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Ether- Tethered Ru(II)/TsDPEN Complexes; Synthesis and Applications to Asymmetric Transfer Hydrogenation.

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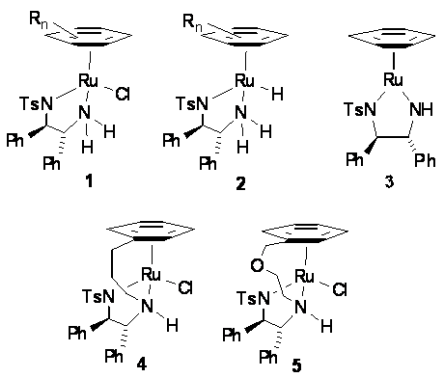
A new type of Ru(II)/TsDPEN catalyst containing an ether-based linking tether has been prepared and shown to exhibit excellent activity in asymmetric transfer hydrogenation reactions of ketones. Related complexes containing a hydroxyl-terminated alkyl chain have also been prepared and tested as asymmetric catalysts. In some cases the activity of the new catalyst type complements that of the closely related alkyl-chain tethered complexes.

Introduction.

The enantioselective reduction of ketones to alcohols is a pivotal reaction in organic chemistry, for which a large number of catalysts have been reported.[1] Of these, a particularly successful class are those based on the combination of a 1,2-monotosylated diamine ligand with a Ru(II) arene unit.[2-7] These catalysts may be employed in both asymmetric transfer hydrogenation (ATH)[3] reactions, i.e. using an organic compound as the hydrogen source, or direct asymmetric hydrogenation (AH)[4] using hydrogen gas. This class of catalyst, typified by structure **1** was first introduced by Noyori et al in 1995.[3a] Complex **1** is effective at ATH using either isopropropanol or formic acid typically as the hydrogen source and also at AH reactions if non-basic conditions are employed. Since their initial discovery, many structural variations of the catalyst have been reported,[5] as well as numerous applications in total synthesis and synthetic methodology.[6]



Mechanistic studies on complex **1** revealed that the catalyst involves conversion of **1** to the hydride **2**, which then transfers two hydrogen atoms to a ketone through an 'outer sphere' mechanism.[7] This transfer results in formation of the 16-electron complex **3** which is subsequently converted back to hydride **2** upon reaction with the terminal hydrogen donor (typically isopropanol or formic acid in the case of ATH),thus completing the catalytic cycle. In 2005, we reported on the synthesis of complex **4**, a structural variation on **1** containing a linking group (a 'tether') between the arene and the diamine unit.[8a] Complex **4** was found to be a highly active catalyst for ATH of ketones, particularly when formic acid/triethylamine (FA/TEA) was employed as the hydrogen source. Since initial report on **4**, we have also reported on the studies of the kinetics of ketone reduction by this complex, on the stereochemistry of ketone and imine reduction, and a number of variations on its structure.[8]

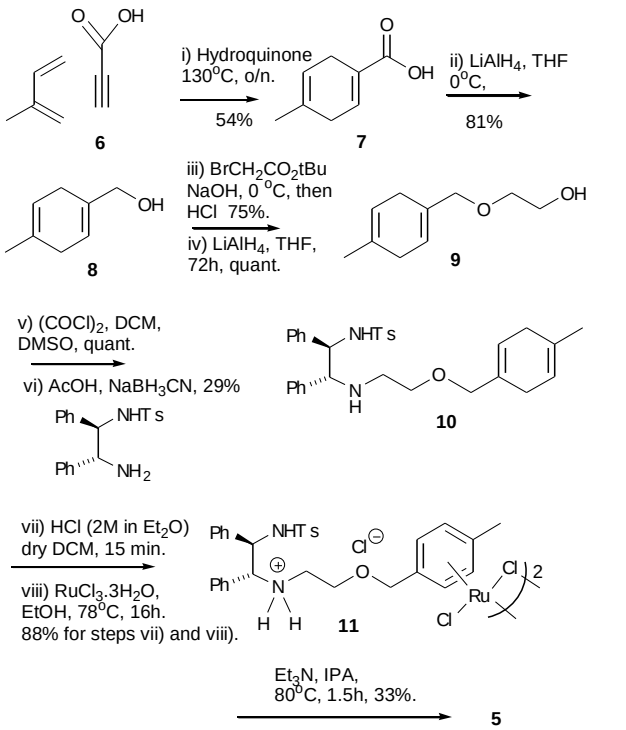
Although complex **4** and its derivatives have proved to be excellent catalysts for ATH reactions, their synthesis still presents a number of challenges when tranferred to the larger scale. In particular, a Birch reduction of an aromatic alcohol is required to deliver a key 1,4-cyclohexadiene for complexation to the ruthenium metal. In a previous report, we have described an alternative approach which is based on a [4+2] cycloaddition strategy to create the required cyclodiene,[8c] however the versatility of the method is limited due to the availability of appropriate starting materials.

In order to provide an improved access to the tethered catalysts, we have recently investigated the use of a very efficient [4+2] cycloaddition of a propargylic acid with a diene, to furnish catalyst **5** containing an ether-based tether between the arene and the diamine.[9] The synthesis and applications of this new class of catalyst are described in this paper.

Results and discussion.

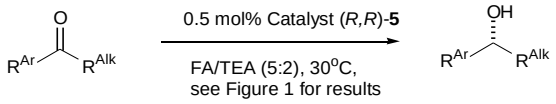
The synthetic route to ether-linked tethered complex **5** is shown in Scheme 1. This starts with the known cycloaddition reaction of propargylic acid **6** with isoprene to give the 1,4-cyclohexadiene **7**. This reaction can be conducted on a large scale without difficulty and is followed by reduction to the alcohol **8**. Extension of the chain was achieved through alkylation with t-butylbromoacetate, then hydrolysis to the acid, followed by a second reduction using $LiAlH_4$ to give **9**. An attempt to form the non-methylated derivative of alcohol **9** by direct Birch reduction

of 2-benzyloxyethanol resulted in cleavage of the ether. Oxidation to the corresponding aldehyde (prone to rearomatisation) was promptly followed by reductive amination with TsDPEN to give **10**, which was complexed with ruthenium trichloride to form the dimer **11**. Dimer **11** could be directly employed in ATH reactions, in common with related complexes which are directly converted from their dimer forms to monomers in situ under ATH conditions (FA/TEA).[8a,e,f] The formation of monomer **5** using triethylamine was successful as judged by the use of mass spectrometry to characterise the complex, and ^{1}H NMR spectroscopic analysis of the crude product. The monomer proved challenging to isolate as a pure complex however, despite our experience with the related complexes.[8] In contrast to the alkyl-chain complexes, which were universally stable to purification by chromatography, **5** appeared to decompose during attempts to purify it. For this reason monomer **5** was either used in crude form or, more conveniently, the dimeric precursor **11** was employed in ATH reactions. As will be demonstrated in a later section, the use of the dimer avoids the need to prepare and isolate the monomeric complex before use.



