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SYNTHESIS OF VERSATILE BIFUNCTIONAL DERIVATIVES OF CHIRAL DIAMINES OBTAINED THROUGH ANCHIMERICALLY ASSISTED NUCLEOPHILIC SUBSTITUTION REACTIONS ON DIASTEREOMERIC PHENYLPROLINOLS

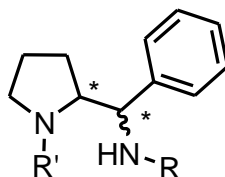
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Abstract Diastereomeric [(*S*)-1-benzylpyrrolidin-2-yl]-(*R*)-[(phenyl)methanamine] and [(*S*)-1-benzylpyrrolidin-2-yl]-(*S*)-[(phenyl)methanamine], were synthesized by selective internal backside nucleophilic substitution of the corresponding activated phenylprolinols. X-Ray diffraction structures of crystalline acetamide derivatives confirmed the anticipated stereochemistry for a S_NiB reaction mechanism. In order to apply this reaction to the synthesis of bifunctional analogs, a series of fragments such as a thiourea moiety and sulfonamide functions were introduced for the functionalization of the primary amino group in the substrate, obtaining more stable and potentially useful derivatives.

INTRODUCTION

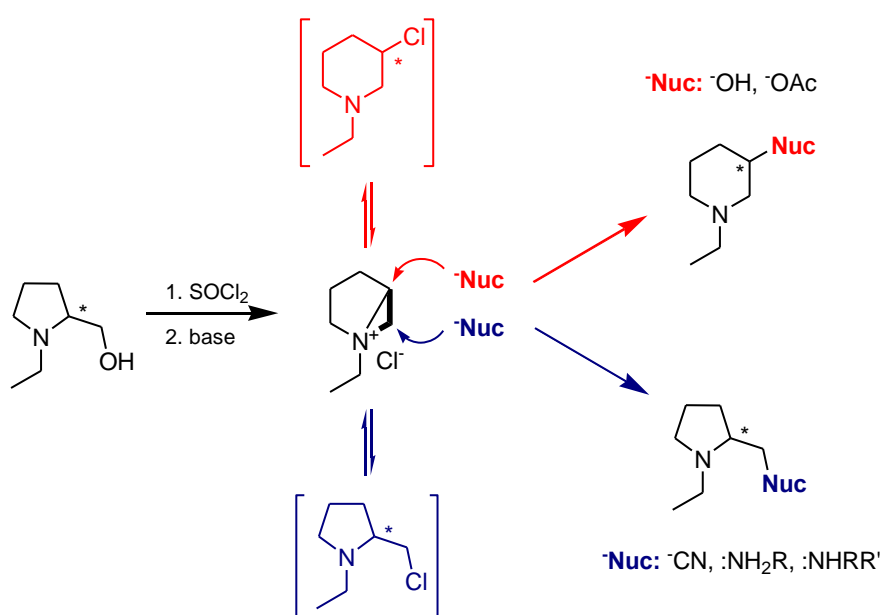
(*N*-Alkyl-pyrrolidin-2-yl)(phenyl)methanamine derivatives (Scheme 1) are useful pharmaceuticals in the treatment of diverse behavioural disorders such as: dementia, schizophrenia, and Parkinson's disease.¹



Scheme 1. Basic structure of pyrrolidine phenylmethanamine derivatives

Furthermore, the development of synthetic methodologies to obtain this type of chiral diamines is important because of the promising structural features which could make these molecules helpful in asymmetric catalysis either as organocatalysts *per se*² or as chiral ligands in coordination complexes used as catalysts.³

One of the principal routes for the preparation of β -aminopyrrolidines consists in the rearrangement reaction of piperidine or pyrrolidine derivatives *via* internal backside nucleophilic substitution ($S_{\text{N}}\text{ib}$).⁴ A salient feature of its mechanism is the anchimeric assistance of the heterocyclic nitrogen (Scheme 2).

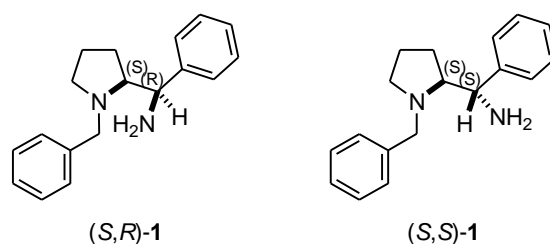


Scheme 2. Mechanism of the nucleophilic displacement reaction on 3-chloromethyl-*N*-ethylpyrrolidine

This anchimeric mechanism is well known since 1948⁵⁻⁷ and it was observed that strong nucleophiles such as amines are likely to favour formation of the pyrrolidinic framework, whereas weaker nucleophiles (OH^- , OAc^-) tend to generate mixtures of 5- and 6-membered ring products. Additionally, it is also worthy to mention that a similar behaviour is observed when linear β -aminoalcohols or polysubstituted pyrrolidinic β -aminoalcohols are used as starting materials in the Mitsunobu reaction.⁸

Nevertheless, the majority of recent studies have pursued the selective formation of six-membered derivatives,⁹ which exhibit biological activity as nonpeptidic NK-1 antagonists,¹⁰ anticancer drugs and anti-malarial agents.¹¹ In this context, the enantioselective ring expansion of prolinols, has been intensively studied by J. Cossy and coworkers,¹² whereas diverse methodologies have been developed to gain access to chiral piperidine derivatives¹³ and analogous nitrogenated heterocycles.¹⁴

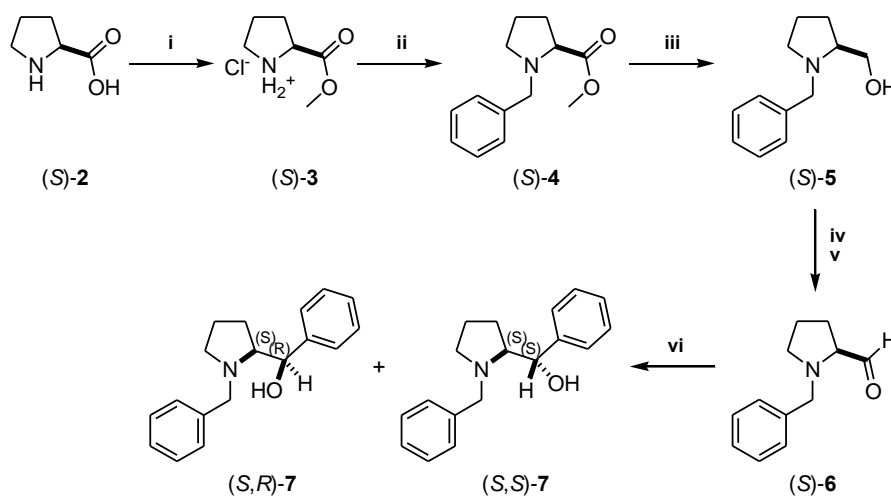
On the other hand, few reports have focused in the development of enantioselective preparation of aminomethyl-pyrrolidine derivatives.^{8b,15} In this report we present our approach for the enantioselective synthesis of [(*S*)-1-benzylpyrrolidin-2-yl]-(*R*)-[(phenyl)methanamine] and [(*S*)-1-benzylpyrrolidin-2-yl]-(*S*)-[(phenyl)methanamine], (*S,R*)-**1** and (*S,S*)-**1**, which are potential chiral building blocks for the preparation of new functionalized (*S*)-proline derivatives (Scheme 3).



