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Further 'tethered' Ru(II) catalysts for asymmetric transfer hydrogenation (ATH) of ketones; the use of a benzylic linker and a cyclohexyldiamine ligand

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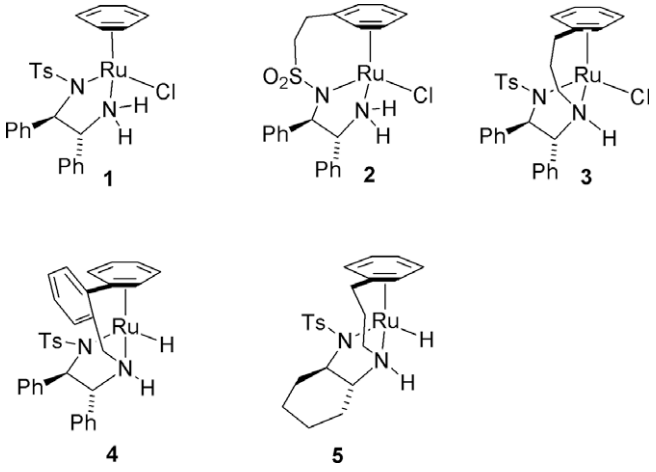
ABSTRACT

The synthesis and characterisation of two new Ru(II) catalysts for the asymmetric transfer hydrogenation (ATH) of ketones is described. In the case of **4**, the novelty lies in the use of a benzyl tethering group between the asymmetric ligand part (TsDPEN) and the η^6-arene ring, which increases the complex rigidity. For **5**, the use of a cyclohexyldiamine as a chiral ligand is described for the first time. In the ATH of ketones in formic acid/triethylamine, alcohols with ees of up to 97% were formed.

1. Introduction

Asymmetric transfer hydrogenation (ATH) of ketones using ruthenium(II) complexes has recently developed into an area of major international research [1–3]. This has largely been the result of initial breakthroughs by Noyori et al., who demonstrated that monotosylated diamine complexes of Ru(II), particularly **1**, form highly enantioselective catalysts for ketone reductions [2a–e]. Aromatic/alkyl ketones, in particular, are excellent substrates because their reduction takes place through a six-centre transition state in which an additional stabilising CH/π interaction favours the approach of one face of the ketone as shown in Fig. 1 [3]. In our recent studies in this area, we have reported the closely related catalysts **2** and **3**, in which the chiral ligand component is attached by a 'tethering' group to the η^6-arene ring located above the ruthenium atom [4]. These complexes also reduce ketones in high enantioselectivity and, in the case of **3**, exhibit significantly higher reactivities in this application.

During the development of this area of research, we wished to investigate the effect of changes to the chiral ligand part and the tethering group. In this paper we report the synthesis and applications of the catalyst containing a benzylic tether, i.e. **4**, in place of the aliphatic one, and of the complex **5**, in which the diphenyl-substituted diamine ligand is replaced with a homochiral *R,R*-1,2-diaminocyclohexane (*R,R*-DAC). 1,2-Diaminocyclohexane



derivatives have been reported to be effective ligands in this application when used in the untethered form [5].

2. Results and discussion

Both new catalysts, **4** and **5**, were prepared from the *R,R*-diamine starting material (Scheme 1 and 2, respectively) by a modification of the route developed for complex **3**. This involved the reductive amination of the appropriate monotosylated diamine

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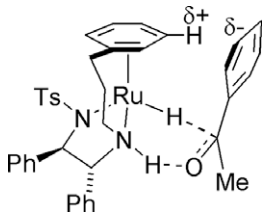
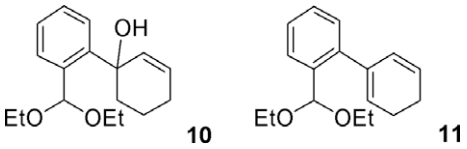
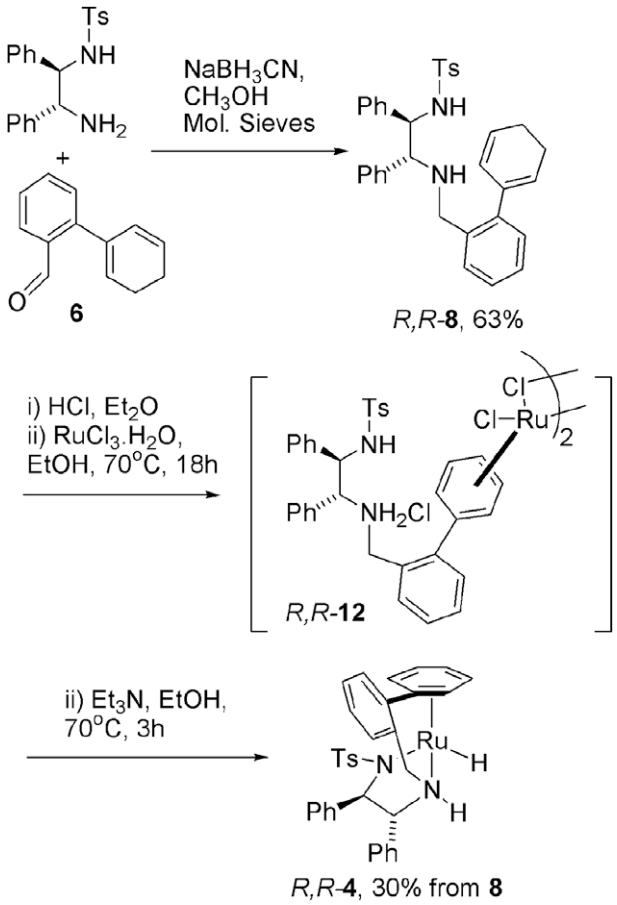


