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Application of Tethered Ruthenium Catalysts to Asymmetric Hydrogenation of Ketones, and the Selective Hydrogenation of Aldehydes

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Abstract. An improved method for the synthesis of tethered ruthenium(II) complexes of monosulfonylated diamines is described, together with their application to hydrogenation of ketones and aldehydes. The complexes were applied directly, in their chloride form, to asymmetric ketone hydrogenation, to give products in excess of 99% ee in the best cases, using 30 bar of hydrogen at 60 °C, and to the selective reduction of aldehydes over other functional groups.
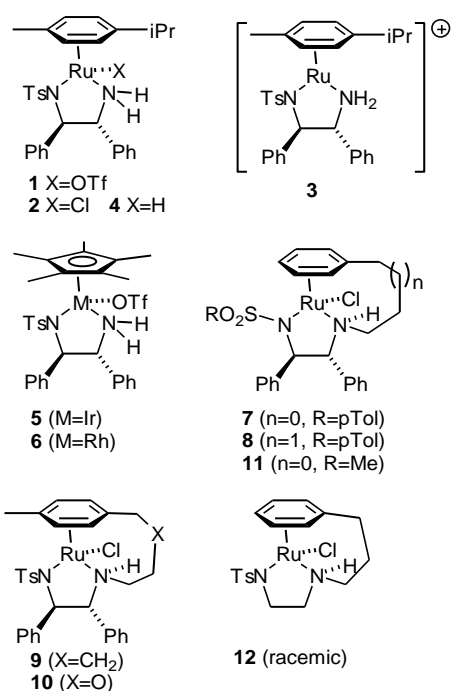
Keywords: Asymmetric catalysis, ketones, aldehydes, alcohols, enantioselectivity, ruthenium, tethered catalysts.
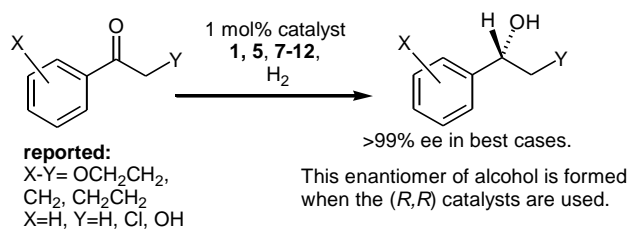
Introduction

Asymmetric hydrogenation of ketones using organometallic catalysts provides a convenient access to enantiomerically pure alcohols.[1-6] The majority of catalysts for asymmetric hydrogenation contain either phosphorus/nitrogen-donor ligands or a combination of each type.[2] Asymmetric hydrogenation catalysts which lack phosphine-based ligands are relatively rare.[3-6] Catalysts of this type[3] can be prepared *in situ* by combining Ru(II), Rh(III) and Ir(III) complexes with chiral diamine ligands,[4] however a number of very efficient, well-defined complexes derived from chiral amines have recently been reported.[5,6]

An important breakthrough in this area was provided by complex **1**,[6] the OTf derivative of the well-established asymmetric transfer hydrogenation catalyst **2**,[7] itself an organometallic complex of the ligand N-tosyl-1,2-diphenyl-ethane-1,2-diamine (TsDPEN). Although complex **2** is reported to be a poor catalyst for ketone hydrogenation, replacement of its chloride with triflate, and conducting the hydrogenation in methanol rather than isopropanol, results in the formation of a much more active hydrogenation system (Scheme 1) which was first tested on a series of chromanone substrates.[3a] The increased activity is due to the ionisation of **1** to form **3**, which then reacts with dihydrogen to form the hydride **4**. It is hydride **4** which then performs the reduction of ketones, through the well-established outer-sphere six-centred transition state mechanism already established in the closely related transfer hydrogenation process.[7]

1 X=OTf
2 X=Cl   **4** X=H
3
5 (M=Ir)
6 (M=Rh)
7 (n=0, R=pTol)
8 (n=1, R=pTol)
11 (n=0, R=Me)
9 (X=CH₂)
10 (X=O)
12 (racemic)

reported:
X-Y= OCH₂CH₂,
CH₂, CH₂CH₂
X=H, Y=H, Cl, OH

>99% ee in best cases.

This enantiomer of alcohol is formed when the (*R,R*) catalysts are used.

This work; Figure 1, Tables 1, 2.

**Scheme 1.** Asymmetric hydrogenation of ketones using Ru/TsDPEN catalysts.

The mechanism of hydrogen activation by **1** has now been extended,[6b,c] and related Ru(II) complexes containing TsDPEN ligands have been reported, including examples in which additional functionalities assist the hydrogen dissociation step.[6e,f] Following the initial disclosure by Noyori et al,[6a] it was found that the closely related Ir complex **5** was also active in the asymmetric reduction of α-hydroxy acetophenone derivatives.[6d] Complexes **1** and **5**, and the related Rh complex **6** have found application in the asymmetric hydrogenation of cyclic and acyclic imines[8] and in the asymmetric reduction of quinoline derivatives.[9]

Recently, we reported the synthesis and applications to asymmetric transfer hydrogenation of a series of complexes which contain a linking group ('tether') between the TsDPEN unit and the arene ring on the ruthenium atom.[10] Complexes **7** (3C tether) and **8** (4C tether) are the most widely used examples of this series[10] and are highly active for ketone transfer hydrogenation when used in formic acid/triethylamine as the hydrogen source and solvent.[10] In our early studies, complex **7** was found to be active at the asymmetric hydrogenation of α-chloroacetophene.[10j] Ikariya et al recently reported the synthesis of both the (CH₂)₄ (4C) tethered complex **9** and the O-tethered derivative **10**, and their application to asymmetric ketone transfer and pressure hydrogenation.[6h] Complex **10**, which was found to be active as a pressure hydrogenation catalyst without modification,[6h] was also prepared by ourselves in contemporaneous studies, although our studies focussed on transfer hydrogenation.[10i] In this paper we describe an improved synthesis of **7,** new catalysts **11** and **12**, and their applications to the asymmetric *hydrogenation* of a range of ketones and the selective reduction of aldehydes.