Scheme 3. Diastereomeric (1-benzylpyrrolidin-2-yl)(phenyl)methanamines

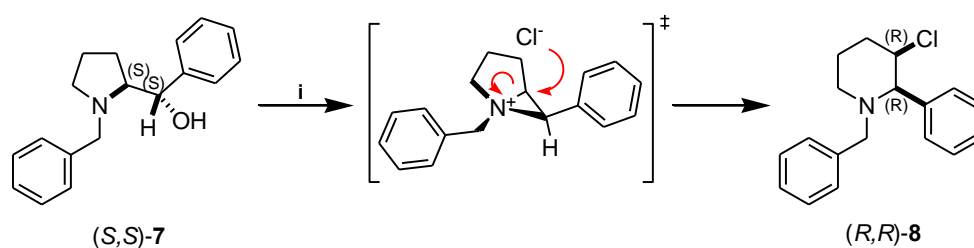
RESULTS AND DISCUSSION

Synthesis of azide precursors via S_N1b reaction on chlorophenylpiperidines derived from enantiopure carbinols (*S,R*)- and (*S,S*)-7**.** Diastereomeric (*N*-benzylpyrrolidin-2-yl)(phenyl)methanols, (*S,R*)- and (*S,S*)-**7** were prepared following a slightly modified synthetic methodology previously reported by Almansa *et al.*^{3a} (Scheme 4). In particular, increased reaction times were used for the Swern oxidation,¹⁶ and the Grignard reaction was carried out at room temperature, and LiBr was used instead of $CeCl_3$ to increase the reactivity of (unstable) aldehyde (*S*)-**6**.¹⁷ Commercially available phenylmagnesium bromide can be used although if prepared in situ, careful removal of bromine (generated from PhBr) is necessary to avoid side reactions.^{18,19}



Scheme 4. Reagents and conditions: (i) 4 equiv $SOCl_2$ added at 0 °C in MeOH then reflux, 3 h, 99% ; (ii) 1.1 equiv $PhCH_2Br$, 2.2 equiv Et_3N , CH_2Cl_2 , rt, 24 h, 90%; (iii) 3 equiv $LiAlH_4$ added at 0 °C to THF soln. and then reflux, 5 h, 98%; (iv) 3.0 equiv DMSO, 1.51 equiv $ClCOCOCl$, CH_2Cl_2 , -78 °C, 3 h; (v) 4.51 equiv Et_3N , 0 °C, 3 h, 99%. (vi) $PhMgBr$, LiBr, THF, rt, overnight.

The conversion of the hydroxy group in (*S,R*)- and (*S,S*)-**7** into the desired amino group was accomplished by first reacting each amino alcohol with methanesulfonyl chloride and then carrying out the displacement reaction with azide, using NaN_3 as the source of *N*-nucleophile. Specifically, the reaction between the amino alcohol (*S,S*)-**7** and mesyl chloride afforded halogenated piperidine (*R,R*)-**8**, which is the product of ring expansion. The immediate internal nucleophilic attack from the pyrrolidinic nitrogen towards the carbon attached to the ephemeral methanesulfonyl group gives rise to the formation of the aziridinium ion, which is opened by a second addition of the chloride ion present in the reaction (Scheme 5). This result is in accordance with those observed with 1-ethylpyrrolidine-2-methanol and other analogs.^{7,12}



Scheme 5. Reagents and conditions: (i) 1.6 equiv. Et_3N , 1.5 equiv MeSO_2Cl , CH_2Cl_2 , rt, 5 h

Light sensitive piperidine (*R,R*)-**8** was recrystallized to give suitable crystals for X-ray diffraction analysis, confirming the predicted relative configuration of both stereocenters (Figure 1).²⁰

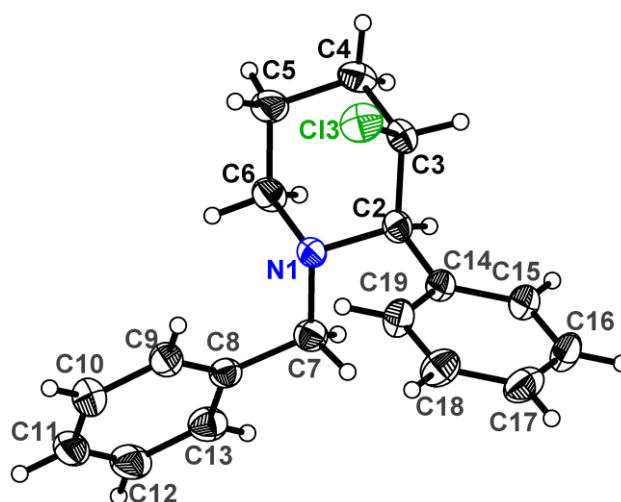
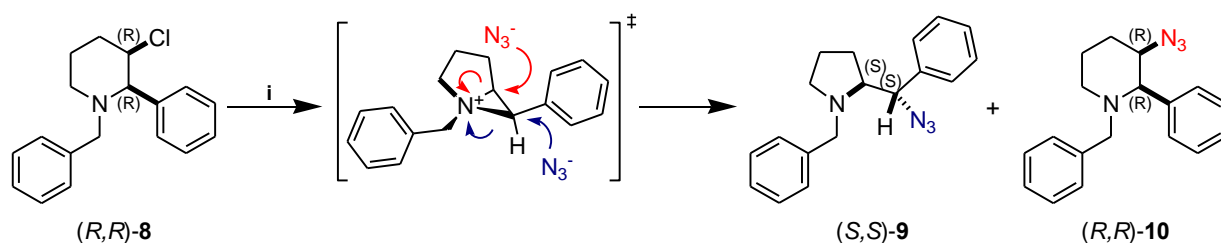


Figure 1. X-Ray diffraction structure and solid-state conformation of (*R,R*)-**8** (thermal ellipsoids shown at 30% probability)

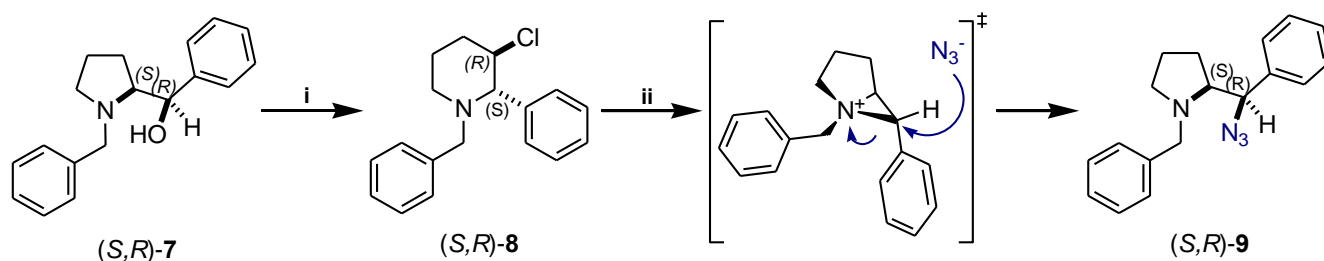
The chlorinated piperidine (*R,R*)-**8** was subjected to nucleophilic substitution reaction conditions using a solution of sodium azide in DMSO-DMF, and irradiated with microwaves for two hours (40 Watts) in order

to reduce the reaction time (ca. 8 h under normal heating conditions). Even though the desired pyrrolidinic derivative (*S,S*)-**9** was obtained, the main product corresponded to (*R,R*)-**10**, originating from ring expansion (Scheme 6).



Scheme 6. Reagents and conditions: (i) 1.1 equiv NaN₃, DMF:DMSO (4:1), MW 40 watts, 55 °C, 2 h, 90% overall yield, (*S,S*)-**9**:(*R,R*)-**10** (1:1.75)

By contrast, amino alcohol (*S,R*)-**7** gave rise to the analogous chloropiperidine (*S,R*)-**8** as described previously by Langlois *et al.*^{9b} However, it is important to point out that when (*S,R*)-**8** reacted with NaN₃ under the same conditions used with (*R,R*)-**8**, this conveniently afforded only the target azide (*S,R*)-**9** (Scheme 7). The regioselective attack of the nucleophile can be explained by the development of a partial positive charge in the transition state, which seems to be more stabilized at the C–Ph atom (Scheme 7).²¹



Scheme 7. Reagents and conditions: (i) 1.6 equiv Et₃N, 1.5 equiv MeSO₂Cl, CH₂Cl₂, rt, 5 h, 89%. (ii) 1.1 equiv NaN₃, DMF:DMSO (4:1), MW, 40 watts, 55 °C, 2 h, 90%.