Scheme 1. Synthesis of catalyst (*R,R*)-**5**.

Complex **5** proved to be an effective catalyst for ketone ATH (Scheme 2, Figure 1). At a loading of 0.5 mol% (supplied as 0.25 mol% dimer **11**), acetophenone was reduced to 1-phenylethanol **12** in 99% ee, with a preference for the *R* product enantiomer. This equates to what would be predicted through the use of the (*R,R*)-enantiomer of diamine employed in the catalyst, provided that it operates through the same mechanism. A further series of acetophenone derivatives were reduced using the catalyst (Figure 1) to give alcohol products **13-28**.



Scheme 2. Reduction reactions used to test catalyst activity.

Of the substrates tested, the majority were reduced in near quantitative conversion and good enantiomeric excesses. Acetophenone derivatives containing para- and meta-chloro substituents and bicyclic derivatives such as tetralone and 4-chromanone were reduced to alcohols **13-16** with similar enantioselectivities to acetophenone itself, An exception was found for the ortho-chloro substituted substrate, reduced to **17** in only 87% ee, reflecting previous observations for similar catalysts.[3,8]

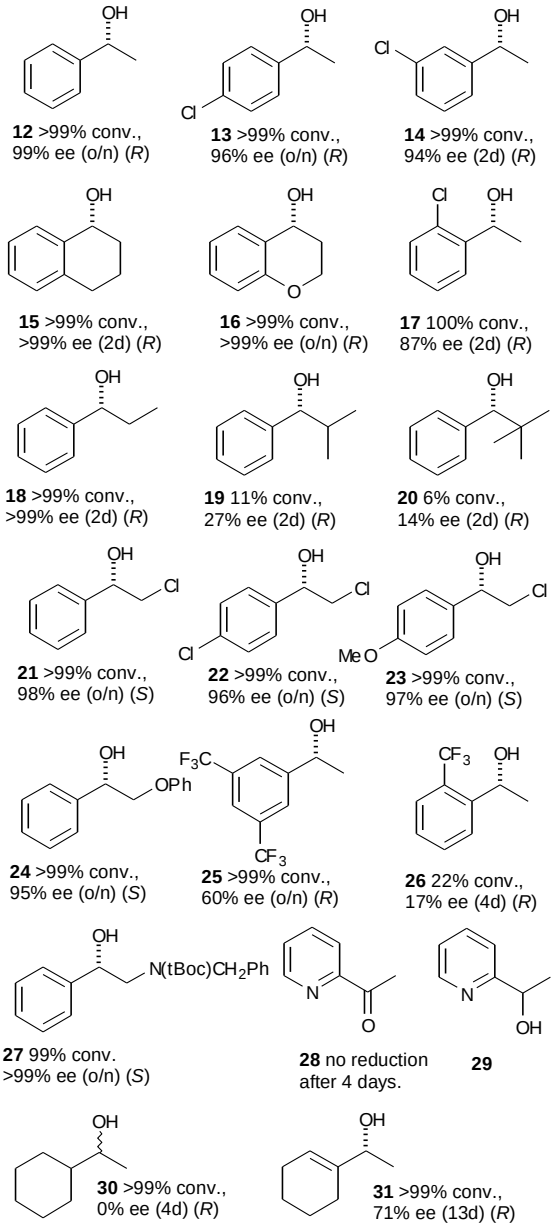
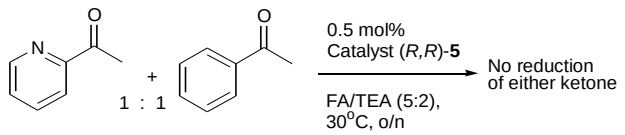


Figure 1. Reduction products formed using catalyst (*R,R*)-**5** (supplied as the dimer **11**).

Propiophenone was reduced in very high ee, to **18**, however increasing the size of the alkyl group resulted in a sharp drop in activity and enantioselectivity, as illustrated by **14** and **20**. This is in some contrast to the alkyl tethered complex (*R,R*)-**4** which is more versatile in this respect. Excellent results were obtained for α-chloroacetophenones, which lead to alcohols **21-23** which are useful intermediates for formation of epoxides and other chiral building blocks. Related substrates containing an O or N heteroatom on the 'alkyl' substituent side could also be reduced in full conversion and high ee (e.g. **24** and **27**). The introduction of electron-withdrawing trifluoromethyl groups into the substrate appears to be detrimental to the enantioselectivity; **25** was formed in just 60% ee whilst the ortho-substituted **26** was reduced in only 22% conversion and a mere 17% ee.

An unexpected result was obtained for 2-acetylpyridine **28**, which was not reduced to the alcohol **29** at all by catalyst (*R,R*)-**5** under the reaction conditions employed. Since 2-acetylpyridine can be fully reduced in high ee by both alkyl-tethered complex (*R,R*)-**4**[8e] and untethered **1**,[6t] we wished to investigate whether the ether-tethered complex was merely a poor catalyst for this substrate or whether the substrate was inhibiting the reaction. To test this, the reduction of a 1:1 mixture of 2-acetylpyridine and acetophenone was attempted with catalyst (*R,R*)-**5**. Remarkably, *neither* ketone was reduced (Scheme 3), suggesting that the 2-acetylpyridine is inhibiting the catalysis, by a mechanism which is presently unclear but may involve an interaction of the (protonated) N atom of the pyridine with the oxygen atom of the side chain. This interaction would not be available to (*R,R*)-**4**, which is not inhibited by this substrate.



Scheme 3. 2-Acetylpyridine inhibits ketone reduction using (*R,R*)-**5**.

The reduction of acetylcyclohexane, which is a useful test ketone for dialkyl substrates, was catalysed by (*R,R*)-**5** with full conversion, however racemic alcohol **30** was formed. This is in contrast to the 69% ee achieved for this substrate using alkyl-tethered (*R,R*)-**4**.[8a] The reduction of a structurally similar but unsaturated ketone to **31**, in contrast, was achieved in full conversion in 71% ee albeit after 13 days of reaction. These results again suggest that the interaction of certain ketones with the ether-tethered catalyst is somewhat different to their interaction with the alkyl-chain version.

