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ARTICLE TYPE

Simple 1,3 diamines and their application as ligands in ruthenium(II) catalysts for asymmetric transfer hydrogenation of aryl ketones.

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Abstract: In this research work simple unsymmetrical 1,3 diamines were studied. The synthesis of the diamines started from non commercial available compounds. *S*-**5a** and *S,S*-**5c** were obtained by biocatalysis with non conventional yeast, *Rhodotorula rubra* MIM 147, with excellent 99% e.e. and d.e. up to 90%. Different approaches of synthesis were applied to the same backbone to study both the steric and electronic effects of the ligands. The reactivity of the corresponding ruthenium complexes was evaluated in the asymmetric hydrogen transfer reduction of acetophenone as standard substrate and of other different aryl ketones, highlighting the flexibility of the six membered chelating ring. A screening of the reaction conditions indicated aqueous media in the presence of HCOONa as hydrogen donor to be the best system for overcoming the lack of stereocontrol thus allowing to obtain 56 % e.e. in the reduction of acetophenone with the complex in which the ligand was the diamine **1,** revealed as the best in terms of reactivity and stereoselectivity also in the reduction of the other different aryl ketones, in particular for α-tetralone, **i** (63 % e.e.).

Introduction

In the last decade asymmetric transfer hydrogenation (ATH) has been revealed as a valid alternative to the use of molecular H_2 in obtaining enantiomerically pure alcohols which can be applied to the synthesis of many fine chemicals, pharmaceuticals and agrochemical products[1].

It is well known that the performance of the catalytic system is strictly related to a synergic effect between the solvent nature and the hydrogen donor. In the recent years the development of ATH in aqueous media has been emerged as a valid alternative to the use of organic solvents for its non toxic, economic and environmental compatible profile.

Since the pioneering work by Noyori and Ikariya groups in 1995[2, 3], the catalysts of choice in ATH reductions of ketones have been established to be the ruthenium(II) complexes chelating different substituted 1,2-diamines such as DPEN and its derivatives, among them the monotosylated compounds were revealed as the most efficient ones[3-11].

All these types of catalysts were based on the presence of ligands forming five membered rings when chelated to the metal centre. Some examples of symmetric 1,4 diamines and few examples of 1,3-diamines were reported in literature,[12-17] mainly used as a typical ruthenium complex [(diphosphine)-$RuCl_2$-(diamine)] for hydrogenation of simple aromatic and aliphatic ketones, in catalytic addition of diethylzinc to aldehyde or in Cu-catalyzed enantioselective Henry reaction.[18-21]

Considering the wide range of 1,2-diamines used as ligands and their utility in asymmetric catalysis, this work reported the synthesis of simple asymmetric monotosylated 1,3-diamines, up to now poorly investigated in ATH (Figure 1) and the evaluation of their catalytic performances.

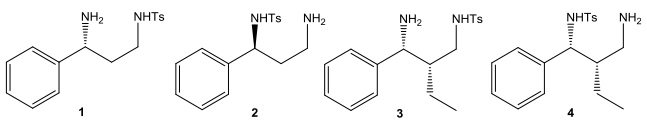


Figure 1. Monotosylated 1,3 diamines.

Results and Discussion

The starting material for the synthesis of these 1,3-diamines was the reduction products of benzoylacetonitrile and its ethylated derivative.

Different approaches using either asymmetric transfer hydrogenation for the reduction of benzoylacetonitrile **5** with iridium(III)[22] and/or ruthenium(II) diamines complexes[23] or whole-cell catalysts[24, 25] were studied. Recently our group displayed the reduction of the substrate **5** and its corresponding ethylated derivative **5b** using Carreira's [Cp*Ir(diamine)(H_2O)]SO_4 complexes in which the diamine ligand CAMPY and its derivatives were used as source of chirality[26] with good stereoselectivity. Unfortunately it was not

enough to use these products as starting materials for the synthesis of enantiomerically pure diamines. Good results were obtained by a biotransformation reaction which has been studied especially by Gotor and Dehli[27-29] employing the fungus *Curvularia lunata*. In these works they underlined the production of the expected side product, 2-(1-hydroxy-1-phenylmethyl)butanenitrile **5c**, during the biotransformation occurring on benzoylacetonitrile **5**.

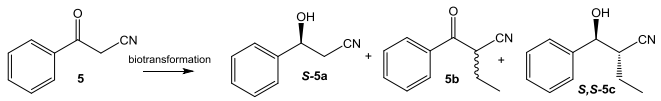


Figure 2. Biotransformation of benzoylacetonitrile by yeasts.

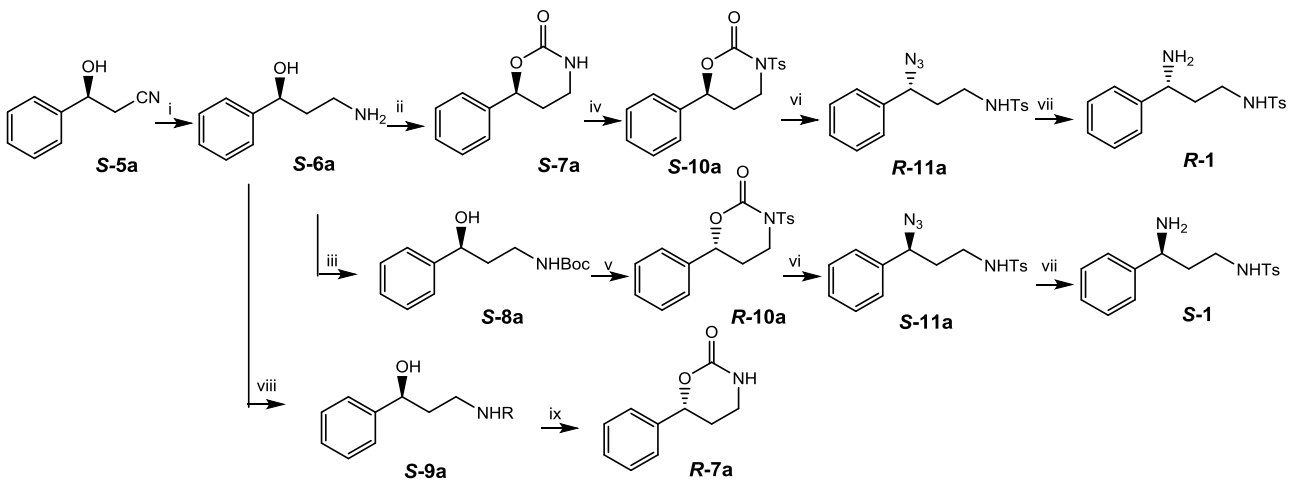
On the basis of the above results we decided to investigate different yeasts able to reduce the same substrate **5** and its derivative **5b**. A screening of different genera and species of yeasts available in our laboratory's library was carried out (data not reported). (Figure 2)

Most of them resulted to produce the ethylated keto-compound **5b** as the major product while the 3-hydroxy-3-phenylpropanenitrile **5** was produced in a minor amount in the presence of glucose as co-substrate.