The contrasting reactivity behaviour in (*S,R*)-**8** and (*R,R*)-**8** might be explained as follows: in the case of the aziridinium ion generated from chloropiperidine (*S,R*)-**8**, the bulky *N*-benzyl and phenyl groups are oriented to the same side (*syn*), which provokes steric repulsion that might induce an elongation and weakening of the N–C(Ph) bond. This effect facilitated the selective azide attack leading to the selective formation of pyrrolidinic product. By contrast, in the case of chloropiperidine (*R,R*)-**8**, the *N*-benzyl group is oriented *anti* to the phenyl group, so that no repulsive steric interaction between these groups takes place, and non-selective azide attack generates a mixture of the five and six-membered heterocyclic products.

Figure 2 compares the NMR spectra of azides (*S,R*)-**9**, (*S,S*)-**9**, and (*R,R*)-**10**, where the assignments were based on one- and two-dimensional NMR experiments. Salient observations are, (1) $^3J_{1/5} = 3.72$ Hz in (*S,R*)-**9** is smaller than $^3J_{1/5} = 7.45$ Hz in (*S,S*)-**9**, which is similar to the trend observed in the corresponding starting amino alcohols (*S,R*)- and (*S,S*)-**7**. (2) Upfield shifts are observed for protons farther from the substituted carbons and for exocyclic methine proton H(5) in azide (*S,S*)-**9**, with respect to those of its (*S,R*)-**9** diastereomer. (3) The methine proton H(1) in (*S,S*)-**9** appears at lower field relative to the same proton in diastereomer (*S,R*)-**9**. (4) The difference in chemical shifts for the AB system in benzylic protons H(6) is largest in (*R,R*)-**10** relative to both diastereomers (*S,S*)-**9** and (*S,R*)-**9**.

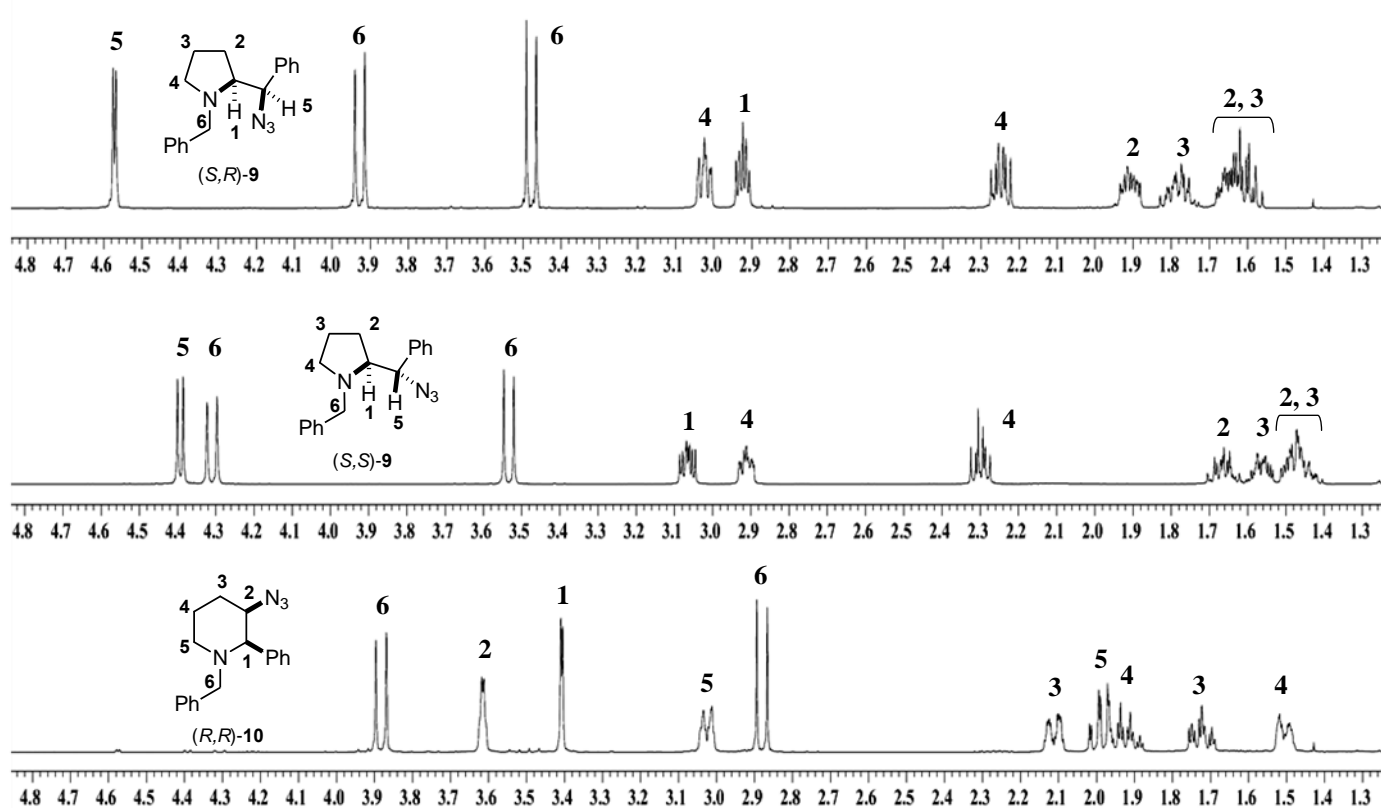
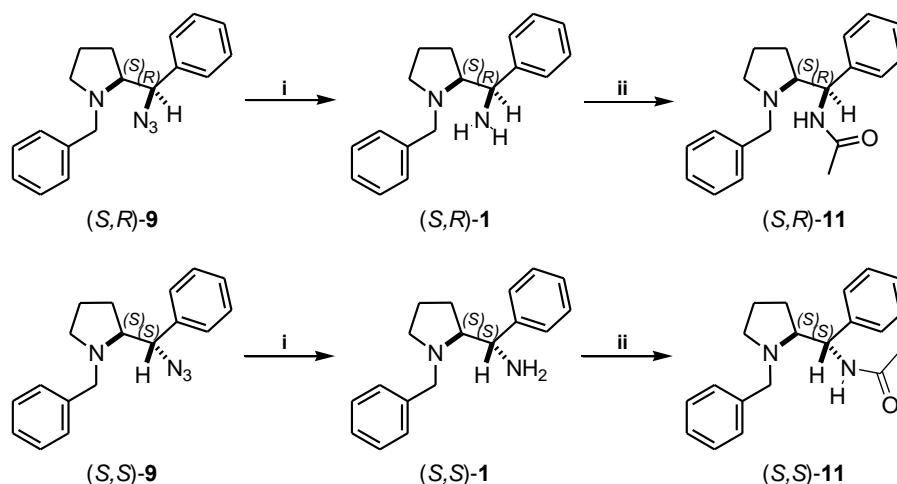


Figure 2. Segments of the ^1H NMR spectra of (*S,R*)-**9**, (*S,S*)-**9** and (*R,R*)-**10**

Confirmation of the configurational assignment by means of X-Ray diffraction analysis.

Reduction of the azide function by means of catalytic hydrogenation afforded the diastereomeric *N*-benzylated diamines, (*S,S*)-**1** and (*S,R*)-**1**, which were acetylated to give crystalline derivatives (*S,S*)-**11** and (*S,R*)-**11** (Scheme 8).



