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"Tethered" Ru(II) Catalysts for Asymmetric Transfer Hydrogenation of Ketones

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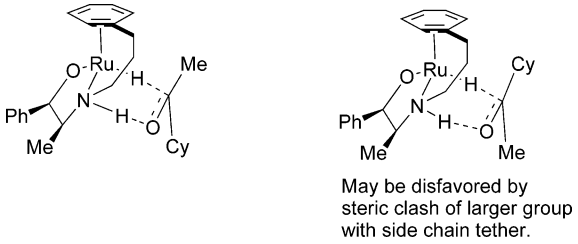

Stereochemically well-defined ruthenium(II) catalysts have been applied to the asymmetric transfer hydrogenation of a series of ketones. In one case, statistical experimental design was employed to optimize the enantiomeric excess of the product. In the case of the TsDPEN-based systems, the replacement of *trans*-1,2-diphenyl substitution with *cis*-, or deletion of one of the phenyl groups, results in significant deterioration of the enantiomeric excess. A new method is described for the synthesis of tethered amino alcohol-containing catalysts.

Introduction

Asymmetric transfer hydrogenation of ketones is an excellent method for the asymmetric synthesis of enantiomerically pure alcohols.[1] The rise in prominence of this method has largely been due to the introduction, by Noyori and co-workers, of powerful new catalyst systems based upon ruthenium(II) complexes of monotosylated diamines[2] and amino alcohols.[3] These catalysts, as well as related ones based on rhodium and iridium, have been further developed in recent years by several international research groups.[4−6] In our research group, we have focused on the use of *cis*-aminoindanol as a ligand and also extension of the range of applications for the new methodology.[7] Recently, we reported the synthesis and applications to ketone reduction of a series of new catalysts in which the homochiral ligand part of the structure is covalently linked to the η^6-arene ring.[7d] Representative examples are complexes **1** and **2**, which are formed in-situ by the treatment of dimers **3** and **4**, respectively, with base under the reaction conditions. These complexes work as well as the untethered version

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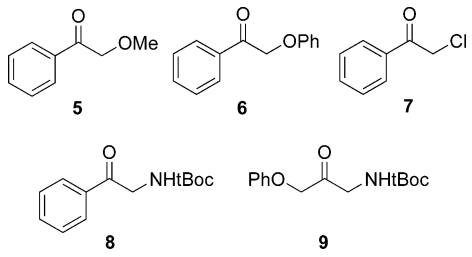
TABLE 1. Asymmetric Reduction of Substrates 5−9 Using Catalyst 2[a]

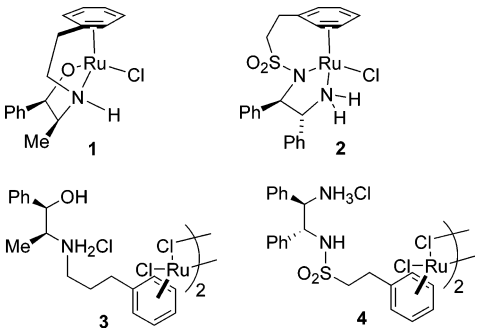


5 6 7 8 9

entry	substrate	time (days)	conversion	ee	*R/S*
1	5	3	100%	84%	S
2	6	2.5	100%	80%	S
3[b]	7	6	100%	81%	S
4	8	4	100%	98%	S
5	9	3	74%	56%	R

[a] Conditions: 0.5 mol % catalyst, HCO_2H:Et_3N (5:2), rt. [b] Propan-2-ol was added to the solution.

with the additional benefit of increased stability due to the "three point" attachment of the ligand to metal. A further benefit is the well-defined structures of the catalysts, which provide a basis for predictable modification toward particular substrate applications.



In this paper, we describe further applications of the "tethered" catalyst systems, as well as the synthesis and applications to ketone reduction of a series of modified TsDPEN-based catalysts. A new method for the preparation of a tethered amino alcohol complex is also described.

Results and Discussion

In our original paper describing the results obtained with complexes **1** and **2**, a series of aryl/alkyl ketones were reduced. The results revealed that **2** was a significantly more effective catalyst than **1**, giving superior yields and enantioselectivities. The use of **2** for the reduction of more challenging substrates, that is, **5**−**9**, was next undertaken. The results are given in Table 1.

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TABLE 2. Optimization of ee and Yield of Reduction of 6 with Respect to Solvent Ratio

	solvent ratios (formic acid/triethylamine)				
	1.3:1	1.6:1	1.9:1	2.2:1	2.5:1
% yield determined by ^{1}H NMR	99.5	99.7	99.3	99.0	99.7
% ee determined by HPLC	89	85	87	92	85

The results indicated that α-tBoc amino ketones could be reduced in very high selectivity provided that an aryl group flanked the ketone. The ee's were lower, however, for α-alkoxy ketones and for ketone **9**, which has no aryl ring next to the site of reduction. This pattern of results closely mimics the results obtained using the nontethered chiral catalyst formed from enantiomerically pure 1,2-(*R*,*R*)-*N*-tosyl diphenylethylenediamine.[7f,g]

The result of the reduction of **6** prompted us to ask whether the ee of the reaction could be improved by altering the reaction conditions. A brief study revealed that the variation of the ratio of solvents could have a dramatic effect on the conversion of acetophenone to 1-phenylethanol. Using a 5:2 (formic acid:triethylamine) or 1:1 mixture, conversions of >95% were obtained in 24 h. However, if the ratio was changed to 1:2 or 3:1, then the conversions dropped dramatically, to 23% and 15%, respectively. However, in all cases, the ee remained high, at ca. 96%.

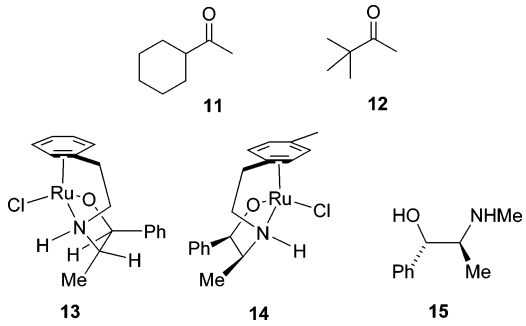
To complete a more systematic study of the reduction of ketone **6**, advantage was taken of the statistical experimental design package MODDE 6.[8] The variables selected for examination were temperature (10−40 °C), ratio of formic acid:triethylamine (4:1 to 1:1), and ketone concentration (0.5−3.5 M). The catalyst (**2**) loading was not changed. Analysis by the software led to the identification of 17 reactions (including three midpoint standards) to determine the effect of each variable. The full results are given in the Supporting Information. The results indicated a good fit to the model; however, two outliers were deleted for the ee fitting and one outlier for the yield fitting.

The results revealed that the ee and yield were both at their highest using a formic acid:triethylamine ratio between 1:1 and 2.5:1. At the higher ratio, both were reduced. The variation of the temperature had only a small effect on both ee and conversion. The ee increased slightly with increased ketone concentration, but the yield dropped slightly. Following these encouraging results, a more focused set of studies were completed (Table 2). The results indicated that a small variation of the formic acid:triethylamine ratio made no difference to the conversion; however, the ee was highest at either 1.3:1 or 2.2:1, and lower between these values. The overall result of these studies was for the ee of the reduction to be improved from 80% to 92%, with essentially quantitative conversion. This encouraging result suggests that the selectivity of reductions using the ruthenium(II) catalysts can be usefully optimized through subtle variation of the reaction conditions.

The asymmetric reduction of alkyl/alkyl substituted ketones, that is, with only alkyl groups flanking the

(8) Modde 6, Umetrics Software Ltd.

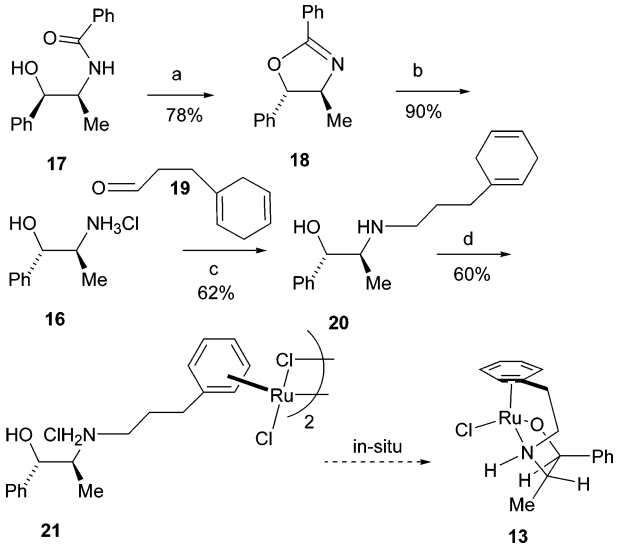
ketone, is known to be a challenging transformation. This is believed to be due to an important stabilizing aryl edge/face interaction between the aryl ring of the catalyst and that of the substrate.[3b] The reduction of cyclohexylmethyl ketone **11** was undertaken to determine whether the tethering might have an effect on the enantioselectivity of this process. Using catalyst **2**, the reduction of **11** was achieved in 84% yield after 63 h, but the ee was rather low, at ca. 19%. (*R*). An unexpectedly improved result was obtained using catalyst **1**, however. Although **2** had been consistently better than **1** in all of our tests on aryl/alkyl ketones, the reduction of **11** with **1** gave a reduction product of 69% ee (*S*) after 2 h (yield: 78%). This reaction was carried out in 2-propanol with an alkoxide base, as the amino alcohol catalysts do not tolerate formic acid/triethylamine conditions. This unexpected result represents one of the best reported results for the reduction of alkyl/alkyl ketones by ATH.[3a,6d−g,7a,c] The reduction of **11** using the equivalent untethered complex, that is, [((1*R*,2*S*)-ephedrine)Ru(*p*-cymene)Cl], under the same conditions gave a product of only 6% ee (*S*) in 27% yield. The tethering group clearly has a dramatic influence on the selectivity of the reduction process. The reduction of pinacolone **12**, by **1**, gave a product of 63% ee (*S*) in quantitative yield. This represents a competitive result, but a poor one in view of the greater steric difference between the substituents flanking the ketone in **12** as compared to **11**.



