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A new class of Rh(III) catalyst containing an aminoalcohol tethered to a tetramethylcyclopentadienyl group for asymmetric transfer hydrogenation of ketones

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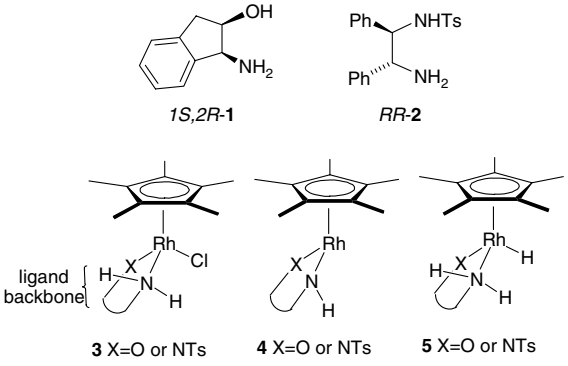
Abstract—The synthesis and application to asymmetric reduction of acetophenone, of a novel class of Rh(III) catalyst containing a tether between the cyclopentadienyl group and a homochiral aminoalcohol, is described. The complex is a highly active catalyst for asymmetric ketone reduction, however it appears to be unstable to the extended reaction conditions. The well-defined stereochemical structure of the catalyst offers potential for significant improvement and 'fine tuning' towards specific substrates.

During the course of a number of investigations into the development of Rh(III) pentamethylcyclopentadienyl catalysts for the asymmetric transfer hydrogenation of ketones, we have focused on the use of homochiral 1,2-aminoalcohols such as **1** and monotosylated diamines such as **2** (Noyori's ligand) to control the enantioselectivity of the reaction.[1,2] An active catalyst is formed by the combination of either ligand with $[RhCl_2(C_5Me_5)]_2$ in an inert solvent with a small amount of base. In this process an 18-electron 'pre-catalyst' **3** is formed, which undergoes subsequent elimination of HCl to form **4**, which in turn abstracts two hydrogen atoms from a solvent molecule (isopropanol or formic acid depending on the conditions employed) to give intermediate **5**. The transfer of these two hydrogen atoms to the substrate results in formation of the alcohol product and regeneration of **4**, thus completing a catalytic cycle.[3]

Although these complexes are capable of generating very high asymmetric inductions in a range of reduction processes, we believed that they could be modified in a productive manner through the tethering of the ligand components, which remain on the metal throughout the catalytic cycle. Through this modification, the cyclopentadienyl ring would be unable to rotate and there would now be a potential to introduce selectively directing groups at specific positions. This would permit the synthesis of 'fine-tuned' reduction catalysts for use with individual classes of substrate. In addition, the 'three-point' attachment of the ligand to the metal was expected to improve the overall stability of the ligand.



Towards this end, we wished to establish methodology for the synthesis of **6**, a complex in which the cyclopentadienyl group is attached to L-norephedrine, an amine, which has been successfully employed as a ligand in this application. X-ray crystallographic analyses of the

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isoelectronic ruthenium(II) complexes **7** have revealed that the favoured diastereoisomer is that in which the phenyl group adjacent to the oxygen atom (in the ligand) lies *trans* to the Ru–Cl bond in the complex equivalent to **3**.[2d,e,i] An analogous structural relationship is found in Rh(III) complexes of monotosylated diamine **2**.[2j,k] Through this diastereoisomeric complexation, the metal is rendered chiral. Assuming that this stereochemistry is retained throughout the catalytic cycle (as demonstrated by Noyori for Ru(II) complexes),[2i] then the metal configuration in turn controls the approach of the ketone to the metal hydride species as depicted in Figure 1; the π-interaction of the phenyl ring with the complexed ring being a significant control element.[4]

Although the tetramethylcyclopentadienyl group is different in structure from an arene ligand, the same π-face stabilisation effect is known to operate through methyl groups on the arene ligand, for example, in the cases of *p*-cymene and hexamethylbenzene.[4] On this basis, it is likely that stereochemical control of ketone reduction using Cp^*/Rh(III) complexes proceeds in a similar manner.