Scheme 8. Reagents and conditions: (i) H_2 , 60-70 psi, EtOH, rt, 2-3 h, 90-96%. (ii) 1.3 equiv Et_3N , 1.2 equiv MeCOCl , THF, rt, 48 h, 62% yield for $(S,R)\text{-11}$ and 90% for $(S,S)\text{-11}$

Figure 3 presents the structure and solid-state conformation of compounds $(S,S)\text{-11}$ and $(S,R)\text{-11}$. In these structures^{22,23} it is possible to confirm the anticipated configurations for the stereogenic centers in each diastereomer, allowing for the unambiguous conclusion that amino alcohol $(S,R)\text{-7}$ led to azide $(S,R)\text{-9}$ by a double nucleophilic attack ($\text{S}_{\text{N}}2\text{ib}$) *via* the aziridinium ion intermediate from piperidine $(S,R)\text{-8}$. A similar conclusion can be reached for amino alcohol $(S,S)\text{-7}$, which gives rise to the corresponding azide $(S,S)\text{-9}$ with overall retention of configuration. The orientation of the hydrogen atoms bonded to the stereogenic carbons is also appreciated. For amide $(S,S)\text{-11}$ these hydrogens are oriented in opposite direction (*anti*) while in the diastereomer $(S,R)\text{-11}$ they are *gauche*-oriented.

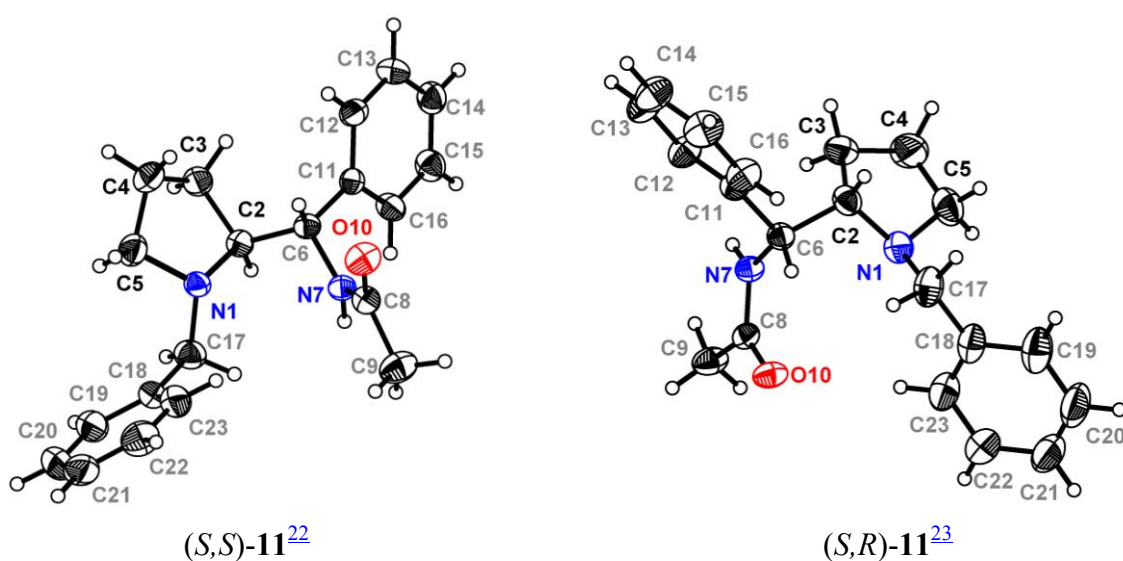
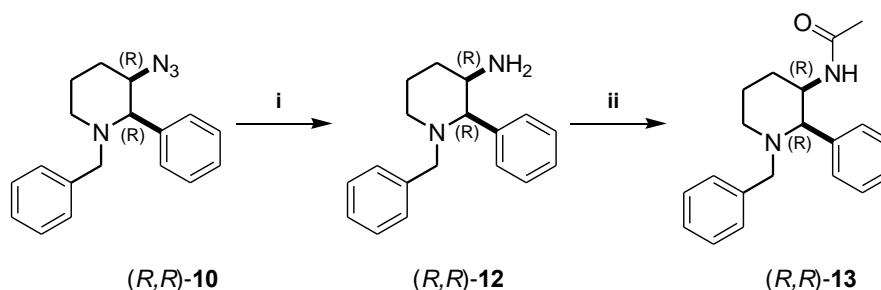


Figure 3. X-Ray crystallographic structure and solid-state conformation of $(S,S)\text{-11}$ and $(S,R)\text{-11}$ (Thermal ellipsoids of 30% probability)

Azido-piperidine (*R,R*)-**10** was reduced according to the same procedure followed in the reduction of (*S,S*)-**9** and (*S,R*)-**9** affording diamine (*R,R*)-**12**, which was also acetylated to give crystalline amide (*R,R*)-**13** (Scheme 9).



Scheme 9. Reagents and conditions: (i) H₂, 70 psi, EtOH, rt, 17 h, 95%. (ii) 1.3 equiv Et₃N, 1.2 equiv MeCOCl, THF, rt, 48 h, 79%.

Figure 4 presents the structure and solid-state conformation of (*R,R*)-**13** obtained by X-ray diffraction analysis. The *cis* configuration of the substituents at the stereogenic carbons is clearly appreciated, and this observation helps discard the possibility of a simple nucleophilic substitution in (*R,R*)-**8**, that would have resulted in inversion of the configuration at C(3).

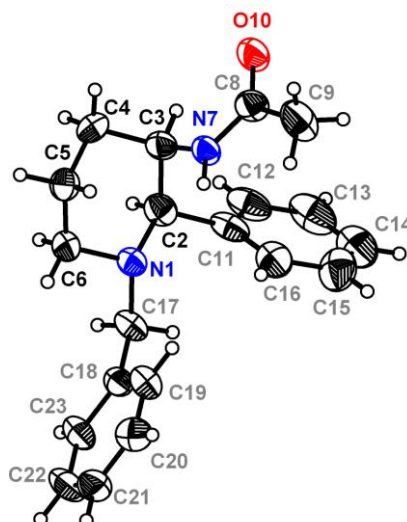
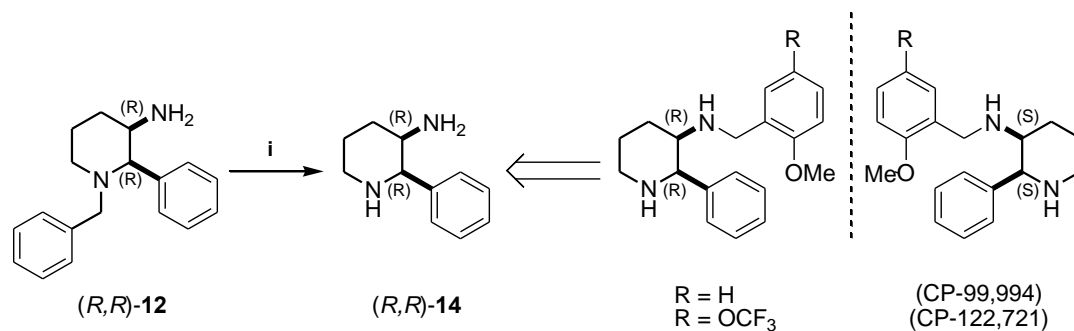


Figure 4. X-Ray diffraction crystallographic structure and solid-state conformation of (*R,R*)-**13** (ellipsoids shown at 30% probability)²⁴

Debenzylation reaction to obtain pharmacophore (*R,R*)-**14**.

Deprotection of diamine (*R,R*)-**12** afforded derivative (*R,R*)-**14**, that offers an attractive strategy for the enantioselective preparation of various commercial drugs such as CP-122,721, CP-99994, among others, which are important neurokinin-1 receptor antagonists (Scheme 10).^{10b,13a}



Scheme 10. Reagents and conditions: (i) 1000 psi H_2 , 15% w-w $Pd(OH)_2$, EtOH, 60 °C, 80%

Conversion of the primary amino group into a thiourea moiety.