Results and Discussion

In our previous approach to the synthesis of **7** and its derivatives,[10b] the reaction between the aldehyde derived from alcohol **13** and (*R,R*)-TsDPEN was employed in order to form intermediate **14a**, which was then converted to dimer **15a** upon reaction with ruthenium trichloride. During attempts to scale up the synthesis, it proved to be inconsistent on a larger scale (10s of grams). In response to this, the direct attachment of alcohol **13** was investigated. It was found that *in situ* formation of the triflate of **13**, with 2,6-lutidine as base, followed by addition of (*R,R*)-TsDPEN with careful control of the temperature, gave **14a** in 70% yield on a 35g scale. Formation of dimer **15a** was completed through a controlled addition of an aqueous solution of ruthenium chloride to the HCl salt of **14a** at 75 °C. The solution of **15a** was then converted to **7** using diisopropylethylamine in DCM at 0 °C, and purified by direct recrystallisation of the celite-filtered product (Scheme 2). From the precursor **15a**, monomer **7** was formed in yields of 67-83%. Both steps could additionally be 'telescoped' to produce **7** directly from diamine **14a** in a one pot process in 63-79% yield. Using this sequence, complexes **11** and **12** (**12** via the mesylated alcohol in the first step) were also produced (Scheme 2), although the yield of **12** over two steps was lower due to a low conversion to the dimer.
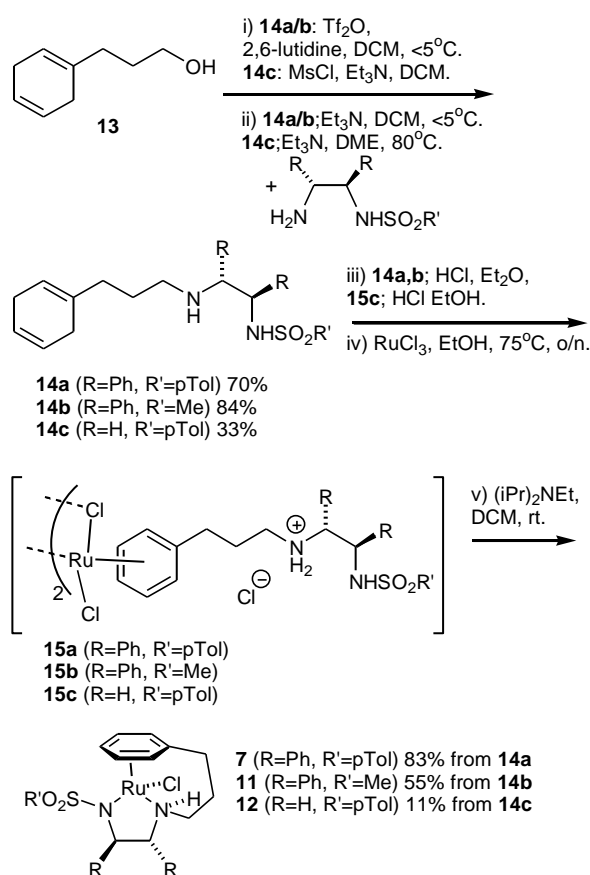
Scheme 2. Synthesis of catalysts **7**, **11** and **12**.

The spectroscopic analysis of catalyst **7** thus generated was found to be facilitated by running ¹H and ¹³C NMR spectra in CD₃NO₂ rather than in CDCl₃. The spectra in CDCl₃ appeared to contain a substantial amount of an 'impurity', which has been observed in previous syntheses,[10b] however the spectra recorded in CD₃NO₂, of an identical sample, revealed no evidence of a similar impurity (see Supporting Information) and were clean other than for a small quantity of residual iPr₂NEt. The observed 'impurity' may be due to another diastereoisomer of the complex, i.e. at the metal or through the

conformation of the linking chain, the ratio of which is solvent dependent. The ratio of the 'impurity' found in the CHCl$_3$ spectra did not, however, change over a range of 213 K to 333 K during a variable temperature ^{1}H NMR study

Having established a suitable route for the practical synthesis of catalysts **7**, **11** and **12**, their application to the asymmetric hydrogenation of ketones was investigated (Scheme 1, Figure 1, Table 1). The application of the unmodified complexes **7**, **11** and **12** to hydrogenation would have the advantage of eliminating the requirement to preform, or form *in situ,*, either the triflate complex or the 16 electron unsaturated species prior to the reaction. In the event, this proved to be the case, and in initial tests at S/C = 100 (Table 1 entries 1, 2), acetophenone was be fully reduced in 94% ee using catalyst **7**. Unexpectedly, the addition of silver salts led to a sharp reduction of catalyst activity (Table 1 entries 3, 10, 12), which is in contrast to the findings of related studies using the untethered catalysts.[8a,f] Increasing the S/C to 500 resulted in a decrease in conversion at 50 °C although this could be restored to >99% within 16h by raising the temperature to 60°C (entries 5 and 6). The ee, at a substrate concentration of 0.5M, was 94.5% (S/C 500) and 93% (S/C 1000) and lower conversions were observed at higher substrate concentration. (entry 9). Reducing the hydrogen pressure gave a slightly inferior result with respect to conversion (entry 7), and at S/C of 2000 the reaction became significantly slower, even at 60 °C (entry 14).

The N-mesylated complex **11** was also efficient in the reaction, although the conversions were lower than for **10**, and again the addition of silver triflate gave an inferior result (entries 15-18). An achiral tethered catalyst can also be employed for racemic ketone hydrogenation; use of complex **12** resulted in

efficient reduction of acetophenone in 16 h at 40°C at S/C of 250 (Table 1, entries 19, 20).

Having established optimal conditions for the hydrogenation reactions, a further series of ketones were evaluated as substrates, with a focus on catalyst **7**, in order to establish its versatility; alcohols **16-29** were formed in these studies (Figure 1, Table 2). Acetophenone derivatives worked well, including electron-rich and –poor substrates, cyclic substrates and those bearing a heteroatom substituent at the α-position. An α-hydroxy ketone worked exceptionally well (**21** formed in >99.5% ee), as did tetralone and chromanone. Given the close similarity of the results, in terms of absolute configuration and enantioselectivity, to those obtained using transfer hydrogenation, we anticipate that the asymmetric reduction step is common to both reduction systems. The process by which the resulting '16e' Ru species is converted back to the hydride is probably identical to that of the untethered complexes.[10b] On this basis, it was not surprising that acetylcyclohexane gave a product of just 66.8% ee, and in the opposite sense to the acetophenone reduction; under transfer hydrogenation conditions, a product of 69% ee (*S*) is formed using (*R,R*)-**7**.[10b]

The reduction of α-chloroacetophenone using **7** required 75 bar H$_2$ pressure. Under these conditions, reduction to (*R*)-**28** in 95% conversion and 94% ee was achieved after 16h (50 °C, MeOH). Reduction of the unsaturated ketone **30** resulted in formation of an inseparable mixture of products of C=O and C=C reduction. Reduction of this mixture gave almost racemic saturated alcohol **33**, which indirectly indicated that there was no enantioselectivity in the reduction.