Fig. 1. Orientation of substrate in ATH by catalyst **3**.

(both are commercially available) with an aldehyde derivative of a 1,4-cyclohexadiene (i.e. **6** and **7**) to give **8** and **9** respectively. Aldehyde **7** is a known molecule [4b], but **8** was prepared by a novel process for this application. Starting from 2-bromobenzaldehyde diethyl acetal, treatment with ^{n}BuLi followed by cyclohexen-2-one provided alcohol **10** in 92% yield [6]. The hydroxyl elimination of **10** using 2,4-dinitrosulfenylchloride provided compound **11** in 46% yield [7]. Mild hydrolysis of **11** furnished **6** in 71% yield and reductive alkylation of *R,R-N*-tosyl,1,2-diphenyl-1,2-ethyldiamine (*R,R*-TsDPEN) using aldehyde **6** generated ligand **8** in 63% yield. Treatment of **8** with $RuCl_3 \cdot H_2O$ in ethanol at 70 °C provided dimer **12** [4b] which was not isolated but converted directly *in situ* to catalyst *R,R*-**4** by its treatment with triethylamine in ethanol at 70 °C for 3 h (overall 30% yield). Complexation of **9** with ruthenium trichloride hydrate furnished the dimer **13**, which was isolated in this form. Dimers such as **13** are known to be converted to the Ru(II) monomers *in situ,* under the reaction conditions employed for the ketone reductions by ATH [4].

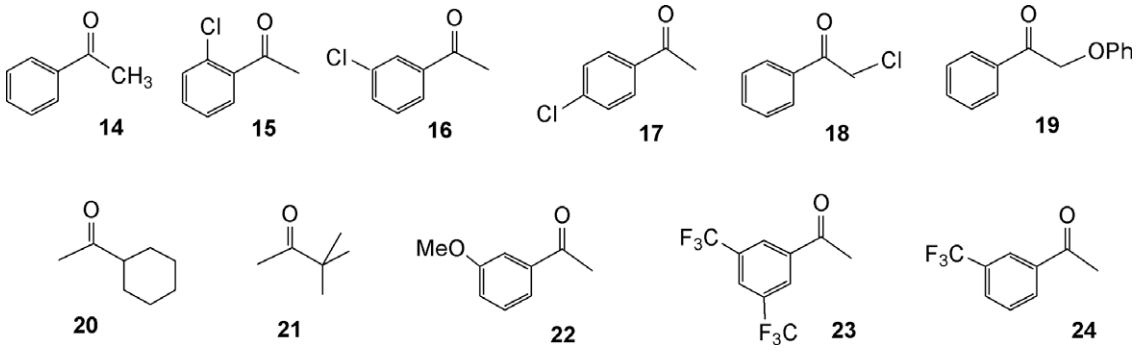




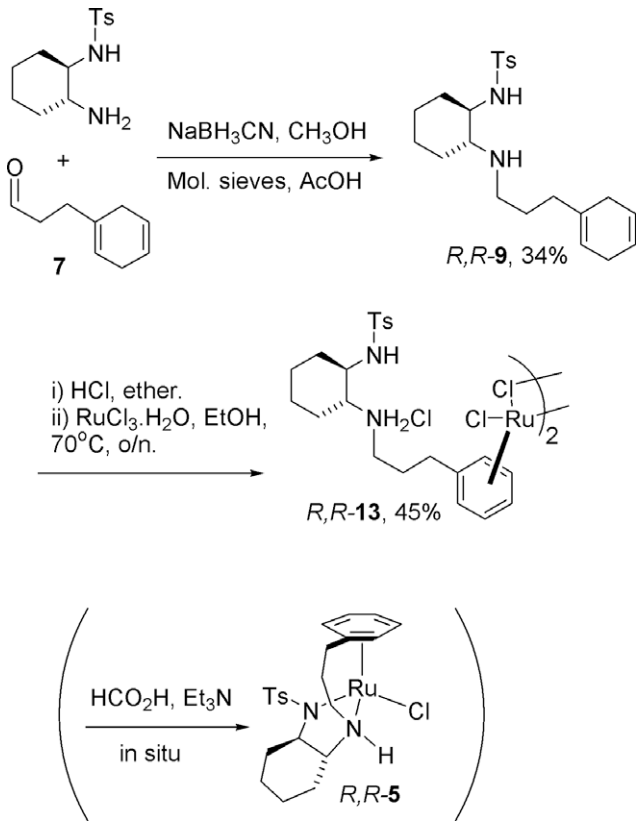
Scheme 1. Synthesis of catalyst *R,R*-**4**.