Chiral thioureas are important compounds due to its great versatility as Brønsted acid activators of prochiral substrates,²⁵ chiral solvating agents in the enantiodiscrimination of carboxylic compounds,²⁶ and more recently as catalysts in organocatalytic Mannich, aza-Henry, and Michael reactions (Figure 5).²⁷

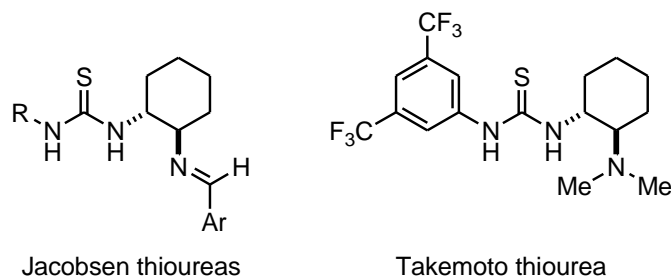
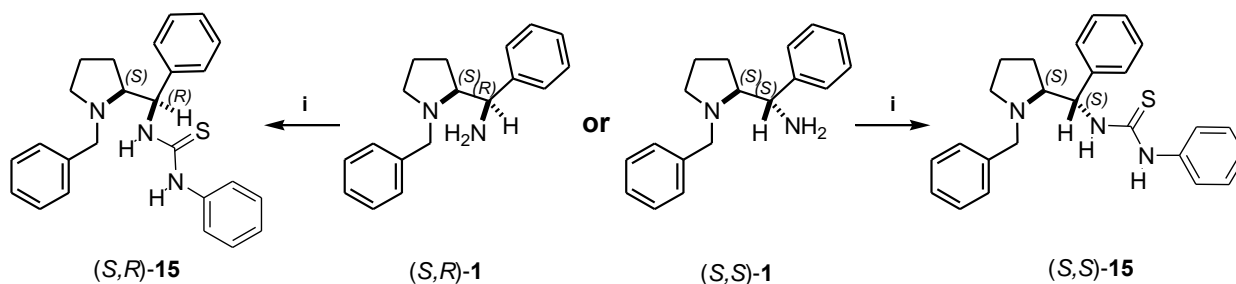


Figure 5. Examples of important thiourea organocatalysts

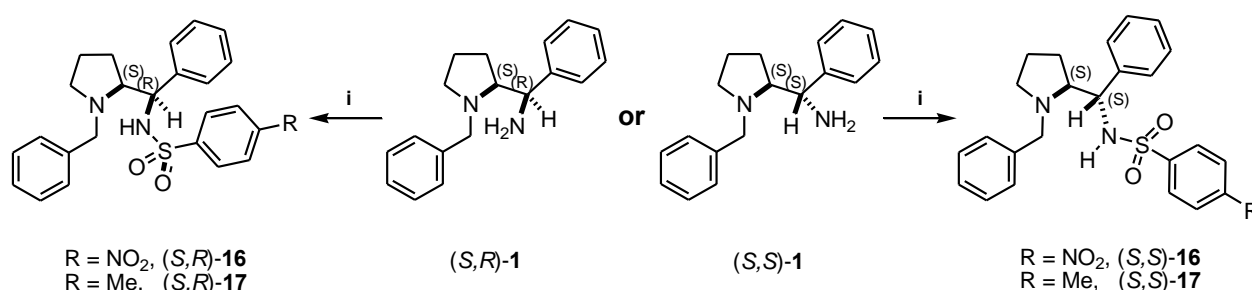
The conversion of primary amino group of derivatives (S,R) -1 and (S,S) -1 into a thiourea moiety was easily carried out by treatment of each diamine with phenyl isothiocyanate at room temperature, giving rise to the expected thioureas (S,R) -15 and (S,S) -15 (Scheme 11).²⁸



Scheme 11. Reagents and conditions: (i) 1.6 equiv $Ph-N=C=S$, THF, rt, 2 days, 70-71% for both diastereomers

Incorporation of a sulfonamide function at the amino group.

We also developed the synthesis of sulfonamide derivatives as described in Scheme 12, and it was possible to obtain a crystal structure of compound (*S,R*)-**17**, which is shown in Figure 6.



Scheme 12. Reagents and conditions: (i) 1.1 equiv Et_3N , 1.05 equiv ArSO_2Cl , THF, rt, 12 h. (*S,R*)-**16**, 67%; (*S,S*)-**16**, 69%; (*S,R*)-**17**, 67%; (*S,S*)-**17**, 78%

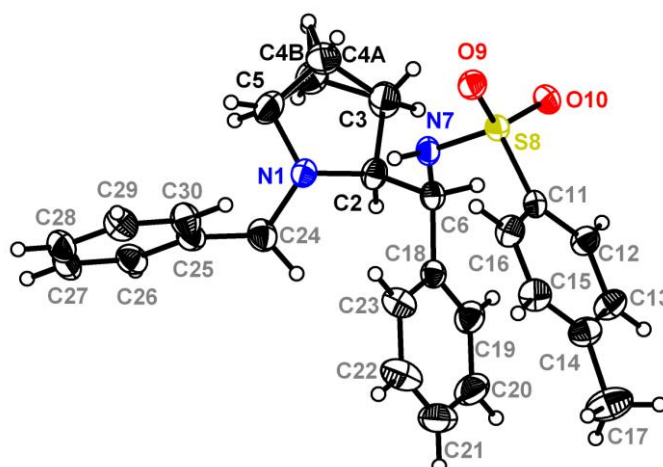


Figure 6. X-Ray diffraction crystallographic structure and solid-state conformation of (*S,R*)-**17** (Thermal ellipsoids shown at 30% probability). Splitting of the position in C(4) was required because of the presence of disorder in the organization of the crystalline lattice of sulfonamide molecules.²⁹

CONCLUSIONS

Pyrrolidinic diamines (*S,R*)-**1** and (*S,S*)-**1** were synthesized by anchimerically assisted nucleophilic substitution reaction ($\text{S}_{\text{N}}\text{iB}$) from carbinols (*S,R*)-**7** and (*S,S*)-**7**, respectively. The overall retention of configuration could be confirmed by analysis of the NMR spectra of azides (*S,R*)-**9** and (*S,S*)-**9** and by examination of X-ray structures of crystalline derivatives (*S,R*)-**11** and (*S,S*)-**11**.

The ring-expansion product (*R,R*)-**10** was obtained solely from the diastereomeric carbinol (*S,S*)-**7**, as corroborated through the X-Ray crystallographic structure of its aminoamide derivative (*R,R*)-**13**. The relevant pharmacophore (*R,R*)-**14** could be readily prepared from (*R,R*)-**10**.

Finally, a variety of bifunctional compounds with potential applications in asymmetric catalysis could be generated in good yields *via* the incorporation of thiourea and sulfonamide moieties in (*S,R*)-**1** and (*S,S*)-**1**.

EXPERIMENTAL

General

Commercially available reagents were used as received. Anhydrous solvents were obtained by routine distillation techniques.³⁰ TLC: Merck DC-F254 plates, detection UV light, iodine vapor. Flash chromatography: Merck silica gel (0.040–0.063 mm). Melting points: Melt Temp 'Electrothermal' apparatus, uncorrected. Optical rotations were measured in a Perkin-Elmer 241 polarimeter. NMR spectra were obtained with JEOL GSX-270 (270 MHz), Bruker Advance 300 (300 MHz), JEOL Eclipse 400 (400 MHz) and Jeol ECA-500 (500 MHz) spectrometers. Chemical shifts (δ) are given in parts per million relative to tetramethylsilane as internal reference, giving coupling constants J in hertz (Hz). IR spectra were recorded on a Varian Model 640 apparatus. Mass spectra were obtained in a Hewlett–Packard HP-5986 instrument 5989-AMS-ENGINE, Thermo Electron Trace-DSQ spectrometer, at 20 eV. High-resolution mass spectra (HRMS) were obtained on one HPLC 1100 coupled to MSDTOF Agilent Technologies apparatus mod. 1069A. Elemental analyses were obtained using a Thermo-Finnigan CHNS/O 1112 apparatus. The structural X-ray crystallographic data were obtained on an Enraf-Nonius Kappa CCD diffractometer. Microwave irradiation experiments were achieved in a single-mode Discover System reactor from CEM Corporation.