To probe this effect further, we elected to examine the reduction of **11** with two further complexes, **13** and **14**. In one of these, **13**, the ephedrine unit was replaced by a pseudoephedrine (**15**) group. This was considered to be worthy of investigation because Noyori has reported that **11** could be reduced in 75% ee and a yield of 93% using [((1*S*,2*S*)-pseudoephedrine)Ru(C_6Me_6)Cl].[3a] Compound **13** was prepared by the route shown in Scheme 1, which first required the preparation of norpseudoephedrine **16** by inversion of the 1-(hydroxyl) chiral center in norephedrine. This was achieved by formation of amide **17**, followed by cyclization to **18**, and finally hydrolysis to **16**, which was isolated in the form of a salt. Reductive amination of **16** with the aldehyde **19**[7d] resulted in formation of **20**, which was converted, in its hydrochloride salt form, to the dimer complex **21**, the direct precursor of **13**. Catalyst **13** was not actually formed and isolated, but was formed in situ during the reduction reaction, as was the case for the work in our preliminary communication.[7d]

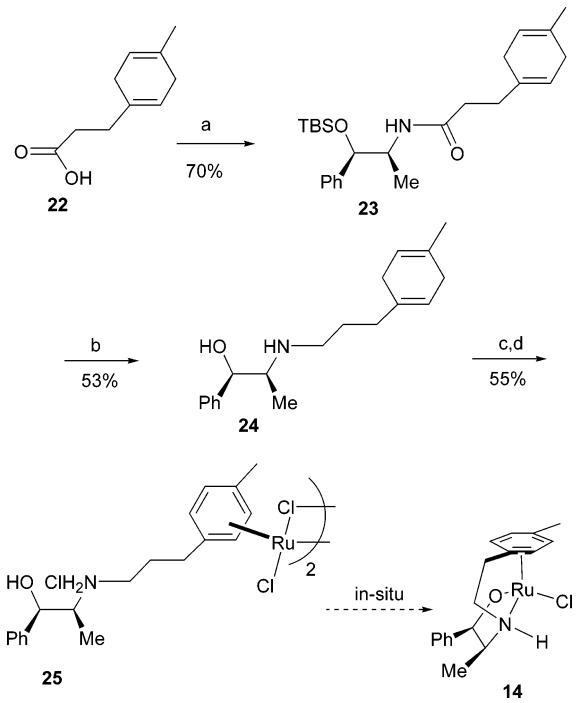
The diastereoisomeric purity of **13** is unknown; therefore, the isomer illustrated corresponds to that which is normally formed by complexes of this type, in which the

SCHEME 1[a]



[a] Reagents and conditions: (a) DIAD, PPh_3, THF, 0−22 °C; (b) 1.2 M HCl (aq), reflux; (c) **19**, 4 Å molecular sieves, NEt_3, DCM then $NaBH_4$, MeOH/H_2O; (d) 2 M HCl in ether then $RuCl_3$, EtOH, reflux.

SCHEME 2[a]



[a] Reagents and conditions: (a) O−TBS norephedrine, EDCI, HOBt, DIPEA; (b) $LiAlH_4$, THF, reflux, 18 h; (c) HCl, Et_2O, DCM, rt, 5 min; (d) $RuCl_3 \cdot H_2O$, EtOH, reflux, 18 h.

substituent adjacent to the oxygen atom in the ligand lies trans to the Ru−Cl or Ru−H bond.[3b,c,5b,c]

The preparation of complex **14** provided an opportunity for an alternative route to be investigated (Scheme 2). The EDCI coupling of diene **22** (formed by Birch reduction) with TBS-protected (1*R*,2*S*)-norephedrine gave amide **23**, which was reduced by lithium aluminum hydride to amine **24**. Formation of the salt of **24** followed by reflux in ethanol with ruthenium(III) chloride resulted

TABLE 3. Summary of Asymmetric Reductions of Acetophenone and 11

complex	ligand configuration	acetophenone reduction: yield, *R*/*S*, ee	cyclohexylmethyl ketone **11** reduction: yield, *R*/*S*, ee
1	(1*R*,2*S*)	96%, *R*, 68% ee[a]	78%, *S*, 69% ee
13	(1*S*,2*S*)	96%, *S*, 12% ee	95%, *R*, 62% ee
14	(1*R*,2*S*)	62%, *R*, 69% ee	66%, *S*, 63% ee
from **15**	(1*S*,2*S*)	99%, *S*, 89% ee[b]	5%, *S*, 70% ee
from ephedrine	(1*S*,2*R*) (1*R*,2*S*)	95%, *S*, 91% ee[c]	27%, *S*, 6% ee

[a] Reference 7d. [b] Reduction of *ortho*-chloroacetophenone (ref 3a). [c] Reference 3a.

in formation of dimer **25**, the direct precursor of **14**, which was not isolated but again formed and used in-situ under the reaction conditions.

Both complexes **13** and **14** were effective at the asymmetric reduction of acetophenone and **11**. In the case of **13**, the reduction of acetophenone gave a product of 12% ee (*S*) in 96% yield, while the reduction of **11** proceeded with selectivity (62% ee (*R*)) similar to that achieved with catalyst **1**, in 95% yield. We also examined the reduction of **11** using (1*S*,2*S*)-pseudoephedrine **15** in a ruthenium(II) complex with hexamethylbenzene as the arene ligand. In our hands, a selectivity (70% ee (*S*)) was achieved that is similar to that reported by Noyori, but the conversion was low (ca. 5%), using the same conditions. These results confirm that both ephedrine and psuedoephedrine represent suitable amino alcohol structures for tethering to the η^6-arene in our complexes. Complex **14** was also an effective reduction catalyst in ATH. Acetophenone was reduced in 62% yield and 69% ee (*R*), and **11** was reduced (reduction with 1.0 mol % Ru atom) in 66% yield and 63% ee (*S*). The introduction of a methyl group on the arene ring therefore does not appear to have a significant effect on either the activity or the selectivity of this class of catalyst.

A comparison of the reductions of acetophenone and **11** is given in Table 3. The absolute configurations of the products indicate that the chiral center adjacent to the hydroxy group (in the ligand) is primarily responsible for the control of enantioselectivity. However, the results from the tethered (first three entries) and untethered catalysts reveal a sharply contrasting trend. In the untethered cases, the configuration of the reduction product from both ketones generally matches that of the 1-position of the ligand (the exception being the virtually racemic final entry). However, for the tethered complexes, the product ee, relative to the ligand 1-position, inverts upon going from acetophenone to **11**. This suggests that a different mode of stereodifferentiation operates in the tethered compounds for alkyl/alkyl ketones as compared to aryl/alkyl ketones. A possibility is that the tether itself contributes to the enantiocontrol; however, the manner of this contribution, whether steric or electronic, is not yet clear. It is possible that the tether may occupy a region close to the arene ring in the complex and therefore make a steric contribution to the selectivity (Figure 1). For the tethered diamine complex **2**, the tether is in a different position relative to the transition state, and possibly too far away from the reduction center to contribute to the enantioselectivity in any significant way. We are currently investigating this effect.

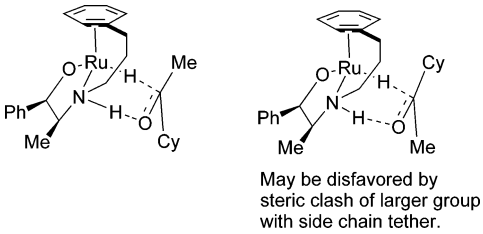
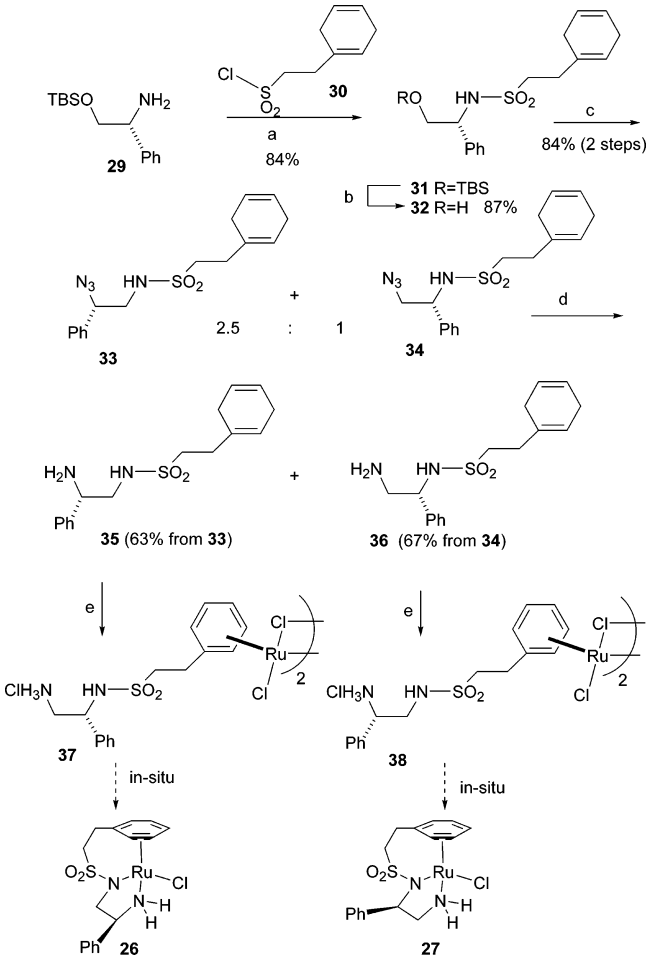


FIGURE 1. Contribution of tether to the control of reduction enantioselectivity.

