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The importance of 1,2-*anti*-disubstitution in monotosylated diamine ligands for ruthenium(II)-catalysed asymmetric transfer hydrogenation

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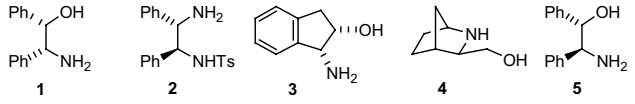
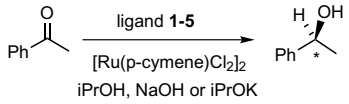
Abstract—The synthesis and applications to transfer hydrogenation of three derivatives of the popular TsDPEN are described. The results clearly demonstrate the importance of both disubstitution and the *anti* arrangement of substituents on this ligand. An explanation for the significance of these results is forwarded.

1. Introduction

The asymmetric transfer hydrogenation of ketones has been the subject of intense international research work in recent years.[1] This has been primarily due to the discovery, by Noyori et al., of highly active catalysts derived from ruthenium (II) complexes of β-amino alcohols such as (*1R,2S*)-1,2-diphenyl-2-(*N*-methyl-amino)-ethan-1-ol **1**[2] and monotosylated 1,2-diamines such as TsDPEN **2** (Scheme 1, Table 1).[3]



In the case of β-aminoalcohols, several diverse types of ligand[4–6] have been successfully employed, including *cis*-aminoindanol **3**[4] and the 2-azanorbornyl derivative **4**.[5] When the diastereoisomer of ephedrine **1**, that is, **5**, is employed as a ligand in the reduction, the resulting alcohol product configuration is unchanged. This suggests that the α-stereogenic centre is the predominant one in controlling the absolute reduction stereochemistry.



Scheme 1.

Table 1

Ligand	Yield, %	Ee, %	*R*/*S*	Ref.
1	97	56	*S*	2
2	95[a]	97	*S*	3a
3	70	91	*S*	4a
4	90	94	*S*	5a
5	97	42	*S*	2

[a] Mesitylene complex used.

For β-aminoalcohol ligands, it has been proposed that the reduction proceeds via the diastereoselective formation of ruthenium hydride **6**, from which hydrogen is transferred to the ketone through the six membered transition state illustrated in Figure 1. The resulting

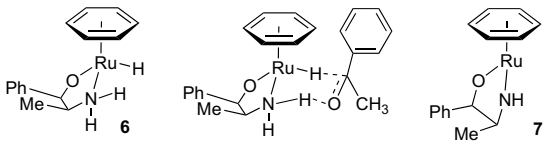


Figure 1.

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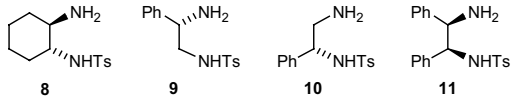
'16-electron' species **7** is subsequently converted back into **6** by hydrogen transfer (from isopropanol or formic acid) through an analogous transition state.[2b,5b]

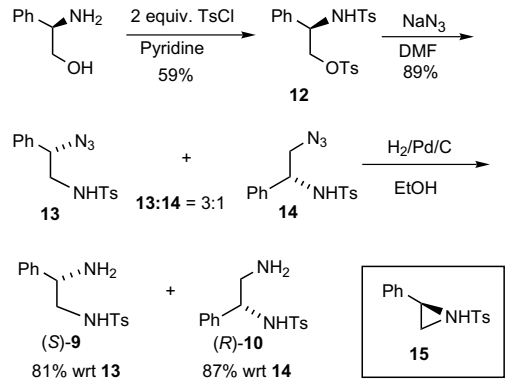
In the case of monotosylated 1,2-diamines, there are very few examples in the literature, other than the diaminocyclohexyl derivative **8**,[7] of effective ligands, which deviate significantly in structure from TsDPEN **2**. However, there are a number of examples of ligands, which bear alternative alkyl- or arylsulfonyl groups, and functionalised aryl rings.[8]

We wished to investigate whether the *anti* orientation, and the 1,2-disubstitution pattern of phenyl groups in TsDPEN were critical to its effectiveness as a ligand in asymmetric transfer hydrogenation. We were also interested in determining which stereogenic centre in **2** was primarily responsible for the overall sense of asymmetric induction during ketone reduction. Towards this end we decided to prepare compounds **9**–**11** which contain, respectively, a deleted phenyl group relative to TsDPEN **2**, and a *syn*-orientation between the phenyl groups. To our knowledge, these ligands have not been reported as ligands for the title application.