Synthesis of (*S*)-proline methyl ester hydrochloride, (*S*)-3**.** SOCl_2 (76 mL, 1.04 mol) was added dropwise to a solution of (*S*)-proline (28.64 g, 0.25 mol) in MeOH (500 mL) at 0 °C. When the addition was complete, the mixture was refluxed for 2.5 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resultant (*S*)-**3** was obtained in 99% yield (42 g, 0.25 mol) as pale yellow oil and was used in the alkylation step without further purification. $[\alpha]_D^{25}$ -34 (c 3.66, MeOH) {lit.,³¹ $[\alpha]_D^{25}$ -33.9 (c 3.55, MeOH)}; δ_{H} (D_2O , 270 MHz): 2.35–2.52 (m, 3H); 2.71–2.78 (m, 1H); 3.64–3.88 (m, 3H); 4.16 (s, 3H). δ_{C} (D_2O , 68 MHz): 23.8, 28.6, 47.0, 54.4, 60.2, 170.9. Spectroscopic data in accordance with those reported in lit.³¹

Synthesis of *N*-benzyl (*S*)-proline methyl ester, (*S*)-4**.** Et_3N (77 mL, 55.9 g, 0.55 mol) was added dropwise to a cold solution of (*S*)-**3** (41.2g, 0.25 mol) in dry CH_2Cl_2 under inert atmosphere. Then, benzyl bromide (33.2 mL, 47.74 g, 0.28 mol) was added to the thick reaction mixture, allowing it to reach room temperature after complete addition. This solution was stirred during 17 h and latter, it was extracted with CH_2Cl_2 (3 x 400 mL). The combined organic layers were dried over MgSO_4 . After filtration and evaporation of the solvents, the crude residue was purified by distillation under reduced pressure (120 °C,

0.5-1 mmHg), giving 49.6 g (0.23 mol) of the product, (*S*)-**4**, as a clear oil in 91% yield. R_f 0.7 (hexane:AcOEt, 7:3), $[\alpha]_D^{25}$ -65 (*c* 3.0, CH₂Cl₂) {Aldrich, 97% ee, $[\alpha]_D^{25}$ -62.0 (neat)}, δ_H (CDCl₃, 300 MHz): 1.71-1.79 (m, 1H); 1.88-2.0 (m, 2H); 2.06-2.17 (m, 1H); 2.39 (dd, 1H, $J = 17$ Hz); 3.0-3.08 (m, 1H); 3.25 (dd, 1H, $J = 6.4$ Hz); 3.57 (d, 1H, $J = 12.75$ Hz); 3.64 (s, 3H); 3.89 (d, 1H, $J = 12.75$ Hz); 7.24-7.35 (m, 5H). δ_C (CDCl₃, 75 MHz): 23.4, 29.8, 52.1, 53.7, 59.2, 65.7, 127.5, 128.6, 129.7, 138.5, 174.9. Chemical shifts in accordance with those reported in the literature.³²

Reduction of amino ester (*S*)-4** to obtain *N*-benzyl (*S*)-prolinol, (*S*)-**5**.** 25.75 g (0.68 mol) of LiAlH₄ were slowly added *via* powder funnel to a cooled solution of (*S*)-**4** (49.6 g, 0.23 mol) in anhydrous THF (400 mL) under N₂. After stirring for one hour at 0 °C, the suspension was allowed to reach room temperature and then, it was refluxed during 3 h. The mixture was cooled again at 0 °C in order to quench the reaction. Quenching was carried out by carefully adding the cold content on 1.5 L of ice, this last in turn contained in a 4 L Erlenmeyer flask equipped with a cooling bath. Once the frost has melted, the resulting magnesia is poured onto a celite pad to remove suspended alkalis and the solid residue was washed with 300 mL of hot AcOEt. The resultant biphasic filtrate was separated and THF was removed from the aqueous layer in a rotary evaporator, extracting again the residual liquid previously cooled with a similar amount of AcOEt. The combined organic layers were dried with Na₂SO₄ and concentrated, and the crude was distilled under reduced pressure (110 °C, 1.5 mmHg), obtaining 41.8 g (0.22 mol) of the desired amino alcohol (*S*)-**5** as a colourless liquid in 97% yield. R_f 0.4 (hexane:AcOEt, 7:3), $[\alpha]_D^{25}$ -60 (*c* 1.0, CHCl₃) {lit.,³³ $[\alpha]_D^{25}$ -59.9 (*c* 1.0, CHCl₃)}, δ_H (CDCl₃, 500 MHz): 1.60-1.69 (m, 2H); 1.78 (sext., 1H, $J = 6.5$ Hz); 1.84-1.92 (m, 1H); 2.23 (dd, 1H, $J = 0.95$ Hz, 8.45 Hz); 2.64-2.59 (m, 1H); 2.92 (quint., 1H, $J = 4.7$ Hz); 3.26 (br, 1H); 3.31 (d, 1H, $J = 12.95$ Hz); 3.45 (dd, 1H, $J = 2.65$ Hz, 10.8 Hz); 3.59 (dd, 1H, $J = 3$ Hz, 10.75 Hz); 3.95 (d, 1H, $J = 12.95$ Hz); 7.18-7.23 (m, 1 H); 7.27 (d, 4H, $J = 4.05$ Hz). δ_C (CDCl₃, 125 MHz): 23.45, 27.94, 54.57, 58.86, 62.41, 64.56, 127.13, 128.53, 128.91, 139.40. IR (ATR, cm⁻¹): ν_{max} 3420, 3060, 3026, 2960, 2872, 2796, 1738, 1602, 1494, 1452, 1374, 1352, 1250, 1210, 1076, 1030, 912, 848, 740, 700. Spectroscopic data in accordance with those reported in the literature.³⁴

Swern Oxidation of *N*-benzylprolinol (*S*)-5** to the corresponding aldehyde, (*S*)-**6**.** 21.05 mL (31.56 g, 0.25 mol) of oxalyl chloride were dissolved with 600 mL of dry CH₂Cl₂ under nitrogen atmosphere in a 2-L three-necked round bottomed flask equipped with magnetic stirring, two addition funnels and two or three evolving gas traps. The solution was cooled at -78 °C and then, 38.6 mL of DMSO (42.4 g, 0.54 mol) were added dropwise, allowing time for the system to depressurise the immediately evolved CO₂. After completion of addition, the reaction mixture was stirred during one hour. Then, 41.8 g (0.22 mol) of (*S*)-**5** dissolved in 100 mL of dry CH₂Cl₂ were added over a period of 20 min. The resulting thick mixture was left under these conditions for 3 h more and latter, Et₃N (142 mL, 103 g, 1.02 mol) were added

leaving the reaction mixture to reach 0 °C and stirring during 3 h at this temperature. Then, 300 mL of brine were added and the organic layer was washed thrice to remove the maximum amount of Me₂S. The organic layer was dried over Na₂SO₄ and after filtration and evaporation of the solvent; the resultant crude aldehyde (*S*)-**6** was dried under vacuum for a prolonged period. Then, 39 g of aldehyde (*S*)-**6** were obtained (94.2% yield) as a crude orange oil which was used in the next step without further purification due to quick decomposition. R_f 0.5 (hexane/AcOEt, 7:3), δ_H (CDCl₃, 270 MHz): 1.79-1.91 (m, 4H); 2.34-2.44 (m, 1H); 2.95-3.02 (m, 1H); 3.06-3.15 (m, 1H); 3.65 (d, 1H, *J* = 12.9); 3.75 (d, 1H, *J* = 12.9); 7.22-7.35 (m, 5H); 9.3 (dd, 1H, *J* = 3.7 Hz, 0.78 Hz). δ_C (CDCl₃, 68 MHz): 23.47, 26.51, 53.99, 59.44, 71.55, 127.34, 128.82, 129.08, 138.31, 202.75. HR-ESI-TOF [M+H]⁺ (*m/z*) calculated for C₁₂H₁₆NO: 190.1226; found: 190.1226, (error = -0.2141). Chemical shifts in accordance with those reported in the literature.³⁵