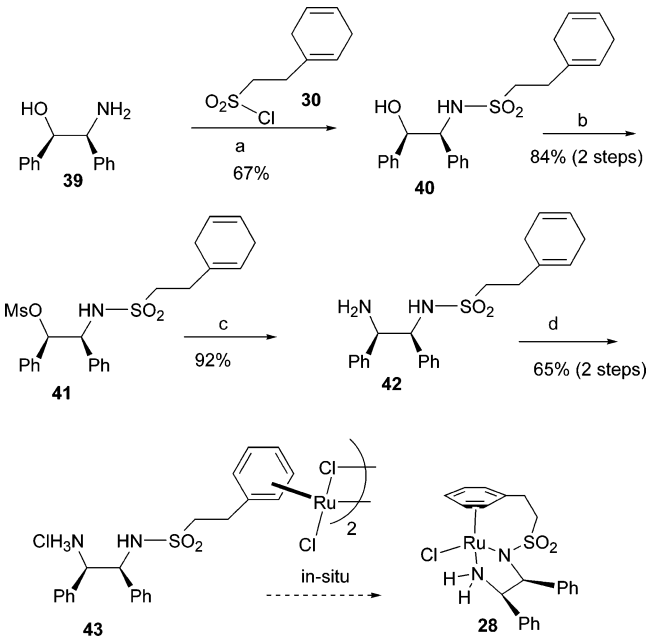
SCHEME 3[a]



[a] Reagents and conditions: (a) **30**, DCM, Et_3N; (b) TBAF, THF; (c) MsCl, DCM, Et_3N then NaN_3, DMF; (d) $LiAlH_4$, THF; (e) 1 M HCl, DCM then $RuCl_3$, EtOH, reflux.

In a previous paper, we have examined the use of modified TsDPEN complexes to investigate the importance of the *trans*-1,2-diphenyl substitution pattern on the reaction selectivity.[7e] Our results indicated that any change to this structure (use of the *cis*-substituted ligand or deletion of either phenyl group) resulted in a dramatic deterioration of the selectivity of reduction. In view of these results, we also wished to examine the effect of similar modifications on the selectivity achieved using complex **2**. Toward this end, we completed the synthesis of complexes **26**−**28**. Scheme 3 illustrates the route to **26** and **27**. The reaction of **29** with known sulfonyl chloride **30** resulted in clean formation of **31**, which was then deprotected to **32**. Reaction of **32** with MsCl,

SCHEME 4 [a]



[a] Reagents and conditions: (a) **30**, DCM, Et_3N; (b) MsCl, DCM, Et_3N; (c) NaN_3, DMF, then H_2/Pd/C, EtOH; (d) 1 M HCl, DCM then $RuCl_3$, EtOH, reflux.

TABLE 4. Acetophenone Reduction Using Complexes 26–28

entry	catalyst	time (days)	conversion	ee (*R*/*S*)
1	*S*-**26**	2	100%	28 (*S*)
2	*R*-**27**	8	94%	24 (*R*)
3	1*S*,2*R*-**28**	8	94%	8 (*S*)

followed by sodium azide, resulted in the formation of **33** and **34** in a 2.5:1 ratio. Product **33** may only be formed via an intermediate aziridine (hence the inversion of configuration), while **34** may be formed by direct displacement or via the aziridine. Reduction of the azide in the mixture of **33** and **34** was readily achieved to give separable products **35** and **36**, respectively, which could be separated by flash chromatography on silica gel. Treatment of each of the amines with acid, followed by reflux with ruthenium trichloride, resulted in formation of the required dimer complexes **37** and **38**, the precursors of **26** and **27**, respectively (which were again formed in situ when used).

Complex **28** was formed by the route shown in Scheme 4. In this route, amino alcohol **39** represented the starting point for reaction with **30** to give intermediate **40**, which, after mesylation, afforded **41**. Reaction of **41** with azide was followed by reduction to **42**. In this case, the azide reaction almost certainly proceeds via an intermediate aziridine, hence the retention of configuration; however, there is no issue of regioselectivity in this example, as the intermediate aziridine is C2-symmetric. Reaction of **42** with acid followed by complexation afforded dimer **43**, the direct precursor of **28**.

The reduction of acetophenone using **26**–**28** was examined (Table 4). All three catalysts were effective at the reduction when it was carried out at the 0.5 mol % level with respect to ruthenium atoms. The conversions were good although the reactions were very slow, and the ee's in all cases were significantly lower that those achieved with **2**. The absolute configuration of the products was related in all cases to that of the catalyst. It is therefore clear that, as for the untethered complexes, the *trans*-relationship between the phenyl groups, and the presence of both phenyls, is a prerequisite for highly enantioselective catalysis of transfer hydrogenation using tosylated diamine catalysts.

Conclusions

In conclusion, we have described the extension of the applications of "tethered" asymmetric transfer hydrogenation catalysts to further substrates and applications. In addition, we have discovered a remarkable and unexpected improvement to the enantioselectivity of the reductions of alkyl/alkyl ketones using the tethered amino alcohol catalysts over the untethered versions. The mechanism by which this is achieved is not clear, but the tether may exert a steric effect in the transition state for reduction. In addition, we have described synthetic approaches to a series of new tethered catalysts, which form the basis for further studies that are now underway.

Experimental Section

General experimental details have been given in a previous publication.[7i] Compounds **5** and **7** were used as purchased, and the known compounds **6**, **8**, and **9** were prepared using known literature routes.[7f,g] Enantiomeric excesses were measured using chiral HPLC or chiral GC methods, the details of which are given in the Experimental Section below. Absolute configurations were established by optical rotation and comparison to literature data. Racemic standards of all alcohol products were prepared by reduction of the precursor ketone with sodium borahydride.

General Procedure for Asymmetric Transfer Hydrogenation Catalyzed by Ruthenium(II) Complex 2. A solution of tethered ruthenium(II) dimer **4** (0.0101 g, 8.57×10^{-3} mmol) in formic acid/triethylamine 5:2 azeotrope (1.5 mL) was stirred in a small flame-dried Schlenk tube under N_2 at 28 °C for 20 min, and then substrate was added (3.33 mmol). The reaction mixture was stirred at 28 °C until completion and then filtered through cotton wool and silica gel in a glass pipet. It was washed several times with a 1:1 solution of ethyl acetate/hexane. The solution was concentrated under reduced pressure to afford the reduction product, which was purified by flash chromatography if required. The same procedure was used for reductions using **26**, **27**, and **28**, with precursor dimers **37**, **38**, and **43**, respectively.

Reduction Product of 2-Chloroacetophenone 7. $[\alpha]^{27}_D$ +38.5 (*S*) (*c* 0.90 in $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) 2.3–2.4 (1H, q, *J* 7.5), 2.92–3.15 (2H, m), 4.25 (1H, dd, *J* 7.5 and 3.7), 6.65–6.80 (5 H, m); ^{13}C NMR (75.5 MHz; $CDCl_3$; Me_4Si) 50.8 (t), 74.1 (d), 126.6 (2 × d), 128.5 (d), 128.6 (2 × d), 141.3 (s)[4a,7h] (Daicel Chiralcel OD 4.6 × 250 mm column, ethanol:hexane = 5:95, 1 mL/min) *S* isomer 9.58 min, *R* isomer 11.82 min.

Reduction Product of 2-Methoxyacetophenone 5. $[\alpha]^{25}_D$ +43.6 (*S*) (*c* 1.30 in CH_2Cl_2); ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) 2.18 (1H, br s), 2.85 (3H, s), 4.28 (1H, br d, *J* 7.5), 6.65–6.80 (5H, m); ^{13}C NMR (75.5 MHz; $CDCl_3$; Me_4Si) 53.96 (q), 72.9 (d), 78.8 (t), 126.6 (2 × d), 127.7 (d), 128.8 (2 × d), 141.1 (s)[9] (Daicel Chiralcel OD 4.6 × 250 mm column, ethanol: hexane = 5:95, 1 mL/min) *S* isomer 8.51 min, *R* isomer 10.18 min.

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Reduction Product of 2-Phenoxyacetophenone 6. $[\alpha]^{27}_D$ +33.0 (*S*) (*c* 1.40 in $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) 2.20 (1H, q, *J* 7.5), 3.25 (2H, q, *J* 7.5), 4.28 (1H, dd, *J* 7.5 and 3.75), 6.05−6.15 (3H, m), 6.40−6.63 (7H, m); ^{13}C NMR (75.5 MHz; $CDCl_3$; Me_4Si) 72.4 (d), 73.7 (t), 115.0 (2 × d), 121.3 (d), 127.2 (2 × d), 128.1 (d), 128.7 (2 × d), 129.8 (2 × d), 141.6 (s), 159.0 (s)[7f,10] (Daicel Chiralcel OD 4.6 × 250 mm column, ethanol:hexane = 5:95, 1 mL/min) *R* isomer 11.99 min, *S* isomer 16.50 min. Alternative conditions that may be useful if unreacted ketone overlaps: ethanol:hexane 7:93, 1 mL/min, *R* isomer 14.38 min, *S* isomer 18.59 min; ethanol:hexane 40:60, *R* isomer 5.52 min, *S* isomer 6.05 min.