The reduction of trifluoromethylated substrates returned some interesting results. Alcohol **29** was

Table 1. Hydrogenation of acetophenone using catalysts **7**, **11** and **12**, with optional additives.[a]

Entry	Catalyst	S/C	Scale [S]/M, additives	T/ °C	Conv /%[b]	Ee /%[b]
1	(*S,S*)-**7**	100	2 mmol [0.5]	40	100	94 (*S*)
2	(*S,S*)-**7**	100	1 mmol [1]	60	100	96 (*S*)
3	(*S,S*)-**7**	100	1 mmol [1] + 1 mol% AgOTf	60	9	Nd[c,d]
4	(*S,S*)-**7**	250	2 mmol [0.5]	50	100	94 (*S*)
5	(*R,R*)-**7**	500	2 mmol [0.5]	50	67	92.5 (*R*)
6	(*R,R*)-**7**	500	2 mmol [0.5]	60	>99	94.5 (*R*)
7	(*R,R*)-**7**	500	10 mmol [1]	60	97[e]	91.5 (*R*)
8	(*S,S*)-**7**	500	2 mmol [0.5]	60	100	93.5 (*S*)
9	(*S,S*)-**7**	1000	5 mmol [1.4]	60	71	94 (*S*)
10	(*S,S*)-**7**	1000	5 mmol [1.4] + 1 mol% AgBF4	60	7	Nd[c,f]
11	(*S,S*)-**7**	1000	3 mmol [1.0]	60	>99	94 (*S*)
12	(*S,S*)-**7**	1000	3 mmol [1.0] +1 mol% AgOTf	60	1	Nd[c,g]
13	(*S,S*)-**7**	1000	2 mmol [0.5]	60	100	93 (*S*)
14	(*S,S*)-**7**	2000	4 mmol [1]	60	49	93 (*S*)
15	(*R,R*)-**11**	200	3 mmol [1]	60	>99	88 (*R*)
16	(*R,R*)-**11**	200	3 mmol [1] + 1 mol% AgOTf	60	<1	Nd[c,f]
17	(*R,R*)-**11**	500	3 mmol [1]	60	62	88 (*R*)
18	(*R,R*)-**11**	1000	3 mmol [1]	60	33	88 (*R*)[h]
19	**12**	100	3 mmol [1]	30	100	-
20	**12**	250	3 mmol [1]	40	100	-

[a] 16 h, MeOH, 30 bar H$_2$, [b] Determined by GC (ChromPack CP-Chirasil-Dex-CB 25 mx0.25mmx0.25μm. 100 °C for 10 min, then to 200 °C @ 10 °C/min, 10 psi He flow, injector: 200 °C; detector (FID): 210 °C. [c] ND = not determined. [d] 7% side product also formed. Using 2 mol% AgOTf the conversion was 4%. [e] 15 bar H$_2$ pressure. [f] 3% side product formed. [g] 4% side product formed. [h] Lower conversions were observed using 5 mmol at [S]=1.4 and 2 mmol at [S]=0.5 M.

3

formed in very low ee of only 8% (>99% conversion) at S/C 500, although this could be raised to 20% ee (*R* using (*S,S*)-**7**) at S/C 50.[11] In contrast the reduction of 1,1,1-trifluoroacetone resulted in formation of **30** in 94% ee ((*S*)-product formed using (*S,S*)-**7**). 1,1,1-Trifluoro-2-propanol **30** is an important chiral building block difficult to access due to its tendency to form self-condensation side-products.[12] This result highlights the potential for using an asymmetric catalysts that works under completely neutral conditions. The low ee for the formation of **29** would suggest that the Ph and CF_3 groups have similar affinity for the ruthenium-bound η^6 arene within the accepted transition states for ketone reductions by these compounds,[7] whilst the high ee and sense of reduction to give **30** indicates that the CF_3 has a higher affinity than the methyl group, as would be anticipated.[11] During the reduction of 1,1,1-trifluoroacetone, a side product, which may be the product of addition of methanol to the substrate, was observed along with incomplete conversion. Addition of ca 10 mol% of water resulted in full reduction to **30**, possibly due to reversal of formation of the observed side product. The reduction of 1,1,1-trifluoroacetone in EtOH and iPrOH was also successful, at 60 °C, giving products of 92 and 90% ee respectively (unchanged configuration).
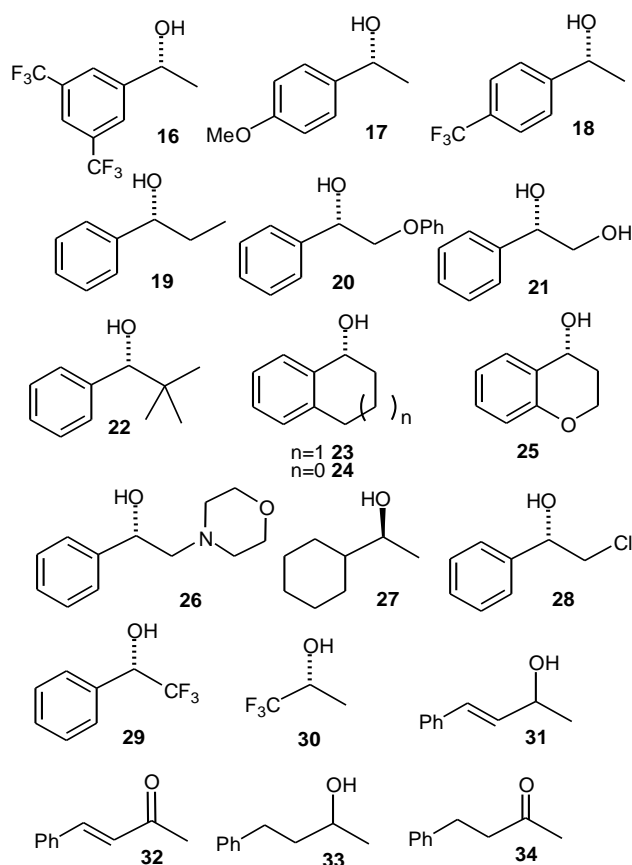

Figure 1. Products of reduction of ketones using catalyst **7**; configuration illustrated matches that obtained using (*R,R*)-catalyst.