The group of red to pinkish yeasts is one of the most interesting biocatalysts[30-33] in the reduction of differently substituted aryl-ketones and among them *Sporobolomyces salmonicolor* is the best known for this application. As expected, this yeast was able to produce the desired product **5a** in a quantitative yield with 80% e.e. in *S* configuration avoiding the use of any co-substrate. In the presence of EtOH as co-substrate this yeast afforded **5a** and **5c** in a 50/50 mixture along with a decreasing enantiomeric excess. Best results were obtained when two similar yeasts were used: *Rhodotorula rubra* MIM 146 and *Rhodotorula rubra* MIM 147. In both cases **5a** was the only product yielded in an excellent 98% e.e. in *S* configuration. With the aim to verify the ability of these two yeasts to reduce and resolve compound **5b**, its racemic mixture was quantitatively synthesised by *Saccharomyces cerevisiae* which mediated non-stereoselective introduction of the ethyl group.[34, 35] With *R. rubra* MIM 146 the conversion of racemic **5b** in **5c** was achieved in 48 h with 78% d.e. and >99% e.e. in *S,S* configuration. The best result was obtained with *R. rubra* MIM 147 which produced *S,S*-**5c** at the same time with >99% e.e. and with a d.e. up to 90% thus allowing to completely separate the two diastereomers by classical chromatographic techniques.

First of all, starting from linear substrate *S*-**5a**, two different types of diamines were synthesised in which the tosyl-amine moiety was set either on aliphatic chain or on the preformed stereocentre. (Scheme 1)

After obtaining the corresponding aminoalcohol **6a** by reduction with $LiAlH_4$, the synthesis proceeded into two different pathways. The cyclisation with CDI in CH_2Cl_2 gave the corresponding (*S*)-6-phenyl-1,3-oxazinan-2-one **7a** with retention of configuration. [36] Successively, the reaction with NaH and TsCl provided 6-phenyl-3-tosyl-1,3-oxazinan-2-one **10a**, with an excellent yield (80% after crystallization). In the second pathway, after protecting the amino group with $(Boc)_2O$, substrate **8a** reacts with TsCl in presence of 4-DMAP and TEA directly giving **10a** with the inversion of configuration at the chiral centre.



R = $-COOCH_2CH_2Si(CH_3)_3$

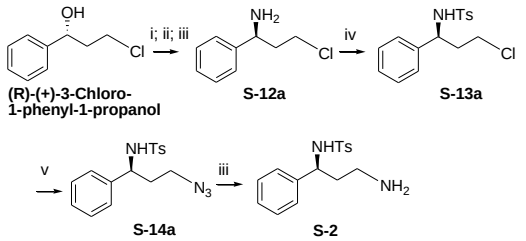
i = $LiAlH_4$, THF, 0°C; ii = CDI, CH_2Cl_2; iii = $(Boc)_2O$, Na_2CO_3, THF/H_2O; iv = NaH, TsCl, THF; v = TsCl, 4-DMAP, TEA, CH_2Cl_2; vi = NaN_3, DMF, 120°C; vii = Pd/C, H_2, CH_3OH, 3h, 20 atm; viii = Teoc-OSu, TEA, CH_2Cl_2, 20 min; ix = MsCl, TEA, THF, 3 h, 0°C.

Scheme 1. Synthesis of linear diamines **1**.

Indeed, under these specific conditions, the formation of TsO- on the benzylic alcohol and the tosylation of the amido moiety allowed by the 4-DMAP, drove a SN_2 reaction. This methodology appears very appealing considering that starting from only one isomer we obtained both the enantiomers of **10a**. (Scheme 1)

The substrates **10a**, with the strong nucleophile NaN_3 in DMF, underwent SN_2 substitution on the chiral centre resulting in the opening of the cycle and the decarboxylation. The corresponding azides were reduced in the presence of Pd/C to monotosylated diamines, *N*-(3-amino-3-phenylpropyl)-4-methylbenzenesulfonamides **1**. For the synthesis of the analogue monotosylated diamine **2**, we planned a procedure starting from *S*-**6a**. The amino moiety was firstly protected with 1-[2-

(trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione (Teoc-OSu). Then the classic procedure, by which the alcoholic function was reacted with mesyl chloride in presence of TEA,[16] was performed unfortunately giving the corresponding oxazinanone *R*-**7a**, with inversion of configuration, as observed when Boc is used as protecting group for the amino moiety. Therefore, an alternative starting material, (*R*)-(+)-3-chloro-1-phenyl-1-propanol, for the synthesis of enantiopure diamine *S*-**2** was studied. The synthesis proceeded as reported in the following scheme. (Scheme 2)



i = MsCl, TEA, THF; ii = NaN_3, DMF, overnight; iii = Pd/C, H_2, CH_3OH, 3 h, 20 atm; iv = TsCl, TEA, CH_2Cl_2; v = NaN_3, DMSO, 100°C, 24 h.

Scheme 2. Synthesis of linear diamines 2.

The second type of diamines was synthesised starting from the reduced ethylated product **5c**. The synthesis of diamine **3** vs **1** mirrored each other from the beginning to the end. (Scheme 3)

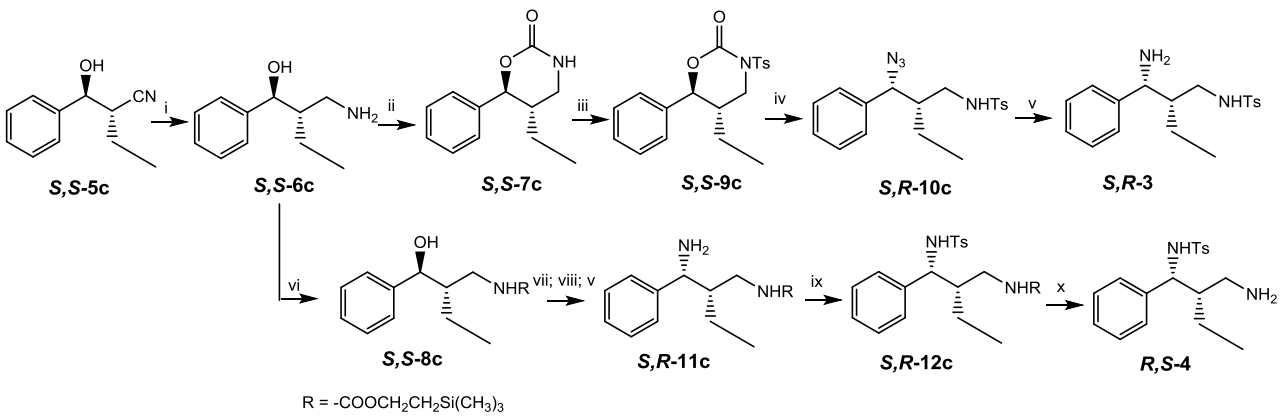
catalyst in ATH. Different reaction conditions were evaluated using acetophenone as test substrate. With regards to solvents, water revealed to be the best choice, as when *i*PrOH or MeOH were employed, the reaction conversion resulted significantly decreased.[5, 38] In the same way the selection of hydrogen donors[39] (HCOOH, HCOONa, azeotropic mixture 5:2=TEA:HCOOH and *i*PrOH) proved HCOONa among others, in ratio 10:1 with the substrate, as the best in terms of the achieved enantioselectivity. In fact by using a different hydrogen donor, a racemic mixture of the product was obtained in all cases. Conversely the temperature variation (20°C, 40°C or 60°C) didn't show any significant effect on enantioselectivity. Table 1 reported the results obtained for the four diamine ligands under the set reaction conditions: water as solvent and HCOONa as hydrogen donor at 40°C.

Table 1. ATH of acetophenone using [Ru(*p*-cymene)(L)Cl] complexes.

Entry	[a] Ligand	Conversion (%)[b]	e.e.%[b]
1	*R*-1	97	56 (*S*)
2	*S*-2	68	33 (*R*)
3	*S*,*R*-3	44	22 (*R*)
4	*R*,*S*-4	18	4 (*R*)

[a] Reactions were carried out at 40°C using 0.5 mmol of substrate with 0.5 mol % of ruthenium complex in 3 mL of water in presence of 10 equiv. HCOONa as hydrogen donor.