Reduction Product of 2-[*N*-(*tert*-Butoxycarbonyl)amino]acetophenone 8. mp 44−45 °C; $[\alpha]_D$ +35.3 (*S*) (*c* 1.10 in $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) 0.58 (9H, s), 2.18 (1H, q, *J* 7.5), 2.30−2.41 (1H, m), 2.60 (1H, br s), 3.95 (1H, dd, *J* 7.5 and 3.75), 4.28 (1H, br s), 6.35−6.50 (5H, m); ^{13}C NMR (75.5 MHz; $CDCl_3$; Me_4Si) 28.1 (3 × q), 48.1 (t), 73.5 (d), 79.5 (s), 125.7 (2 × d), 127.5 (d), 127.9 (2 × d), 141.7 (s), 156.7 (s)[7g] (Daicel Chiralcel OD 4.6 × 250 mm column, ethanol:hexane = 5:95, 1 mL/min) *R* isomer 8.82 min, *S* isomer 9.93 min.

Reduction Product of 1-(*N*-*tert*-Butoxycarbonylamino)-2-oxo-3-phenoxypropane 9. Colorless oil. ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) 1.46 (9H, s), 3.26−3.35 (2H, m), 3.44−3.52 (1H, m), 3.91−4.01 (2H, m), 4.10 (1H, br s), 5.02 (1H, br s), 6.89−6.93 (3H, m), 7.25−7.35 (2H, m); ^{13}C NMR (75.5 MHz; $CDCl_3$; Me_4Si) 28.8 (3 × q), 44.9 (t), 69.8 (t), 70.3 (d), 80.3 (s), 114.9 (2 × d), 121.6 (d), 129.9 (2 × d), 158.8 (s). 56.1% ee (*R*) by HPLC (Chiralcel OD column, ethanol:hexane = 10:90 (1 mL/min), *R* isomer 8.2 min, *S* isomer 12.8 min).[7g]

General Procedure for Asymmetric Transfer Hydrogenation Catalyzed by Ruthenium(II) Complexes 1, 13, and 14. To a suspension of ruthenium dimer (0.004 mmol) in 2-propanol (15 cm^3) was added a 0.1 M solution of potassium hydroxide (0.85 cm^3, 0.085 mmol), and the solution was stirred at 28 °C for 20 min. Substrate (1.70 mmol) was added, and the reaction mixture was stirred at 28 °C for 2 h, diluted with hexane (30 cm^3), filtered (silica), washed (50% EtOAc/hexane), and concentrated under vacuum to give the reduction product. The residue was purified by flash chromatography where necessary.

Procedure for Reduction by Amino Alcohol Ligands. A suspension of ruthenium dimer (0.0125 mmol) and amino alcohol (0.050 mmol) in 2-propanol (4 cm^3) was heated at 80 °C for 20 min, cooled to 28 °C, and a 0.1 M solution of potassium hydroxide (0.85 cm^3, 0.085 mmol) was added. A solution of substrate (1.70 mmol) in 2-propanol (45 cm^3) was added, and the reaction mixture was stirred at 28 °C for 2 h, diluted with hexane (30 cm^3), filtered (silica), washed (50% EtOAc/hexane), and concentrated under vacuum to give the reduction product. The residue was purified by flash chromatography where necessary.

Reduction Product of Cyclohexyl/methyl Ketone 11. Colorless oil. Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 100 °C, P = 7 psi, ketone 17.6 min, *R* isomer 26.3 min, *S* isomer 26.9 min); $[\alpha]^{18}_D$ −1.61 (*c* 1.80 in $CHCl_3$) 19% ee (*R*) (lit.[11] $[\alpha]_D$ +3.51 (*c* 3.1 in $CHCl_3$) 95% ee (*S*)); ^1H NMR (400 MHz; $CDCl_3$; Me_4Si) 0.92−1.32 (6H, m), 1.15 (3H, d, *J* 6.3), 1.46 (1H, br s), 1.63−1.88 (5H, m), 3.54 (1H, dt, *J* 6.3 and 6.3); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) 20.4 (q), 26.2 (2 × overlapping t), 26.5 (t), 28.4 (t), 28.7 (t), 45.1 (d), 72.2 (d).

Reduction Product of Pinacolone 12. Colorless oil. Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 80 °C, P = 7 psi, ketone 5.5 min, *R* isomer 8.7 min, *S* isomer 8.9 min); $[\alpha]^{23}_D$ +2.0 (*c* 0.9 in CCl_4) 63% ee (*S*) (lit.[12] $[\alpha]^{29}_D$ −43.0 (*c* 1.5 in CCl_4) 99% ee (*R*)); ^1H NMR (400 MHz; $CDCl_3$; Me_4Si) 0.89 (9H, s), 1.12 (3H, d, *J* 6.5), 1.58−1.82 (1H, br s), 3.44−3.52 (1H, m); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 17.8 (q), 25.4 (3 × q), 34.9 (s), 75.6 (d).

Synthesis of *N*-((1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl)-benzamide 17. To a stirred solution of 1*R*,2*S*-norephedrine (5.00 g, 33.1 mmol) and triethylamine (3.34 g, 33.1 mmol) in dichloromethane (25 cm^3) at 0 °C was added dropwise a solution of benzoyl chloride (4.65 g, 33.1 mmol) in dichloromethane (5 cm^3). The reaction mixture was allowed to warm to room temperature, and a dense white precipitate was formed that was filtered and washed with water (200 cm^3). The solid was then dissolved in dichloromethane (600 cm^3), washed with water (200 cm^3), dried ($MgSO_4$), and concentrated under vacuum to give **17** (6.42 g, 76%) as a white solid (Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.25; H, 6.7; N, 5.5. Found: C, 74.85; H, 6.55; N, 5.55); mp 170−171 °C; $[\alpha]^{30}_D$ +42.3 (*c* 0.85 in MeOH); IR (ν, cm^{-1}) (solid) 3353 (OH), 3286 (NH), 1636 (C=O), 753 and 697 (Ph); ^1H NMR (400 MHz; DMSO-d_6) 1.12 (3H, d, *J* 6.8), 4.13−4.22 (1H, m), 4.73 (1H, dd (apparent t), *J* 8.3 and 8.3), 5.46 (1H, d, *J* 4.8), 7.19−7.54 (8H, m), 7.77−7.80 (2H, m), 8.20 (1H, d, *J* 8.3); ^{13}C NMR (100.6 MHz; DMSO-d_6) 14.8 (q), 51.1 (d), 74.4 (d), 126.2 (d), 126.7 (d), 127.2 (d), 127.7 (d), 128.1 (d), 130.9 (d), 134.8 (s), 143.7 (s), 165.5 (s). HRMS found (EI) 256.1337 $[MH]^+$. $C_{16}H_{18}NO_2$ requires 256.1338 (0.1 ppm error). MS *m/z* (EI) 256 (M^+, 10%), 238 (15), 149 (85), 148 (90), 105 (100), 79 (45), 77 (80).

Synthesis of (4*S*,5*S*)-4-Methyl-2,5-diphenyl-4,5-dihydrooxazole 18.[13] To a stirred solution of **17** (5.00 g, 19.6 mmol) and triphenylphosphine (6.41 g, 24.4 mmol) in THF (125 cm^3) at 0 °C was added diisopropylazodicarboxylate (4.94 g, 24.4 mmol). The reaction mixture was allowed to warm to room temperature, stirred overnight, and concentrated under vacuum. The crude product was purified by flash column chromatography (7.5% EtOAc/hexane to 15% EtOAc/hexane) to give **18** (3.60 g, 78%) as a colorless oil; $[\alpha]^{21}_D$ +82.6 (*c* 1.15 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.49 (3 H, d, *J* 6.8), 4.21 (1 H, dq, *J* 7.9 and 6.8), 5.10 (1 H, d, *J* 7.9), 7.29−7.53 (8 H, m), 8.00−8.04 (2H, m); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) 21.4 (q), 71.0 (d), 88.2 (d), 125.7 (d), 127.8 (s), 128.3 (d), 128.4 (2 × overlapping d), 128.8 (d), 131.4 (d), 140.6 (s), 162.8 (s).

Synthesis of (1*S*,2*S*)-2-Amino-1-phenyl-propan-1-ol (Norpseudoephedrine) 16·HCl.[14] A stirred solution of **18** (3.60 g, 15.2 mmol) in 1.2 M HCl (100 cm^3) was heated at reflux for 30 h. The reaction mixture was allowed to cool to room temperature, and a precipitate formed that was removed by filtration and washed with water (100 cm^3). The aqueous layer was washed with EtOAc (100 cm^3), ether (100 cm^3), and dichloromethane (100 cm^3) and then concentrated under vacuum to give **16·HCl** (2.56 g, 90%) as a white solid; $[\alpha]^{23}_D$ +41.2 (*c* 1.05 in H_2O); ^1H NMR (400 MHz; DMSO-d_6) 0.98 (3H, d, *J* 6.8), 3.23 (1H, dq, *J* 8.8 and 6.8), 4.48 (1H, dd, *J* 8.8 and 4.0), 6.22 (1H, d, *J* 4.0), 7.31−7.42 (5H, m), 8.16 (3H, br s); ^{13}C NMR (100.6 MHz; DMSO-d_6) 14.9 (q), 52.4 (d), 74.4 (d), 127.0 (2 × d), 127.9 (2 × d), 128.3 (2 × d), 141.4 (s).