We reasoned that the synthesis of complex **6**, as the single diastereoisomer illustrated, could be achieved upon reaction of precursor **10** with 1 equiv of rhodium(III) trichloride. The synthesis of **6** was thus completed as illustrated in Scheme 1.[5] The reaction of *ortho*-bromobenzyl bromide with L-(1*R*,2*S*)-norephedrine followed by treatment of the product with 2,2-dimethoxypropane furnished the key intermediate **8** in excellent yield. Bromine/lithium exchange in **8** upon treatment with 1 equiv of *t*-BuLi at −78 °C was followed by addition of 2,3,4,5-tetramethylcyclopentenone **11**. This resulted in the formation of **9** in reasonable yield as a mixture of isomers. In the next step **9** was treated with strong acid overnight, resulting in both hydrolysis of the aminal ring and dehydration to form the cyclopentadiene group in **10**. This intermediate exhibited a very complex ^{1}H NMR spectrum as would be expected due to cyclopentadiene isomerisation. Upon treatment with 1 equiv of $RhCl_3$ for 48 h the exchange reaction resulted in direct formation of the required catalyst **6** in essentially quantitative conversion.[6]

Complex **6**, a red/brown crystalline solid, was characterised by ^{1}H NMR spectroscopy, which exhibited the four singlet signals expected of four diastereomerically distinct methyl groups on the cyclopentadienyl ring. In addition the complex was of the correct mass as determined by high resolution mass spectrometry. Since we have not yet been able to confirm the stereochemistry of **6** by X-ray crystallography, we have assigned the relative stereochemistry on the basis of the structures of closely related complexes derived from L-ephedrine and its derivatives.[2]

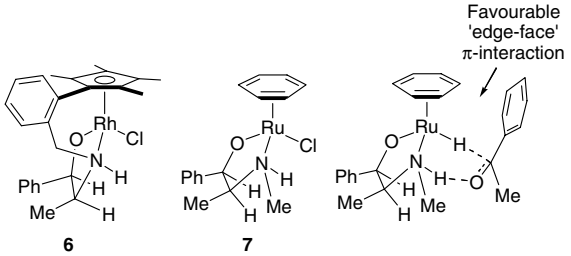
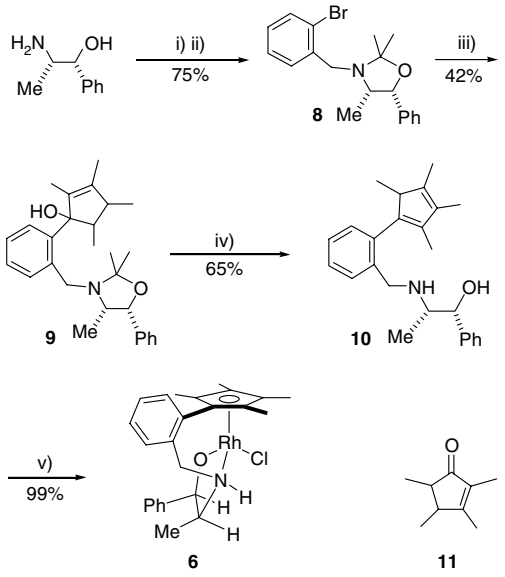


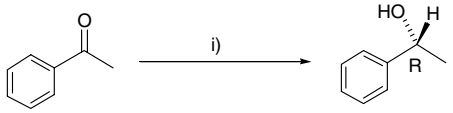
Figure 1.



Scheme 1. Reagents and conditions: (i) *o*-$BrC_6H_4CH_2Br$, Et_3N, DCM, 94%. (ii) $(CH_3)_2C(OCH_3)_2$, TsOH, 91%. (iii) *t*-BuLi, Et_2O, −78 °C, then **10**, Et_2O, −78 °C–rt, o/n. (iv) 2 M H_2SO_4, Et_2O, rt, o/n. (v) $RhCl_3{\cdot}H_2O$, MeOH, reflux, 48 h.