[b] Conversion was determined by NMR and e.e. was determined by HPLC after 48 h.



i = $LiAlH_4$, THF, 0°C; ii = CDI, CH_2Cl_2; iii = NaH, TsCl, THF; iv = NaN_3, DMF, 120°C; v = Pd/C, H_2, CH_3OH, 3h, 20 atm; vi = Teoc-OSu, TEA, Ch_2Cl_2, 20 min; vii = MsCl, TEA, THF, 3h, 0°C; viii = NaN_3, DMF, overnight; ix = TsCl, TEA, CH_2Cl_2, overnight; x = $ZnBr_2$, CH_3NO_2.

Scheme 3. Synthesis of ethylated diamines **3** and **4**.

In the case of diamine **4**, the methodology was the same of that initially thought for diamine **2** but in this case the formation of oxazinanone **7c** didn't take place and after removing the Teoc protecting group with $ZnBr_2$,[37] diamine **4** was obtained in quantitative yield.

The so synthesised diamines were reacted with [Ru(*p*-cymene)Cl_2]$_2$ to give the corresponding ruthenium(II) complexes assuming a six membered ring conformation. The synthesis of the ruthenium(II) complexes here reported was realised by refluxing in toluene for 3 h and utilised without further purification as pre-

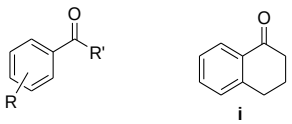
Unexpectedly the presence of an additional chiral centre in position 2 of the ligands **3** and **4** didn't improve the enantioselectivity but on the contrary it negatively influenced the stereoselectivity of the catalysts along with a significant decrease in the reaction rate (entries 3 and 4 *vs* 1 and 2). The results obtained by changing the position of tosyl moiety confirmed the importance of stereogenic centre to be in proximity of the amine involved in the catalytic cycle contributing to increase both the reaction conversion and enantioselectivity through a steric and/or an electronic effect (entries 1 *vs* 2 and 3 *vs* 4).

The reactivity and selectivity of the complexes carrying the linear

diamines **1** and **2** were studied in ATH of different aryl ketones. (Table 2)

The best results both in terms of reaction rate and enantioselectivity were achieved with the catalyst bearing diamine ligand ***R*-1** if compared to catalyst carrying ***S*-2** diamine (entries 1-9 *vs* 10-18). In particular in the reduction of α-tetralone, an appreciable 63 % e.e. was achieved with a yield of 70 % in 48 h (entry 9).[40-42]

Table 2. ATH of different aryl ketones.



i

a R= *o*-CH_3; R'= CH_3
b R= *m*-OCH_3; R'=CH_3
c R= *p*-CF_3; R'= CH_3
d R= H; R'= CH_2CH_3
e R= H; R'= $(CH_2)_2COOEt$
f R=H; R'= CH_2COOEt
g R= H; R'= CH_2CN
h R= H; R'= $CH(CH_2CH_3)CN$

Entry[a]	Ligand	Substrate	Conversion (%)[b]	e.e.%[b]
1	*R*-**1**	a	40	0
2		b	70	41 (*S*)
3		c	95	40 (*S*)
4		d	46	18 (*S*)
5		e	43	23 (*S*)
6		f	50	35 (*S*)
7		g	-	-
8		h	-	-
9		i	70	63 (*S*)
10	*S*-**2**	a	5	0
11		b	15	34 (*R*)
12		c	35	24 (*R*)
13		d	8	15 (*R*)
14		e	-	-
15		f	15	5 (*R*)
16		g	-	-
17		h	-	-
18		i	10	0

[a] Reactions were carried out at 40°C using 0.5 mmol of substrate with 0.5 mol % of ruthenium complex in 3 mL of water in presence of 10 equiv. HCOONa as hydrogen donor.

[b] Conversion was determined by NMR and e.e. was determined by HPLC after 48 h.

Conclusions

Easily prepared 1,3-diamines were developed starting from chiral substrates. The production of the starting material was realised by a biocatalytic approach using a non-conventional yeast, *Rhodotorula rubra* MIM 147, achieving very good results in terms of stereoselectivity, yield and recovery.

The catalytic data showed that when a six membered ring was formed by employing 1,3 diamines as source of chirality, enlarged if compared to the one obtained by using 1,2 ligands, a lower optical induction was observed due to the flexibility of the chelating ring as already underlined for the diphosphine ligands.[43] Nevertheless the right combination between the hydrogen donor and the solvent proved to drastically influence the catalytic performance of this type of catalysts as well as the electronic and steric properties of the substrate.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD on Bruker DRX Avance 300 MHz equipped with a non-reverse probe at 25°C. Chemical shifts (in ppm) were referenced to residual solvent proton/carbon peak. FTIR spectra were collected by using a Perkin Elmer (MA, USA) FTIR Spectrometer "Spectrum One" in a spectral region between 4000 and 450 cm^{-1} and analysed by transmittance technique with 32 scansions and 4 cm^{-1} resolution. Polarimetry analyses were carried out on Perkin Elmer 343 Plus equipped with Na/Hal lamp. ESI-MS analyses were performed by using a Thermo Finnigan (MA, USA) LCQ Advantage system MS spectrometer with an electronspray ionisation source and an 'Ion Trap' mass analyser. The MS spectra were obtained by direct infusion of a sample solution in MeOH under ionisation, ESI positive. Catalytic reactions were monitored by gas chromatography analysis using a chiral stationary phase column (MEGA DMT β, 25 m, internal diameter 0.25 mm) or by HPLC analysis with Merck-Hitachi L-7100 equipped with Detector UV6000LP and chiral column (OD-H Chiralcel or AD Chiralpak) and with JASCO PU-2080 Plus (OJ-H Chiralcel). Commercially reagent grade solvents were dried according to standard procedures and freshly distilled under nitrogen before use.

Enzymatic synthesis of *rac*-2-benzoylbutanenitrile 5b: Commercial Baker's yeast (50 g L^{-1}) was suspended in a phosphate buffer (200 mL, 0.1 M, pH 7) containing 50 g L^{-1} of glucose and 5 g L^{-1} of the substrate **5**. The biotransformation system was shaken with mechanic stirrer at 28°C. When the total conversion was achieved, the cells were separated by centrifugation. Both the aqueous phases and the cells mixture were extracted with diethyl ether (3x50 mL), dried with Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2/hexane/ethyl acetate = 4:1:1) to give 860 mg of **5b** (86% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.7 Hz, 3H, -CH_3), 2.02-2.15 (m, 2H, -CH_2-), 4.30 (dd, J = 6.2, 4.3 Hz, 1H, -CH-), 7.49-7.56 (m, 2H, arom), 7.65 (d, J = 7.6 Hz, 1H, arom), 7.95 (d, J = 6.7 Hz, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.88, 170.91, 134.63, 133.93, 130.38, 129.31, 128.92, 128.68, 41.38, 23.77, 11.89 ppm; IR ν = 3467, 2975, 2936, 2249, 1694, 1597, 1449, 1265, 1233, 1208, 1000, 696 cm^{-1}; Elemental analysis for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09; found: C, 76.13; H, 6.34; N, 7.98; MS (ESI) of $C_{11}H_{11}NO$ *m/z* 196.1 ($[M+Na]^+$).