Grignard reaction to obtain the mixture of diastereomeric amino alcohols (*S,R*)- and (*S,S*)-7**.** 27.5 g (1.13 mol) of clean Mg and 200 mL of anhydrous THF were added in a 1-L round-bottomed flask equipped with a magnetic stir bar and conditioned with inert atmosphere. Afterwards, 119 mL (177 g, 1.13 mol) of freshly distilled bromobenzene were added dropwise to the cooled heterogeneous mixture. Once the content became homogeneous, 17.9 g (0.21 mol) of LiBr dissolved in 100 mL of anhydrous THF were added at 0 °C to the Grignard solution and stirred during 1 h at this temperature. Then, 39 g (0.21 mol) of (*S*)-**6** dissolved in dry THF (100 mL) were added *via* cannula and the final solution was stirred during 4 h at 0 °C and left to reach room temperature overnight. The reaction was quenched by adding in cold 200 mL of a saturated aqueous solution of NH₄Cl. When Grignard reagent was eliminated, filtering and washing of solid precipitates, and extraction of residual liquids were carried out following the same techniques described above for (*S*)-**5**. AcOEt was evaporated under vacuum obtaining the diastereomeric mixture crude. Amino alcohols were separated by column chromatography using gradient (hexane:AcOEt, 95:5→85:15), obtaining 23.71 g (0.09 mol) of (*S,R*)-**7** and 21.9 g (0.08 mol) of (*S,S*)-**7** (d. r. 52:48, 81% overall yield).

(*R*)-[(2*S*)-1-Benzylpyrrolidin-2-yl](phenyl)methanol, (*S,R*)-7**.** Yellow oil; R_f 0.55 (hexane/AcOEt, 7:3) [α]_D²⁵ -69 (*c* 1.16, CHCl₃) {lit.,^{3a} [α]_D²⁵ -69.2 (*c* 1.3, CHCl₃)}, δ_H (CDCl₃, 400 MHz): 1.28-1.43, 1.6-1.83 (1H and 3H, respectively, 2m, CH₂CH₂CH), 2.36 (1H, q, *J* = 8.65 Hz, 1 x CH₂CHHN), 2.89-2.98 (1H, m, CH-CHOH), 3.03-3.14 (1H, m, 1 x CH₂CHHN), 3.5, 4.22 (1H each, 2d, *J* = 12.88 Hz each, CH₂Ph), 4.93 (1H, d, *J* = 2.92 Hz, CH-OH), 7.34-7.59 (10H, m, ArH); δ_C (CDCl₃, 100 MHz): 23.3, 24.1 (CH₂CH₂CH), 54.81 (CH₂CH₂N), 58.36 (NCH₂Ph), 69.28 (CH₂CHN), 70.22 (CH-OH), Ar: 125.61, 126.9, 127.31, 128.24, 128.55, 128.91, 139.11 (*C-ipso*), 141.63 (*C-ipso*). Chemical shifts and other spectroscopic data are in agreement with those reported in the literature.^{3a}

(S)-[(2S)-1-Benzylpyrrolidin-2-yl](phenyl)methanol, (S,S)-7. White solid, mp 72-74 °C (AcOEt/hexane); R_f 0.33 (hexane/AcOEt, 7:3); $[\alpha]_D^{25} +118.3$ (c 1.04, CHCl₃) {lit.,^{3a} $[\alpha]_D^{25} +101.8$ (c 1.1, CHCl₃)}, δ_H (CDCl₃, 270 MHz): 1.71–1.84, 1.91–2.04 (3H and 1H, respectively, 2m, CH₂CH₂CH), 2.36–2.48, 2.92–3.01 (1H each, 2m, CH₂CH₂N), 3.05–3.14 (1H, m, -CHN), 3.35, 3.66 (1H each, 2d, $J = 12.9$ Hz each, N-CH₂Ph), 4.39 (1H, d, $J = 5.2$ Hz, *CH-OH), 7.20–7.41 (10H, m, ArH); δ_C (CDCl₃, 68 MHz): 24.26, 29.33 (CH₂CH₂CH), 54.22 (CH₂CH₂N), 61.19 (NCH₂Ph), 70.15 (CH₂CHN), 75.19 (CH-OH), Ar: 126.12, 127.03, 127.10, 128.24, 128.32, 128.65, 139.40 (C-*ipso*), 143.69 (C-*ipso*). Chemical shifts and other spectroscopic data are in agreement with those reported in the literature.^{3a}

General procedure for the synthesis of 1-benzyl-3-chloro-2-phenylpiperidines. A determined amount of the required diastereomer **7** was dissolved with CH₂Cl₂ in a three-necked round-bottomed flask equipped with magnetic stirring and conditioned with nitrogen atmosphere. Subsequently, 1.6 equivalents of Et₃N and 1.5 equivalents of MeSO₂Cl are simultaneously added at 0 °C. The reaction mixture was left stirring during three more hours at this temperature. After this time, the reaction was ended by extracting twice with saturated aqueous solution of NaHCO₃ and latter with brine, then the organic layer was dried with Na₂SO₄. Activated charcoal is incorporated to the organic phase and the mixture was slightly heated before pouring onto a compressed celite pad in a porous glass filter. Solvent was evaporated under reduced pressure and the resultant oil is dissolved again in a minimum volume of heated hexane:AcOEt (95:5) mixture. The saturated solution is cooled thus precipitating colourless crystals which were filtrated and dried under vacuum.

(2R,3R)-1-Benzyl-3-chloro-2-phenylpiperidine, (R,R)-8. The general procedure described above was followed with 5.5 g (0.02 mol) of (S,S)-**8**, 4.6 mL (3.34 g, 0.03 mol) of Et₃N and 2.4 mL (3.55 g, 0.03 mol) of MeSO₂Cl and 100 mL of CH₂Cl₂ to afford the desired piperidine (R,R)-**8** (5.8 g, 98.4% yield), as a colourless solid, mp 94-96 °C (AcOEt/hexane); R_f 0.58 (hexane/AcOEt, 9:1); $[\alpha]_D^{25} +20$ (c 1.07, CHCl₃), δ_H (CDCl₃, 500 MHz): 1.48-1.55, (m, 1H, CH₂-CH₂-CH₂-), 1.96 (tdd, 1H, $J = 13.5, 3.5, 3.2$ Hz, -CHCl-CH₂-), 2.04 (td, 1H, $J = 12.0, 3.2$ Hz, -CH₂-N), 2.14-2.25 (m, 2H, -CHCl-CH₂-CH₂-), 2.93 (d, 1H, $J = 14.0$ Hz, NCH₂Ph), 3.06 (ddd, 1H, $J = 12.0, 5.0, 3.2$ Hz, -CH₂-CH₂-N), 3.54 (d, 1H, $J = 2.2$, -CHPh-CHCl-), 3.93 (d, 1H, $J = 14.0$ Hz, NCH₂Ph), 4.22 (ddd, 1H, $J = 3.2, 2.2, 1.7$ Hz, CHPh-CHCl), 7.18-7.37 (m, 8H, ArH), 7.46-7.51 (m, 2H, Ar). δ_C (CDCl₃, 125 MHz): 20.07 (CH₂-CH₂-CH₂-), 33.56 (-CHCl-CH₂-), 53.28 (CH₂-N), 59.17 (NCH₂Ph), 64.00 (-CHCl-), 71.38 (-CHPh-CHCl-), ArC: 126.73, 127.57, 127.93, 128.14, 128.57, 129.00, 138.85 (NCH₂Ph, *Cipso*), 140.52 (-CHPh-CHCl-, *Cipso*). IR (ATR, cm⁻¹): ν_{max} 3060, 3023, 2954, 2929, 2804, 1600, 1492, 1449, 1315, 1304, 1133, 1099, 1065, 1028, 996, 941, 885, 755, 737, 703, 640, 600. HR-ESI-TOF [M+H]⁺ calculated for C₁₈H₂₁ClN: 286.1357; found: 286.1357 (error = -0.0139).