2. Results and discussion

The approach that we designed for the synthesis of ligands **9** and **10** is outlined in Scheme 2. Tosylation of commercially available (*R*)-phenylglycinol gave **12**,[9] which was converted to a 3:1 mixture of inseparable isomers **13** and **14** upon reaction with sodium azide in DMF. Whilst **14** may be produced by direct displacement of the OTs group, the formation of **13** requires the reaction to proceed via the formation of aziridine **15**. Attack of azide at the 1-position of the aziridine would then be expected to take place with inversion of configuration. Also, **15** was isolated as the major product when *R*-phenylglycinol was tosylated in the presence of triethylamine with no formation of **12** observed.



Scheme 2.

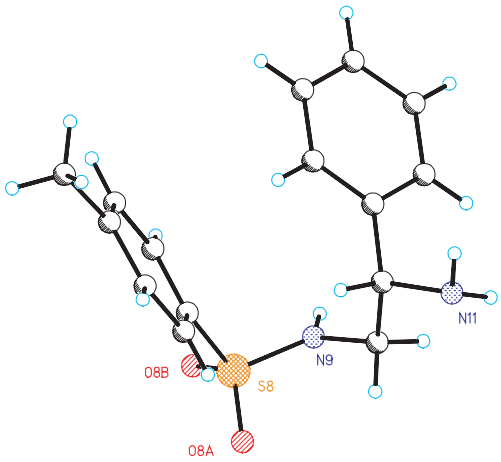
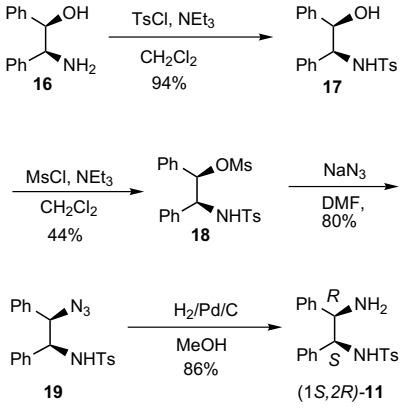


Figure 2. X-ray crystallographic structure of **9**.

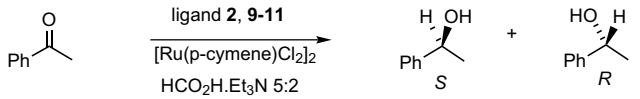
The synthesis of ligands **9** and **10** was completed by reduction of the azide to amine using catalytic hydrogenation. At this point the isomers could be separated by flash chromatography on silica gel. In order to fully confirm both the regiochemistry and absolute stereochemistry of the products of this reaction, an X-ray crystallographic structural analysis of **9** was completed (Fig. 2). To confirm that no racemisation had taken place during formation of **13** from **12** (i.e., no S_N1 opening of intermediate **15**) racemic **9** was synthesised via the same route outlined in Scheme 2 using racemic phenylglycinol. Subsequent HPLC analysis of **9** gave an ee of 100%.

Ligand **11** was prepared from amino alcohol **16** by the route illustrated in Scheme 3, which was based on a precedent in the patent literature.[10] Tosylation of **16** to give **17** was followed by mesylation to give **18**. The reaction of **18** with sodium azide resulted in formation of **19**, in excellent yield and with full diastereocontrol. This reaction presumably proceeds via a C_2-symmetric aziridine, thus eliminating the requirement for regioselective ring opening. Reduction of **19** to **11** was achieved using catalytic hydrogenation.