General procedure of biotransformation with *Rhodotorula rubra* MIM 147

Rhodotorula rubra MIM 147 was routinely maintained on malt extract slants (8 g L^{-1}, yeast extract 5 g L^{-1}, agar 15 g L^{-1}, pH 5.6). The strain, grown on malt extract slants for 72 h at 28 °C, was inoculated into 1000 mL Erlenmeyer flasks containing 150 mL of the same liquid medium and incubated on a reciprocal shaker (100 spm) for 48 h at 28°C. Cells obtained by

centrifugation (4000×g for 15 min at 4°C) of the culture broth (1 L) were washed with deionised water (3x200 mL). After lyophilisation 20 g/L of yeast was suspended in 500 mL of 0.1M phosphate buffer pH = 7 containing 50 g L^{-1} of glucose. The substrates dissolved in DMSO were added to the biotransformation system in 2 g L^{-1} (**5**) or 1 g L^{-1} (***rac*-5b**) of substrate concentration and 1% of solvent. The biotransformation system was shaken with mechanic stirrer at 28°C for 48 h. The cells were separated by centrifugation and both were extracted with diethyl ether (3x150 mL), dried with Na_2SO_4 and the solvent was removed in *vacuo*. The crude product was purified by flash chromatography (ethyl acetate/cyclohexane = 7:3) to give 786 mg of ***S*-5a** (78% yield) or 287 mg of ***S,S*-5c** (57% yield).

***S*-5a:** All characterization data are in agreement with previously reported literature.[22, 23, 44, 45] $[\alpha]^{20}_D$ = -63.8 (c=1, $CHCl_3$); HPLC data: HPLC data for **5a**: OJ-H Chiralcel, eluent: hexane: 2-propanol = 90:10, flow = 1.0 mL/min, λ = 216 nm; rt: (*S*) = 24.5 min, (*R*) = 30.8 min.

***S,S*-5c:** ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.09 (t, *J* = 7.7 Hz, 3H, -CH_3), 1.51-1.69 (m, 2H, -CH_2-), 2.76-2.83 (m, 1H, -CH-), 4.79 (d, *J* = 6.2 Hz, 1H, -CH-), 7.33-7.56 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.71, 128.69, 128.05, 127.04, 76.57, 24.85, 10.38 ppm; IR *v* = 3390, 2964, 1494, 1453, 160, 1103, 1038, 702 cm^{-1}; Elemental analysis for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99; found: C, 75.23; H, 7.32; N, 7.89; MS (ESI) of $C_{11}H_{13}NO$ *m/z* 198.3 ($[M+Na]^+$). $[\alpha]^{20}_D$= -46.4 (c=0.5, $CHCl_3$). HPLC data: Chiralcel OD-H, eluent: hexane: 2-propanol = 95:5, flow = 0.8 mL/min, λ = 216 nm; rt: (*R,S*) = 26.9 min, (*S,S*) = 28.6 min, (*S,R*) = 34.2 min, (*R,R*) = 36.4 min.

General Synthesis of aminoalcohol 6a or *S,S*-6c: To a solution of **5a** or ***S,S*-5c** (1.72 mmol) in anhydrous THF (10 mL), $LiAlH_4$ was added (100 mg, 2.6 mmol) and the resulting mixture was stirred under nitrogen atmosphere at 0°C. After 1 hour, some water was carefully added in order to quench the excess of $LiAlH_4$ and the solution was then reduced in volume and extracted with dichloromethane (3x15mL). The organic layers were dried on Na_2SO_4, filtered and evaporated to give the product.

(*S*)-3-ammino-1-phenylpropan-1-ol *S*-6a: pale yellow oil (200 mg, 77% yield). $[\alpha]^{20}_D$= -44.38 (c=0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78-1.82 (m, 2H, -CH_2-), 2.48-2.52 (br, 2H, NH_2) 2.95-2.98 (m, 2H, -CH_2-), 4.92 (dd, *J* = 4.03, 8.06 Hz, 1H, -CH-), 7.21-7.38 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.16, 128.43, 128.14, 127.20, 125.85, 125.54, 75.44, 40.57, 39.87 ppm; IR *v* = 3360, 2917, 2874, 1601, 1492, 1453, 1337, 1062 cm^{-1}; MS (ESI) of $C_9H_{13}NO$ *m/z* 152.0 ($[M+H]^+$), 174.1 ($[M+Na]^+$).

(1*S*,2*S*)-2-(aminomethyl)-1-phenylbutan-1-ol *S,S*-6c: yellow oil (215 mg, 84% yield). $[\alpha]^{20}_D$= -18.3 (c=2.0, $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$): δ = 0.88 (m, 3H, -CH_3); 1.26-1.30 (m, 2H, -CH_2-); 2.87-2.91 (m, 2H, -CH_2-); 2.95-2.97 (m, 1H, -CH-); 3.09 (br, 2H, NH_2); 4.71(d, *J* = 6.59 Hz, 1H, -CH-); 5.2 (s, 1H, OH); 7.23-7.38 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.05, 128.31, 128.07, 127.14, 126.73, 126.55, 79.45, 47.11, 43.42, 22.36, 11.79 ppm; IR *v* = 3367, 3305, 2960, 2929, 2874, 1601, 1493, 1453, 1043, 1026, 701 cm^{-1}; MS (ESI) of $C_{11}H_{17}NO$ *m/z* 180.1 ($[M+H]^+$).

General synthesis of oxazinanones 7a or *S,S*-7c: *N,N'*-carbonyldiimidazole (204 mg, 1.35 mmol) was added to a solution of **6a** or ***S,S*-6c** in CH_2Cl_2 at room temperature and the resulting mixture was stirred for 12 h. Then, the solvent was evaporated and the residue solved in ethylacetate and washed with aqueous HCl (0.1 M) and water. After drying and elimination of the solvent, crystallization by diffusion of hexane into the acetone solution afforded the product.

(*S*)- 6-phenyl-1,3-oxazinan-2-one *S*-7a: white solid (179 mg, 75% yield). $[\alpha]^{20}_D$= -37.4 (c=0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14-2.17 (m, 2H, -CH_2-), 3.39-2.44 (m, 2H, -CH_2-), 5.34 (dd, *J* = 2.93, 9.53 Hz, 1H, -CH-), 5.81 (s, 1H, NH), 7.26-7.39 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.61, 138.67, 128.85, 128.59, 125.85, 78.83, 39.17, 28.91 ppm; IR *v* = 3389, 2966, 2878, 1797, 1682, 1494, 1456, 800, 702 cm^{-1}; Elemental analysis for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; found: C, 67.68; H, 6.24; N, 7.88; MS (ESI) of $C_{10}H_{11}NO_2$ m/z 200.1 ($[M+Na]^+$).

(5*S*,6*S*)-5-ethyl-6-phenyl-1,3-oxazinan-2-one *S,S*-7c: white solid (177 mg, 72% yield). $[\alpha]^{20}_D$= -7.0 (c=0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.33 Hz, 3H, -CH_3), 1.21-1.25 (m, 2H, -CH_2-), 2.02-2.05 (m, 1H, -CH-), 3.12 (t, *J* = 9.89 Hz, 1H, -C*H*H-), 3.43-3.49 (m, 1H, -CH*H*-), 4.97 (d, *J* = 8.79 Hz, 1H, -CH-), 5.27 (s, 1H, NH), 7.29-7.36 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.38, 138.14, 128.86, 128.75, 128.55, 127.15, 126.05, 84.04, 43.81, 38.79, 22.31, 11.09 ppm; IR *v* = 3435, 2961, 2925, 2854, 1698, 1457, 1355, 802, 761 cm^{-1}; Elemental analysis for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; found: C, 70.13; H, 7.33; N, 6.79; MS (ESI) of $C_{12}H_{15}NO_2$ *m/z* 206.1 ($[M+H]^+$).