Table 2: Hydrogenation of ketones with catalyst **7**.[a]

Prod-uct	Catalyst	t	T/ °C	Conv. /%[b]	Ee /%[b]
16	(*R,R*)-**7**	24h	60	>99%	70 (*R*)
17	(*R,R*)-**7**	16h	60	99.3	91.1 (*R*)
18	(*R,R*)-**7**	16h	60	>99.9	88.2 (*R*)
19	(*R,R*)-**7**	48h	60	99.9	89.7 (*R*)
20	(*R,R*)-**7**	24h	60	99.9	84.4 (*S*)
21	(*R,R*)-**7**	24h	60	>99	>99.5 (*S*)
22	(*R,R*)-**7**	48h	60	73.7	68.8 (*R*)
23	(*R,R*)-**7**	48h	60	99.9	99.3 (*R*)
24	(*R,R*)-**7**	48h	60	99.5	97.5 (*R*)
25	(*R,R*)-**7**	24h	60	99.9	99.0 (*R*)
26	(*R,R*)-**7**	48h	60	87.7[d]	>95% (*S*)[e]
27	(*R,R*)-**7**	48h	60	99.95	66.8 (*S*)
28[f]	(*S,S*)-**7**	16h	50	95	94 (*R*)
29[g]	(*S,S*)-**7**	18h	60	>99	8 (*R*)
30[h]	(*S,S*)-**7**	18h	50	94	92 (*S*)
30[i]	(*S,S*)-**7**	18h	50	>99	94 (*S*)
31,33	(*R,R*)-**7**	24h	60	80.3[c]	4.7% (*S*)

[a] MeOH, S/C=500, 30 bar H_2, 1 mmol scale, [S] = 0.5 M except where indicated. [b] Determined by GC (ChromPack CP-Chirasil-Dex-CB 25 m x 0.25mm x 0.25μm. 100 °C for 10 min, then to 200 °C @ 10 °C /min, 10 psi He flow, injector: 200 °C; detector (FID): 210 °C. [c] 37.3% unsaturated alcohol **31**, 30.9% saturated alcohol **33**, 12.1% saturated ketone **34**, reduction of the mixture gave the saturated alcohol **33** in 4.7% ee. [d] Conversion determined by ^{1}H NMR. [e] Only one enantiomer is visible in ^{1}H NMR using Mosher's method. [f] S/C=200, 1.3 mmol, [S] = 0.13 M, 75 bar H_2. [g] 2 mmol, [S] = 0.7M, product of 20% ee obtained at S/C = 50. [h] ca 6% side product also formed under these conditions (see SI). [i] 10 mol% H_2O added, <1% side product formed.

The tethered catalysts also proved to be effective at catalysis of reduction of a series of aldehydes **33 – 37** (Table 3). Although the chiral catalyst (*S,S*)-**7** worked well, it is preferable to use the non-chiral analogue **12**. During initial studies on benzaldehyde (**33**) in methanol, using **7**, dimethylacetal **38a** was formed in high yield alongside the desired alcohol. This could be eliminated by the addition of at least 5% (volume) of water to the solvent; even within 8h at 60 °C, almost complete reduction was observed, with only a trace of the acetal in the product. This parallels the observation made in the reduction to **30**, i.e. water may be assisting the conversion of the unwanted acetal to aldehyde substrate. The water content could be increased to 10% without detriment to the rate, however at >25% water loading the rate was seen to decrease, and longer reaction times were required for full reduction. In neat water, 26.2% conversion to alcohol was achieved under the standard conditions.

4

35, 36, 37 (aldehydes), 38 (O₂N-), 39 (Ph cinnamaldehyde)

40a X=H
40b X=OMe
40c X=Br
40d X=NO₂

41
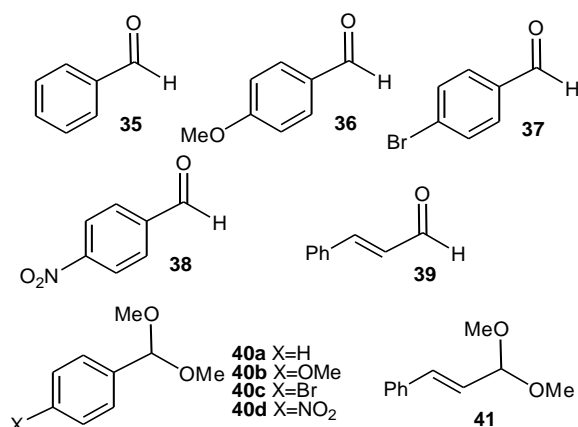
Solvents other than methanol, including iPrOH, DCM, toluene, cyclohexanol, dioxane and DMF, were significantly inferior, affording less than 5% alcohol within 24h at 60 °C and 30 bar. Using achiral catalyst **12**, a 90:10 MeOH:H$_2$O ratio of solvents gave the optimal selectivity, with 99.5% of the desired alcohol product formed. These conditions were applied to the reduction of aldehydes **36-39**, and were found to work well, with minimal reduction of either the bromide (none visible) or the nitro (2.8% 4-aminobenzyl alcohol identified) group, or formation of the corresponding acetals **40** or **41** under the conditions used. Aldehyde **39** provided a very difficult test of selectivity, however using catalyst **12**, 96.1% of the unsaturated alcohol product was formed alongside products of reduction of the C=C bond.

Conclusion

In conclusion, tethered Ru(II) catalysts **7**, **11** and **12** can be prepared in high yield and purity, and can be used effectively in asymmetric pressure hydrogenation of ketones, as the chlorides, without the need for activation by additives. The tethered catalysts are also effective for highly chomoselective aldehyde reduction.

Experimental Section

General experimental details are given in the Supporting information.

Synthesis of tethered ligand (*R,R*)-14a.

A solution of 3-(1,4-cyclohexadien-1-yl)-1-propanol **13** (22.1 g, 0.16 mol, 1.6 eq.) and 2,6-lutidine (d: 0.92 g/mL; 24.5 mL, 0.21 mol, 2.10 eq.) in anhydrous CH$_2$Cl$_2$ (500 mL) was cooled to 0°C under N$_2$. A solution of trifluoromethane sulfonic anhydride (d: 1.677; 29.1 mL, 0.17 mol, 1.7 eq.) in anhydrous CH$_2$Cl$_2$ (100 mL) was added slowly, keeping the internal temperature below 5°C. The resulting amber solution was stirred for 30 min at 0°C, 60 min rt, and cooled back to 0°C. A solution of (*R,R*)-TsDPEN (36.6 g, 0.10 mol) and triethylamine (d: 0.726; 33.5 mL, 0.24 mol, 2.4 eq.) in anhydrous CH$_2$Cl$_2$ (100 mL) was added slowly, keeping the internal temperature below 5°C. At the end of the addition, stirring was continued for 30 min at 0°C. and then at rt overnight (17.5 h). The reaction was diluted with CH$_2$Cl$_2$ (500 mL), washed with sat. aq. NaHCO$_3$ (2×500 mL, 1×250 mL), water (2×300 mL), brine (250 mL), dried over MgSO$_4$, and concentrated

Table 3. hydrogenation of aldehydes with catalysts **7** and **12**.[a]