2.1. Applications to ketone reduction

A range of ketones (**14**–**24**, the orientation of the diagrams reflects the relative functional group positions in Table 1) were reduced to alcohols using catalysts **4** and **5** and formic acid/triethylamine as both the solvent and the source of hydrogen. Catalyst **4** demonstrated a slower rate of ATH in formic acid/triethylamine at 28 °C as compared to other tethered catalysts [4b], possibly due to its bulky tethered structure. However, acetophenone and a series of further ketones were fully reduced at slightly higher temperatures (ca. 40 °C). Substituted chloro-derivatives of acetophenone were more reactive, being fully converted to the alcohols at 28 °C with significant enantiomeric excesses (Table 1). In addition, two dialkylketones (**20** and **21**) were reduced with **4**, however the enantiomeric excesses were poor in both cases. The reversed enantioselectivities for these reductions, relative to acetophenone derivatives, suggest that (weaker) steric factors are directing the reaction, rather than electronic ones.

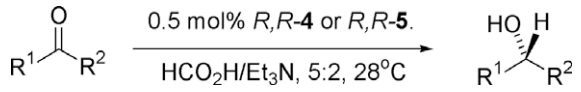


Using complex **5**, acetophenone **14** was fully reduced to 1-phenyl ethanol in 92% enantiomeric excess (ee) within 10–12 h at 28 °C (Table 1) whereas reduction of acetylcyclohexane **20** using 0.5 mol% of this catalyst gives a product of 59% ee (*S*). Again this reflects the lower level of transition state organization when an aryl ring is absent from the ketone substrate.



Scheme 2. Synthesis of catalyst *R,R*-**5**.

Table 1
Asymmetric ketone reduction using catalysts *R,R*-**4** and *R,R*-**5**[a]



Catalyst	Ketone	*T* (°C)	Time (h)	Conversion (%)	ee (%)[b]	*R/S*
4	**14**	28	66	43	97	*R*
4	**14**	40	24	100	95	*R*
4	**15**	28	16	100	69	*R*
4	**16**	28	24	97	88	*R*
4	**17**	40	24	100	89	*R*
4	**18**	28	24	100	92	*S*
4	**19**	28	24	92	93	*S*
4	**19**	40	5	99	91	*S*
4	**20**	40	24	100	51	*S*
4	**21**	40	24	97	33	*S*
5	**14**	28	12	100	92	*R*
5	**16**	28	24	100	86	*R*
5	**17**	28	24	100	86	*R*
5	**18**	28	24	100	83	*S*
5	**19**	28	24	100	85	*S*
5	**20**	28	24	100	59	*S*
5	**21**	28	24	25	26	*S*
5	**22**	28	24	95	88	*R*
5	**23**	28	24	100	51	*R*
5	**24**	28	18	100	83	*R*

[a] Reactions were carried out in a 2 M solution of ketone in a formic acid/triethylamine (5:2) azeotrope mixture, using catalyst loading = 0.5 mol%, S/C = 200 under N_2 atmosphere.
[b] Determined by GC or HPLC: GC; cyclodextrin-β-236M-19, 50 m, HPLC: Chiracel OD- 250 × 4.6 mm, mobile phase typically 90% hexane:10% IPA: 0.1% Et_2NH; flow rate: 0.7 mL/min.

In addition to several of the same acetophenone derivatives as were used with **4**, we examined ketone **23**, since its reduction product is an intermediate in the synthesis of the Merck drug aprepitant [8], and **24**, a building block of the agricultural fungicide MA-20565 [9]. Whilst both were fully converted to alcohols, **24** was reduced in good ee (but lower than that of similar ketones) ketone **23** was reduced in rather poor yield. Other substituted acetophenones gave higher enantioselectivities with full conversions. The reaction of acetophenone **14** using catalyst **5** was studied by ^1H NMR spectroscopy (Fig. 2). A graph of conversion versus reaction time demonstrated that acetophenone has completely converted to the product 1-phenylethanol (*R* > *S* enantiomer) in nearly 10 h. The highly linear nature of the graph suggests zero-order kinetics at the early stages of the reaction, i.e. the rate is relatively unsensitive to the concentration of ketone. This suggests that the rate-limiting step is the regeneration of the 'Ru–H' species in the catalytic cycle, rather than the rate of hydrogen transfer from the metal hydride to the substrate, as has been observed previously for this class of tethered catalyst [4c]. The initial slow rate is also observed when dimer precursors are employed as catalysts, and reflects the conversion of dimer to monomer prior to reduction, i.e. an induction period during catalyst formation [4d].