With ligands **9**–**11** in hand, we examined their application to the asymmetric transfer hydrogenation of ace-



Scheme 3.



Scheme 4.

Table 2

Ligand	Time	Conv., %	Ee, %	*R*/*S*
(*R*,*R*)-**2**	22 h	100	98	*R*
(*S*)-**9**	48 h	95	69	*S*
(*R*)-**10**	13 day	46	33	*R*
(1*S*,2*R*)-**11**	220 h	32	70	*S*

tophenone (Scheme 4, Table 2). Since the new ligands were all monotosylated diamines, the reduction was carried out in a formic acid/triethylamine azeotrope, which is known to give superior results and avoids the problem of reaction reversibility. β-Aminoalcohol ligands are not compatible with these conditions. Ligand (*R*,*R*)-**2** was also tested in order to provide a baseline for comparison.

The results obtained have an interesting and unexpected pattern. Both centres direct reduction in the same sense. With *cis*-**11** the centres are mismatched, but the dominant centre is the *S* centre adjacent to the NHTs group. This is surprising because **9** gave a higher ee than **10**, suggesting that the α-NH_2 centre in **11** would be expected to be dominant. Also, the ee obtained using **11** was higher than that with either **9** or **10**. Ligands **10** and **11** also induced much lower rate accelerations in the reactions than either **2** or **9**. It is clear that both substituents in monotosylated diamine ligands are required to be present for optimal results in terms of both rate and ee. In analogy with the β-aminoalcohol ligands, the principal directing effect comes from the absolute configuration of the stereogenic centre most distant from the basic amine. However it is clear from the results that the substituents on the stereogenic centre adjacent to basic amine also contribute a vital directing role to the reaction, possibly through a steric repulsion effect, or possibly a π-attractive interaction with the substrate.

In conclusion, **2** is an ideal ligand for ruthenium-catalysed transfer hydrogenation because (a) the stereogenic centres are matched and (b) the *trans* orientation provides an extra element of overall stereocontrol and rate enhancement.

3. Experimental section

All reactions, unless otherwise stated, were run under an atmosphere of nitrogen at ambient temperature (18–22 °C). A temperature of 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by TLC using aluminium backed silica gel 60 (F254) plates, visualised using UV 254 nm and phosphomolybdic acid, ninhydrin, potassium permanganate or vanillin dips as appropriate. Flash column chromatography was carried out routinely using 60 Å silica gel (Merck). Reagents were used as received from commercial sources unless otherwise stated. NMR spectra were recorded on a Bruker DPX (300 or 400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million downfield from TMS. Coupling constants (J) are measured in hertz. IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR Golden Gate. Mass spectra were recorded on a 7070E VG mass spectrometer. Melting points were recorded on a Stuart Scientific SMP 1 instrument and are uncorrected. Optical rotations were measured with an AA1000 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Determination of enantiomeric excesses by HPLC analysis was achieved using a Merck-Hitachi L-6200A HPLC pump, Merck-Hitachi L-4000 UV absorbance detector, Axiomm 727 data module and a Daicel Chiralcel OD 4.6×25 cm column.

3.1. Representative procedure for test reduction of acetophenone

A mixture of (*p*-cymene)ruthenium(II)chloride dimer (7.7 mg, 0.0125 mmol) and (*R*,*R*)-TsDPEN **2** (9.2 mg, 0.0250 mmol) in formic acid/triethylamine 5:2 azeotrope (2.5 mL) was stirred in a flame dried Schlenk tube at 28 °C for 30 min. Acetophenone (0.600 g, 5.00 mmol) was added and the reaction mixture was stirred at 28 °C, following by TLC. After 22 h, the reaction mixture was filtered (silica washed with ethyl acetate) and concentrated under vacuum to give the crude product. The residue was purified by flash chromatography (5% EtOAc/hexane to 10% EtOAc/hexane) to give *R*-phenylethanol[4a] (0.586 g, 96%) as a clear liquid; 98% ee (*R*) by HPLC [Chiralcel OD, 5% ethanol/hexane (1.0 mL min^{-1}), *R* isomer 8.3 min, *S*-isomer 9.6 min]; $[\alpha]_D = +49$ (*c* 1.0, $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.47 (3H, d, *J* 6.4, CH_3), 2.04 (1H, br s, OH), 4.86 (1H, q, *J* 6.4, PhC*H*CH_3), 7.33–7.35 (5H, m, Ph); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 24.9 (q), 70.2 (d), 125.2 (2×d), 127.2 (d), 128.3 (2×d), 145.6 (s).