Synthesis of (1*S*,2*S*)-2-(3-Cyclohexa-1,4-dienylpropylamino)-1-phenylpropan-1-ol 20. To a suspension of 4 Å molecular sieves in dichloromethane (17 cm^3) was added sequentially **19**[7d] (0.860 g, 6.32 mmol), triethylamine (0.639 g, 6.32 mmol), and **16·HCl** (1.187 g, 6.32 mmol). The reaction mixture was stirred overnight, filtered, and concentrated under vacuum. The residue was dissolved in methanol (35 cm^3), and sodium borohydride (0.956 g, 25.30 mmol) was added, stirred for 1 h, diluted with water (25 cm^3), and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered, and then concentrated under vacuum. The residue was purified by flash column

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chromatography to give **20** (1.062 g, 62%) as a white solid; mp 68−69 °C; $[\alpha]^{21}_D$ + 98.7 (*c* 1.1 in $CHCl_3$); IR (ν, cm^{-1}) (solid) 3311 (OH), 1669 (C=C), 757 and 700 (Ph); ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) 0.95 (3H, d, *J* 6.4), 1.56−1.68 (2H, m), 2.03 (2H, t, *J* 7.7), 2.44−2.84 (7H, m), 4.12 (1H, d, *J* 8.3), 5.41−5.46 (1H, m), 5.65−5.77 (2H, m), 7.21−7.38 (5H, m); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) 16.6 (q), 26.8 (t), 28.1 (t), 28.9 (t), 35.1 (t), 46.8 (t), 60.0 (d), 77.8 (d), 118.7 (d), 124.3 (d), 127.0 (2 × d), 127.6 (d), 128.2 (2 × d), 134.5 (s), 142.4 (s). HRMS found (EI) 270.1861 $[M - H]^+$. $C_{18}H_{24}NO$ requires 270.1858 (1.1 ppm error). MS *m/z* (EI) 272 (MH^+, 30%), 164 (100), 91 (45), 79 (25), 77 (20).

Synthesis of (1*S*,2*S*)-1-Phenyl-2-(3-phenylpropylamino)-propan-1-ol Ammonium Chloride Ruthenium Dimer 21. To a stirred solution of **20** (0.600 g, 2.21 mmol) in diethyl ether (10 cm^3) was added a 2 M solution of HCl in diethyl ether (3.30 mL, 6.60 mmol), and the reactants were stirred for 20 min. The solvent was removed from the resulting precipitate under vacuum, the resulting hydrochloric acid salt of **20** was dissolved in ethanol (20 cm^3), and ruthenium trichloride trihydrate (0.387 g, 1.48 mmol) was added. The reaction mixture was heated at reflux overnight and then cooled to 0 °C. The precipitate was collected by filtration and washed with ethanol (5 × 10 cm^3) and then dichloromethane (5 × 10 cm^3) to give **21** (0.421 g, 60%) as a dark green solid; IR (ν, cm^{-1}) (solid) 3303 (OH), 767 and 706 (Ph); ^1H NMR (400 MHz; DMSO-d_6) 0.99 (6H, d, *J* 6.5), 2.01−2.08 (4H, m), 2.56−2.62 (4H, m), 3.08 (4H, br s), 4.58 (2H, d, *J* 8.8), 5.84 (6H, d, *J* 5.3), 6.05 (4H, t, *J* 5.3), 6.40 (2H, br s,), 7.32−7.50 (10H, m), 8.55 (2H, br s), 8.55 (2H, br s); ^{13}C NMR (100.6 MHz; DMSO-d_6) 12.5 (2 × q), 24.9 (2 × t), 29.5 (2 × t), 43.0 (2 × t), 58.0 (2 × d), 73.4 (2 × d), 83.6 (2 × d), 85.2 (2 × (2 × d)), 88.7 (2 × (2 × d)), 106.1 (2 × s), 127.2 (2 × (2 × d)), 128.1 (2 × d), 128.4 (2 × (2 × d)), 141.3 (2 × s). HRMS found (LSIMS): 405.0516 (monomeric species formed in-situ). $^{101}RuC_{18}H_{23}NOCl$ requires 405.0524 (2.1 ppm error). MS *m/z* (LSIMS) 406 (monomer$^+$, 10%), 270 (100).

Preparation of 3-(4-Methyl-cyclohexa-1,4-dienyl)-propionic Acid 22.[15] To a stirred solution of 3-(4-*iso*propylphenyl)propionic acid (3 g, 17.68 mmol) in NH_3 at −78 °C was added ^{t}BuOH over a period of 30 min. Lithium was added in small portions until the deep blue color of solution persisted. The reaction mixture was stirred for a further 6 h at this temperature and then left to stir at room temperature overnight for the excess NH_3 to evaporate. EtOAc (30 mL) was added, and the mixture was acidified with 6 M HCl. This was followed by an extraction with EtOAc (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was obtained as a pale beige solid (2.24 g, 76%) and after NMR confirmation was used in the next step without further purification; mp 100−103 °C; ^1H NMR (400 MHz; MeOD) 5.50−5.49 (1H, m), 5.44−5.42 (1H, m), 2.64−2.57 (4H), 2.47−2.43 (2H, m), 2.32−2.28 (2H, m), 1.69 (3H, s); ^{13}C NMR (100 MHz; MeOD) 177.7, 135.1, 132.4, 122.4, 119.8, 33.8, 33.5, 32.9, 31.2, 23.6.

Preparation of *N*-[(1*S*,2*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-2-phenyl-ethyl]-3-(4-methyl-cyclohexa-1,4-dienyl)-propionamide 23. A stirred solution of 3-(4-methyl-cyclohexa-1,4-dienyl)-propionic acid, 22 (1.00 g, 6.02 mmol, 1.0 equiv), (1*R*,2*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-2-phenyl-ethylamine (2.40 g, 9.02 mmol, 1.5 equiv),[7i] and HOBt (1.22 g, 9.02 mmol, 1.5 equiv) in dry THF (35 mL) was stirred for 30 min. After this time, EDCI (1.73 g, 9.02 mmol, 1.5 equiv) and DIPEA (5.10 mL, 30.08 mmol, 5.0 equiv) were added. Stirring was continued for a further 18 h at room temperature, and solvent was evaporated in vacuo. After purification by flash column chromatography, the product 23 was isolated as a colorless oil (1.74 g, 70%). $[\alpha]^{24}_D$ −34.0 (*c* 1.00, $CHCl_3$); IR (ν, cm^{-1}) 3290, 2927, 2855, 1636, 1541, 1471, 1251, 1088, 833, 775, 699; ^1H NMR (300 MHz; $CDCl_3$; $Si(CH_3)_4$) 7.36−7.20 (5H, m), 5.61 (1H, d, *J* = 8.7 Hz), 5.47 (1H, brs), 5.41−5.40 (1H, m), 4.88 (1H, d, *J* = 2.4 Hz), 4.19−4.08 (1H, m), 2.64 (4H, m), 2.34−2.27 (4H, m), 1.67 (3H, s), 0.95 (9H, s), 0.91 (3H, d, *J* = 6.8 Hz), 0.03 (3H, s), −0.15 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$; $Si(CH_3)_4$) 172.0, 142.2, 134.0, 131.6, 128.4, 127.6, 126.5, 119.6, 118.7, 76.5, 51.6, 35.5, 33.1, 32.0, 30.3, 26.3, 23.4, 18.6, 13.5, −4.3, −4.8; MS *m/z* (EI) 413 (M^+, 4%), 356 (43), 289 (12), 221 (100), 192 (15), 134 (21), 118 (31), 73 (61); HRMS found: M^+, 413.2750. $C_{25}H_{39}NO_2Si$ requires 413.2750.

Preparation of (1*R*,2*S*)-2-[3-(4-Methyl-cyclohexa-1,4-dienyl)-propylamino]-1-phenyl-propan-1-ol 24. To a solution of $LiAlH_4$ (550 mg, 14.50 mmol, 4.0 equiv) in dry THF (5 mL) was added *N*-[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-2-phenyl-ethyl]-3-(4-methyl-cyclohexa-1,4-dienyl)-propionamide **23** (1.5 g, 3.63 mmol, 1.0 equiv) in dry THF (10 mL). The reaction mixture was refluxed for 18 h and cooled to room temperature. The mixture was quenched with H_2O (3 mL) and 15% NaOH (3 mL), filtered through a plug of Celite, and evaporated in vacuo. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by recrystallization (EtOAc/hexane) afforded the product **24** as white crystals (549 mg, 53%); mp 63−65 °C; $[\alpha]^{24}_D$ −4.7 (*c* 1.00, $CHCl_3$); IR (ν, cm^{-1}) 3292, 3055, 2849, 2813, 1448, 1427, 1368, 1131, 985, 901, 769, 695; ^1H NMR (300 MHz; $CDCl_3$; $Si(CH_3)_4$) 7.25−7.22 (5H), 5.43−5.42 (2H, m), 4.72 (1H, d, *J* = 4.0 Hz), 2.94−2.86 (1H, m), 2.76−2.63 (2H, m), 2.59 (4H, s), 2.06−2.01 (2H, m), 1.68 (3H, s), 1.64−1.57 (2H, m), 0.80 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$; $Si(CH_3)_4$) 141.9, 134.8, 131.7, 128.4, 127.4, 126.5, 119.1, 118.9, 73.4, 58.8, 47.3, 35.2, 32.0, 30.3, 28.5, 23.4, 15.3; MS *m/z* (FAB) 286 ($M + H^+$, 100%), 178 (65), 154 (31); HRMS found: $M + H^+$, 286.2164. $C_{19}H_{28}NO$ requires 286.2171.