Complex **6** proved to be an effective catalyst for the asymmetric reduction of acetophenone in isopropanol, a useful test substrate, which allows comparisons with other systems (Scheme 2, Table 1).[7] It also furnished a reduction product of *R* configuration, which would be predicted based on the stereochemical argument above, with the assumption that the tethering does not adversely effect the control by the ligand. A small amount of base is required to activate the catalyst by promoting the elimination of HCl in order to form a 16-electron intermediate, which then enters the catalytic cycle.

Perhaps the most striking feature of the reduction reactions, which were studied using a 0.1 M concentration of ketone at the 1 and 5 mol% catalyst levels, was the very high *activity* demonstrated (selected results are given in Table 1). At the 1 mol% level the reduction was 50% complete within 10 min, whilst at the 5 mol% level the reaction was 95% complete after this time. Unfortunately, at the lower catalyst loading, the reaction



Scheme 2. Reagents and conditions: (i) 1–5 mol% tethered catalyst **6**, 2.5 mol% KO*t*-Bu, *i*-PrOH, 4 h, rt.

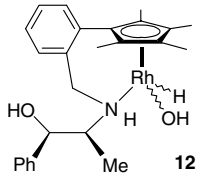
Table 1. Asymmetric reduction of acetophenone using **6**

Catalyst (mol%)	Time (min)	Conversion (%)	Enantiomeric excess (%)
1	1	18.5	74.9
1	5	41.2	72.1
1	10	50.4	68.6
1	60	62.1	55.8
1	o/n	86.2	41.6
5	1	78.2	73.5
5	5	92.7	70.5
5	10	95.0	68.0
5	60	96.4	64.2
5	o/n	98.2	62.5

Conversions were followed by ^{1}H NMR and enantiomeric excesses by chiral HPLC.

failed to go to completion and the rate of conversion dropped dramatically after the first few minutes. Even at the higher catalyst loading the reaction failed to go fully to completion, even when left overnight. In a control reaction, the combination of *N*-benzyl-L-ephedrine with rhodium trichloride did not result in the formation of a catalyst capable of acetophenone reduction. The use of 5 mol% of complex **6** in formic acid/triethylamine (o/n, rt) resulted in the formation of racemic alcohol in 41% conversion. This result was not unexpected, as amino alcohol ligands are not generally compatible with formic acid/triethylamine conditions.

The enantiomeric excesses also demonstrated an interesting trend. After a promising high selectivity early in the reaction, the ees dropped in the later stages of the reaction. That this drop was not due to significant reversibility of the reaction was demonstrated by treatment of *R*-1-phenylethanol of 97% ee with 5 mol% of the catalyst in isopropanol and 1 equiv of acetone to reproduce the environment generated at the end of the reaction. The reaction mixture was followed at various times up to 24 h after the addition of KOH and at no time was the alcohol observed to racemise. Having ruled out significant racemisation of the product by catalyst, we reasoned that the loss of enantioselectivity may be accounted for by the transient formation of a slow-reacting decomposition product, which served to reduce the remaining ketone in a racemic manner. This would result in a lower overall observed enantioselectivity. Such an intermediate could be **12**, formed by breakage of the O–Rh bond, which then subsequently decomposes further to an unreactive material under the reaction conditions. However the 5 mol% catalyst figures in Table 1 suggest that there must also be *some* racemisation taking place (i.e., 1.4% conversion increase from 10 to 60 min would not give an ee drop of 3.8% if the new product was entirely racemic). It is perhaps possible that our racemisation test, which employed *fresh* catalyst, did not fully reproduce the conditions at the end of the reaction.



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In conclusion, we have successfully completed the synthesis and testing of the first example of a Rh(III) catalyst for transfer hydrogenation in which both ligand components are tethered. Whilst this is a highly active catalyst for ketone reduction, and furnishes a product of the predicted configuration (*R*) based on the design principles, it does not remain stable under the reaction conditions. Studies are currently underway to improve the stability of the catalyst in order to deliver a finely-tunable reagent for targeted use on specific substrates.