3.2. Synthesis of toluene-4-sulfonic acid (*R*)-2-phenyl-2-(toluene-4-sulfonylamino)-ethyl ester 12[9]

To a stirred solution of *R*-phenyl glycinol (0.463 g, 3.38 mmol) in pyridine (6 mL) at 0 °C was added *para*-toluene sulfonyl chloride (1.415 g, 7.42 mmol). The reaction mixture was stirred overnight and then the resulting dark brown solution was diluted with water (20 mL), extracted with diethyl ether (5×10 mL), washed with satd $NaHCO_3$ solution (10 mL) and satd NaCl solution (10 mL), dried ($MgSO_4$), filtered and concentrated under vacuum to give the crude product. The residue was purified by flash chromatography (5% EtOAc/hexane to 25% EtOAc/hexane) to give **12** (0.886 g, 59%) as a white solid; mp 114.0–114.5 °C; $[\alpha]_D^{24} = -26.3$ (*c* 1.60, $CHCl_3$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.39 (3H, s, OTs-CH_3), 2.44 (3H, s, NTs-CH_3), 4.14 (2H, ABX system, *J* 16.0, 6.0 and 6.0, CH_aH_bOTs), 4.53 (1H, q, *J* 6.0, C*H*PhNHTs), 5.09 (1H, d, *J* 6.0, NH), 7.02–7.26 (7H, m, ArH *o* to CH_3 on NTs and Ph),

7.29 (2H, d, *J* 8.2, ArH *o* to CH_3 on NTs), 7.58 (2H, d, *J* 8.2, ArH *o* to SO_2 on OTs), 7.64 (2H, d, *J* 8.2, ArH *o* to SO_2 on NTs); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 21.9 (q), 22.1 (q), 56.8 (d), 71.6 (t), 127.3 (2×d), 127.6 (2×d), 128.3 (2×d), 128.7 (d), 129.1 (2×d), 129.9 (2×d), 130.3 (2×d), 132.6 (s), 136.4 (s), 137.3 (s), 143.9 (s), 145.6 (s).

3.3. Synthesis of *N*-((*S*)-2-azido-2-phenyl-ethyl)-4-methyl-benzenesulfonamide 13 and *N*-((*R*)-2-azido-1-phenyl-ethyl)-4-methyl-benzenesulfonamide 14