[1*R*,2*S*)-2-[3-(4-Methyl-cyclohexa-1,4-dienyl)-propylamino]-1-phenyl-propan-1-ol-$RuCl_2$]$_2$ 25.[7d] To a stirred solution of (1*R*,2*S*)-2-[3-(4-methyl-cyclohexa-1,4-dienyl)-propylamino]-1-phenyl-propan-1-ol **24** (150 mg, 5.26 mol, 1.2 equiv) in dry DCM (5 mL) was added 2 M HCl/Et_2O (0.66 mL, 13.1 mol, 3.0 equiv) dropwise. The reaction mixture was stirred at room temperature for 5 min and concentrated in vacuo. EtOH (10 mL) was added followed by hydrate ruthenium(III) trichloride (91 mg, 4.38 mol, 1.0 equiv), and the reaction mixture was refluxed for 18 h. The solution was evaporated, and after washing with DCM (3 × 5 mL), the product **25** was obtained as a dark green solid (121 mg, 55%); mp >300 °C (decomposition); $[\alpha]^{24}_D$ −27.4 (*c* 0.80, DMSO); IR (ν, cm^{-1}) 2357, 2340, 2011, 1587, 1400, 1311, 1042, 980, 754, 672 (weak sample); ^1H NMR (300 MHz; DMSO) 7.40−7.38 (5H, m), 7.30 (1H, brs), 6.13 (1H, d, *J* = 3.9 Hz), 5.88−5.83 (4H, m), 5.12 (1H, brs), 3.45−3.29 (1H, m), 3.10 (2H, brs), 2.51−2.49 (2H, m), 2.11 (3H, s), 2.02−1.98 (2H, m), 0.92 (3H, d, *J* = 6.4 Hz). ^{13}C NMR (100 MHz; DMSO) 141.1, 128.2, 127.4, 126.0, 100.3, 99.8, 88.1, 87.0, 69.5, 58.2, 44.4, 28.9, 25.4, 18.2, 9.5; MS *m/z* (FAB) 420 ($M - H^+$, 19%), 382 (5), 340 (1), 307 (31), 284 (14), 219 (9), 154 (100), 139 (11); HRMS found: $M - H^+$, 420.0680. $C_{19}H_{25}NOClRu$ requires 420.0668, that is, ruthenium monomer formed spontaneously. Note: The ^1H NMR spectrum was partially masked by DMSO and H_2O peaks.

Synthesis of (*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethylamine 29.[16] To a stirred solution of *R*-phenyl glycinol (2.500 g, 18.2 mmol), triethylamine (3.680 g, 36.5 mmol), and 4-(dimethylamino)pyridine (0.446 g, 3.7 mmol) in dichloromethane (25 cm^3) was added a solution of *tert*-butyl-chloro-dimethyl-silane (2.746 g, 18.2 mmol) in dichloromethane (15 cm^3). The reaction mixture was stirred overnight, diluted with water (50 cm^3), and extracted with dichloromethane (2 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered,

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and concentrated under vacuum to give the crude product. The residue was purified by flash chromatography (2% MeOH/DCM) to give **29** (3.510 g, 77%) as a colorless oil; $[\alpha]^{23}_D$ −26.5 (*c* 1.15 in $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) −0.08 (6H, s), 0.83 (9H, s), 1.64 (2H, br s), 3.43 (1H, dd, *J* 9.8 and 8.3), 3.64 (1H, dd, *J* 9.8 and 4.0), 3.99 (1H, dd, *J* 8.3 and 4.0), 7.16−7.28 (5 H, m); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) −5.0 (2 × q), 18.7 (s), 26.3 (3 × q), 58.0 (d), 70.0 (t), 127.3 (2 × d), 127.7 (d), 128.7 (2 × d), 143.1 (q).

Synthesis of 2-Cyclohexa-1,4-dienyl-ethanesulfonic Acid [(*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethyl]-amide 31. To a solution of **29** (2.515 g, 10.0 mmol) and triethylamine (2.020 g, 20.0 mmol) in dichloromethane (25 cm^3) was added a solution of **30**[7d] (2.067 g, 10.0 mmol) in dichloromethane (25 cm^3). The reactants were stirred overnight, diluted with water (40 cm^3), and extracted with dichloromethane (2 × 50 cm^3). The combined extracts were washed with water (50 cm^3), dried ($MgSO_4$), filtered, and concentrated under vacuum to give the crude product. The residue was purified by flash chromatography (5% EtOAc/hexane to 15% EtOAc/hexane) to give **31** (3.532 g, 84%) as a white solid; mp 60−61 °C; $[\alpha]^{23}_D$ −16.1 (*c* 1.6 in $CHCl_3$); IR (ν, cm^{-1}) (solid) 3254 (NH), 1321 and 1119 (SO_2N), 755 and 699 (Ph); ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) −0.11 (6H, s), 0.76 (9H, s), 2.22 (2H, t, *J* 8.0), 2.26−2.30 (2H, m), 2.50−2.54 (2H, m), 2.62−2.76 (2H, m), 3.61 (1H, dd, *J* 10.2 and 6.3), 3.78 (1H, dd, *J* 10.2 and 4.2), 4.47 (1H, ddd, *J* 6.3, 5.3 and 4.2), 5.01 (1H, d, *J* 5.3), 5.20 (1H, m), 5.54 (2H, m), 7.21−7.27 (5H, m); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) −5.2 (2 × q), 18.7 (s), 26.2 (3 × q), 27.0 (t), 29.1 (t), 31.4 (t), 52.5 (t), 59.5 (d), 67.3 (t), 120.9 (d), 124.1 (d), 124.4 (d), 127.8 (2 × d), 128.6 (d), 129.0 (2 × d), 131.5 (s), 139.2 (s). HRMS found (LSIMS): 422.2185 $[MH]^+$. $C_{22}H_{36}NO_3SSi$ requires 422.2185 (0.2 ppm error). MS *m/z* (LSIMS): 422 (MH^+, 20%), 364 (20), 235 (100), 154 (10), 138 (10).

Synthesis of 2-Cyclohexa-1,4-dienyl-ethanesulfonic Acid ((*R*)-2-Hydroxy-1-phenyl-ethyl)-amide 32. To a solution of **31** (3.450 g, 8.20 mmol) in THF (20 cm^3) at 0 °C was added a 1 M solution of tetrabutylammonium fluoride in THF (9.8 cm^3, 9.80 mmol). The reactants were stirred overnight, diluted with water (20 cm^3), and extracted with dichloromethane (3 × 40 cm^3). The combined extracts were washed with water (50 cm^3), dried ($MgSO_4$), filtered, and concentrated under vacuum to give the crude product. The residue was purified by flash chromatography (1% MeOH/DCM to 5% MeOH/DCM) to give **32** (2.185 g, 87%) as a white solid (Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.5; H, 6.9, N, 4.55. Found: C, 62.2; H, 6.9; N, 4.5); mp 66.5−68.0 °C; $[\alpha]^{23}_D$ −26.3 (*c* 1.40 in $CHCl_3$); IR (ν, cm^{-1}) (solid) 3526 (OH), 3322 (NH), 1306 and 1125 (SO_2N), 752 and 703 (Ph); ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) 2.15−2.26 (4H, m), 2.48−2.52 (2H, m), 2.70−2.85 (2H, m), 2.91−2.94 (1H, m), 3.65−3.75 (2H, m), 4.50−4.54 (1H, m), 5.17 (1H, m), 5.26 (2H, m), 5.72 (1H, d, *J* 7.5), 7.17−7.35 (5H, m); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) 27.0 (t), 28.9 (t), 31.4 (t), 52.5 (t), 60.2 (d), 66.7 (t), 121.1 (d), 124.1 (d), 124.4 (d), 127.4 (2 × d), 128.7 (d), 129.4 (2 × d), 131.4 (s), 138.8 (s). HRMS found (LSIMS): 308.1330 $[MH]^+$. $C_{16}H_{22}NO_3S$ requires 308.1320 (3.1 ppm error). MS *m/z* (LSIMS): 308 (MH^+, 15%), 242 (40), 188 (35), 121 (50), 107 (100).

Synthesis of 2-Cyclohexa-1,4-dienyl-ethanesulfonic Acid ((*S*)-2-Azido-2-phenyl-ethyl)-amide 33 and 2-Cyclohexa-1,4-dienyl-ethanesulfonic Acid ((*R*)-2-Azido-1-phenyl-ethyl)-amide 34. To a solution of 32 (1.884 g, 6.10 mmol) and triethylamine (0.929 g, 9.20 mmol) in dichloromethane (30 cm^3) was added a solution of methane sulfonyl chloride (1.055 g, 9.20 mmol) in dichloromethane (12 cm^3). The reactants were stirred overnight, diluted with water (50 cm^3), and extracted with dichloromethane (2 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum to give a thick pale yellow oil, which was dissolved in DMF (30 cm^3). Sodium azide (1.098 g, 16.89 mmol) was added, and the reaction mixture was heated at 80 °C for 2 h. The reaction mixture was cooled to room temperature and stirred overnight, diluted with water (50 cm^3), and extracted with diethyl ether (4 × 50 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried ($MgSO_4$), filtered, and concentrated under vacuum using a 50:50 MeOH:heptane azeotrope to remove the DMF to give an inseparable mixture of 33 and 34 (1.637 g, 81%) as a yellow oil; IR (ν, cm^{-1}) (thin film) 3281 (NH), 2100 (N_3), 1319 and 1145 (SO_2), 759 and 710 (Ph); ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) 2.26−3.41 (8H, m), 3.48 (major isomer, 1H, br s), 3.59−3.69 (minor isomer, 2H, m), 4.64−4.65 (minor isomer, 1H, m), 4.71−4.77 (major isomer, 2H, m), 5.30 (minor isomer, 1H, m), 5.38 (minor isomer, 1H, d, *J* 7.8), 5.49 (major isomer, 1H, m), 5.64 (minor isomer, 2H, m), 5.70 (major isomer, 2H, m), 7.20−7.44 (5H, m); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) 27.0 (minor isomer, t), 27.1 (major isomer, t), 29.0 (minor isomer, t), 29.2 (major isomer, t), 31.5 (minor isomer, t), 31.6 (major isomer, t), 48.6 (major isomer, t), 51.8 (major isomer, t), 52.6 (minor isomer, t), 56.8 (minor isomer, t), 57.5 (minor isomer, t), 66.5 (major isomer, d), 121.2 (minor isomer, d), 121.4 (major isomer, d), 124.0 (overlapping major isomer, d and minor isomer, d) 124.5 (minor isomer, d), 124.6 (major isomer, d), 127.2 (minor isomer, 2 × d), 127.5 (major isomer, 2 × d), 129.2 (major isomer, d), 129.3 (minor isomer, d), 129.5 (minor isomer, 2 × d), 129.6 (major isomer, 2 × d), 131.4 (minor isomer, s), 131.5 (major isomer, s), 136.6 (major isomer, s), 136.8 (minor isomer, s). HRMS found (LSIMS): 333.1393 $[MH]^+$, $C_{16}H_{21}N_4O_2S$ requires 333.1385 (2.3 ppm error). MS *m/z* (EI) 290 ($[M - N_3]^+$, 15%), 198 (25), 134 (25), 118 (25), 106 (100), 91 (60), 77 (50).