General synthesis of tosyl-oxazinanones *S*-10a or *S,S*-9c: To a solution of ***S*-7a** or ***S,S*-7c** (1.69 mmol) in anhydrous THF at 0°C the stoichiometric amount of NaH was added (68 mg, 1.69 mmol). After thirty minutes the solution of tosyl chloride in THF (387 mg, 2.03 mmol) was dropped into the former solution and stirred at room temperature overnight. The resulting solution was quenched with water and extracted with trichloromethane (3x10 mL). The collected organic layers were dried on Na_2SO_4, filtered and evaporated to give a yellow oil then purified by crystallization in dichloromethane/hexane to provide the product.

(*S*)-6-phenyl-3-tosyl-1,3-oxazinan-2-one *S*-10a: white solid (440 mg, 80% yield). $[\alpha]^{20}_D$= -24.7 (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25-2.29 (m, 2H, -CH_2-), 2.45 (s, 3H, -CH_3), 4.00-4.08 (m, 2H, -CH_2-), 5.34 (dd, *J* = 2.93, 9.53 Hz, 1H, -CH-), 7.23-7.37 (m, 7H, arom), 7.94 (d, *J* = 8.43 Hz, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.82, 145.44, 137.61, 135.37, 129.68, 129.16, 129.06, 129.03, 125.75, 79.67, 44.22, 29.89, 21.93 ppm; IR *v* = 3436, 2976, 2923, 1709, 1354, 1174, 1148 cm^{-1}; Elemental analysis for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23; found: C, 61.57; H, 5.13; N, 4.20; MS (ESI) of $C_{17}H_{17}NO_4S$ *m/z* 354.1 ($[M+Na]^+$).

5*S*,6*S*)-5-ethyl-6-phenyl-3-tosyl-1,3-oxazinan-2-one *S,S*-9c: white solid (351 mg, 58% yield). $[\alpha]^{20}_D$= -5.8 (c=0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85-0.89 (m, 3H, -CH_3), 1.31-1.35 (m, 2H, -CH_2-), 2.05-2.12 (m, 1H, -CH-), 2.46 (s, 3H, -CH_3), 3.65 (dd, *J* = 2.19, 9.53 Hz, 1H, -C*H*H-), 4.11 (dd, *J* = 5.13, 6.59 Hz, 1H, -CH*H*-), 4.96 (d, *J* = 8.43 Hz, 1H, -CH-), 7.19-7.43 (m, 7H, arom), 7.91-7.97 (m, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.89, 145.33, 136.82, 135.52, 129.66, 129.28,

129.12, 128.97, 126.89, 84.63, 48.41, 40.31, 22.39, 21.85, 11.06 ppm; IR ν = 3426, 2964, 2882, 2101, 1719, 1353, 1175, 1158, 885, 700 cm^{-1}; Elemental analysis for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90; found: C, 63.52; H, 5.93; N, 3.94; MS (ESI) of $C_{19}H_{21}NO_4S$ *m/z* 360.2 ($[M+H]^+$).

Synthesis of (*R*)-6-phenyl-3-tosyl-1,3-oxazinan-2-one *R*-10a: To a solution of **8a** (270 mg, 1.08 mmol) in fresh-distilled dichloromethane, 4-dimethylaminopyridine (99 mg, 0.81 mmol) and triethylamine (2 mL, 14.04 mmol) were added. The reaction mixture was then cooled to -10°C and stirred for half an hour. A solution of tosyl chloride (267 mg, 1.4 mmol) in dichloromethane was then dropped into the former solution and stirred overnight allowing the reaction mixture to reach room temperature. The reaction was monitored by TLC using dichloromethane/diethyl ether 1:1 as eluent. After 24 h the reaction is completed. The desired product was obtained as a white solid by slow diffusion of hexane into the acetone solution (152 mg, 43% yield). $[\alpha]^{20}_D$= +24.7 (c=0.25, $CHCl_3$). All characterization data are in agreement with previously reported for ***S*-10a**.

General synthesis of azido benzensulfonamides 11a or *S,R*-10c: To a solution of **10a** or ***S,S*-9c** in anhydrous DMF (0.30 mmol), NaN_3 was added (98.2 mg, 1.51 mmol). The solution was refluxed at 120°C for 3.5 h under N_2 atmosphere. After cooling to room temperature, water was added and the solution was extracted with diethyl ether (3x10 mL). The collected organic layers were dried on Na_2SO_4, filtered and evaporated to give the product.

(*R*)-*N*-(3-azido-3-phenylpropyl)-4-methyl benzensulfonamide *R*-11a: orange oil (49 mg, 50% yield). $[\alpha]^{20}_D$= +61.2 (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86-1.90 (m, 2H, -CH_2-), 2.42 (s, 3H, -CH_3), 3.00-3.05 (m, 2H, -CH_2-), 4.52 (t, *J* = 7.33 Hz, 1H, -CH-), 5.16 (t, *J* = 7.12 Hz, 1H, NH) 7.19-7.37 (m, 7H, arom) 7.73 (d, *J* = 8.43 Hz, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.79, 138.96, 137.02, 130.01, 129.15, 128.74, 127.34, 127.03, 63.78, 40.47, 36.24, 21.73 ppm; IR ν = 3283, 3063, 3032, 2927, 2876, 2099, 1663, 1598, 1454, 1326, 1160, 1093, 909, 815 cm^{-1}; MS (ESI) of $C_{16}H_{18}N_4O_2S$ *m/z* 353.2 ($[M+Na]^+$).

(*S*)-*N*-(3-azido-3-phenylpropyl)-4-methylbenzen sulfonamide *S*-11a: orange oil (50 mg, 51% yield). $[\alpha]^{20}_D$= -75.0 (c=0.25, $CHCl_3$). All characterization data are in agreement with previously reported for ***R*-11a**.

***N*-((*S*)-2-((*R*)-azido(phenyl)methyl)butyl)-4-methylbenzen sulfonamide *S,R*-10c:** pale yellow oil (73 mg, 68% yield). $[\alpha]^{20}_D$= +103.5 (c=0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81-0.86 (m, 3H, -CH_3), 1.24-1.29 (m, 2H, -CH_2-), 1.73-1.79 (m, 1H, -CH-), 2.44 (s, 3H, -CH_3), 2.89 (t, *J* = 6.23 Hz, 2H, -CH_2-), 4.59-4.63 (m, 2H, -CH- + NH), 7.13-7.36 (m, 7H, arom), 7.69 (d, *J* = 6.59 Hz, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.76, 138.25, 136.95, 131.09, 130.71, 130.55, 130.40, 128.32, 86.06, 49.84, 41.75, 23.82, 21.43, 12.49 ppm; IR ν = 3282, 2964, 2933, 2101, 1711, 1666, 1328, 1160, 1093, 911 cm^{-1}; MS (ESI) of $C_{18}H_{22}N_4O_2S$ *m/z* 359.3 ($[M+H]^+$).

General synthesis of amino benzensulfonamides *R*-1, *S*-1 or *S,R*-3: In a stainless steel autoclave (20 mL), equipped with temperature control and a magnetic stirrer, purged five times with hydrogen, a solution of **11a** or ***S,R*-10c** (0.15 mmol) in methanol with 1% of Pd/C was transferred. The autoclave was pressurised at 20 atm and kept under stirring at room temperature for four hours. The mixture was then filtered on Celite and the solvent was evaporated in *vacuo* to give the product.