Compound **12** (0.780 g, 1.75 mmol) and sodium azide (0.171 g, 2.63 mmol) were stirred in DMF (22 mL) at 85 °C for 2.5 h. The reaction mixture was cooled to room temperature, diluted with water (22 mL) and extracted with diethyl ether (5 × 15 mL). The combined extracts were washed with water (2 × 20 mL), saturated sodium chloride solution (1 × 20 mL), dried ($MgSO_4$), filtered and concentrated under vacuum to give **13** and **14** (0.492 g, 89%) as an inseparable oil mixture in the ratio **13**/**14** = 3:1 from ^{1}H NMR; ν_{max}/cm^{-1} (thin film) 3286 (NH), 2100 (N_3), 1319 and 1154 (SO_2N), 812 (*p*-subst. Ph), 751 and 699 (Ph); δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.39 (minor isomer, 3H, s, CH_3), 2.43 (major isomer, 3H, s, CH_3), 3.08 (major isomer, 1H, ABX system, *J* 13.6, 5.0 and 4.0, CHCH_aH$_b$NH), 3.23 (major isomer, 1H, ABX system, *J* 13.6, 5.0 and 3.0, CHCH_aH$_b$NH), 3.57 (minor isomer, 2H, d, *J* 5.5, CH_2CHNH), 4.46 (minor isomer, 1H, dt, *J* 6.0 and 5.5, CH_2C*H*NH), 4.59 (major isomer, 1H, dd, *J* 9.0 and 5.0, CH_2CH_3), 4.75 (major isomer, 1H, br t, *J* 5.5, CH_2NHSO_2), 5.10 (minor isomer, 1H, br d, *J* 6.0, CH_2CHNH), 7.09–7.40 (both isomers, 7H, m, Ph and ArH *o* to CH_3), 7.62 (minor isomer, 2H, d, *J* 8.5, ArH *o* to SO_2), 7.73 (major isomer, 2H, d, *J* 7.7, ArH *o* to SO_2); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 21.9 (major isomer+minor isomer, 2×overlapping q), 48.5 (major isomer, t), 56.4 (minor isomer, t), 57.5 (minor isomer, d), 65.8 (major isomer, d), 127.2 (minor isomer, 2×d), 127.4 (major isomer, 2×overlapping 2×d), 127.5 (minor isomer, 2×d), 128.6 (minor isomer, d), 129.1 (minor isomer, 2×d), 129.4 (major isomer, d), 129.5 (major isomer, 2×d), 129.9 (minor isomer, 2×d), 130.3 (major isomer, 2×d), 136.7 (major isomer, s), 137.3 (major isomer, s), 137.5 (minor isomer, s), 138.0 (minor isomer, s), 143.9 (minor isomer, s), 144.2 (major isomer, s). Found (EI): 317.1070 $[MH]^+$, $C_{15}H_{17}N_4O_2S$ requires 317.1072 (0.8 ppm error); *m*/*z* (CI) 317 (MH^+, 5%), 274 (35), 260 (60), 184 (65), 155 (95), 106 (70), 91(100).

3.4. Synthesis of *N*-((*S*)-2-amino-2-phenyl-ethyl)-4-methyl-benzenesulfonamide 9 and *N*-((*R*)-2-amino-1-phenyl-ethyl)-4-methyl-benzenesulfonamide 10

To a stirred solution of **13** and **14** (0.316 g, 1.0 mmol) in ethanol (15 mL) was added 10% palladium on charcoal (0.032 g). The reaction vessel was evacuated, filled with H_2 from a balloon and stirred overnight. The reaction vessel was purged with N_2, filtered (Celite) and concentrated under vacuum to give the crude products. The residue was purified by flash chromatography (2% MeOH/DCM to 6% MeOH/DCM) giving first **9** (0.175 g, 81% wrt amount of starting material containing appropriate azide regioisomer) as a white solid (Found: C, 61.65; H, 6.2; N, 9.45. $C_{15}H_{18}N_2O_2S$ requires: C, 62.0; H, 6.25; N, 9.65); mp 97–98 °C; 100% ee (*S*) by HPLC (Chiralcel OD, 10% ethanol/hexane (1.0 mL min^{-1}), *S*-isomer 14.7 min, (*R*)-isomer 16.9 min); $[\alpha]_D^{20} = +85$ (*c* 1.50, $CHCl_3$); ν_{max}/cm^{-1} (solid) 3400 (NH), 3338 and 3286 (NH_2), 1598 (NH_2), 1315 and 1149 (SO_2N), 750 and 700 (Ph); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.35–2.08 (2H, br s, NH_2), 2.42 (3H, s, NTs-CH_3), 2.95 (1H, ABX system, *J* 12.7, 8.5 and 2.5 CH_aH$_b$NHTs), 3.15 (1H, ABX system, *J* 12.7, 5.0 and 2.5 CH_aH$_b$NHTs), 3.97 (1H, m, C*H*PhNH$_2$), 7.20 (2H, d, *J* 8.1, ArH *o* to CH_3 on NTs), 7.24–7.32 (5H, m, Ph), 7.71 (2H, d, *J* 8.1, ArH *o* to SO_2 on NTs); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 21.9 (q), 50.7 (t), 55.5 (d), 126.6 (2×d), 127.5 (2×d), 128.2 (d), 129.2 (2×d), 130.1 (2×d), 137.3 (s), 143.0 (s), 143.8(s). Found (EI): 291.1179 $[M]^+$, $C_{15}H_{18}N_2O_2S$ requires 291.1167 (4.2 ppm error); *m*/*z* (EI) 291(M^+, 5%), 155 (5), 106 (100), 91 (15), 79 (15), 69 (5). NH not observed in ^{1}H NMR.