Substrate.	Catalyst	solvent	t/h	T / °C	Conv. /% [b]	alcohol:acetal[b]
35	(*S,S*)-**7**	MeOH	24	60	100	62:38
35	(*S,S*)-**7**	MeOH:H$_2$O 95:5	8	60	99.97	99.94:0.03
35	(*S,S*)-**7**	MeOH:H$_2$O 90:10	16	60	100	99.9:<0.01
35	(*S,S*)-**7**	MeOH:H$_2$O 75:25	24	60	99.8	99.8:<0.01
35	(*S,S*)-**7**	MeOH:H$_2$O 50:50	24	60	99.8	99.8:<0.01
35	(*S,S*)-**7**	MeOH:H$_2$O 25:75	24	60	72.2	71.8:0.4
35	**12**	MeOH	24	60	99.8	33.7:66.1
35	**12**	MeOH:H$_2$O 95:5	4	60	44.6	12.3:32.3
35	**12**	MeOH:H$_2$O 95:5	8	60	99.6	98.7:0.9
35	**12**	MeOH:H$_2$O 95:5	16	40	59.1	7.4:51.7
35	**12**[h]	MeOH:H$_2$O 95:5	8	60	51.4	2.7:47.2
35	**12**	MeOH:H$_2$O 90:10	16	60	99.6	99.5:0.1
36	**12**	MeOH:H$_2$O 90:10	16	60	99.6	99.6:0
37	**12**	MeOH:H$_2$O 90:10	16	60	99.9	99.8:0.1[g]
38	**12**	MeOH:H$_2$O 90:10	16	60	99.2	94.8:4.4[c]
39	(*S,S*)-**7**	MeOH	24	60	83.95	59.2:22.8[d]
39	**12**	MeOH:H$_2$O 90:10	24	60	99.95	96.1:0.3[e]
39	**12**	MeOH:H$_2$O 90:10	16	60	67.6	62.4:2.6[f]

[a] MeOH, 30 bar H$_2$, S/C 500, 1 mmol scale [S]=0.5 M except where indicated. [b] conversion and alcohol:dimethoxy acetal ratio determined by GC. [c] 4.4% is sum of 4-aminobenzylalcohol (2.8%) and 3 unidentified impurities in GC. [d] also + 1.2% saturated alcohol + 0.75% saturated aldehyde. [e] also 3.5% saturated alcohol, 0.06% saturated aldehyde [f] also 1.3% saturated alcohol + 0.6% saturated aldehyde, 0.7% other unidentified' product. [g] also <0.1% impurity at rt 8.1 in GC. [h] S/C = 1000.

under reduced pressure to give a highly viscous, amber oil. Ethanol (250 mL) was added, and the mixture was stirred until a solid formed. Additional ethanol (450 mL) was added, and the mixture was heated to 70°C until a clear solution was obtained, which was allowed to cool to room temperature overnight. The thick suspension (solvent not visible, voluminous product) was filtered, and the off-white precipitate was washed with ethanol, hexane, and dried under high vacuum to give **14a** (34.10 g, 0.0702 mol, 70%), NMR purity >98% (^{1}H NMR). The spectroscopic data matches that already reported for this known compound.[10b]

Synthesis of tethered ligand (*S*,*S*)-14b.HCl.

A solution of 3-(1,4-cyclohexadien-1-yl)-1-propanol **13** (8.3 g, 60.0 mmol, 1.20 eq.) and 2,6-lutidine (8.3 mL, 70.0 mmol, 1.40 eq.) in anhydrous CH_2Cl_2 (250 mL) was cooled to 0°C under N_2. A solution of triflic anhydride (10.7 mL, 62.5 mmol, 1.25 eq.) in anhydrous CH_2Cl_2 (40 mL) was added slowly, keeping the internal temperature below 5°C. The resulting amber solution was stirred for 30 min at 0°C, 90 min at rt, and cooled to 0°C. A solution of (*S*,*S*)-MsDPEN (14.52 g, 50.0 mmol) and triethylamine (11.2 mL, 80.0 mmol, 1.6 eq.) in anhydrous CH_2Cl_2 (90 mL) was added slowly, keeping the internal temperature below 5°C. At the end of the addition, stirring was continued for 30 min at 0°C and then at rt overnight (20.5 h). The reaction mixture was diluted with CH_2Cl_2 (total volume: ca. 500 mL), washed with sat. aq. $NaHCO_3$ (2×250 mL, 1×150 mL), water (2×200 mL), brine (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a highly viscous, amber oil (26.5 g). The crude product was filtered through a layer of silica gel (7 cm thick, 9 cm in diameter) with EtOAc/hexane 2/1 as eluent. The product was obtained with the first two fractions (200 mL each) but still contained an impurity, which eluted first (TLC in EtOAc, R_f(impurity): 0.76, R_f(tethered MsDPEN): 0.66; visualised with UV @ 254 nm or with basic $KMnO_4$). Evaporation of the solvents under reduced pressure yielded the crude product as a yellow-to-orange oil, which slowly solidified (20.2 g). The solid was dissolved in methyl *t*butyl ether (MTBE) (500 mL) and the solution was cooled to ca. 0°C. A 1.25 M solution of HCl in MeOH (120 mL, 150 mmol) was added with vigorous stirring. After 45 min at 0°C the thick suspension was filtered, the solid was washed with MTBE, and dried under high vacuum to give **14b** (17.13 g, 0.0384 mol, 77%), NMR purity >98% (^{1}H NMR). A second batch of product was obtained by working up the mother liquor: The combined filtrate and washings were evaporated to dryness under reduced pressure until a solid was obtained, which was triturated with ethyl acetate (40 mL) at 70°C for 1 hour. After cooling to rt, the mixture was filtered and the filter cake was washed with EtOAc. The off-white solid was then dried under high vacuum (1.66 g, 3.72 mmol, 7%), NMR purity >98% (^{1}H NMR). Mp 186°C; $[α]_D^{26}$ -

20.25 (*c* 1 in CHCl$_3$); (found (ESI): M$^+$ + H - HCl 411.2099). $C_{24}H_{31}N_2O_2S$ requires M, 411.2101); $υ_{max}$ 3676, 2972, 2901, 1590, 1455, 1395, 1329, 1157, 1066, 985, 756, 698 and 664 cm^{-1}; $δ_H$ (400 MHz, CDCl$_3$) 10.08 (1H, br s, HN$^+$*H*), 8.81 (1H, d, *J* 9.1 , N*H*Ms), 8.61 (1H, br s, HN$^+$*H*), 7.52-7.51 (2H, m, C*H*Ar), 7.38-7.36 (2H, m, C*H*Ar), 7.25-7.24 (3H, m, C*H*Ar), 7.20-7.14 (3H, m, C*H*Ar), 5.57 (2H, s, HC=C*H* x 2), 5.26 (1H, s, C=C*H*), 5.23 (1H, d, *J* 10.0, C*H*Ph), 4.91 (1H, d, *J* 10.4, C*H*Ph), 2.97-2.94 (1H, m, NH$_2$C*H*^{a}H^b), 2.85-2.83 (1H, m, NH$_2$CH^a*H*^{b}), 2.65 (3H, s, C*H*$_3$), 2.50-2.48 (2H, m, =C-C*H*$_2$-C=), 2.44-2.40 (2H, m, =C-CH$_2$-C=), 2.16-1.82 (4H, m, 2 x CH$_2$); $δ_C$ (100 MHz, CDCl$_3$) 137.1, 132.7, 130.9, 129.6, 129.5, 129.1, 128.8, 128.4, 128.2, 124.01 (x 2), 119.5, 65.5, 61.1, 45.7, 42.1, 34.1, 28.6, 26.6, 22.9; *m/z* (ESI) 411.1 (M$^+$ + 18 - 36).