The sense of reduction would in each case suggest that the catalyst (*R,R*)-**5** operates through a mechanism which is analogous to that of comple (*R,R*)-**4** (Figure 2A). This involves a key stabilising CH/π interaction between the η^6-arene ring of the catalyst and the aromatic ring of the substrate. In the case of 2-acetyl pyridine, an additional interaction can be evisaged between the protonate heterocyclic ring and the oxygen atom in the tether (Figure 2B). This would stabilise the complex between the catalyst and both the substrate and product to the point where product is not released, hence preventing catalyst turnover as reflected in the competition experiment (Scheme 3). This additional interaction is not available to complex (*R,R*)-**4**, which is not inhibited in the same way. The reduction to form alcohol **31** could be directed by a similar CH/π interaction as for the acetophenone derivatives (Figure 2C).

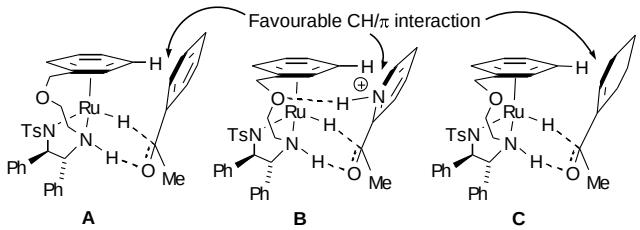
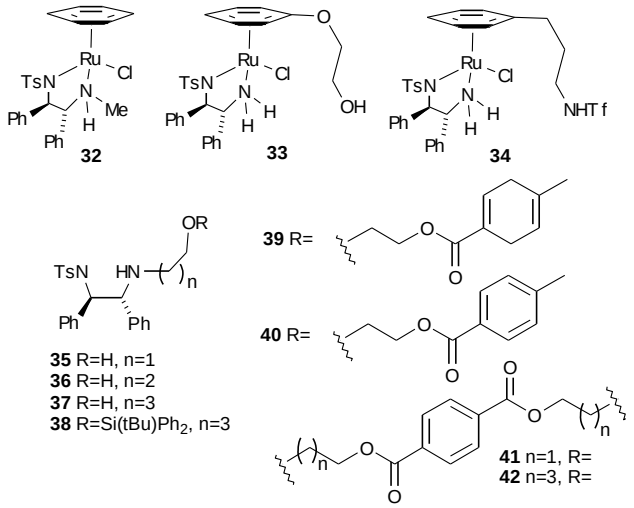


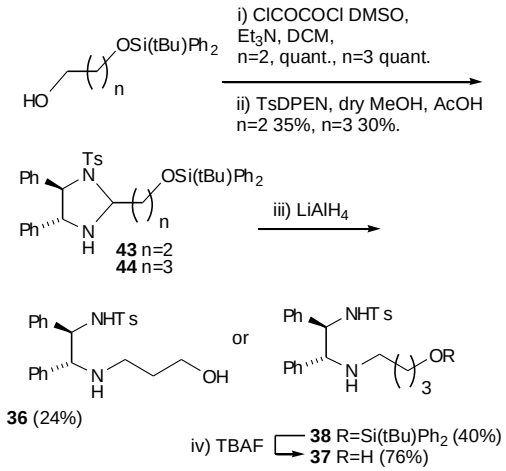
Figure 2. Substrate reduction modes using (*R,R*)-**5**.

Having established that an ether-tethered catalyst was viable for ATH of ketones, we wished to investigate the effect of an ether- or alcohol-containing chain on the basic nitrogen atom without it being tethered to the η^6-arene ring. Such a modification provides a potential means for attaching the catalyst to a heterogeneous support. In a recent study,[10] we have found that the 'basic' nitrogen atom of the TsDPEN ligand in catalyst **1** can be monosubstituted without loss of catalytic activity or selectivity, provided that the substituent is a linear alkyl group; branched or sterically-hindered substituents cause a sharp reduction of activity. In contrast to extensive studies on the primary amine-containing TsDPEN, a relatively small number of successful applications of N-alkylated TsDPEN-derived catalysts have been been reported.[11] These include applications to C=C reduction[11a] and use in reversible formate decarboxylation studies.[11b,c] In addition, the application of N'-alkylated derivatives of N-tosyl-1,2-diaminocyclohexane (TsDAC) to ketone and imine ATH has been reported.[11d,e] Although we had not previously studied oxygen-containing chains, one report on the successful use in ATH of a TsDPEN ligand containing a PEG chain has been published.[11f] There appear to be no published studies on the use of N-hydroxy-functionalised substituents, which have the potential to interact with the ruthenium atom in an analogous manner to a previously-reported catalyst **33** containing a 2-hydroxyethyl group on the η^6-arene ring.[5p] In other related examples published by Ikariya, an NTf group at the end of a 3-carbon chain from the η^6-arene ring, i.e. in **34**, was reported to give improved results in the asymmetric hydrogenation reaction of ketones, speculated to result from an intramolecular assistance of the heterocyclic cleavage of dihydrogen during the catalytic cycle.[4g,i]

Towards this end, we have prepared derivatives of TsDPEN **35-40** which contain a linear chain of 2-4 C atoms terminated by either an hydroxy, silyl ether or ester group. In addition two ligands, **41** and **42** were prepared, containing two diamine units connected by a diester unit.

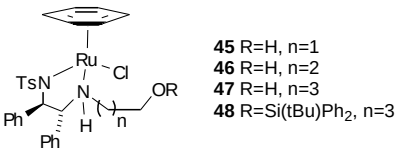


Ligand **35**, containing a hydroxyethyl group, has already been prepared during the course of a related project.[12a] Ligand **36**, bearing a hydroxypropyl group, was prepared by the sequence shown in Scheme 4. Starting from the known monosilyated diol,[12b] oxidation to the aldehyde[12b] was followed by aminal formation with TsDPEN (in all cases the (*R,R*) enantiomer was used). Reduction of **43** with $LiAlH_4$ resulted in formation of **36** through aminal reduction coupled to desilylation under the same conditions.



Scheme 4. Preparation of ligands **36**-**38**.

Ligands **37** and **38**, both containing linear 4C groups, were prepared by an analogous sequence[12c] via **44**, with the difference that the $LiAlH_4$ treatment at the end of the sequence did not simultaneously remove the silyl group, i.e. the product was silyl ether **38**. The silyl group was, however, removed in a subsequent step using TBAF to furnish **37**. The ester-containing ligands were prepared by reaction of N-hydroxyethylTsDPEN **35** with the precursor acids using a combination of DCC and DMAP as the coupling reagent. Dimeric ligands **41** and **42** were prepared by an analogous process starting from the 1,4-dicarboxylic acid. A number of isolated complexes **45**-**48** were also prepared by reaction of **35**-**38** with $[(\eta^6\text{-benzene})RuCl_2]_2$ (noting that the use of a η^6-benzene gives significantly improved results over other η^6-arenes when N-alkylated TsDPENs are employed in ATH reactions).