An X-ray crystal structure of **9** was undertaken. $C_{15}H_{18}N_2O_2S$, $M = 290.37$, orthorhombic, space group $P2_12_12_1$, $a = 5.6168(12)$, $b = 12.340(2)$, $c = 21.000(3)$ Å, $U = 1455.5(4)$ Å^3 (by least squares refinement on 2442 reflection positions), $T = 180(2)$ K, $\lambda = 0.71073$ Å, $Z = 4$, $D(cal) = 1.325$ Mg m^{-3}, $F(000) = 616$. μ(MoK-α) = 0.225 mm^{-1}. Crystal character: colourless block. Crystal dimensions 0.24 × 0.08 × 0.08 mm. The full data has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 235426.

Further elution gave **10** (0.066 g, 87% wrt amount of starting material containing appropriate azide regioisomer) as a white solid (Found: C, 61.8; H, 6.25; N, 9.55. $C_{15}H_{18}N_2O_2S$ requires: C, 62.0; H, 6.25; N, 9.65); mp 109–110 °C; $[\alpha]_D^{20} = -62$ (*c* 0.85, $CHCl_3$); ν_{max}/cm^{-1} (solid) 3408 (NH), 3343 and 3288 (NH_2), 1602 (NH_2), 1308 and 1149 (SO_2N), 748 and 699 (Ph); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.28–1.60 (2H, br s, NH_2), 2.37 (3H, s, NTs-CH_3), 2.89 (2H, m, CH_aH_bNH$_2$), 4.25 (1H, t, *J* 6.0, C*H*PhNHTs), 7.09 (2H, d, *J* 7.8, ArH *o* to CH_3 on NTs), 7.14–7.23 (5H, m, Ph), 7.58 (2H, d, *J* 7.8, ArH *o* to SO_2 on NTs); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 21.9 (q), 47.9 (t), 59.7 (d), 127.1 (2×d), 127.5 (2×d), 127.9 (d), 128.8 (2×d), 130.1 (2×d), 137.8 (s), 139.4 (s), 143.5 (s). Found (EI): 291.1156 $[M]^+$, $C_{15}H_{18}N_2O_2S$ requires 291.1167 (3.8 ppm error); *m*/*z* (EI) 291(M^+, 10%), 260 (25), 155 (25), 106 (100), 91 (55). NH not observed in ^{1}H NMR.

3.5. Synthesis of *N*-((1*S*,2*R*)-2-hydroxy-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide 17

To a solution of (1*R*,2*S*)-2-aminodiphenylethanol **16** (0.808 g, 3.79 mmol) and triethylamine (0.574 g, 5.69 mmol) in dichloromethane (15 mL) was added a solution of *para*-toluene sulfonyl chloride (0.903 g, 4.74 mmol) in dichloromethane (5 mL) and the reactants