Synthesis of 2-Cyclohexa-1,4-dienyl-ethanesulfonic Acid ((*S*)-2-Amino-2-phenyl-ethyl)-amide 35 and 2-Cyclohexa-1,4-dienyl-ethanesulfonic Acid ((*R*)-2-Amino-1-phenyl-ethyl)-amide 36. To a suspension of lithium aluminum hydride (0.178 g, 4.68 mmol) in THF (15 cm^3) was cautiously added a solution of 33 and 34 (1.557 g, 4.68 mmol) in THF (45 cm^3). The reactants were heated at reflux, cooled, and stirred overnight. The reaction was quenched with water (3 cm^3), filtered (Celite-washed with 50% MeOH/DCM), and concentrated under vacuum to give the crude product. The residue was purified by flash chromatography (1% MeOH/DCM to 8% MeOH/DCM) giving first 35 (0.672 g, 63% with respect to the amount of starting material containing appropriate azide regioisomer) as a white solid (Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.7; H, 7.25; N, 9.15%. Found: C, 62.95; H, 7.25; N, 8.85); mp 101−103 °C; $[\alpha]^{20}_D$ +23.0 (*c* 0.95 in $CHCl_3$); IR (ν, cm^{-1}) (solid) 3357 and 3289 (NH_2), 1307 and 1128 (SO_2N), 759 and 698 (Ph); ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) 2.39 (2H, m), 2.54−2.58 (2H, m), 2.65−2.69 (2H, m), 3.03−3.08 (2H, m), 3.16 (1H, dd, *J* 12.9 and 8.0), 3.32 (1H, dd, *J* 12.9 and 5.0), 4.08 (1H, dd, *J* 8.0 and 5.0), 5.46 (1H, m), 5.70 (2H, m), 7.29−7.37 (5H, m); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) 27.1 (t), 29.2 (t), 31.6 (t), 50.8 (t), 51.2 (t), 56.1 (d), 121.1 (d), 124.0 (d), 124.6 (d), 126.7 (2 × d), 128.2 (d), 129.2 (2 × d), 131.7 (s), 143.1 (s). HRMS found (LSIMS): 307.1467 $[MH]^+$. $C_{16}H_{23}N_2O_2S$ requires 307.1480 (4.4 ppm error). MS *m/z* 307 (MH^+, 100%), 305 (30).

Further elution gave **36** (0.238 g, 67% with respect to the amount of starting material containing appropriate azide regioisomer) as a white solid; mp 108−109 °C; $[\alpha]_D$ −18.9 (*c* 1.55 in $CHCl_3$); IR (ν, cm^{-1}) (solid) 3364 and 3295 (NH_2), 1295 and 1124 (SO_2N), 740 and 698 (Ph); δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.24−2.36 (4H, m), 2.58−2.61 (2H, m), 2.69−2.89 (2H, m), 2.96 (1H, dd, *J* 12.9 and 7.3), 3.05 (1H, dd, *J* 12.9 and 5.3), 4.45 (1H, dd, *J* 7.3 and 5.3), 5.30 (1H, m), 5.63 (2H, m), 7.29−7.36 (5H, m); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) 27.0 (t), 29.0 (t), 31.5 (t), 48.2 (t), 52.5 (t), 59.9 (d), 121.0 (d), 124.1 (d), 124.4 (d), 127.3 (2 × d), 128.5 (d), 129.4 (2 × d), 131.5 (s), 140.2 (s). HRMS found (LSIMS): 307.1479 $[MH]^+$. $C_{16}H_{23}N_2O_2S$ requires 307.1480 (0.5 ppm error). MS *m/z* (LSIMS) 307 (MH^+, 40%), 147 (5), 132 (15), 120 (100).

Synthesis of (*S*)-1-Phenyl-2-(2-phenyl-ethanesulfonyl-amino)-ethylammonium Chloride Ruthenium Dimer 37.

To a solution of **35** (0.400 g, 1.31 mmol) in dichloromethane (20 cm^3) was added a 1 M solution of HCl in diethyl ether (6.5 cm^3, 6.50 mmol), and the reactants were stirred for 20 min. The solvent was removed under vacuum, and the resulting hydrochloric acid salt of **35** (0.453 g, 1.31 mmol) was dissolved in ethanol (12 cm^3) and ruthenium trichloride trihydrate (0.173 g, 0.66 mmol) was added. The reactants were heated at reflux overnight and then cooled to 0 °C. The precipitate was collected by filtration and washed with ethanol (5 × 10 cm^3) to give **37** (0.198 g, 58%) as a dark green solid; mp 261 °C (dec); IR (ν, cm^{-1}) (solid) 3484 (NH), 1594 and 1496 (NH_3^+), 1321 and 1135 (SO_2N), 763 and 700 (Ph); ^1H NMR (400 MHz; DMSO-d_6) 2.84 (4H, t, *J* 7.5), 3.42−3.48 (8H, m), 4.33 (2H, br s), 5.83 (2H, t, *J* 5.5), 5.89 (4H, dd, *J* 5.8 and 5.5), 6.04 (4H, t, *J* 5.8), 7.42−7.53 (10H, m), 7.66 (2H, t, *J* 6.0), 8.48 (6H, br s); ^{13}C NMR (100.6 MHz; DMSO-d_6) 27.2 (2 × t), 46.4 (2 × t), 49.9 (2 × t), 54.8 (2 × d), 84.8 (2 × d), 86.8 (2 × (2 × d)), 88.5 (2 × (2 × d)), 103.3 (2 × s), 128.3 (2 × (2 × d)), 128.9 (2 × d), 129.2 (2 × (2 × d)), 135.8 (2 × s). HRMS found (LSIMS): 440.9990 (monomeric species formed in-situ). $^{102}RuC_{16}H_{20}N_2O_2SCl$ requires 440.9978 (2.9 ppm error). MS *m/z* (LSIMS) 441 (monomer$^+$, 70%), 405 (M − HCl$^+$, 70), 232 (100).

Synthesis of (*R*)-2-Phenyl-2-(2-phenyl-ethanesulfonylamino)-ethylammonium Chloride Ruthenium Dimer 38. To a solution of **36** (0.224 g, 0.73 mmol) in dichloromethane (10 cm^3) was added a 1 M solution of HCl in diethyl ether (3.7 cm^3, 3.70 mmol), and the reactants were stirred for 20 min. The solvent was removed from the resulting precipitate under vacuum, and the resulting hydrochloric acid salt of **36** (0.250 g, 0.73 mmol) was dissolved in ethanol (12 cm^3) and ruthenium trichloride trihydrate (0.095 g, 0.37 mmol) was added. The reactants were heated at reflux overnight and then cooled to 0 °C. The precipitate was collected by filtration and washed with ethanol (5 × 10 cm^3) to give **38** (0.138 g, 72%) as a dark green solid; mp 261 °C (dec); IR (ν, cm^{-1}) (solid) 3484 (NH), 1587 and 1495 (NH_3^+), 1320 and 1130 (SO_2N), 759 and 702 (Ph); ^1H NMR (400 MHz; DMSO-d_6) 2.60−2.92 (8H, m), 3.06−3.16 (4H, m) 4.60 (2H, m), 5.52 (2H, d, *J* 5.8), 5.74 (2H, d, *J* 6.0), 5.80 (2H, t, *J* 5.5), 5.99 (4H, m), 7.39−7.51 (10H, m), 7.99 (6H, m), 8.25 (2H, d, *J* 9.3); ^{13}C NMR (100.6 MHz; DMSO-d_6) 27.3 (2 × t), 44.4 (2 × t), 52.0 (2 × t), 55.9 (2 × d), 84.9 (2 × d), 86.7 (2 × (2 × d)), 88.5 (2 × (2 × d)), 103.1 (2 × s), 127.6 (2 × (2 × d)), 128.8 (2 × d), 129.4 (2 × (2 × d)), 139.2 (2 × s). HRMS found (LSIMS): 440.9982 (monomeric species formed in-situ). $^{102}RuC_{16}H_{20}N_2O_2SCl$ requires 440.9978 (0.9 ppm error). MS *m/z* (LSIMS) 441 (monomer$^+$, 100%), 405 (M − HCl$^+$, 75).

