-2.33 (1H, m, $CH_2CH_2CH_2$), 2.33-2.24 (2H, m, $CH_2CH_2CH_2$), 2.17 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 141.90, 139.52, 139.32, 134.40, 130.41, 130.12, 128.52, 127.94, 126.74, 126.24, 125.20, 88.05, 87.12, 85.97, 85.05, 84.79, 84.59, 79.14, 66.42, 53.53, 48.40, 28.60, 23.77, 21.14; *m/z* ESI-MS $[M\text{-}Cl]^+$ 599.1; HRMS found 599.1314 ($C_{31}H_{33}ClN_2O_2RuS$- Cl requires 599.1308, error = -1.0 ppm).

Reduction of acetophenone 15 and imine 16 or its salt:

In neat FA/TEA: A mixture of imine/ketone (50 mg), catalyst (1 mol%) in FA:TEA (5:2) (0.2 mL) was stirred at 30 °C for 18-22 h under an inert atmosphere. For reaction monitoring, an aliquot of the reaction mixture was filtered through a plug of silica and analyzed by chiral GC for % conversion and ee.

In solvent: A mixture of imine/ketone (50 mg), catalyst (1 mol%) and FA:TEA (5:2) (0.2 mL) in solvent (0.4 mL) was stirred at 30 °C for 18-22 h under an inert atmosphere. For reaction monitoring, an aliquot of the reaction mixture was filtered through a plug of silica and analyzed by chiral GC, with comparison to an authentic sample of the required material, for % conversion and ee, (retention times given in ESI).

400MHz NMR Kinetic study of the reduction of acetophenone: To a 5 mm NMR tube were added catalyst (0.01 mmol), and formic acid/triethylamine 5:2 complex (1 mL). After 30 minutes, acetophenone was added (120 mg, 1 mmol) followed by 0.05 mL of C_6D_6 hence providing a substrate solution of initially ca. 0.86M. The reaction was followed by ^{1}H-NMR until the specified conversion was achieved. The conversion was calculated by the integration of the methyl peak from the starting material at ca. 2.44 ppm and the CH from the product at ca. 4.87 ppm. Note that the exact positions of these peaksvary slightly depending on the exact nature of each sample (solvent, concentration etc.). At the end of the reaction the reaction mixture was flushed through a short pad of silica using EtOAc to elute. The alcohol was isolated by flash chromatography on silica gel and its ee was determined by chiral GC with comparison to an authentic sample of the required material, for % conversion and ee, (retention times given in ESI).

400MHz NMR Kinetic study for reduction of imine: To a 5 mm NMR tube were added catalyst (0.005 mmol), and formic acid/triethylamine 5:2 complex (0.25 mL). After 30 minutes a solution of imine **16** (0.5 mmol) in acetonitrile (0.8 mL) was added followed by 0.05 mL of C_6D_6 hence providing a substrate solution of initially ca. 0.45M. The reaction was followed by ^{1}H-NMR until complete reduction was observed. The conversion was calculated by the integration of the aromatic proton peak from the starting material (two singlets at ca. 6.99, 6.69 ppm) and the product (two singlets at ca.

6.50, 6.40 ppm). Note that the exact positions of these peaksvary slightly depending on the exact nature of each sample (solvent, concentration etc.). At the end of the reaction the reaction mixture was flushed through a short pad of silica using EtOAc to elute. The amine product was isolated by flash chromatography on silica gel and its ee was determined by chiral GC with comparison to an authentic sample of the required material, for % conversion and ee, (retention times given in ESI).

700 NMR reactions for reduction of imine: To a 5 mm NMR tube were added the imine 16 (0.731 mmol), catalyst (1 or 3 mol%), and formic acid/triethylamine 5:2 complex (0.6 mL), followed by 0.05 mL of C_6D_6. The reaction was followed by ^{1}H-NMR with hydride detection until the maximum level of reduction was observed. The conversion was calculated, and the product isolated, by following the procedure in the paragraph above.

Acknowledgements

We thank Warwick University for support of RS through a scholarship, EPSRC for financial support of JEDM (EP/F019424) and EPSRC/AstraZeneca for support of FKC via a collaborative studentship. The X-ray diffractometer was funded through the AWM Science City Advanced Materials project and ERDF support.

Notes and references

[a] *Department of Chemistry, The University of Warwick, Coventry, CV4 7AL UK. Fax: (+44) 24 7652 3260; Tel: (+44) 24 7652 4112; E-mail: m.wills@warwick.ac.uk.*

[b] *Cancer & Infection Chemistry, AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG.*

† Electronic Supplementary Information (ESI) available: [experimental details, X-ray structure and NMR spectra]. See DOI: 10.1039/b000000x/