were stirred overnight. The solvent was removed from the resulting precipitate under vacuum and the crude solid was suspended in water (20 mL), filtered and washed with water (2×20 mL) and dichloromethane (10 mL) to give **17** (1.297 g, 94%) as a white solid; mp 207–209 °C; $[\alpha]_D^{19} = -29.2$ (*c* 0.55, acetone); ν_{max}/cm^{-1} (solid) 3458 (OH), 3323 (NH), 1311 and 1149 (SO_2N), 746 and 699 (Ph); δ_H (400 MHz; DMSO-d_6) 2.31 (3H, s, NTs-CH_3), 4.32 (1H, dd, *J* 9.4 and 6.7, PhC*H*NH), 4.45–4.90 (1H, br s, OH), 4.65 (1H, d, *J* 6.7, PhC*H*OH), 7.05–7.22 (12H, m, 2×Ph and ArH *o* to CH_3 on NTs), 7.33 (2H, d, *J* 8.0, ArH *o* to SO_2 on NTs), 8.14 (1H, d, *J* 9.4, NH); δ_C (100.6 MHz; DMSO-d_6) 21.2 (q), 63.7 (d), 75.8 (d), 126.6 (2×d), 126.8 (d), 127.1 (2×d), 127.3 (d), 127.4 (2×d), 127.9 (2×d), 128.6 (2×d), 129.3 (2×d), 139.0 (s), 139.3 (s), 142.0 (s),143.1 (s). Found (LSIMS) 350.1211 $[MH-H_2O]^+$, $C_{21}H_{20}NO_2S$ requires 350.1215 (1.0 ppm error); *m*/*z* (EI) 306 (80%), 260 (65), 201 (85), 106 (100), 91 (55), 77 (45).

3.6. Synthesis of methanesulfonic acid (1*R*,2*S*)-1,2-diphenyl-2-(toluene-4-sulfonylamino)-ethyl ester 18

To a suspension of **17** (0.404 g, 1.11 mmol) and triethylamine (0.168 g, 1.67 mmol) in dichloromethane (5 mL) was added a solution of methane sulfonyl chloride (0.152 g, 1.33 mmol) in dichloromethane (2.5 mL). The reaction mixture was stirred overnight, diluted with water (10 mL) and extracted with dichloromethane (2×10 mL). The combined extracts were washed with water (10 mL) and concentrated under vacuum to give the crude product. The residue was purified by flash column chromatography (DCM to 5% MeOH/DCM) to give **18** (0.216 g, 44%) as a white solid; mp 118–119 °C; $[\alpha]_D^{19} = -34.5$ (*c* 0.50, acetone); ν_{max}/cm^{-1} 3266 (NH), 1341 and 1186 (SO_2O), 1327 and 1167 (SO_2N), 762 and 695 (Ph); δ_H (400 MHz; acetone-d_6) 2.33 (3H, s, NTs-CH_3), 2.65 (3H, s, OMs-CH_3), 4.81 (1H, m, PhC*H*NHTs), 5.81 (1H, d, *J* 6.8, PhC*H*OMs), 7.11–7.34 (13H, m, 2×Ph, ArH *o* to CH_3 on NTs and NH), 7.44 (2H, d, *J* 8.3, ArH *o* to SO_2 on NTs); δ_C (100.6 MHz; acetone-d_6) 21.7 (q), 38.9 (q), 63.3 (d), 86.2 (d), 128.0 (2×d), 128.7 (2×d), 129.0 (d), 129.2 (2×d), 129.5 (2×d), 129.7 (2×d), 130.0 (d), 130.4 (2×d), (ipso carbons not distinguishable). Found (LSIMS): 446.1092 $[MH]^+$, $C_{22}H_{24}NO_5S_2$ requires 446.1096 (0.9 ppm error); *m*/*z* (LSIMS) 446 (MH^+, 1%), 350 (20), 260 (10), 154 (100), 137 (70).