Synthesis of TsDPEN Ru dimer (*R*,*R*)-15a.

Procedure 1. To a stirred suspension of (*R*,*R*)-tethered-diamine **14a** (11.68 g, 24 mmol) in EtOH (500 mL) was added concentrated HCl (3 mL, 37 %, 36 mmol) at 60°C and the solution was stirred for 30 minutes. The solution was then heated to 75°C and to this was added RuCl$_3$ in H$_2$O (assay 19.23% in Ru, d=1.628, 6.46 mL, 20 mmol) in EtOH (50 mL) dropwise over 1 hour. The solution was then stirred at 75°C overnight. The solution was then cooled, hexane (600 mL) added with vigorous stirring and solution filtered. The solids obtained were then washed with hexane, collected and dried under high vacuum to give a light brown solid (~15g, carried forward). The isolated product **15a.** was shown to be >95% pure by ^{1}H NMR (CDCl$_3$). No further purification was attempted and this material was carried forward to the next step. The spectroscopic data matched that previously reported for this known compound.[10b]

Procedure 2. To a stirred suspension of (*R*,*R*)-diamine **14a** (2.9 g, 6.0 mmol) in DCE (20 mL) was added HCl (3 mL, 37 %, 36 mmol) at 50°C and solution was stirred for 30 minutes. The resulting suspension was then heated to 75°C and to this was added RuCl$_3$ in H$_2$O (assay 19.23% in Ru, d=1.628, 1.62 mL, 5 mmol) in isopropylacohol (IPA) (20 mL) added dropwise over 1 hour. The solution was then stirred at 75°C overnight. The solution was then cooled, hexane (100 mL) added with vigorous stirring and the solution was filtered. The solids obtained were then washed with hexane, collected and dried under high vacuum to give a light brown solid (~6 g, carried forward). The dimer **15a** was isolated as a crude solid and shown to be >90% pure by ^{1}H NMR (CDCl$_3$).[10b]

Procedure 3. To a stirred suspension of (*R*,*R*)-diamine **14a** (2.9 g, 6.0 mmol) in toluene (20 mL) was added HCl (3 mL, 37 %, 36 mmol) at 50°C and the solution was stirred for 30 minutes. The resulting suspension was then heated to 75°C and to this was

added $RuCl_3$ in H_2O (assay 19.23% in Ru, d=1.628, 1.62 mL, 5 mmol) in IPA (20 mL) dropwise over 1 hour. The solution was then stirred at 75°C overnight. The solution was then cooled, hexane (100 mL) added with vigorous stirring and solution filtered. The solids obtained were then washed with hexane, collected and dried under high vacuum to give a light brown solid (~6 g, carried forward). The dimer **15a** was isolated as a crude solid and shown to be >90% pure by ^{1}H NMR ($CDCl_3$).

Synthesis of [Ts-teth-DPEN Ru Cl] (monomer) 7.

Procedure 1. To a stirred solution of the (*R,R*)-dimer **15a** (14g carried forward, ~10.1 mmol) in DCM (300 mL) at 0°C was added N,N-diisopropylethylamine (20.9 mL, 120 mmol) and the solution was stirred at room temperature for 1 hour. The solution was then filtered over celite, IPA (300 mL) added and the DCM removed by rotary evaporation. The resulting suspension was then filtered and product collected as a dark orange solid. The solid was then further dried under high vacuum over night to give **7** as a fine orange powder (10.6g, 0.0171 mol, 83 % from **14a**). The isolated product was shown to be >95% pure by ^{1}H NMR ($CDCl_3$). A detailed ^{1}H NMR study was conducted on a 700 MHz instrument fitted with a cryoprobe in $CDCl_3$ and CD_3NO_2 (see supporting information). The data matched that previously reported for this known compound.[10b]

Procedure 2. To a stirred solution of the (*R,R*)-dimer **15a** (14g, ~10.1 mmol) in IPA (1 L) at 50°C was added N,N-diisopropylethylamine (20.9 mL, 120 mmol) and the solution was stirred at 85°C for 2 hours. The solution was then cooled, evaporated to a third of its original volume and then filtered to give a dark orange solid. The solid was then further dried under high vacuum over night to give **7** as a fine orange powder (8.5g, 13.7 mmol, 67 %). The isolated product was shown to be >95% pure by ^{1}H NMR ($CDCl_3$).

Synthesis of (*R,R*)-7 in one-pot from diamine 14a.

Procedure 1. To a stirred suspension of (*R,R*)-diamine **14a** (2.9 g, 6.0 mmol) in toluene (20 mL) was added HCl (0.75 mL, 37 %, 9 mmol) at 50°C and the solution was stirred for 30 minutes. The resulting suspension was then heated to 75°C and to this was added $RuCl_3$ in H_2O (assay 19.23% in Ru, d=1.628, 1.62 mL, 5 mmol) in IPA (10 mL) dropwise over 1 hour. The solution was then stirred at 75°C overnight (16 h). The solution was then cooled to 0°C, toluene (30 mL) added and *N,N*-diisopropylethylamine (4.35 mL, 25 mmol) added dropwise with stirring. The solution was then allowed to warm to rt and then heated to 80°C for 30 mins. The solution was cooled, diluted with DCM (50 mL), filtered over neutral alumina (1 g / mmol) and the pad was washed with further portions of DCM (2 x 20 mL). The filtrate

was evaporated to remove the solvent, IPA (50 mL) added and solution stirred at rt for 1h. The resulting slurry was then filtered to give an orange solid, which was dried under high vacuum for 2 hours to give **7** (2.3 g, 3.71 mmol, 63 %). After the initial heating phase a thick precipitate formed which resulted in the stirring of the solution failing. Addition of the toluene and N,N-diisopropylethylamine however resulted in re-dissolution of the solids as the monomer formation proceeded. Isolated product was shown to be >95% pure by ^{1}H NMR ($CDCl_3$).