(*R*)-*N*-(3-amino-3-phenylpropyl)-4-methyl benzensulfonamide *R*-1: yellow oil, without any further purification step (43 mg, 95% yield). $[\alpha]^{20}_D$= +8.0 (c=0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89 (dd, *J* = 5.87, 12.09 Hz, 2H, -CH_2-), 2.42 (s, 3H, -CH_3), 2.91-2.95 (m, 2H,-CH_2-), 4.04 (t, *J* = 5.87 Hz, 1H, -CH-), 4.25-4.54 (br, 2H, NH_2), 7.17-7.29 (m, 7H, arom), 7.72 (d, *J* = 8.07 Hz, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.10, 142.74, 136.82, 129.60, 128.73, 127.64, 127.05, 126.29, 54.34, 40.71, 36.43, 21.42 ppm; IR ν = 3350, 3293, 2917, 2099, 1650, 1598, 1454, 1323, 1156, 1094, 951, 815 cm^{-1}; MS (ESI) of $C_{16}H_{20}N_2O_2S$ *m/z* 305.2 ($[M+H]^+$).

(*S*)-*N*-(3-amino-3-phenylpropyl)-4-methylbenzen sulfonamide *S*-1: pale yellow oil (45 mg, quantitative yield). $[\alpha]^{20}_D$= -7.6 (c=0.24, $CHCl_3$). All characterization data are in agreement with previously reported for ***R*-1**.

***N*-((*S*)-2-((*R*)-amino(phenyl)methyl)butyl)-4-methylbenzene sulfonamide *S,R*-3**: white solid (44.3 mg, 89% yield). $[\alpha]^{20}_D$= +4 (c=0.3, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD): δ = 0.85-0.87 (m, 3H, -CH_3), 1.19-1.22 (m, 2H, -CH_2-), 1.73-1.76 (m, 1H, -CH-), 2.45 (s, 3H, -CH_3), 2.86-2.91 (m, 2H, -CH_2-), 4.15 (d, *J* = 3.29 Hz, 1H, -CH-), 7.05-7.33 (m, 7H, arom), 7.75 (d, *J* = 8.06 Hz, 2H, arom) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ = 143.51, 140.92, 136.64, 129.53, 128.54, 127.68, 126.96, 55.94, 45.51, 42.45, 20.27, 19.18, 9.75 ppm; IR ν = 3436, 3292, 2963, 2925, 1631, 1320, 1151, 1093, 803, 704 cm^{-1}; Elemental analysis for $C_{18}H_{24}N_2O_2S$: C, 65.03; H, 7.28; N, 8.43; found: C, 64.97; H, 7.23; N, 8.39; MS (ESI) of $C_{18}H_{24}N_2O_2S$ *m/z* 333.0 ($[M+H]^+$).

Synthesis of *tert*-butyl-(*S*)-(3-hydroxy-3-phenylpropyl) carbamate *S*-8a: To a solution of **6a** (520 mg, 2.94 mmol) in a mixture of THF/water 1:1, Na_2CO_3 was added (720 mg, 6.76 mmol). The solution was then cooled to 0°C and a solution of di-*tert*-butyl dicarbonate (770 mg, 3.53 mmol) in 5 mL THF was added dropwise. After 1 h stirring at 0°C, the solution was warmed to room temperature and stirred for further 3 h. The reaction was monitored by TLC using dichloromethane/diethyl ether 1:1 as eluent. After 4 h the reaction was complete and water was added to the mixture and extracted with diethyl ether (3x10 mL) to give the product as a yellow oil (575 mg, 78% yield). $[\alpha]^{20}_D$= -18.9 (c=0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H, -C(CH_3)$_3$), 1.75-1.79 (m, 2H, -CH_2-), 3.16-3.20 (m, 1H, -C*H*-), 3.37-3.63 (m, 2H, -C*H*- + OH), 4.64 (m, 1H, -CH-), 5.23 (br, 1H, NH), 7.25-7.31 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.05, 144.54, 128.65, 127.59, 125.87, 79.76, 71.95, 39.77, 37.83, 28.63 ppm; IR ν = 3363, 3274, 2975, 1677, 1546, 1291, 1180, 1025, 981 cm^{-1}; MS (ESI) of $C_{14}H_{21}NO_3$ *m/z* 274.10 ($[M+Na]^+$).

General synthesis of Teoc-amino alcohols *S*-9a or *S,S*-8c: The synthesis proceeded according to methodology reported in literature.[46]

2-(trimethylsilyl)ethyl (*S*)-(3-hydroxy-3-phenylpropyl)carba mate *S*-9a: colourless oil (405 mg, 93% yield). $[\alpha]^{20}_D$= -12.3 (c=1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 9H, -C(CH_3)$_3$), 0.89 (t, *J* = 8.43 Hz, 2H, -CH_2-), 1.75 (q, *J* = 6.6 Hz, 2H, -CH_2-), 3.11-3.27 (m, 2H, -CH_2-), 4.05 (t, *J* = 8.43 Hz, 2H, -CH_2-), 4.60-4.66 (q, *J* = 5.50 Hz, 1H, -CH-), 5.42 (br, 1H, NH),

7.14-7.26 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.19, 157.58, 144.78, 128.60, 127.67, 127.43, 125.98, 125.88, 71.97, 70.66, 63.14, 39.32, 25.60, 17.95, -1.27 ppm; IR ν = 3403, 2953, 1743, 1694, 1525, 1251, 1062, 860, 838 cm^{-1}; MS (ESI) of $C_{15}H_{25}NO_3Si$ *m/z* 318.2 ([M+Na]$^+$).

2-(trimethylsilyl)ethyl ((*S*)-2-((*S*)-hydroxy (phenyl)methyl) butyl)carbamate *S,S*-8c: white oil (374 mg, 82% yield). $[\alpha]^{20}_D$= -9.5 (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 9H, -C(CH_3)$_3$), 0.93 (t, *J* = 4.03 Hz, 3H, -CH_3), 0.97-1.02 (m, 2H, -CH_2-), 1.17-1.28 (m, 2H, -CH_2-), 1.69-1.75 (m, 1H, -CH-), 3.18-3.25 (m, 1H, -C*H*H-), 3.49-3.63 (m, 1H, -CH*H*-), 4.15 (t, *J* = 9.16 Hz, 2H, -CH_2-), 4.48 (d, *J* = 7.7 Hz, 1H, -CH-), 5.10 (br, 1H, NH), 7.24-7.34 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.93, 143.54, 129.25, 128.60, 127.79, 126.77, 74.23, 63.44, 63.39, 47.73, 41.74, 21.61, 19.16, 17.99, 12.13, 1.24 ppm; IR ν = 3391, 2958, 1694, 1519, 1251, 1064, 1041, 860, 837 cm^{-1}; MS (ESI) of $C_{17}H_{29}NO_3Si$ *m/z* 346.3 ([M+Na]$^+$).

Synthesis of (*R*)- 6-phenyl-1,3-oxazinan-2-one *R*-7a: A solution of ***S*-9a** (405 mg, 1.37 mmol) and triethylamine (380 µL, 2.74 mmol) in anhydrous THF (10 ml), was cooled to 0°C. Mesyl chloride (130 µL, 1.64 mmol) in THF (2 mL) was added dropwise. The reaction was stirred for 2 h, filtrated and the solvent evaporated in *vacuo*. ***R*-7a** was obtained as a white solid (179 mg, 74% yield). $[\alpha]^{20}_D$= +40.0 (c=0.5, $CHCl_3$). All characterization data are in agreement with previously reported for ***S*-7a**.