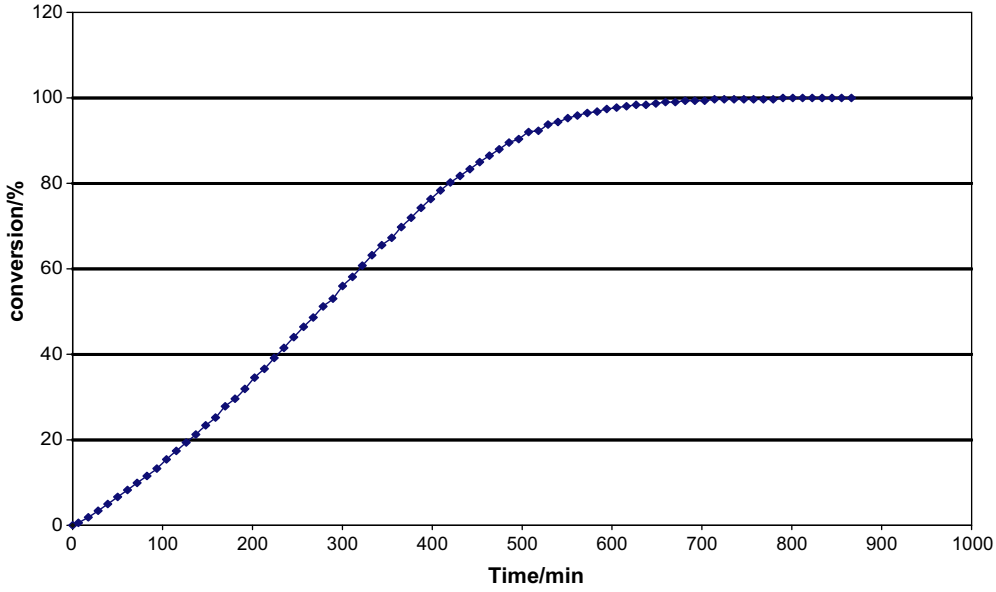


Fig. 2. Reaction/time profile for ATH of acetophenone by catalyst **5** followed by ^1H NMR spectroscopy.

In conclusion, two new organometallic catalysts have been prepared and have demonstrated good activity in ATH of ketones using formic acid/triethylamine as the solvent and hydrogen source. Although neither gave an improved performance relative to catalyst **3**, they both represent effective catalysts for the required application. The results for catalyst **5** suggest that cyclohexyldiamine may be considered a reasonable viable alternative to the more commonly employed trans-diphenyl (TsDPEN) system.

3. Experimental

3.1. General

General experimental conditions and instrumentation have been previously reported [4d].

3.2. Synthesis of 1-(2-diethoxymethyl-phenyl)-cyclohexen-2-ol (**10**) [6]

2-Bromobenzaldehyde diethyl acetal (5.0 g, 1.93 mmol) in THF was cooled to −78 °C and a solution of ^{n}BuLi in hexane (2.5 M, 8.40 mL, 0.021 mol) was added dropwise. After maintaining the reaction at this temperature for 1 h, a solution of cyclohexen-2-one (2.0 mL, 0.021 mol) was added dropwise. The reaction was allowed to warm to r.t. and stirred for further 3 h. The reaction was quenched by the addition of toluene (20 mL) and water (20 mL). The organic layer was separated and washed with saturated brine (20 mL) and then dried with anhydrous $MgSO_4$. The solvent was removed to give **10** (5.33 g, 1.78 mmol, 92%) as a light yellow oil. ν_{max}(neat)/cm^{-1}: 3428, 2973, 2930, 2868, 1706, 1444, 1371, 1271, 1055, 1004, 750, 735; ^{1}H NMR (300 MHz; $CDCl_3$): δ *7.80–7.22* (m, 4H), 6.20 (s, 1 H), 5.98 (m, 1 H), 5.83 (d, 1 H, J = 10.0 Hz, 1H), 3.75–3.46 (m, 4H, m), 3.33 (s, 1H), 2.15–1.92 (m, 4H), 1.83 (m, 1H), 1.56 (m, 1H), 1.24 (t, J = 7.0 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 144.0, 136.0, 133.0, 128.5, 127.4, 127.1, 126.9, 126.5, 99.1, 61.9, 61.6, 38.3, 24.2, 18.5, 14.6; HRMS (ESI) *m/z* ((M+Na)$^+$) Calc. for $C_{17}H_{24}NaO_3$; 299.1616. Found: 299.1611 (1.6 ppm error).