Synthesis of 2-Cyclohexa-1,4-dienyl-ethanesulfonic Acid ((1*S*,2*R*)-2-Hydroxy-1,2-diphenyl-ethyl)-amide 40. To a stirred solution of 1*R*,2*S*-2-aminodiphenylethanol **39** (1.03 g, 4.84 mmol) and triethylamine (0.73 g, 7.26 mmol) in dichloromethane (14 cm^3) was added **30**[7] (1.00 g, 4.84 mmol). The reaction mixture was stirred overnight and concentrated under vacuum to give the crude product. The residue was suspended in water (10 cm^3), filtered, and washed with water (5 cm^3) and then recrystallized to give **40** (1.24 g, 67%) as a white solid; mp 146−147 °C (ethanol); $[\alpha]^{24}_D$ −18.5 (*c* 0.55 in DMSO); IR (ν, cm^{-1}) (solid) 3412 (NH), 3186 (OH), 1350 and 1131 (SO_2N), 757 and 697 (Ph); ^1H NMR (400 MHz; DMSO-d_6) 1.93 (2H, t, *J* 8.0), 2.23 (2H, t, *J* 8.5), 2.29−2.54 (4H, m), 4.36 (1H, dd, *J* 9.0 and 6.2), 4.74 (1H, dd, *J* 6.2 and 4.8), 5.10 (1H, m), 5.46 (1H, d, *J* 4.8), 5.61 (2H, m), 7.21−7.36 (10H, m), 7.76 (1H, d, *J* 9.0); ^{13}C NMR (100.6 MHz; DMSO-d_6) 26.1 (t), 28.0 (t), 30.3 (t), 50.8 (t), 63.2 (d), 75.5 (d), 119.2 (d), 123.8 (d), 126.9 (d), 127.1 (2 × d), 127.6 (2 × overlapping (2 × d)), 128.2 (2 × d), 131.4 (s), 140.6 (s), 143.2 (s) (NB, not all aromatic CH signals observed). HRMS found (LSIMS): 384.1614 [MH]$^+$. $C_{22}H_{26}NO_3S$ requires 384.1633 (5.0 ppm error). MS *m/z* (LSIMS) 384 (MH$^+$, 20%), 366 (100), 276 (35), 197 (75), 180 (140).

Synthesis of Methanesulfonic Acid (1*R*,2*S*)-2-(2-Cyclohexa-1,4-dienyl-ethanesulfonylamino)-1,2-diphenyl-ethyl Ester 41. To a stirred solution of **40** (0.800 g, 2.09 mmol) and triethylamine (0.316 g, 3.13 mmol) in dichloromethane (10 cm^3) was added a solution of methane sulfonyl chloride (0.359 g, 3.13 mmol). The reaction mixture was stirred overnight, diluted with water, separated, and concentrated under vacuum to give the crude product. The residue was then recrystallized to give **41** (0.889 g, 92%) as white crystals; mp 113 °C (ethanol); $[\alpha]^{24}_D$ −37.6 (*c* 1.55 in $CHCl_3$); IR (ν, cm^{-1}) (solid) 3274 (NH), 3186 (OH), 1350 and 1176 (SO_2N), 744 and 698 (Ph); ^1H NMR (400 MHz; $CDCl_3$; Me_4Si) 2.22−2.28 (2H, m), 2.35 (2H, t, *J* 8.0), 2.58−2.62 (2H, m), 2.69−2.85 (2H, m), 2.73 (3H, s), 4.92 (1H, dd, *J* 8.3 and 4.8), 5.02 (1H, d, *J* 8.3), 5.26 (1H, m), 5.63 (2H, m), 5.87 (1H, d, *J* 4.8), 7.08−7.34 (10H, m); ^{13}C NMR (100.6 MHz; $CDCl_3$; Me_4Si) 27.0 (t), 28.9 (t), 31.3 (t), 39.3 (q), 52.7 (t), 62.1 (d), 85.3 (d), 121.0 (d), 124.0 (d), 124.4 (d), 127.3 (2 × d), 128.0 (2 × d), 128.8 (overlapping d, 2 × d and 2 × d), 129.6 (d), 131.3 (s), 134.7 (s), 136.3 (s). HRMS found (LSIMS): 366.1510 [MH − CH_3SO_3H]$^+$. $C_{22}H_{24}NO_2S$ requires 366.1528 (5.0 ppm error). MS *m/z* (LSIMS) 460 (M − H$^+$, 20%), 366 (100), 274 (80), 196 (20), 180 (90).

Synthesis of 2-Cyclohexa-1,4-dienyl-ethanesulfonic Acid ((1*S*,2*R*)-2-Amino-1,2-diphenyl-ethyl)-amide 42. To a stirred solution of **41** (0.740 g, 1.61 mmol) in DMF (10 cm^3) was added sodium azide (0.313 g, 4.82 mmol). The reaction mixture was stirred at 105 °C for 3 h, cooled to room temperature, diluted with water (20 cm^3), and extracted with diethyl ether (3 × 30 cm^3). The combined extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum to give a pale yellow oil (0.500 g, 1.18 mmol), which was dissolved in THF (10 cm^3) and added to a suspension of lithium aluminum hydride (0.045 g, 1.18 mmol) in THF (5 cm^3). The reaction mixture was stirred overnight at room temperature, refluxed for 2 h, cooled, quenched with water (0.5 cm^3), filtered (Celite), and concentrated under vacuum to give **42** (0.372 g, 60% over two steps) as a white solid; mp 138−140 °C; $[\alpha]^{24}_D$ −24.5 (*c* 2.45 in $CHCl_3$); IR (ν, cm^{-1}) (solid) 3364 (NH), 1578 (NH_2), 1310 and 1147 (SO_2N), 756 and 696 (Ph); ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) 2.10 (2H, t, *J* 8.1), 2.20 (2H, t, *J* 7.9), 2.43−2.75 (4H, m), 3.57 (1H, br s), 4.21 (1H, d, *J* 5.8), 4.59 (1H, d, *J* 5.8), 5.11 (1H, m), 5.54 (2H, m), 6.98−7.20 (10H, m); ^{13}C NMR (75.5 MHz; $CDCl_3$; Me_4Si) 25.6 (t), 27.5 (t), 29.9 (t), 50.9 (t), 59.6 (d), 62.0 (d), 119.4 (d), 122.6 (d), 123.0 (d), 126.1 (2 × d), 126.7 (2 × d), 126.9 (d), 127.1 (d), 127.4 (2 × overlapping (2 × d)), 130.0 (s), 136.8 (s), 140.2 (s). HRMS found (LSIMS): 383.1787 [MH]$^+$. $C_{22}H_{27}N_2O_2S$ requires 383.1793 (1.7 ppm error). MS *m/z* (LSIMS) 383 (MH$^+$, 100%), 312 (25),196 (50).

Synthesis of 2-Phenyl-ethanesulfonic Acid ((1*S*,2*R*)-2-Amino-1,2-diphenyl-ethyl)-ammonium Chloride Ruthenium Dimer 43. To a stirred solution of **42** (0.300 g, 0.75 mmol) in dichloromethane (10 cm^3) was added a 1 M solution of HCl in diethyl ether (3.80 cm^3, 3.80 mmol), and the reactants were stirred for 20 min. The solvent was removed from the resulting precipitate under vacuum, and the resulting hydrochloric acid salt of **42** (0.326 g, 0.75 mmol) was dissolved in ethanol (9 cm^3) and ruthenium trichloride trihydrate (0.131 g, 0.50 mmol) was added. The reaction mixture was heated at reflux overnight and then cooled to 0 °C. The precipitate was collected by filtration and washed with ethanol (5 × 10 cm^3) to give **43** (0.196 g, 33%) as a dark green solid; mp 248 °C (dec); IR (ν, cm^{-1}) (solid) 3483 (NH), 1578 and 1496 (NH_3^+), 1321 and 1132 (SO_2N), 760 and 700 (Ph); ^1H NMR (250 MHz; DMSO-d_6) 3.20−3.50 (8H, m, peaks obscured by overlap with H_2O resonance), 4.49 (2H, m), 4.81 (2H, t, *J* 9.3), 5.33 (2H, d, *J* 5.5), 5.54 (2H, d, *J* 5.5), 5.75 (2H, t, *J* 4.9), 5.94 (4H, dd, *J* 5.5 and 4.9), 7.41−7.50 (20H, m), 8.23 (2H, d, *J* 9.3), 8.36 (6H, m); ^{13}C NMR (75.5 MHz; DMSO-d_6) 27.0 (2 × t), 51.6 (2 × t), 58.4 (2 × d), 60.5 (2 × d), 84.7 (2 × d), 86.3 (2 × (2 × d)), 88.4 (2 × (2 × d)), 103.0 (2 × s), 128.5 (2 × (2 × d)), 128.8 (2 × d), 128.9 (2 × (2 × d)), 129.0 (overlapping 2 × d and 2 × (2 × d)), 129.3 (2 × (2 × d)), 135.5 (2 × s), 138.2 (2 × s). HRMS found (LSIMS): 517.0284 (monomeric species formed in-situ). ^{102}-

$RuC_{22}H_{24}N_2O_2SCl$ requires 517.0291 (1.2 ppm error). MS *m/z* (LSIMS) 517 (monomer$^+$, 70%), 481 (M − HCl$^+$, 45), 381 (60).

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Supporting Information Available: General experimental details, ^1H and ^{13}C NMR of all new compounds lacking elemental analyses, and details of statistical experimental design treatment of the reduction of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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