In the ATH of acetophenone, each of the catalysts, both pre-prepared, and formed in situ, proved to be effective and gave a product of high enantiomeric excess (Table 1). The N-alkylated complexes were somewhat less active than the unsubstituted and tethered complexes, however, with a typical reaction time of 4 days being required for full reduction at rt at 0.5 mol% catalyst loading. Catalyst **45**, with the shortest chain, was the least active, requiring 10 days to achive >99% conversion to product. This may indicate that there is some reversible interaction of the OH group with the Ru(II) atom, thereby reducing its effective concentration in the reaction. This would have a close analogy to the effect observed by White for hydroxyethyl-substituted complex **33**.[5p] As the chain becomes longer, this reduction in activity is attenuated and, for the 4C complex, there is essentially no difference in activity between the silylated **48** and the free OH complex **47**, as would be expected on entropic grounds. In general, the isolated complexes were more active than the complexes formed in situ.

Table 1: Reduction of acetophenone using catalysts **45**-**48** and in situ complexes formed between **39(or 35)**-**42** and $[(benzene)RuCl_2]_2$.[a]

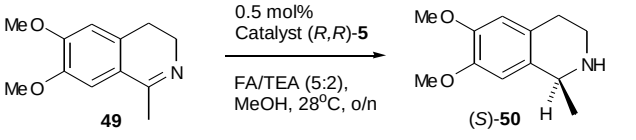
Entry	Catalyst	Time/Days	Conversion / %	Ee / % (*R/S*)
1	**35/Ru**	13	>99	92 (*R*)
2	**36/Ru**	8	31	92
3	**37/Ru**	6	93	94
4	**38/Ru**	6	>99	95
5	**45**	3	88	93 (*R*)
6	**46**	2	>99	94 (*R*)
7	**47**	2	>99	95 (*R*)
8	**48**	2	>99	95 (*R*)
9	**39/Ru**	5	98	95 (*R*)
10	**40/Ru**	5	97	96 (*R*)
11	**41/Ru**	5	92	96 (*R*)
12	**42/Ru**	8	>99	95 (*R*)

[a] For **45**-**48** the isolated catalysts were employed, for **35**-**42** the catlaysts were preformed by reaction of ligand with $[(benzene)RuCl_2]_2$, 28 °C, 5:2 FA:TEA, 0.5 mol% catalyst wrt Ru loading.

The ester-terminated complexes formed from **39**-**42** were also efficient catalysts for the ATH of acetophenone, giving products of 95-96% ee in high conversion. The presence of a nearby ester appears entirely compatible with catalyst activity. It should be noted that all of the reactions in Table 1 were follow over time in order to confirm that no racemisation was taking place during their course (see supporting information).

Finally, we have established that the ether-linked catalyst (*R,R*)-**5** is a suitable catalyst for the reduction of cyclic imines.[13] Although successful imine reduction by Ru/TsDPEN complexes and related catalysts has been reported under both ATH[13] and

AH[14] conditions, we elected to focus our studies on ATH reactions. The reduction of **49** to amine **50** was achieved with full conversion and in 87% ee using 0.5 mol% of (*R,R*)-**5** (supplied as 0.25 mol% of dimer (*R,R*)-**11**) (Scheme 5). The sense of reduction matches that previously reported for closely related catalysts such as (*R,R*)-**1** and **4**, suggesting a similar mode of action in both cases.



Scheme 5. Asymmetric reduction of a cyclic imine.

Conclusions

In conclusion, we have demonstrated that a functional tethered Ru(II)/arene/TsDPEN derivative containing an ether chain, i.e. (*R,R*)-**5** can be prepared through a sequence that avoids the requirement for formation of a 1,4-cyclohexadiene via a Birch reduction. The resulting catalyst can be used in monomer form or by direct addition of the dimer precursor to the ATH reaction mixture. In some cases, ketones are reduced with enantioselectivities which are similar to the alkyl-tethered complexes such as (*R,R*)-**5**, however in some cases the results contrast. This is particularly notable for 2-acetylpyridine which appears to inhibit the ether-tethered catalyst, but not the alkyl-tethered. Complexes containing a straight-chain substituent attached to a hydroxy, ether or ester function also act as effective catalysts. This may represent a useful means for the attachment of the catalyst to a heterogeneous support.

Experimental section.

Synthesis of 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)acetic acid..

To a flame-dried flask containing (4-methylcyclohexa-1,4-dienyl)methanol **9** (3.73 g, 30.0 mmol), *tert*-butyl bromoacetate (6.92 g, 5.20 cm^3, 35.5 mmol) and TBAB (1.94 g, 6.01 mmol) was added NaOH solution (9.27 g in 9.27 cm^3 H_2O, 232 mmol) at 0 °C. The reaction mixture was then stirred at 70 °C for 3 days. Saturated NaCl solution (60 cm^3) was then added to the reaction mixture and then it was extracted using Et_2O (3 x 90 cm^3) to remove starting materials and other impurities. Conc. HCl was then added to the aqueous layer to obtain pH 1, and it was then extracted again using Et_2O (3 x 90 cm^3), dried ($MgSO_4$), filtered and concentrated to give the product as an orange oil (4.10 g, 22.5 mmol, 75 %); ν_{max} 2963, 2855, 2819, 1724, 1426, 1244, 1196, 1106, 1055, 952, 903, 834, 786, 764, 734 and 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.99 (1 H, br s, COO*H*), 5.74 (1 H, s, C*H*=CCH_2O), 5.44 (1 H, s, C*H*=CCH_3), 4.08 (2 H, s, OCH_2COOH), 4.02 (2 H, s, CH=CCH_2O), 2.71-2.59 (4 H, m, $CH_2C(CH_3)$=CCH_2) and 1.67 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 175.51 (*C*OOH), 130.95 (*C*), 130.74 (*C*), 124.22 (C*H*), 118.25 (C*H*), 75.53 (CH_2), 65.93 (CH_2), 31.33 (CH_2), 27.64 (CH_2) and 22.97 (CH_3); *m/z* (ESI-MS) 181.0 $[M-H]^+$. Found (ESI-HR-MS): 205.0840 $[M+Na]^+$, $C_{10}H_{14}NaO_3$ requires 205.0835 (-2.5 ppm error).