3.3. Synthesis of 1-cyclohexa-1,5-dienyl-2-diethoxymethyl-benzene (**11**) [7]

2,4-Dinitrosulfenylchloride was added to a cooled solution (0 °C) of alcohol **10** (2.5 g, 8.4 mmol) and triethylamine (2.9 mL, 36 mmol) in dichloromethane (40 mL). After 10 min, the reaction was allowed to warm to r.t. and was stirred overnight. After 18 h, pentane (20 mL) was added and the mixture was filtered and evaporated, providing 2.5 g of a black oil which was purified by silica gel column chromatography (0 → 2% v/v ethyl acetate/pentane) to afford **11** as a light yellow oil (1.09 g, 3.87 mmol, 46%). ν_{max}(neat)/cm^{-1}: 3035, 2973, 2929, 2869, 1708, 1675, 1594, 1529, 1444, 1341, 1052, 760, 693; ^{1}H NMR (300 MHz; $CDCl_3$): δ *7.68–7.12* (m, 4H), 6.06 (m, 1H), 5.88 (m, 2H), 5.55 (s, 1H), 3.63 (m, 2H), 3.46 (m, 2H), 2.45 (m, 2H), 2.32 (m, 2H), 1.21 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 142.6, 136.9, 136.0, 128.1, 128.0, 126.9, 125.4, 124.8, 123.7, 100.2, 62.0, 28.5, 23.1, 15.2; HRMS (ESI) *m/a* ((M+Na)$^+$) Calc. for $C_{17}H_{22}NaO_2$: 281.1509. Found: 281.1512 (1.0 ppm error).

3.4. Synthesis of 2-cyclohexa-1,5-dienyl-benzaldehyde (**6**)

Acetal **11** (1.0 g, 3.56 mmol) was dissolved in THF (20 mL), a 1% HCl solution (10 mL) was added and the reaction was stirred overnight at r.t. After 18 h, aq. $NaHCO_3$ (10 mL) was added and the organic phase was extracted with diethylether (3 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated, providing the crude product which was purified by silica gel column chromatography (0 → 1% v/v ethyl acetate/pentane) to afford **6** as a light yellow oil (0.47 g, 2.54 mmol, 71%). ν_{max}(neat)/cm^{-1}: 3030, 2931, 2825, 2742, 1686, 1649, 1594, 1254, 1223, 1192, 992, 826, 760, 726, 693; ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.17 (s, 1H), 7.94–7.10 (m, 4H), 6.08 (m, 1H), 5.95 (m, 1H), 5.84 (d, J = 5.7 Hz, 1H), 2.56 (m, 2H), 2.36 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 192.3, 146.9, 133.9, 133.8, 133.4, 128.4, 128.0, 127.9, 127.1, 124.6, 28.3, 22.9; HRMS (ESI) *m/z* ((M+H)$^+$) Calc. for $C_{13}H_{13}O$: 185.0963. Found: 185.0961 (1.0 ppm error).

3.5. Synthesis of N-[2-(2-cyclohexa-1,5-dienyl-benzylamino)-1R,2R-diphenyl-ethyl]-4-methyl-benzenesulfonamide (**8**) [6]

To a stirred solution of (1R,2R)-TsDPEN (0.55 g, 1.62 mol) and molecular sieves (1 g) in dry methanol (20 mL), was added aldehyde **6** (0.30 g, 1.62 mmol) followed by 3 drops of glacial acetic acid. The reaction was followed by TLC until the imine was formed (3 h) and then sodium cyanoborohydride (0.37 g, 5.8 mmol) was added and the reaction left to stir overnight at r.t. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure. The residue was dissolved in chloroform (15 mL), washed with saturated $NaHCO_3$ solution (15 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude solid which was purified by silica gel column chromatography (0 → 30% v/v ethyl acetate/hexane) to afford the product **8** as a yellow solid (0.57 g, 1.02 mmol, 63%). m.p. 40–42 °C; $[\alpha]_D^{27} = -26$ (c 0.97, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3262, 3029, 2923, 2820, 1598, 1493, 1453, 1323, 1153, 1091, 925, 812, 756, 700; ^{1}H NMR (300 MHz; $CDCl_3$): δ *7.36–6.91* (m, 18H), 6.18 (brs, 1H), 5.92 (m, 1H), 5.75 (m, 1H), 5.60 (d, J = 5.1 Hz, 1H), 4.28 (d, J = 7.3 Hz, 1H), 3.67 (d, J = 7.3 Hz, 1H), 3.59 (d, J = 12.6 Hz, 1H), 3.40 (d, J = 12.6 Hz, 1H), 2.28 (s, 3H), 2.14 (m, 2H), 2.04 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 143.3, 142.6, 138.9, 138.5, 137.7, 137.0, 129.5, 129.1, 128.6, 128.4, 128.0, 127.6, 127.5, 127.4, 127.3, 127.2, 127.0, 136.2, 125.4, 124.8, 123.2, 67.3, 63.1, 49.1, 28.3, 23.0, 21.4; HRMS (ESI) *m/z* ((M+Na)$^+$) Calc. for $C_{34}H_{34}N_2NaSO_2$: 557.2225. Found: 557.2238 (2.3 ppm error).