General synthesis for insertion of amino group in 1 position *S*-12a or *S,R*-11c: A solution of (*R*)-(+)-3-chloro-1-phenyl-1-propanol or *S,S*-**8c** (0.68 mmol) and triethylamine (190 µL, 1.36 mmol) in anhydrous THF (5 mL), was cooled to 0°C. Mesyl chloride (65 µl, 0.81 mmol) in THF (1 mL) was added dropwise. The reaction was stirred for 2 h, filtrated and the solvent evaporated in *vacuo*. The mesylated intermediate was used without any other purification step. The compound was dissolved in dry DMF (5 mL) and NaN_3 (65 mg, 1 mmol) was added. After stirring for 12 h at room temperature, water (2 mL) was added and the solution was extracted with diethyl ether (3x10 mL). The collected organic layers were washed with an aqueous solution of $NaHCO_3$, dried on Na_2SO_4, filtered and evaporated to give the azido compound. In a stainless steel autoclave (20 mL), equipped with temperature control and a magnetic stirrer, purged five times with hydrogen, a solution azido intermediate (0.67 mmol) in methanol with 1% of Pd/C was transferred. The autoclave was pressurised at 20 atm and kept under stirring at room temperature for four hours. The mixture was then filtered on Celite and the solvent was evaporated in *vacuo* to give the product

Intermediate (1-azido-3-chloropropyl)benzene: (130 mg, 97% yield). $[\alpha]^{20}_D$= -123.8 (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99-2.45 (m, 2H, -CH_2-), 3.35-3.54 (m, 1H, -C*H*H-), 3.56-3.82 (m, 1H, -CH*H*-), 4.75 (dd, *J* = 8.4, 6.0 Hz, 1H, -CH-), 6.99-7.81 (m, 5H, arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.80, 129.24, 128.86, 127.15, 63.33, 41.57, 39.16. ppm; IR ν = 3032, 2964, 2919, 2098, 1678, 1454, 1244, 760, 700 cm^{-1}; MS (ESI) of $C_9H_{10}ClN_3$ *m/z* 196.7 ([M+H]$^+$).

(*S*)-3-chloro-1-phenylpropan-1-amine *S*-12a: yellow pale oil (100 mg, 89% yield). $[\alpha]^{20}_D$= +5.4 (c=1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12 (dd, *J* = 13.5, 7.0, 3.1 Hz, 2H, -CH_2-), 3.01 (br, 2H, NH_2), 3.35-3.48 (m, 1H, -C*H*H-), 3.52-3.65 (m, 1H, -CH*H*-), 4.15 (t, *J* = 7.0 Hz, 1H, -CH-), 7.21-7.39 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ = 143.80, 128.64, 127.82, 127.49, 126.78, 126.48, 126.24, 57.51, 53.38, 41.56, 41.15, 30.01, 9.77 ppm; IR ν = 3352, 3270, 2933, 1602, 1453, 1348, 1072 cm^{-1}; MS (ESI) of $C_9H_{12}ClN$ *m/z* 170 ([M+H]$^+$).

Intermediate 2-(trimethylsilyl)ethyl((*S*)-2-((*R*)-azido(phenyl) methyl)butyl)car-bamate: $[\alpha]^{20}_D$= +51.8 (c=1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 9H, -C(CH_3)$_3$), 0.92 (t, *J* = 7.70 Hz, 3H, -CH_3), 1.25-1.39 (m, 2H, -CH_2-), 1.43-1.50 (m, 2H, -CH_2-), 1.83-1.86 (m, 1H, -CH-), 3.08-3.14 (t, *J* = 6.23 Hz, 2H, -CH_2-), 4.13 (t, *J* = 9.89 Hz, 2H, -CH_2-), 4.54 (d, *J* = 6.6 Hz, 1H, -CH-), 7.28-7.40 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.98, 138.29, 129.03, 128.72, 128.48, 128.25, 127.44, 126.65, 77.89, 77.26, 76.62, 68.22, 63.25, 45.93, 41.33, 20.67, 17.98, 11.36, -1.25 ppm; IR ν = 3339, 2956, 2100, 1704, 1524, 1250, 1176, 860, 838 cm^{-1}; MS (ESI) of $C_{17}H_{28}N_4O_2Si$ *m/z* 374.3 ([M+Na]$^+$).

2-(trimethylsilyl)ethyl ((*S*)-2-((*R*)-amino(phenyl) methyl) butyl)carbamate *S,R*-11c: colourless oil (76 mg, 35% total yield for three steps) $[\alpha]^{20}_D$= +6.46 (c=1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 9H, -C(CH_3)$_3$), 0.95 (t, *J* = 8.03 Hz, 3H, -CH_3), 1.15-1.42 (m, 4H, 2 x –CH_2-), 1.63-1.74 (m, 1H, -CH-), 2.85 (br, 2H, NH_2), 3.08-3.21 (m, 2H, –CH_2-), 4.09-4.13 (m, 3H, –CH_2- + -CH-), 5.85 (br, 1H, NH), 7.21-7.38 (m, 5H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.19, 143.25, 128.60, 128.25, 127.41, 127.03, 126.65, 126.17, 62.99, 57.91, 45.98, 41.94, 20.10, 17.99, 11.90, -1.25 ppm; IR ν = 3339, 2596, 1704, 1519, 1250, 860, 837 cm^{-1}; MS (ESI) of $C_{17}H_{30}N_2O_2Si$ *m/z* 323.2 ([M+H]$^+$).

General synthesis for sulphonamides in 1 position *S*-13a or *S,R*-12c: To a solution of *S*-**12a** or *S,R*-**11c** (0.53 mmol) in fresh-distilled dichloromethane, triethylamine (112 µL, 0.79 mmol) was added. The reaction mixture was then cooled to 4°C and stirred for half an hour. A solution of tosyl chloride (126 mg, 0.66 mmol) in dichloromethane was then dropped into the former solution and stirred overnight allowing the reaction mixture to reach room temperature. The reaction was monitored by TLC using EtOAc/hexane 1:1 as eluent.

(*S*)-*N*-(3-chloro-1-phenylpropyl)-4-methyl benzen sulfonamide *S*-13a: The product was obtained as a white solid by slow diffusion of hexane into the chloroform solution. (80 mg, 50% yield). $[\alpha]^{20}_D$= -6.5 (c=0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92–2.57 (m, 2H, -CH_2-), 2.35 (s, 3H, -CH_3), 3.19–3.27 (m, 1H, -C*H*H-), 3.32–3.51 (m, 1H, -CH*H*-), 4.52 (q, *J* = 7.4 Hz, 1H, -CH-), 5.55 (d, *J* = 7.6 Hz, 1H, NH), 7.00-7.16 (m, 7H, arom), 7.57 (d, *J* = 8.2 Hz, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.39, 139.81, 137.62, 129.95, 129.47, 128.88, 128.56, 127.96, 127.30, 126.79, 126.36, 55.98, 41.31, 40.16, 21.64 ppm; IR ν = 3436, 3265, 2965, 1600, 1458, 1325, 1161 cm^{-1}; Elemental analysis for $C_{16}H_{18}ClNO_2S$: C, 59.34; H, 5.60; N, 4.33; found: C, 58.98; H, 5.52; N, 4.21; MS (ESI) of $C_{16}H_{18}ClNO_2S$ *m/z* 346.3 ([M+Na]$^+$).