*Synthesis of 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)ethanol (**9**).*

2-((-4-Methylcyclohexa-1,4-dienyl)methoxy)acetic acid (4.10g, 22.5 mmol) in THF (28 cm^3) was added dropwise to a solution of $LiAlH_4$ (2.56 g, 67.5 mmol) in THF (138 cm^3) with stirring at 0 °C. After addition, the solution was allowed to stir at r.t for 72h. The solution was then cooled to 0 °C and quenched with a 50 : 50 mixture of water and THF (28 cm^3: 28 cm^3), followed by water (28 cm^3). Rochelle salt (40 g, 142.12 mmol) was then added followed by DCM (41 cm^3) and was further allowed to stir for 3 hrs. The remaining solution was then filtered off through celite, dried ($MgSO_4$), filtered and concentrated to give (**9**) as a light orange oil (3.92 g, quantitative conversion, includes traces of solvent) which was characterised in crude form due to reoxidation during chromatography; ν_{max} 3393, 2855, 2819, 1446, 1428, 1351, 1259, 1142, 1105, 1051, 951, 908, 889, 842, 783, 764 and 712 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.71 (1 H, s, C*H*=CCH_2O), 5.44 (1 H, s, C*H*=CCH_3), 3.93 (2 H, s, CH=CCH_2O), 3.73 (2 H, t, *J* 4.8, OCH_2CH_2OH), 3.50 (2 H, *J* 4.8, OCH_2CH_2OH), 2.70-2.58 (4 H, m, $CH_2C(CH_3)$=CCH_2), 2.17 (1 H, br s, O*H*) and 1.68 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 132.04 (*C*), 130.90 (*C*), 122.55 (*C*H), 118.34 (*C*H), 75.26 (*C*H_2), 70.75 (*C*H_2), 61.92 (*C*H_2), 31.31 (*C*H_2), 27.74 (*C*H_2) and 23.01 (*C*H_3); *m/z* (ESI-MS) 191.0 $[M+Na]^+$. Found (ESI-HR-MS): 191.1045 $[M+Na]^+$, $C_{10}H_{16}NaO_2$ requires 191.1043 (-1.1 ppm error).

Synthesis of 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)acetaldehyde.

The solution of oxalylchloride (2M in DCM, 15.14 cm^3, 30.28 mmol) in anhydrous DCM (30 cm^3) was cooled to -78 °C, and was slowly added a solution of dimethylsulfoxide (4.73 g, 4.30 cm^3, 60.56 mmol) in DCM (15 cm^3) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 2-((4-methylcyclohexa-1, 4-dien-1-yl) methoxy) ethanol **9** (3.92 g, 23.3 mmol) in DCM (50 cm^3) was slowly added at the same temperature. After stirring for 40 min at -78 °C, Et_3N (14.22 g, 19.59 cm^3, 139.58 mmol) was added and the reaction mixture was allowed to warm up to r.t. After 30 mins, water (100 cm^3) was added, and extracted with DCM, dried ($MgSO_4$), filtered and then concentrated under vacuum to give the product as a orange-brown oil (4.78 g, quantitative conversion, includes traces of solvent) which was characterised in crude form due to reoxidation and decomposition during attempts to purify; ν_{max} 2855, 2820, 1736, 1428, 1380, 1217, 1142, 1099, 952, 908, 752, 733 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.72 (1 H, s, C*H*O), 5.73 (1 H, s, C*H*=CCH_2O), 5.44 (1 H, s, C*H*=CCH_3), 4.03 (2 H, s, OCH_2CHO), 3.99 (2 H, s, CH=CCH_2O), 2.72-2.57 (4 H, m, $CH_2C(CH_3)$=CCH_2) and 1.68 (3 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 200.98 (*C*HO), 131.16 (*C*), 130.84 (*C*), 124.03 (*C*H), 118.21 (*C*H), 75.82 (*C*H_2), 74.82 (*C*H_2), 31.33 (*C*H_2), 27.69 (*C*H_2) and 22.99 (*C*H_3); *m/z* (ESI-MS) 189.2 $[M+Na]^+$. Found (ESI-HR-MS): 189.0901 $[M+Na]^+$, $C_{10}H_{14}NaO_2$ requires 189.0886 (-7.6 ppm error).

Synthesis of 4-methyl-N-((1R, 2R)-2-((2-((4-methylcyclohexa-1, 4-dien-1-yl)methoxy)ethyl)amino)-1, 2-

*diphenylethyl)benzenesulfonamide (**10**).*

To a suspension of powdered molecular sieves (4 Å, 4.2 g) in dry methanol (250 cm^3) was added 2-((4-methylcyclohexa-1,4-dienyl)methoxy)acetaldehyde (2.90 g, 17.43 mmol), (*R*, *R*)-TsDPEN (7.10 g, 19.37 mmol) and glacial acetic acid (51 drops). The reaction mixture was stirred at r.t. and monitored by TLC. After 2 hrs, the imine had formed, and sodium cyanoborohydride (1.30 g, 21.05 mmol) was added. The reaction was left overnight at r.t. The molecular sieves were removed by filtration, and the solution was concentrated under reduced pressure. The residue was re-dissolved in DCM (300 cm^3). The organic phase was washed with saturated $NaHCO_3$ (300 cm^3) and brine (300 cm^3), dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by flash chromatography (10→50 % v/v ethyl acetate/pet ether) to give (**10**) as a colourless oil (2.58 g, 5.00 mmol, 29 %); $[\alpha]_D^{26}$ -5.6 (*c* 0.5, $CHCl_3$); ν_{max} 3270, 3029, 2855, 1599, 1495, 1454, 1397, 1327, 1218, 1184, 1156, 1092, 1027, 931, 812, 752, 699 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36 (2 H, d, *J* 8.2, $NHSO_2Ar$(*o*-2C*H*)), 7.15-6.90 (12 H, m, $2C_6H_5$ + $NHSO_2Ar$ (*m*-2C*H*)), 6.30 (1 H, br s, N*H*Ts), 5.62 (1 H, s C*H*=CCH_2O), 5.45 (1 H, s, , C*H*=CCH_3), 4.24 (1 H, d, *J* 7.6, TsNHC*H*), 3.77 (2 H, s, CH=CCH_2O), 3.66 (1 H, d, *J* 7.6, NHC*H*), 3.45-3.32 (2 H, m, $NHCH_2CH_2OCH_2$), 2.65-2.54 (5 H, m, $NHCH_{(1)}H_{(2)}CH_2OCH_2$ + $CH_2C(CH_3)$=CCH_2), 2.48-2.41 (1 H, m, $NHCH_{(1)}H_{(2)}CH_2OCH_2$), 2.33 (3 H, s, $NHSO_2ArCH_3$), 1.73 (1 H, br s, N*H*CH) and 1.69 (3 H, s, $CH_2C(CH_3)$=CCH_2); δ_C (101 MHz, $CDCl_3$) 142.62 (*C*), 139.21 (*C*), 138.42 (*C*), 137.12 (*C*), 132.17 (*C*), 130.92 (*C*), 129.08 (*C*H), 128.30 (*C*H), 127.92 (*C*H), 127.77 (*C*H), 127.55 (*C*H), 127.46 (*C*H), 127.26 (*C*H), 127.12 (*C*H), 122.00 (*C*H), 118.42 (*C*H), 75.00 (CH_2), 69.00 (CH_2), 67.83 (CH_3), 63.10 (CH_3), 46.74 (CH_2), 31.33 (CH_2) and 27.74 (CH_2); *m/z* (ESI-MS) 539.2 $[M+Na]^+$. Found (ESI-HR-MS): 517.2519 $[M+H]^+$, $C_{31}H_{37}N_2O_3S$ requires 517.2519 (0.1 ppm error).