3.6. Synthesis of N-{2-[(Biphenyl-2-ylmethyl)-amino]-1R,2R-diphenyl-ethyl}-4-methyl-benzenesulfonamide chloro ruthenium monomer (**4**) [4b]

To a stirred solution of **8** (0.32 g, 0.57 mmol) in dichloromethane (10 mL) was added a 1 M solution of HCl in diethyl ether (1.8 mL, 1.8 mmol). After stirring for 30 min, the solvent was removed under vacuum. The resulting precipitate was dissolved in ethanol (10 mL) and ruthenium trichloride trihydrate (0.12 g, 0.6 mmol) was added. The reaction mixture was heated at 70 °C overnight to give **12** which was converted *in situ* in the monomer **4** by the addition of triethylamine (0.17 mL, 1.2 mmol) to the mixture at 70 °C followed stirring at this temperature for a further 3 h. The solvent was removed under reduced pressure and the residue was washed with $NaHCO_3$ solution (10 mL). The organic layer was separated and dried over anhydrous $MgSO_4$ providing the crude monomer which was purified by fluorisil column chromatography (1:1 v/v ethyl acetate/hexane and then 0 → 20% v/v MeOH/dichloromethane) to afford the pure monomer **4** as a black solid (0.107 g, 0.169 mmol, 30%). m.p. > 300 °C; $[\alpha]_D^{27} = -633$ (c 0.0012, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3059, 3029, 2926, 2869, 1598, 1493, 1453, 1441, 1270, 1130, 1083, 1026, 937, 809, 748, 698, 661; ^{1}H NMR (400 MHz; $CDCl_3$): δ *7.65–6.35* (m, 18H), 6.10 (brs, 1H), 6.04 (brs, 1H) 5.16 (brs, 1H), 5.10 (brs, 1H), 4.93 (d, J = 10.8 Hz, 1H), 4.72 (d, J = 13.3 Hz, 1H), 4.08 (d, J = 10.5 Hz, 1H), 3.84 (d, J = 13.4 Hz, 1H), 3.29 (brt, J = 11.4 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (75 MHz;

$CDCl_3$): δ 141.6, 139.2, 138.1, 135.0, 133.4, 132.5, 131.4, 129.8, 129.6, 129.2, 128.5, 128.4, 127.7, 127.0, 126.6, 126.1, 96.6, 78.8, 76.0, 68.7, 53.2, 21.0. HRMS (ESI) *m/z* ($(M-Cl)^+$) Calc. for $C_{34}H_{31}N_2SO_2Ru$: 633.1139. Found: 633.1124 (2.3 ppm error).

3.7. Synthesis of N-[(1R,2R)-2-(3-cyclohexa-1,4-dienyl)propylamino)cyclohexyl]-4-methylbenzenesulfonamide (**9**)

To a suspension of 4Å molecular sieves (1.0 g) in dichloromethane (15 cm^3), aldehyde **7** (0.650 g, 4.78 mmol) followed by *R,R*-TsDAC (1.41 g, 5.25 mmol) was added. The reaction mixture was stirred overnight, filtered, concentrated under vacuum and dissolved in anhydrous CH_3OH (15 mL) to which sodium cyanoborohydride (0.600 g, 9.55 mmol) was added slowly with stirring. Glacial acetic acid (0.5 mL) was added and the reaction was stirred overnight, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to give **9** (0.629 g, 1.61 mmol, 34%) as viscous pale yellow oil. (Anal. Calc. for $C_{22}H_{32}N_2O_2S$: C, 68.0; H, 8.3; N, 7.21. Found: C, 68.5; H, 8.6; N, 6.7%; $[\alpha]_D^{20} = +35.9$ (c 0.5 in $CHCl_3$); ν_{max}/cm^{-1} (viscous solid): 3151, 1329, 1158, 817, 660; ^1H NMR (400 MHz, $CDCl_3$; Me_4Si): δ *7.85–7.75* (d, *J* = 12 Hz, 2H), 7.30–7.25 (d, *J* = 12 Hz, 2H), 5.70–5.90 (brs, 2H, brs), 5.70 (brs, 2H), 5.35 (brs, 1H), 2.80–3.10 (m, 2H), 3.60–3.50 (m, 2H), 2.40–2.30 (m, 2H), 2.10–1.10 (m, 14H), 2.35 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$; Me_4Si): δ 21.6, 23.5, 24.2, 26.4, 26.7, 28.6, 31.2, 34.1, 44.4, 54.3, 60.9, 77.1, 119.9, 124.0, 126.4, 127.3, 128.6, 130.3, 132.3, 136.3, 144.6. MS *m/z* (LSIMS): 389 (MH^+ 100%), 154 (40%). HRMS (LSIMS) *m/z* ($(M+H)^+$) Calc. for $C_{22}H_{33}N_2O_2S$ 389.22. Found: 389.227.

3.8. Synthesis of N-[(1R,2R)-2-(3-cyclohexa-1,4-dienyl)propylamino)cyclohexyl]-4-methylbenzenesulfonamide ammonium chloride ruthenium dimer (**13**)