2-(trimethylsilyl)ethyl ((*S*)-2-((*R*)-((4-methylphenyl)sulfonamido)(phenyl)methyl) butyl)carbamate *S,R*-12c: colourless oil (100 mg, 40% yield). $[\alpha]^{20}_D$ = + 20.4 (c=0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 9H, -C(CH_3)$_3$), 0.88 (t, *J* = 8.06 Hz, 3H, -CH_3), 0.96 (t, *J* = 8.06 Hz, 2H, -CH_2-), 1.34-1.48 (m, 2H, -CH_2-),1.81-1.93 (m, 1H, -CH-), 2.30 (s, 3H, -CH_3), 3.18-

3.24 (m, 2H, -CH_2-), 4.18 (t, J = 6.78 Hz, 2H, -CH_2-), 4.49-4.56 (m, 1H, -CH-), 5.29 (br, 1H, NH), 5.49-5.53 (br, 1H, NH), 6.89-6.98 (m, 2H, arom), 7.04-7.14 (m, 5H, arom), 7.53 (d, J = 8.43, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.13, 143.34, 139.22, 137.52, 129.49, 128.44, 127.17, 126.56, 63.26, 58.20, 47.04, 41.22, 29.90, 21.63, 18.00, 11.82, -1.23 ppm; IR ν = 3382, 2597, 1694, 1532, 1251, 1160, 860, 838, 702 cm^{-1}; MS (ESI) of $C_{24}H_{36}N_2O_4SSi$ *m/z* 477.3 ([M+H]$^+$).

Synthesis of (*S*)-*N*-(3-azido-1-phenylpropyl)-4-methylbenzen sulfonamide *S*-14a: Compound **13a** (40 mg, 0.124 mmol) was dissolved in dry DMSO (5 mL) and NaN_3 (80 mg, 1.24 mmol) was added. After 24 h at 100°C, the solution was cooled to room temperature, water (2 mL) was added and the mixture was extracted with diethyl ether (3x5 mL). The collected organic layers were washed with an aqueous solution of $NaHCO_3$, dried on Na_2SO_4, filtered and evaporated to give the product ***S*-14a** as a white solid (40 mg, 97% yield). $[\alpha]^{20}_D$= -14.3 (c=0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.8-2.10 (m, 2H, -CH_2-), 2.57 (s, 3H, -CH_3), 3.01-3.33 (m, 2H, -CH_2-), 4.31 (dd, J = 8.1, 14.8 Hz, 1H, -CH-), 6.65 (d, J = 8.2 Hz, 1H, NH), 6.98-7.16 (m, 7H, arom), 7.46 (d, J = 7.8, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.43, 140.02, 137.72, 129.60, 129.45, 128.90, 128.57, 127.95, 127.28, 126.77, 126.56, 126.29, 56.12, 48.28, 36.59, 21.59 ppm; IR ν = 3232, 2963, 2091, 1599, 1455, 1323, 1156, 1088 cm^{-1}; Elemental analysis for $C_{16}H_{18}N_4O_2S$: C, 58.16; H, 5.49; N, 16.96; found: C, 58.26; H, 5.51; N, 17.08; MS (ESI) of $C_{16}H_{18}N_4O_2S$ *m/z* 353.3 ([M+Na]$^+$).

Synthesis of (*S*)-*N*-(3-amino-1-phenylpropyl)-4-methylbenzen sulfonamide *S*-2: In a stainless steel autoclave (20 mL), equipped with temperature control and a magnetic stirrer, purged five times with hydrogen, a solution of **14a** (40 mg, 0.121 mmol) in methanol with 1% of Pd/C was transferred. The autoclave was pressurised at 20 atm and kept under stirring at room temperature for four hours. The mixture was then filtered on Celite and the solvent was evaporated in *vacuo* to give the product ***S*-2** as a yellow pale oil (35 mg, 95% yield). $[\alpha]^{20}_D$= +5.4 (c=1.5, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85–2.05 (m, 2H, -CH_2-), 2.30 (s, 3H, -CH_3), 2.77-2.9 (m, 2H, -CH_2-), 4.46 (t, J = 6.5 Hz, 1H, -CH-), 6.97-7.16 (m, 7H, arom), 7.46 (d, J = 7.8 Hz, 2H, arom) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.82, 141.22, 138.12, 129.89, 129.36, 128.45, 127.21, 126.77, 126.56, 57.69, 38.89, 38.47, 21.57 ppm; IR ν = 3352, 3270, 2933, 2103, 1652, 1453, 1328, 1152, 1091, 953, 817 cm^{-1}; MS (ESI) of $C_{16}H_{20}N_2O_2S$ *m/z* 305.4 ([M+H]$^+$).

Synthesis of *N*-((*1R,2S*)-2-(aminomethyl)-1-phenylbutyl)-4-methylbenzenesulfonamide *R,S*-4: The synthesis proceeded as reported in literature.[37] The product was recovered as colourless oil (58 mg, 87% yield). $[\alpha]^{20}_D$ = +6.5 (c=1.3, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): δ = 0.86 (t, J = 7.33 Hz, 3H,-CH_3), 1.37-1.43 (m, 2H, -CH_2-), 2.25 (s, 3H, -CH_3), 2.46 (d, J = 6.97 Hz, 1H, -CH-), 3.73-3.82 (m, 2H, -CH_2-), 4.50 (d, J = 5.50 Hz, 1H, -CH-), 7.01-7.10 (m, 5H, arom), 7.43-7.51 (m, 4H, arom) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ = 143.16, 138.47, 138.03, 129.02, 128.21, 127.12, 126.84, 126.76, 65.67, 58.19, 44.69, 20.10, 19.71, 10.32 ppm; IR ν = 3252, 3063, 2968, 2353, 1661, 1598, 1455, 1325, 1159, 1091, 969, 814 cm^{-1}; MS (ESI) of $C_{18}H_{24}N_2O_2S$ *m/z* 333.4 ([M+H]$^+$).

Typical procedure for asymmetric transfer hydrogenation (ATH): A 10 mL Schlenk tube was loaded with [$RuCl_2$(*p*-cymene)]$_2$ (1 mmol), diamine ligand (2.2 mmol) and charged with distilled toluene (3 mL). The solution was refluxed at 110°C for 3 h. The solvent was removed in *vacuo*. To a solution of keto-substrate (0.5 mmol) in water (2 mL), [Ru(*p*-cymene)(diamine)Cl] (0.0025 mmol) in 20 μL DMSO and HCOONa as hydrogen donor (5 mmol, 10 eq.) were added. The reaction mixture was stirred at 40°C for 48 h and extracted with ethyl acetate (2x5 mL). The combined organic layers were dried with Na_2SO_4 and analysed by HPLC.

Analytical HPLC conditions: Chiralcel OD-H, eluent: hexane: ethanol = 95:5, flow = 0.8 mL/min, λ = 216 nm:

1-phenylethan-1-ol: rt: substrate 4.8 min, (*R*) = 5.4 min, (*S*) = 6.0 min.

1-(o-tolyl)ethan-1-ol: rt: substrate 6.3 min, (*R*) = 8.4 min, (*S*) = 9.0 min.

1-(3-methoxyphenyl)ethan-1-ol: rt: substrate 7.5 min, (*R*) = 12.6 min, (*S*) = 15.8 min.

1-(4-(trifluoromethyl)phenyl)ethan-1-ol: rt: substrate 6.3 min, (*S*) = 8.1 min, (*R*) = 8.4 min.

1-phenylpropan-1-ol: rt: substrate 7.1 min, (*R*) = 9.9 min, (*S*) = 10.9 min.

ethyl 4-hydroxy-4-phenylbutanoate: rt: substrate 12.8 min, (*R*) = 13.9 min, (*S*) = 14.6 min.

ethyl 3-hydroxy-3-phenylpropanoate: rt: substrate 7.7 min, (*S*) = 11.6 min, (*R*) = 14.6 min.

1,2,3,4-tetrahydronaphthalen-1-ol: rt: substrate 7.1 min, (*S*) = 8.7 min, (*R*) = 9.1 min.

Notes and references

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