*Synthesis of ether linked "tethered" dimer (**11**).*

To a stirred solution of 4-methyl-*N*-((1*R*,2R)-2-(2-((4-methylcyclohexa-1,4-dienyl)methoxy)ethylamino)-1,2-diphenylethyl)benzenesulfonamide **10** (1.38 g, 2.67 mmol) in DCM (39 cm^3) was added 1.25 M HCl in EtOH (6.4 cm^3, 8.01 mmol). The reaction mixture was stirred for 2 hrs and concentrated under vacuum. To a suspension of the residue in IPA (28 cm^3) was added trihydrated ruthenium trichloride (880 mg, 4.22 mmol). The reaction mixture was stirred at reflux temperature for 2 days. It was then filtered off and washed with cold IPA to give (**11**) as a dark blue solid (1.70 g, 1.18 mmol, 88 %); ν_{max} 3676, 2988, 2902, 1454, 1406, 1394, 1382, 1324, 1250, 1230, 1155, 1066, 1057, 892, 812, 763, 699 and 669 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 9.47 (2 H, br s, 2 x $NH_{(1)}H_{(2)}^+Cl^-$), 8.90 (2 H, br s, 2 x $NH_{(1)}H_{(2)}^+Cl^-$), 8.55 (2 H, d, *J* 9.8, 2 x N*H*Ts), 7.35-6.70 (28 H, m, 2 x (14 x Ar-*H*)), 6.05-5.75 (8 H, m, 2 x (4 x Ru-Ar-*H*)), 4.80 (2 H, t, *J* 9.8, 2 x $CHNH_2^+Cl^-$), 4.63-4.50 (2 H, m, 2 x C*H*NHTs), 4.38 (3.2 H, s, 2 x ArCH_2O), 4.31 (0.8 H, s, 2 x ArCH_2O), 3.90-3.75 (4 H, m, 2 x $NH_2^+Cl^-CH_2CH_2O$), 3.10-2.97 (4 H, m, 2 x $NH_2^+Cl^-CH_2CH_2O$), 2.21 (6 H, s, 2 x CH_3Ts), 2.15 (4.8 H, s, 2 x CH_3Ar) and 2.12 (1.2 H, s, 2 x CH_3Ar); δ_C (101 MHz, DMSO-d_6) 142.66 (2 x *C*), 138.06 (2 x *C*), 135.90 (2 x *C*), 131.93 (2 x *C*), 129.52 (2 x (2 x *C*H)), 129.50 (2 x *C*H and 2 x (2 x *C*H)), 129.21 (2 x (2 x *C*H)), 128.55 (2 x *C*H), 128.28 (2 x (2 x *C*H)), 128.15 (2 x (2 x *C*H)), 126.88 (2 x (2 x *C*H)), 122.62 (2 x *C*H), 118.73 (2 x *C*H), 102.76 (2 x *C*), 94.90 (2 x *C*), 65.59 (2 x *C*H), 62.48 (2 x (2 x *C*H)), 60.85 (2 x *C*H), 56.78 (2 x (2 x CH_2)), 48.61 (2 x CH_2), 26.00 (2 x CH_3) and 21.53 (2 x CH_3); *m/z* (ESI-MS) 615.0 $[Monomer+H]^+$. Found (ESI-HR-MS): 615.1266 $[Monomer+H]^+$, $C_{31}H_{33}N_2O_3{}^{102}RuS$ (monomer formed *in situ* from dimer and loss of 3 x HCl) requires 615.1257 (-2.0 ppm error). Optical rotation could not be obtained due to the product being highly coloured.

*Synthesis of ether linked "tethered" monomer (**5**).*

To a suspension of dimer **11** (98 mg, 0.067 mmol) in IPA (9 cm^3) was added Et_3N (0.06 cm^3, 0.42 mmol). After stirring at 80 °C for 1.5 hrs, the hot IPA solution was filtered through a layer of cotton wool and filter paper to remove impurities. The solution was then concentrated, re-dissolved in DCM and washed with water. The organic layer was then dried (Na_2SO_4), filtered and concentrated to give the monomer (**5**) as an orange solid (29 mg, 0.0446 mmol, 33 %). The crude product was isolated, and LRMS and HRMS were carried out to confirm the presence of product. Several purification attempts on the crude product led to decomposition of the material; δ_H (300 MHz, $CDCl_3$) 7.30 (2 H, d, *J* 8.0, ArH), 7.15-7.10 (4 H, m, ArH), 6.85 (2 H, d, *J* 8.0, ArH), 6.80-6.70 (2 H, m, ArH), 6.70-6.55 (4 H, m, ArH), 6.15-6.05 (1 H, m, RuArH), 5.75 (1H, d, *J* 6.4, RuArH), 5.65 (1H, d, *J* 6.4, RuArH), 5.50-5.40 (1 H, m RuArH), 4.92 (1 H, brd, *J* 14.2, CHPh), 4.55-4.45 (2 H, m, CHPh + NH), 4.05-3.88 (4 H, m, 2 x CH_2), 3.65-3.55 (1 H, m, C*H*H), 3.20-3.05 (1 H, m, CH*H*), 2.60 (3 H, s, CH_3), 2.24 (3 H, s, CH_3). *m/z* (ESI-MS) 615.0 $[Monomer+H]^+$. Found (ESI-HR-MS): 615.1264 $[Monomer+H]^+$, $C_{31}H_{33}N_2O_3{}^{102}RuS$ requires 615.1257 (-1.8 ppm error).

Ketone and Imine Reduction.

General procedure for the preparation of secondary alcohols.

Method A (Racemic): To a stirred solution of ketone/imine (1 mmol) in methanol (12 cm^3) was added $NaBH_4$ (3.0 eq.) portion-wise and the reaction mixture was allowed to stir until completion while monitoring the conversion by TLC, after completion the solution was diluted with saturated $NH_4Cl_{(aq)}$ (12 cm^3) and extracted with dichloromethane (3 x 12 cm^3). The combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the racemic secondary alcohol. The product was identified by comparison of its spectroscopic data to that reported (see Supporting Information).