1. (a) T. Ikariya, K. Murata and R. Noyori, *Org. Biomol. Chem*. 2006, **4**, 393-406. (b) S. Gladiali and E. Alberico, *Chem. Soc. Rev*. 2006, **35**, 226-236. (c) T. Ikariya and A. J. Blacker, *Acc. Chem. Res.* 2007, **40**, 1300-1308. (d) S. E. Clapham, A. Hadzovic and R. H. Morris, *Coord. Chem. Rev*. 2004, **248**, 2201-2237.
2. (a) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc*. 1995, **117**, 7562-7563. (b) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya and R. Noyori, *J. Am. Chem. Soc*. 1996, **118**, 2521-2522. (c) K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.* 1997, **119**, 8738-8739. (d) K. Murata, K. Okano, M. Miyagi, H. Iwane, R. Noyori and T. Ikariya, *Org. Lett*. 1999, **1**, 1119-1121.
3. (a) N. Uematsu, A. Fujii, S. Hasjiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.* 1996, **118**, 4916-4917. (b) J. Blacker and J. Martin, in Asymmetric Catalysis on an Industrial Scale: Challenges, Approaches and Solutions; H.-U. Blaser and E. Schmidt, Eds, Wiley, 2004, 201-216. (c) C. P. Casey, T. B. Clark and I. A. Guzei, *J. Am. Chem. Soc.* 2007**, 129**, 11821-11827. (d) J. S. M. Samec, A. H. Éll, J. B. Åberg, T. Primalov, L. Eriksson and J.-E. Bäckvall, *J. Am. Chem. Soc*. 2006, **128**, 14293-14305. (e) C. P. Casey and J. B. Johnson, *J. Am. Chem. Soc.* 2005, **127**, 1883-1894. (f) J. B. Åberg, J. S. M. Samec and J.-E. Bäckvall, *Chem. Commun*. 2006, 2771-2773. g) D. J. Blackmond, M. Ropic and M. Stefinovic, *Org. Proc. Res. Dev*. 2006, **10**, 457 – 463. (h) G. D. Williams, R. A. Pike, C. E. Wade and M. Wills, *Org. Lett*. 2003, **5**, 4227 – 4230.
4. K. J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem. Int. Ed.* 1997, **36**, 285-288.
5. (a) M. Yamakawa, I. Yamada and R. Noyori, *Angew. Chem. Int. Ed.* 2001, **40**, 2818-2821. (b) R. Noyori, M. Yamakawa and S. Hashiguchi, *J. Org. Chem.* 2001, **66**, 7931-7944. (c) M. Yamakawa, H. Ito and R. Noyori, *J. Am. Chem. Soc*. 2000, **122**, 1466-1478. (d) D. A. Alonso, P. Brandt, S. J. M. Nordin and P. G. Andersson, *J. Am. Chem. Soc.* 1999, **121**, 9580-9588. (e) P. Brandt, P. Roth and P. G. Andersson, *J. Org. Chem.* 2004, **69**, 4885-4890.
6. (a) C. P. Casey and J. B. Johnson, *J. Org. Chem.* 2003, **68**, 1998-2001. (b) X. Wu, J. Liu, D. Di Tommaso, J. I. Iggo, C. R. A. Catlow, J. Bacsa and J. Xiao, *Chem. Eur. J.* 2008, **14**, 7699-7715.
7. (a) J. E. D. Martins, G. J. Clarkson and M. Wills, *Org. Lett*. 2009, **11**, 847 – 850. (b) M. P. Magee and J. R. Norton, *J. Am. Chem. Soc.* 2001, **123**, 1778-1779. (c) R. M. Bullock, *Chem. Eur. J.* 2004, **10**, 2366-2374.
8. (a) T. Honjo, S. Sano, M. Shiro and Y. Nagao, *Angew. Chem. Int. Ed.* 2005, **44**, 5838-5841. (b) T. Honjo, M. Nakao, S. Sano, M. Shiro, K. Yamaguchi, Y. Sei and Y. Nagao, *Org. Lett*. 2007, **9**, 509-512.
9. X ray data for **7**; CCDC no. 793889, $C_{31}H_{37}ClN_2O_3RuS$, M = 654.21, Triclinic, space group P1 a = 10.3603(2), b = 11.0519(3), c = 14.0747(3) Å , α = 90.6376(19)˚, β = 103.5283(17)˚, γ = 107.614(2)˚, U = 1487.56(6) Å^3 (by least squares refinement on 22067 reflection positions), T =100(2)K, λ = 0.71073 Å, Z = 2, D(cal) = 1.461 Mg/m^3, F(000) = 676. mu(MoK-α) = 0.721 mm^{-1}. Crystal character: orange block. Crystal dimensions 0.40 x 0.18 x 0.14 mm. Further details are given in the SI.
10. T. Koike and T. Ikariya, *Adv. Synth. Catal*. 2004, **346**, 37-41.
11. (a) A. M. Hayes, D. J. Morris, G. J. Clarkson and M. Wills, *J. Am. Chem. Soc.* 2005, **127**, 7318 – 7319. (b) D. J. Morris, A. M. Hayes, and M. Wills, *J. Org. Chem.* 2006, **71**, 7035-7044.
12. (a) F. K. Cheung, C. Lin, F. Minissi, A. Lorente Crivillé, M. A. Graham, D. J. Fox and M. Wills, *Org. Lett.* 2007, **9**, 4659-4662. (b) F. K. (K.) Cheung, A. J, Clarke, G. J. Glarkson, D. J. Fox, M. A. Graham, C. Lin, A. Lorente Crivillé and M. Wills, *Dalton Trans.* 2010, **39**, 1395 – 1402.
13. X-ray data for **8**; CCDC no. 793888, $C_{31}H_{33}ClN_2O_2RuS$, M = 634.17, Orthorhombic, space group P2(1)2(1)2(1) a = 8.39707(8), b = 9.14896(9), c = 35.0858(3) Å , α = 90˚, β = 90˚, γ = 90˚, U = 2695.44(4) Å^3 (by least squares refinement on 7176 reflection positions), T =100(2)K, λ = 1.54184 Å, Z = 4, D(cal) = 1.563 Mg/m^3, F(000) = 1304. mu(MoK-α) = 6.436 mm^{-1}. Crystal character: orange block. Crystal dimensions 0.2108 x 0.1391 x 0.0319 mm. Further details are given in the SI.
14. A. J. Blacker, E. Clot, S. B. Duckett, O. Eisenstein, J. Grace, A. Nova, R. N. Perutz, D. J. Taylor and A. C. Whitwood, *Chem. Commun.* 2009, 6801-6803.