3.7. Synthesis of *N*-((1*S*,2*R*)-2-azido-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide 19

To a solution of **18** (0.145 g, 0.33 mmol) in dimethylformamide (2 mL) was added sodium azide (0.064 g, 0.98 mmol) and the reactants were heated at 105 °C for 4 h, cooled and stirred overnight. Water (5 mL) was added and the resulting precipitate was collected by filtration and washed with water (5 mL) and methanol (5 mL) to give **19** (0.103 g, 80%) as a white solid; mp 148–149 °C; $[\alpha]_D^{19} = -62.8$ (*c* 0.55, acetone); ν_{max}/cm^{-1} (solid) 3254 (NH), 2108 (N_3), 1318 and 1161 (SO_2N), 751 and 703 (Ph); δ_H (400 MHz; acetone-d_6) 2.33 (3H, s, NTs-CH_3), 4.66 (1H, dd, *J* 7.5 and 6.0, PhC*H*NH), 5.02 (1H, d, *J* 7.5, PhCH_3), 7.11–7.32 (13H, m, 2×Ph, ArH *o* to CH_3 on NTs and NH), 7.43 (2H, d, *J* 8.3, ArH *o* to SO_2 on NTs); δ_C (100.6 MHz; acetone-d_6) 21.7 (q), 63.4 (d), 71.2 (d), 128.0 (2×d), 128.7 (d), 129.0 (2× overlapping 2×d), 129.5 (2×d), 129.6 (overlapping d and 2×d), 130.4 (2×d), 138.0 (s), 139.0 (s), 140.0 (s), 143.8 (s). Found (LSIMS): 393.1373 $[MH]^+$, $C_{21}H_{20}N_4O_2S$ requires 393.1385 (3.0 ppm error); *m*/*z* (LSIMS) 393 (MH^+, 10%), 350 (15), 307 (40), 260 (30), 154 (100), 137 (70).

3.8. Synthesis of *N*-((1*S*,2*R*)-2-amino-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide 11

To a solution of **19** (0.080 g, 0.21 mmol) in methanol (4 mL) was added 10% palladium on charcoal (0.008 g). The reaction vessel was evacuated, filled with H_2 from a balloon and stirred overnight. The reaction vessel was purged with N_2, filtered (Celite) and concentrated under vacuum to give **11** (0.066 g, 86%) as a white solid (Found: C, 68.45; H, 6.0; N, 7.35. $C_{21}H_{22}N_2O_2S$ requires: C, 68.8; H, 6.0; N, 7.65); mp 169–171 °C; 100% ee (1*S*,2*R*) by HPLC (Chiralcel OD, 10% ethanol/hexane (1.0 mL min^{-1}), 1*R*,2*S* isomer 18.1 min, 1*S*,2*R* isomer 21.6 min); $[\alpha]_D = +34.8$ (*c* 0.65, $CHCl_3$); ν_{max}/cm^{-1} 3362 (NH), 3306 and 3262 (NH_2), 1597 (NH_2), 1321 and 1156 (SO_2N), 755 and 696 (Ph); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.57 (2H, br s, NH_2), 2.24 (3H, s, CH_3), 4.04 (1H, d, *J* 5.5, PhC*H*NH_2), 4.39 (1H, d, *J* 5.5, PhC*H*NHTs), 5.60 (1H, br s, NH), 6.76 (2H, d, *J* 7.9, ArH *o* to CH_3 on NTs), 6.85–7.25 (10H, m, 2×Ph), 7.38 (2H, d, *J* 7.9, ArH *o* to SO_2 on NTs); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 21.8 (q), 60.8 (d), 63.4 (d), 127.4 (2×d), 127.5 (2×d), 127.9 (d), 128.2 (overlapping d and 2×d), 128.3 (2×d), 128.8 (2×d), 129.7 (2×d), 137.2 (s), 137.7 (s), 141.3 (s), 143.4 (s). Found (CI): 367.1465 $[MH]^+$, $C_{21}H_{23}N_2O_2S$ requires 367.1465 (4.2 ppm error); *m*/*z* (EI) 367 (MH^+, 5%), 260 (20), 155 (15), 106 (100), 91 (25), 77 (15), 65 (10).

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