Method B (Asymmetric using "tethered" Ru (II) dimer for ketones): A solution of ruthenium dimer (0.0025 mmol) in formic acid/triethylamine (5:2) azeotrope (0.5 cm^3) was stirred in a flame dried Schlenk tube at 28 °C for 30 minutes. Ketone (1 mmol) was added and dichloromethane (0.5 cm^3) was added if required to dissolve the substrate. The reaction mixture was stirred at 28 °C and monitored by TLC. After completion, the reaction mixture was diluted with dichloromethane (6.7 cm^3) and washed with $NaCO_3$ solution (3 x 5 cm^3). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the desired alcohol. The product was identified by comparison of its spectroscopic data to that reported, and the ee

determined by chiral GC or HPLC analysis (see Supporting Information).

Method C (Asymmetric using "tethered" Ru (II) dimer for imines): A solution of ruthenium dimer (0.0025 mmol) and imine (1 mmol) in methanol (1.6 cm^3) was stirred in a flame dried Schlenk tube at 28 °C for 10 minutes. Formic acid/triethylamine (5 : 2) azeotrope (0.5 cm^3) was then added. The reaction mixture was stirred at 28 °C and monitored by TLC. After completion, $NaHCO_3$ solution (5 cm^3) was added, and was extracted with dichloromethane (3 x 6.7 cm^3). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the desired amine. The product was identified by comparison of its spectroscopic data to that reported, and the ee determined by chiral GC or HPLC analysis (see Supporting Information).

*Synthesis of catalyst (**45**).*

A mixture of benzeneruthenium (II) chloride dimer (40 mg, 0.08 mmol), *N*-((1*R*, 2*R*)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **35** (46 mg, 0.11 mmol) and triethylamine (0.06 cm^3, 0.43 mmol) in IPA (2.4 cm^3) was heated at 80 °C for 1 hr. The solution was then cooled to r.t, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (4.8 cm^3) and then washed with water (2.4 cm^3) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na_2SO_4), filtered and then concentrated under reduced pressure to give (**45**) as a brown solid (58 mg, 0.093 mmol, 85 %); Mp 250-253 °C (dec); $[\alpha]_D^{27}$ +120 (*c* 0.02, $CHCl_3$); ν_{max} 3435, 3063, 3030, 2917, 1730, 1599, 1494, 1453, 1435, 1398, 1266, 1128, 1084, 1059, 1003, 932, 834, 808, 749, 697 and 663 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.55-6.65 (14 H, m, 14 x Ar-*H*), 6.01 (6 H, s, 6 x Ar-*H*), 4.86 (1 H, d, *J* 10.3, C*H*NTs), 4.51 (1 H, d, *J* 10.3, C*H*NH), 3.80-3.40 (1 H, br m, C$H_{(1)}H_{(2)}$OH), 3.35-3.10 (1 H, br m, CH$_{(1)}H_{(2)}$OH), 2.50-2.25 (2 H, br m, CH_2NH) and 2.20 (3 H, s, CH_3Ts) note; ^{1}H NMR peaks are broadened for this compound, which may reflect a restricted rotation; δ_C (101 MHz, $CDCl_3$) 140.12 (*C*), 130.67 (*C*H), 128.84 (*C*H), 128.36 (5 x *C*H), 128.21 (*C*H), 127.63 (2 x *C*H), 126.86 (4 x *C*H), 83.67 (6 x *C*H), 82.89 (2 x *C*H), 74.28 (2 x *C*H_2) and 21.22 (*C*H_3); *m/z* (ESI-MS) 589.0 $[M\text{-}Cl]^+$. Found (ESI-HR-MS): 589.1106 $[M\text{-}Cl]^+$, $C_{29}H_{31}N_2O_3{}^{102}RuS$ requires 589.1100 (-0.3 ppm error).

*Synthesis of catalyst (**46**).*

A mixture of benzeneruthenium (II) chloride dimer (13 mg, 0.025 mmol), *N*-((1*R*, 2*R*)-2-((3-hydroxypropyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **36** (14 mg, 0.033 mmol) and triethylamine (0.018 cm^3, 0.13 mmol) in IPA (0.75 cm^3) was heated at 80 °C for 1 hr. The solution was then cooled to r.t, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (1.5 cm^3) and then washed with water (0.75 cm^3) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na_2SO_4), filtered and then concentrated under reduced pressure giving (**46**) as a brown solid (13.4 mg, 0.021 mmol, 64 %); Mp 210-213 °C (dec); $[\alpha]_D^{27}$ -360 (*c* 0.02, $CHCl_3$); ν_{max} 3436, 3204, 3064, 3029, 2922, 2853, 1730, 1600, 1494, 1454, 1437, 1381, 1267, 1185, 1128, 1083, 1054, 1004, 912, 812, 759, 698, 682 and 658 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30-6.50 (14 H, m, 14 x Ar-*H*), 5.90 (6 H, s, 6 x Ru-Ar-*H*), 4.18-4.05 (1 H, br m, C*H*NTs), 3.99-3.86 (1 H, br m, C*H*NH), 3.68-3.58 (1 H, br m, C$H_{(1)}H_{(2)}$OH), 3.57-3.46 (1 H, br m, CH$_{(1)}H_{(2)}$OH), 3.16-3.04 (1 H, br m, C$H_{(1)}H_{(2)}$NH), 2.96-2.82 (1 H, br m, CH$_{(1)}H_{(2)}$NH), 2.22 (3 H, s, CH_3Ts), 2.12-2.01 (2 H, br m, CH_2CH$_2$OH) and 1.41-1.33 (1 H, br m, N*H*) note; ^{1}H NMR peaks are broadened for this compound, which may reflect a restricted rotation; δ_C (101 MHz, $CDCl_3$) 141.50 (*C*), 139.64 (*C*), 139.54 (*C*), 136.91 (*C*), 128.60 (2 x *C*H), 128.50 (2 x *C*H), 128.17 (*C*H), 128.07 (4 x *C*H), 127.54 (2 x *C*H), 127.06 (2 x *C*H), 126.37 (*C*H), 84.72 (6 x *C*H), 81.43 (*C*H), 69.84 (*C*H), 61.27 (*C*H_2), 53.62 (*C*H_2), 29.70 (*C*H_2) and 21.23 (*C*H_3); *m/z* (ESI-MS) 603.0 $[M\text{-}Cl]^+$. Found (ESI-HR-MS): 603.1259 $[M\text{-}Cl]^+$, $C_{30}H_{33}N_2O_3{}^{102}RuS$ requires 603.1257 (0.1 ppm error).