Procedure 2. To a stirred suspension of (*S,S*)-diamine **14a** (14.5 g, 30 mmol) in toluene (100 mL) under nitrogen was added HCl (3.75 mL, 37 %, 45 mmol) at 50°C and the solution was stirred for 30 minutes. The resulting suspension was then heated to 75°C and to this $RuCl_3$ in H_2O (assay 19.23% in Ru, d=1.628, 8.1 mL, 25 mmol) in IPA (50 mL) was added dropwise over 1 hour. The solution was then stirred at 75°C overnight (16 h). The solution was cooled to 0°C, DCM (100 mL) and *N,N*-diisopropylethylamine (21.75 mL, 125 mmol) were added dropwise with stirring. The solution was then allowed to warm to rt and stirred for 2h. The solution was then filtered over neutral alumina (1 g / mmol) and pad washed with further portions of 10/90 IPA/DCM (2 x 50 mL). The combined filtrate was evaporated to remove the solvent IPA (200 mL) was added and solution stirred at room temperature for 2h. The resulting slurry was then filtered to give an orange solid, which was washed with cold IPA (30 mL) and dried under high vacuum for 2 hours to give **7** (12.3 g, 19.8 mmol, 79 %). The same observations were made as for procedure 1. Crude Isolated product was shown to be >95% pure by ^{1}H NMR ($CDCl_3$).

Synthesis of (*S,S*)-11 in one-pot from 14b.

Procedure 1. To a stirred suspension of (*S,S*)-diamine.HCl **14b** (2.67 g, 6.0 mmol) in toluene (20 mL) at 75°C under nitrogen $RuCl_3$ in H_2O (assay 19.23% in Ru, d=1.628, 1.62 mL, 5 mmol) in IPA (10 mL) was added dropwise over 1 hour. The solution was then stirred at 75°C overnight (16 h). The solution was cooled to 0°C, DCM (30 mL) added and *N,N*-diisopropylethylamine (4.35 mL, 25 mmol) was added dropwise with stirring. The solution was allowed to warm to rt and stirred for 2h. The solution was diluted with DCM (50 mL), filtered over neutral alumina (1 g / mmol) and pad washed with further portions of DCM (2 x 20 mL). The combined filtrate was evaporated to remove solvent, IPA (50 mL) was added and the solution stirred at room temperature for 1h. The resulting slurry was then filtered to give **11** as an orange solid, which was dried under high vacuum for 2 hours (1.8 g, 3.31 mmol, 55 %). After the initial heating phase a thick precipitate was not observed in comparison to the Ts example. The isolated product was shown to be >95% pure by ^{1}H NMR ($CDCl_3$). Mp 187°C; $[\alpha]_D^{26}$ -460 (*c* 0.05 in $CHCl_3$); (found (ESI): M^+ - Cl, 509.0836. $C_{24}H_{27}N_2O_2RuS$ requires M, 509.0837); ν_{max} 2972, 1730, 1452, 1261, 1109, 1058,

958, 905, 805 and 699 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.17-7.15 (3H, m, C*H*Ar), 7.04-7.01 (3H, m, C*H*Ar), 6.95-6.93 (2H, m, C*H*Ar), 6.85-6.83 (2H, m, C*H*Ar), 6.24 (1H, t, *J* 5.5 , C*H*Ar), 6.06 (1H, t, *J* 5.7, C*H*Ar), 5.99 (1H, t, *J* 5.7, C*H*Ar), 5.19 (1H, d, *J* 5.6 , C*H*Ar), 5.03 (1H, d, *J* 5.6, C*H*Ar), 4.46-4.43 (1H, m, N*H*), 4.05 (1H, d, *J* 10.7, MsNC*H*), 3.67 (1H, t, *J* 11.4, HNC*H*), 2.90-2.83 (1H, m, CH*H*), 2.71-2.65 (4H, s overlapping m, C*H*$_3$ with CH*H* overlapping), 2.55-2.49 (1H, m, CH*H*), 2.35-2.29 (1H, m, CH*H*), 2.27-2.17 (1H, m, CH*H*), 2.02-1.93 (1H, m, CH*H*); δ_C (100 MHz, CDCl$_3$) 142.4, 136.7, 128.8, 128.5, 128.0, 127.63, 127.58, 126.7, 99.7, 93.6, 92.8, 81.9, 79.2, 77.8, 72.8, 69.8, 48.8, 41.3, 29.7, 26.8; *m/z* (ESI) 509.0 (M$^+$ + 1 - 35).

Procedure 2. To a stirred suspension of (*S,S*)-diamine.**14b.**HCl (8.03 g, 18 mmol) in toluene (60 mL) at 75°C under nitrogen RuCl$_3$ in H$_2$O (assay 19.23% in Ru, d=1.628, 4.86 mL, 15 mmol) in IPA (30 mL) was added dropwise over 1 hour. The solution was then stirred at 75°C overnight (16 h). The solution was then cooled to 0°C, DCM (100 mL) and *N,N*-diisopropylethylamine (15.66 mL, 90 mmol) were added dropwise with stirring. The solution was allowed to warm to room temperature and was stirred for 2h. The solution was filtered over neutral alumina (1 g / mmol) and pad washed with further portions of 10/90 IPA/DCM (2 x 50 mL). The combined filtrate was evaporated to remove the solvent, IPA (200 mL) added and the solution was stirred at room temperature for 2h. The resulting slurry was filtered to give **11** as an orange solid, which was washed with cold IPA (30 mL) and dried under high vacuum for 2 hours (5.0 g, 9.2 mmol, 51 %). The crude isolated product was shown to be >95% pure by ^{1}H NMR (CDCl$_3$).

Synthesis of achiral tethered catalyst 12.

Synthesis of ligand 14c. To a stirred solution of 3-(1,4-cyclohexadien-1-yl)-1-propanol **13** (1.21 g, 9.18 mmol) in DCM (25 mL), NEt$_3$ (2.7 mL, 19.28 mmol) was added and the resulting solution was cooled to 0°C. A solution of methane sulfonyl chloride (1.1 mL, 13.8 mmol) was added over a period of 20 min by keeping the internal temperature below 5° C. After 30 min the reaction mixture was allowed to warm up to rt and stirred overnight. The reaction was quenched with saturated NaHCO$_3$ solution. The reaction was worked up with water, brine and dried over Na$_2$SO$_4$. The mesylate derivative (96% yield) was carried forward directly to the next step. A solution of the mesylate derivative in 10 mL of DME was added slowly over a period of 5 min to a stirred solution of monotosylated ethylenediamine (1.98 g, 9.25 mmol) in 1,2-dimethoxy ethane (20 mL) and NEt$_3$ (2.7 mL, 19.43 mmol) at 60° C. The resulting solution was heated to 80 °C and stirred overnight. The reaction was quenched with saturated NaHCO$_3$ solution. The reaction was worked up with water, brine and dried over Na$_2$SO$_4$. The desired ligand **14c** (1.0 g, 3.0