Acknowledgements

We thank the EPSRC and Avecia for support of a CASE studentship (D.J.C.). A.M.K. thanks the Brazilian iAe for study leave. Professor D. Games and Dr. B. Stein of the EPSRC National Mass Spectroscopic service (Swansea) are thanked for HRMS analysis of certain compounds. We also acknowledge the generous loan of ruthenium and rhodium salts by Johnson–Matthey limited and the use of the EPSRC Chemical Database Service at Daresbury.[8]

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5. For an example of a tethered Cp/Ru system see: Brunner, H.; Valerio, C.; Zabel, M. *New J. Chem.* **2000**, *24*, 275.
6. *N-2-(2,3,4,5-Tetramethylcyclopentadienyl)benzyl-(*L*)-norephedrine rhodium(III) chloride* **6**. Rhodium(III) chloride hydrate (0.197 g, 0.748 mmol) was added to a stirred solution of *N*-2-(2,3,4,5-tetramethylcyclopentadienyl)benzyl-(L)-norephedrine **8** (0.27 g, 0.748 mmol) in methanol (15 mL) at room temperature. The reaction mixture was heated under reflux and stirred for 72 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to give the crude product, which was washed with DCM to give the product **6** as a red/brown solid (0.37 g, 99%). ^{1}H NMR (300 MHz, CDCl3): $\delta = 7.07$–7.95 (1H, m, ArH), 7.59–7.13 (8H, m, ArH), 5.20 (1H, br s, NH), 4.81 (1H, d, $J = 13.1$ Hz, CHPh), 4.21 (1H, m, CH_2Ar), 2.9 (1H, m, C*H*Me), 1.84 (3H, s, CpMe), 1.76 (3H, s, CpMe), 1.65 (3H, s, CpMe), 1.53 (3H, s, CpMe), 0.91 (3H, d, $J = 6.4$ Hz, CH*Me*). ^{13}C NMR (300 MHz, CDCl3): $\delta = 9.3$ (CH_3), 9.5 (*C*H_3), 12.2 (CH_3), 10.5 (*C*H_3), 12.5 (*C*H_3), 54.8 (*C*H_2), 59.2 (*C*H), 72.8 (*C*H), 125.8, 126.1, 126.5, 127.2, 128.5, 128.7, 128.9, 129.0, 129.5, 129.7, 130.5, 131.9, 133.6, 137.6, 142.0 (Ar–*C*). IR (neat) = 3882, 3226, 2978, 2359, 2342, 2211, 2190, 2084, 2064, 1968, 1634, 1447, 1373, 1266, 1197, 1151, 1098, 1022, 968, 749, 730, 700, 262. MS (FAB+): 498 (MH^+, 15%), 374 (21%), 307 (24%), 154 (100%), 136 (75%), 148 (35%), 132 (22%), 106 (14%), 91 (23%), 84 (100%). HRMS (FAB) calcd for $C_{25}H_{29}$ ClNORh = 498.10254, found 498.10664.
7. *N-2-(2,3,4,5-Tetramethylcyclopentadienyl)benzyl-(*L*)-norephedrine rhodium(III) chloride* **6** *catalysed transfer hydrogenation of acetophenone; typical procedure (5 mol%).* *N*-2-(2,3,4,5-Tetramethylcyclopentadienyl)benzyl-(L)-norephedrine rhodium(III) chloride **6** (0.025 g, 0.05 mmol) was stirred in acetophenone (0.120 g, 1 mmol) under nitrogen in a flame dried Schlenk tube for 30 min. Degassed propan-2-ol (10 mL) was added and the reaction mixture was stirred for 2 h. Sodium *tert*-butoxide (1.0 mL, 0.1 M solution in propan-2-ol) was added. Samples were filtered through silica, concentrated under reduced pressure and analysed by NMR and HPLC. After 2 min the conversion was 78.2% and ee 73.5% by HPLC analysis [Chiracel OD, hexane/ethanol = 95:5 (1.0 mL/min)], *R* isomer 8.30 min, *S* isomer 9.35 min.
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