*Synthesis of catalyst (**47**).*

A mixture of benzeneruthenium (II) chloride dimer (28 mg, 0.056 mmol), *N*-((1*R*, 2*R*)-2-((4-hydroxybutyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **37** (32 mg, 0.074 mmol) and triethylamine (0.04 cm^3, 0.29 mmol) in IPA (2.2 cm^3) was heated at 80 °C for 1 hr. The solution was then cooled to r.t, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (4.4 cm^3) and then washed with water (2.2 cm^3) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na_2SO_4), filtered and then concentrated under reduced pressure giving (**47**) as orange brown crystals (43 mg, 0.066 mmol, 89 %); Mp 220-223 °C (dec); $[\alpha]_D^{26}$ -480 (*c* 0.02, $CHCl_3$); ν_{max} 3428, 3062, 2863, 1599, 1494, 1455, 1437, 1385, 1267, 1127, 1083, 1054, 992, 915, 809, 750, 697, 681 and 656 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (2 H, d, *J* 7.8, 2 x Ar-*H*), 7.15-7.00 (3 H, m, 3 x Ar-*H*), 6.80 (3 H, d, *J* 7.8, 3 x Ar-*H*), 6.75-6.64 (4 H, m, 4 x Ar-*H*), 6.56 (2 H, d, *J* 6.8, 2 x Ar-*H*), 5.90 (6 H, s, 6 x Ar-Ru-*H*), 3.99 (1 H, t, *J* 10.2, C*H*NTs), 3.92 (1 H, t, *J* 10.2, C*H*NH), 3.76 (1 H, br m, CHN*H*), 3.60 (2 H, br m, CH$_2$O*H*), 3.44-3.30 (1 H, br m, C$H_{(1)}H_{(2)}$NH), 2.85-2.65 (1 H, br m, CH$_{(1)}H_{(2)}$NH), 2.22 (3 H, s, CH_3Ts), 2.16-1.98 (1 H, br m, C$H_{(1)}H_{(2)}$CH$_2$NH), 1.80-1.66 (1 H, br m, CH$_{(1)}H_{(2)}$CH$_2$NH), 1.64-1.48 (1 H, br m, C$H_{(1)}H_{(2)}$CH$_2$OH) and 1.43-1.29 (1 H, br m, CH$_{(1)}H_{(2)}$CH$_2$OH); δ_C (101 MHz, $CDCl_3$) 141.80 (*C*), 139.57 (*C*), 139.45 (*C*), 137.10 (*C*), 128.66 (2 x *C*H), 128.56 (2 x *C*H), 128.24 (*C*H), 128.06 (4 x *C*H), 127.43 (2 x *C*H), 127.04 (2 x *C*H), 126.32 (*C*H), 86.64 (6 x *C*H), 80.89 (*C*H), 69.61 (*C*H), 61.62 (*C*H_2), 54.82 (*C*H_2), 29.83 (*C*H_2), 25.43 (*C*H_2) and 21.23 (*C*H_3); *m/z* (ESI-MS) 617.0 $[M\text{-}Cl]^+$. Found (ESI-HR-MS): 617.1414 $[M\text{-}Cl]^+$, $C_{31}H_{35}N_2O_3{}^{102}RuS$ requires 617.1406 (-2.03 ppm error).

*Synthesis of catalyst (**48**).*

A mixture of benzeneruthenium (II) chloride dimer (28 mg, 0.056 mmol), *N*-((1*R*, 2*R*)-2-((4-((*tert*-butyldiphenylsilyl)oxy)butyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **38** (50 mg, 0.074 mmol) and triethylamine (0.04 cm^3, 0.29 mmol) in IPA (2.2 cm^3) was heated at 80 °C for 1 hr. The solution was then cooled to r.t, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (4.4 cm^3) and then washed with water (2.2 cm^3) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na_2SO_4), filtered and then concentrated under reduced pressure giving (**48**) as orange brown crystals (58 mg, 0.065

mmol, 88 %); Mp 205-208 °C (dec); $[\alpha]_D^{26}$ -240 (*c* 0.02, $CHCl_3$); ν_{max} 3067, 2930, 2856, 1600, 1494, 1455, 1428, 1387, 1361, 1262, 1189, 1126, 1108, 1083, 992, 915, 822, 759, 728, 697 and 657 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.60 (4 H, d, *J* 7.2, 4 x Ar-*H*), 7.45-7.25 (6 H, m, 6 x Ar-*H*), 7.13-6.99 (4 H, m, 4 x Ar-*H*), 6.90-6.79 (4 H, m, 4 x Ar-*H*), 6.74 (2 H, t, *J* 7.2, 2 x Ar-*H*), 6.65 (2 H, d, *J* 6.5, 2 x Ar-*H*), 6.59 (2 H, d, *J* 7.2, 2 x Ar-*H*), 5.79 (6 H, s, 6 x Ar-*H*), 3.97 (1 H, d, *J* 10.3, C*H*NHTs), 3.84 (1 H, t, *J* 11.4, C*H*NH), 3.70 (1 H, t, *J* 11.4, CHN*H*), 3.61-3.50 (2 H, m, CH_2OSi), 3.30-3.10 (1 H, br m, C$H_{(1)}H_{(2)}$NH), 2.85-2.70 (1 H, br m, CH$_{(1)}H_{(2)}$NH), 2.22 (3 H, s, CH_3Ts), 2.15-2.01 (1 H, br m, C$H_{(1)}H_{(2)}CH_2$NH), 1.72-1.60 (1 H, br m, CH$_{(1)}H_{(2)}CH_2$NH), 1.58-1.46 (1 H, br m, C$H_{(1)}H_{(2)}CH_2$OSi), 1.42-1.27 (1 H, br m, CH$_{(1)}H_{(2)}CH_2$OSi) and 1.03 (9 H, s, 3 x CH_3); δ_C (101 MHz, $CDCl_3$) 141.54 (*C*), 139.83 (*C*), 139.46 (*C*), 137.01 (*C*), 133.55 (4 x *C*H), 133.76 (*C*), 133.62 (*C*), 129.72 (2 x *C*H), 128.68 (2 x *C*H), 128.59 (2 x *C*H), 128.27 (*C*H), 128.01 (2 x *C*H), 127.77 (5 x *C*H), 127.68 (2 x *C*H), 127.46 (*C*H), 127.04 (2 x *C*H), 126.37 (*C*H), 84.51 (6 x *C*H), 81.05 (*C*H), 69.67 (*C*H), 63.16 (CH_2), 54.88 (CH_2), 30.12 (CH_2), 27.00 (3 x CH_3), 25.39 (CH_2), 21.26 (CH_3) and 19.25 ($(CH_3)_3C$); *m/z* (ESI-MS) 855.0 $[M-Cl]^+$. Found (ESI-HR-MS): 855.2596 $[M-Cl]^+$, $C_{47}H_{53}N_2O_3{}^{102}RuSSi$ requires 855.2584 (0.13 ppm error).

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Notes and references

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† Electronic Supplementary Information (ESI) available: [General experimental details, characterisation and ee determination information for reduction products, details of preparation of ligands and intermediates to organometallic catalysts, ^1H and ^{13}C NMR spectra]. See DOI: 10.1039/b000000x/.

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