mmol, 33% yield based on the starting alcohol) was isolated, as a yellow oil, by column chromatography with EtOAc as eluent (R$_f$ value 0.1 in EtOAc; visualised with UV @ 254 nm or with basic KMnO$_4$). (found (ESI): M$^+$ + H, 335.1798 C$_{18}$H$_{27}$N$_2$O$_2$S requires M, 335.1788); υ_{max} 2925, 2362, 2325, 1597, 1448, 1322, 1155, 1092, 1034, 814, 752 and 659 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.76-7.74 (2H, m, Ar*H*), 7.31-7.28 (2H, m, Ar*H*), 5.70 (2H, br s, C*H*=C*H*), 5.38 (1H, br s, =C*H*), 2.99-2.97 (2H, m, C*H*$_2$NH), 2.68-2.65 (4H, m, -C*H*$_2$-C= and =CH-C*H*$_2$-CH=), 2.57-2.53 (2H, m, C*H*$_2$-NH), 2.46-2.42 (5H, m, C*H*$_2$ and C*H*$_3$ overlapping), 1.96-1.90 (2H, m, -NH-C*H*$_2$-), 1.54-1.45 (2H, m, -CH$_2$-C*H*$_2$-CH$_2$); δ_C (100 MHz, CDCl$_3$) 143.3, 136.9, 134.4, 129.7, 127.1, 124.3, 118.6, 48.9, 48.0, 42.4, 35.0, 28.9, 27.5, 26.8, 21.5; *m/z* (ESI) 335.2 (M$^+$ + 1), 357.1 (M$^+$ + 23).

Synthesis of monomer 12. To a stirred solution of tethered ethylenediamine ligand **14c** (0.270 g, 0.808 mmol) in EtOH (15 mL) was added concentrated HCl (0.12 mL, 35%, 1.212 mmol) at 0°C. The solution was heated at 60°C for 30 minutes. After this time the solution was heated to 75°C and a solution of RuCl$_3$ (0.110 g, 0.533 mmol) in EtOH (15 mL) and water (0.5 mL) was added dropwise over 20 min. The solution was stirred at 75°C overnight. The solution was cooled, hexane (60 mL) was added with vigorous stirring and the resulting solid collected by filtration. The solid was then washed with hexaneand dried under high vacuum to give **15c** as a dark brown solid (0.006 g, 0.0055 mmol, 1.3%). The filtrate was concentrated to give an orange powder (0.040 g, 0.037 mmol, 9.2%). Both these solids were combined with those from other reactions and used directly in the next reaction. The isolated product was >95% pure by ^{1}H NMR: δ_H (300 MHz, DMSO-d6) 8.74 (4H, br s, N*H*$_2$), 7.91 (2H, br s, N*H*), 7.74-7.72 (4H, m, Ar*H*), 7.46-7.44 (4H, m, Ar*H*), 6.05-6.02 (4H, m, Ru-Ar*H*), 5.84-5.80 (6H, m, Ru-Ar*H*), 3.01 (12H, br s, C*H*$_2$), 2.57-2.54 (4H, m, C*H*$_2$), 2.42 (8H, m, C*H*$_3$ + C*H* overlapping), 1.95 (4H, br s, -C*H*$_2$-). To a stirred solution of dimer **15c** (0.238 g, 0.220 mmol) in DCM (50 mL) at 0°C was added N,N-diisopropylethylamine (3.0 mL, 1.696 mmol) and the solution was stirred at room temperature for 2 hours. The solution was then filtered over celite and the DCM was removed by rotary evaporation. EtOH was added to the resulting paste which was stored in the freezer for 3 hours before the cold solution was filtered and an orange precipitate collected. The dark precipitate was washed with further portions of cold EtOH. The desired ruthenium complex was isolated by column chromatography with EtOAc (R$_f$ value 0.2 in EtOAc; visualised with UV @ 254 nm and phosphomolybdic acid) (205 mg, 0.44 mmol, quant). Mp 125°C (decomposed); (found (ESI): M$^+$ -Cl, 433.0525. C$_{18}$H$_{23}$N$_2$O$_2$RuS requires M, 433.0522); υ_{max} 3675, 3169, 2970, 2901, 1447, 1406, 1266, 1105, 1075, 1049, 984, 864, 850, 810 and 661 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.73 (2H, d, *J* 8.2, C*H*Ar), 7.15 (2H, d, *J* 8.2, C*H*Ar), 6.36 (1H, t, *J* 5.6, C*H*Ar), 5.96 (1H, t, *J*

5.6, C*H*Ar), 5.83 (1H, t, *J* 5.8, C*H*Ar), 5.01 (1H, d, *J* 5.6, C*H*Ar), 4.91 (1H, d, *J* 5.8, C*H*Ar), 3.79 (1H, br s N*H*), 3.30-3.23 (1H, m, CH*H*), 3.03 (1H, dd, *J* 11.5 and 4.2, CH*H*), 2.79-2.71 (1H, m, CH*H*), 2.66-2.62 (1H, m, CH*H*), 2.43-2.36 (3H, m, C*H*$_2$ + CH*H*), 2.34 (3H, s, C*H*$_3$), 2.27-2.19 (2H, m, C*H*$_2$), 2.08-1.99 (1H, m, CH*H*); δ_C (100 MHz, CDCl$_3$) 140.5, 140.2, 128.7, 127.4, 98.8, 92.8, 91.3, 78.6, 78.1, 73.5, 57.7, 52.2, 47.5, 29.5, 28.6, 21.4; *m/z* (ESI) 432.9 (M$^+$ + 1 - 35).

Hydrogenation of ketones and aldehydes with (*R,R*)- and (*S,S*)-7, 11 and 12.

Catalyst (0.005 mol) and any required additive were weighed into a glass reaction tube. The tubes were placed in a Biotage Endeavour (at JM) or a Parr hydrogenator (at Warwick) and flushed with nitrogen. Acetophenone was added, followed by MeOH. The reaction was purged with hydrogen gas, heated and pressurised. The reaction was heated and pressurised with H$_2$ for 16 hours then analysed by GC (Full results are given in the Tables, spectroscopic and chromatographic data are in the SI).

Acknowledgements

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Application of Tethered Ruthenium Catalysts to Asymmetric Hydrogenation of Ketones, and the Selective Hydrogenation of Aldehydes

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7 (R=Ph, R'=pTol)
11 (R=Ph, R'=Me)
12 (R=H, R'=pTol)

>99% ee in best cases.
This enantiomer of alcohol is formed when the (*R,R*) catalysts are used.

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