To a stirred solution of **9** (0.357 g, 0.92 mmol) in dichloromethane (10 cm^3) was added a 1 M solution of HCl in diethyl ether (3 cm^3, 3.00 mmol). After stirring for 30 min, the solvent was removed from the resulting precipitate under vacuum, dissolved in ethanol (20 cm^3) and ruthenium trichloride trihydrate (0.179 g, 0.69 mmol) was added. The reaction mixture was heated at 70 °C overnight and then cooled to r.t. The precipitate was collected by filtration and washed with ethanol (5 × 10 mL) to give **13** (0.230 g, 0.21 mmol, 45%) as a dark green powder; decomposition temperature >250 °C. $[\alpha]_D^{20} = -134.7$ (c 0.0125 in DMSO); ν_{max}/cm^{-1} (solid) 2942, 1448, 1325, 1158, 772, 666; ^1H NMR (400 MHz, DMSO-d_6): δ 9.66 (brs, 1H), 9.55 (brs, 1H), 8.66–8.56 (brs, 1H), 7.25–7.92 (m, 4H), 6.04–5.83 (m, 5H), 3.58–3.43 (m, 2H), 2.52–2.41 (m, 4H), 2.37 (s, 3H), 1.44–1.04 (m, 10H); ^{13}C NMR (100.4 MHz, DMSO-d_6): δ 21.1, 23.6, 23.0, 30.8, 39.5, 52.8, 83.7, 85.2, 85.4, 85.6, 88.7, 88.9, 106.0, 126.6, 128.4, 128.5, 129.9, 138.4, 138.3, 143.1. MS (LSIMS) *m/z* 523.07 (monomeric species formed *in situ*$^+$, 100%). $^{102}RuC_{22}H_{29}N_2O_2S^{35}Cl$ requires 522.07.

3.9. Reduction of ketones using tethered R,R Ru(II) catalysts **4** and **5**

A solution of ruthenium monomer **4** (0.0104 mmol) or dimer **13** (0.0052 mmol) in formic acid: triethylamine 5:2 azeotrope (2.08 mL) was stirred in a flame dried Schlenk tube at 28 °C for 1 h. Ketone substrate (4.16 mmol; S/C (monomer) = 200) was added and the reaction mixture was stirred at 28 °C for 24 h. The reaction mixture was filtered (silica), washed with 40% EtOAc/hexane and concentrated under vacuum to give the reduction product. The residue was purified by flash column chromatography on silica gel.

3.10. Analysis of asymmetric reduction products

1-Phenylethanol: Enantiomeric excess was determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 115 °C, *P* = 15 psi, ketone 9.1 min, *R* isomer 13.3 min, *S* isomer 14.1 min); $[\alpha]_D^{22} = +49.0$ (c 1.0 in $CHCl_3$) 95% ee (*R*) (cat **4**) (lit. [10] $[\alpha]_D^{23} = +48.6$ (c 1.0 in CH_2Cl_2); 96% ee (*R*)); ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.47 (d, *J* = 6.4 Hz, 3H), 2.04 (brs, 1H), 4.86 (q, *J* = 6.4 Hz), 7.33–7.35 (m, 5 H).

1-(2′-Chlorophenyl)ethanol: Enantiomeric excess was determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 150 °C, *P* = 10 psi, ketone 6.4 min, *R* isomer 11.2 min, *S* isomer 12.1 min); 69% ee (*R*) (cat **4**) (lit. [11] $[\alpha]_D^{20} = +41$ (c 1.0 in $CHCl_3$) 67% ee (*R*); ^1H NMR (400 MHz; $CDCl_3$): δ 7.56 (dd, *J* = 7.8 and 1.8 Hz, 1H), 7.32–7.25 (m, 2H), 7.18 (td, *J* = 7.7 and 1.8 Hz, 1H), 5.26 (dq, *J* = 6.3 and 2.8 Hz, 1H), 2.33 (brd, *J* = 3.0 Hz, 1H), 1.46 (d, *J* = 6.5 Hz, 3H).

1-(3′-Chlorophenyl)ethanol: Enantiomeric excess was determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 150 °C, *P* = 10 psi, ketone 11.1 min, *R* isomer 16.4 min, *S* isomer 16.9 min); 88% ee (*R*) (cat **4**) (lit. [6] $[\alpha]_D^{24} = +38.2$ (c 0.9 in $CHCl_3$) 96% ee (*R*); ^1H NMR (400 MHz; $CDCl_3$): δ 7.36 (brs, 1H), 7.30–7.20 (m, 3H), 4.85 (q, *J* = 6.4 Hz, 1H), 2.15 (brs, 1H), 1.46 (d, *J* = 6.4 Hz, 3H).

1-(4′-Chlorophenyl)ethanol: Enantiomeric excess was determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 150 °C, *P* = 10 psi, ketone 11.5 min, *R* isomer 16.5 min, *S* isomer 17.1 min); 89% ee (*R*) (cat **4**) (lit. [6] $[\alpha]_D^{29} = +52.6$ (c 0.56 in Et_2O) 95% ee (*R*); ^1H NMR (400 MHz; $CDCl_3$): δ 7.29 (dd, *J* = 5.3 and 3.0 Hz, 4H), 4.85 (brs, 1H), 7.30–7.20 (m, 3H), 4.85 (q, *J* = 6.5 Hz, 1H), 2.11 (brs, 1H), 1.5 (d, *J* = 6.5 Hz, 3H).

2-Chloro-1-phenylethanol: Enantiomeric excess was determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 140 °C, *P* = 10 psi, ketone 20.6 min, *S* isomer 24.9 min, *R* isomer 25.8 min); 83% ee (*S*) (cat **5**) (lit. [12] $[\alpha]_D^{25} = -47.5$ (c 1.7 in cyclohexane); 96% ee (*R*), >99% yield, ^1H NMR (400 MHz; $CDCl_3$): δ 7.37–7.39 (m, 5H), 4.87 (dd, *J* = 3.5, 8.8 Hz, 1H), 3.72 (dd, *J* = 3.5, 11.2 Hz, 1H), 3.62 (dd, *J* = 8.8, 11.2, 1H), 2.77 (brs, 1H).

1-Cyclohexyl-ethanol: Enantiomeric excess was determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 92 °C, *P* = 9 psi, ketone 25.4 min, *R* isomer 40.5 min, *S* isomer 41.1 min); 59% ee (*S*) (cat **5**) (lit. [13,4b] $[\alpha]_D$ = +3.51 (c 3.1 in $CHCl_3$) 95% ee (*S*)); ^1H NMR (400 MHz; $CDCl_3$; Me_4Si): δ 3.54 (dt, *J* = 6.5, 6.3 Hz, 1H), 1.63–1.88 (m, 5H), 1.46 (brs, 1H), 1.15 (d, *J* = 6.3 Hz, 3H), 0.92–1.32 (m, 6H).

3,3-Dimethylbutan-2-ol: Enantiomeric excess was determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 80 °C, *P* = 7 psi, ketone 5.5 min, *S* isomer 8.7 min, *R* isomer 8.9 min); 33% ee (*S*) (cat **4**) (lit. [14] $[\alpha]_D^{29} = -43.0$ (c 1.5 in CCl_4) 99% ee (*R*)); ^1H NMR (400 MHz; $CDCl_3$; Me_4Si): δ 3.52–3.44 (m, 1H). 7.37–7.39 (m, 5H), 4.87 (dd, *J* = 3.5, 8.8 Hz, 1H), 3.72 (dd, *J* = 3.5, 11.2 Hz, 1H), 3.62 (dd, *J* = 8.8, 11.2, 1H), 2.77 (brs, 1H), 1.58–1.82 (brs, 1H), 1.12 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H).

2-Phenoxy-1-phenylethanol: Enantiomeric excess by HPLC was determined by ^1H NMR (Chiracel HPLC OD: 250 x 4.6 mm, mobile phase = 90% Hexane: 10% IPA: 0.1% Et_2NH, Flow rate: 0.7 mL/min, ketone 29.6 min, *S* isomer 38.2 min, *R* isomer 19.9 min) 93% ee (*S*) (cat **4**) (lit. [15a] $[\alpha]_D^{20} = -27.0$ (c 2.0, CHCl3) 72% yield. (*R*), lit. [15b] $\alpha]_D^{23} = +23.0$ (c 0.81, CH_2Cl_2) 97% ee (*S*), ^1H NMR (400 MHz; $CDCl_3$): δ 7.46–7.25 (m, 7H), 6.99–6.91 (m, 3H), 5.12 (dd, *J* = 3.2, 8.8 Hz, 1H), 2.77 (brs, 1H).

1-(3-Methoxyphenyl)ethanol: Enantiomeric excess was determined determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 140 °C, *P* = 15 psi, ketone 13.3 min, *R* isomer 18.2 min, *S* isomer 18.9 min); 88% ee (*R*) (cat **5**) $[\alpha]_D^{22} = +32.9$ (c 0.75 in MeOH) 97% ee (*R*) (lit. [16] $[\alpha]_D^{21} = -34.9$ (c 0.849 in MeOH)

>99% ee, 90% Conv. (*S*)); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.26 (dd, J = 8.0, 8.0 Hz, 1H), 6.96–6.92 (m, 2H), 6.83–6.79 (m, 1H), 4.86 (q, J = 6.4, 1H), 3.81 (s, 3H), 1.94 (brs, 1 H), 1.48 (d, J = 6.5 Hz, 3H).

1-(3,5-bis-Trifluoromethylphenyl)ethanol: Enantiomeric excess was determined determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 110 °C, P = 8 psi, ketone 9.3 min, *R* isomer 27.7 min, *S* isomer 29.8 min); 51% ee (*R*) (cat **5**) $[\alpha]_D^{22} = -24$ (c 1.00 in CH_3OH), (lit. [8a] $[\alpha]_D^{22} = +16$ (c 1.204 in $CHCl_3$) 99% ee (*R*)).

1-(3-Trifluoromethylphenyl)ethanol: Enantiomeric excess was determined determined by GC analysis (Chrompac cyclodextrin-β-236M-19, 50 m, T = 120 °C, P = 10 psi, ketone 10.0 min, *R* isomer 20.2 min, *S* isomer 21.5 min); 83% ee (*R*) (cat **5**) $[\alpha]_D^{22} = +28.4$ (c 1.26 in CH_3OH), (lit. [6] $[\alpha]_D^{22} = +27.1$ (c 1.60 in CH_3OH) 96% ee (*R*)).

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