(2*S*,3*R*)-1-Benzyl-3-chloro-2-phenylpiperidine, (*S,R*)-8. The general procedure described for the synthesis of piperidines was followed with 4.0 g (0.02 mol) of (*S,R*)-8, 3.34 mL (2.43 g, 0.02 mol) of Et₃N and 1.74 mL (2.58 g, 0.02 mol) of MeSO₂Cl and 80 mL of CH₂Cl₂ to afford the desired piperidine (*S,R*)-8 (4.27 g, 99% yield), as a colourless solid, mp 60-61 °C (AcOEt/hexane); R_f 0.67 (hexane/AcOEt, 9:1); [α]_D²⁵ +25 (c 1.0, CHCl₃), {lit.,^{9b} [α]_D²⁹⁸ +27(c 1.6, CHCl₃)}, δ_{H} (CDCl₃, 500 MHz): 1.63-1.81 (m, 3H); 2.00-2.06 (m, 1H); 2.35-2.40 (m, 1H); 2.87 (d, 1H, *J* = 13.5 Hz); 2.93 (m, 1H); 3.19 (d, 1H, *J* = 9.55 Hz); 3.68 (d, 1H, *J* = 13.5 Hz); 3.96 (ddd, 1H, *J* = 11.55, 9.55, 4.5 Hz); 7.18-7.49 (m, 10H, ArH). δ_{C} (CDCl₃, 125 MHz): 25.41, 36.38, 52.23, 59.50, 63.66, 75.64, 126.85, 127.93, 128.19, 128.45, 128.58, 139.38, 141.44. **HR-ESI-TOF [M+H]⁺** calculated for C₁₈H₂₁ClN: 286.1357; found: 286.1358 (error = 0.3559). Chemical shifts are in agreement with those reported in the literature.^{9b}

General procedure for the nucleophilic substitution reaction employing NaN₃. A determined amount of the required piperidine **8** were dissolved in 10-20 mL of DMF, and added to a 100-mL long-necked flask (special for MW equipment use) containing 1.1 equiv of NaN₃ previously homogenized in 30-40 mL of DMF:DMSO (9:1). This mixture was stirred and later, the flask was placed inside the microwave equipment to irradiate the reaction with 40 Watts of power in order to heat at 55 °C. The reaction was irradiated during 2 h under controlled temperature by using simultaneous external cooling with compressed air. At the end of this period, the reaction was cooled to room temperature and subsequently added to a flask with 100 mL of brine at 0 °C to facilitate the extraction with petroleum ether (3 x 50 mL). The combined organic layers were washed with 30 mL of water to remove residual polar solvents, dried with Na₂SO₄ and concentrated in the rotary evaporator. The crude was dried under reduced pressure and purified by flash chromatography (2% AcOEt in hexane) to give the corresponding azides.

(*S*)-2-[(*R*)-Azido(phenyl)methyl]-1-benzylpyrrolidine, (*S,R*)-9. The general procedure described above was followed with 2.54 g (9 mmol) of chloropiperidine (*S,R*)-8, 0.64 g (10 mmol) of NaN₃ and 50 mL of DMF:DMSO (4:1) to afford 2.3 g (8 mmol) of the desired azide (*S,R*)-9 as a clear oil in 89 % yield, R_f 0.59 (hexane:AcOEt, 9:1), [α]_D²⁵ -97 (c 1.0, CHCl₃), δ_{H} (CDCl₃, 500 MHz): 1.55-1.69 (m, 2H, CH₂CH₂CH), 1.71-1.84 (m, 1H, CH₂CH₂CH), 1.87-1.96 (m, 1H, CH₂CH₂CH), 2.25 (ddd, 1H, *J* = 9.9, 9.35, 6.3 Hz, CH₂CH₂N), 2.92 (ddd, 1H, *J* = 8.8, 4.65, 4.1 Hz, NCHCH₂), 3.03 (ddd, 1H, *J* = 9.2, 7.1, 2.1 Hz, CH₂CH₂N), 3.48, 3.93 (d, 1H each, *J* = 12.89 Hz, NCH₂Ph), 4.57 (d, 1H, *J* = 4.1 Hz, CHCHN₃), 7.21-7.35 (m, 10H, ArH); δ_{C} (CDCl₃, 125 MHz): 23.59 (CH₂-CH₂-CH₂-), 26.00 (CH₂CH₂CH), 54.86 (CH₂CH₂N), 59.71 (NCH₂Ph), 67.2 [CH(Ph)N₃], 69.65 (NCHCH₂), ArC: 126.87, 126.98, 127.56, 128.26, 128.36, 128.81, 138.46 (NCH₂Ph, *Cipso*), 139.40 [CH(Ph)N₃, *Cipso*]. **IR (ATR, cm⁻¹):** ν_{max} 2967, 2796, 2097 (N₃), 1495, 1452, 1351, 1288, 1269, 1122, 1074, 1029, 846, 740, 697. **MS (IE) m/z (%):** 65.1 (22.96), 77.1 (8.88), 89.1 (8.2), 90.1 (8.88), 91.1 (100), 92.1 (9.62), 104.1 (13.7), 118.1 (25.06), 146

(11.38), 160.2 (29.52), 194.2 (10.52), 236.3 (10.6). **HR-ESI-TOF** $[M+H]^+$ (m/z) calculated for $C_{18}H_{21}N_4$: 293.1760; found: 293.1764, (error = 1.1143).

(S)-2-[(S)-Azido(phenyl)methyl]-1-benzylpyrrolidine, (S,S)-9, and (2R,3R)-3-azido-1-benzyl-2-phenyl piperidine, (R,R)-10. The general procedure described above was followed with 2.73 g (9.6 mmol) of chloropiperidine (*R,R*)-**8**, 0.64 g (10.5 mmol) of NaN_3 and 50 mL of DMF:DMSO (4:1) to obtain 0.86 g (3 mmol, 31% yield) of the desired azide (*S,S*)-**9** and 1.5 g (5.3 mmol, 55% yield) of azidopiperidine (*R,R*)-**10** both as colourless oils.

(S)-2-[(S)-Azido(phenyl)methyl]-1-benzylpyrrolidine, (S,S)-9. R_f 0.41 (hexane:AcOEt, 9:1), $[\alpha]_D^{25} +84$ (c 1.0, $CHCl_3$). δ_H ($CDCl_3$, 500 MHz): 1.39-1.52 (m, 2H, one for each CH_2CH_2CH), 1.53-1.61 (m, 1H, CH_2CH_2CH), 1.61-1.72 (m, 1H, CH_2CH_2CH), 2.30 (td, 1H, $J = 9.42, 6.3$ Hz, CH_2CH_2N), 2.91 (ddd, 1H, $J = 10.0, 6.52, 2.97$ Hz, CH_2CH_2N), 3.07 (ddd, 1H, $J = 8.95, 7.45, 3.94$ Hz, $NCHCH_2$), 3.53, 4.31 (d, 1H each, $J = 13.03$ Hz, NCH_2Ph), 4.39 (d, 1H, $J = 7.45$ Hz, $CHCHN_3$), 7.22-7.43 (m, 10H, ArH); δ_C ($CDCl_3$, 125 MHz): 23.72 ($CH_2-CH_2-CH_2-$), 28.51 (CH_2CH_2CH), 54.70 (CH_2CH_2N), 61.02 (NCH_2Ph), 67.43 [$CH(Ph)N_3$], 71.19 ($NCHCH_2$), ArC: 126.81, 127.84, 128.02, 128.22, 128.39, 128.83, 138.16 (NCH_2Ph , *Cipso*), 139.82 [$CH(Ph)N_3$, *Cipso*]. **IR (ATR, cm^{-1}):** ν_{max} 3032, 2970, 2939, 2866, 2796, 2090 (N_3), 1493, 1453, 1343, 1275, 1249, 1098, 1027, 917, 870, 818, 751, 699, 657, 606. **MS (EI) m/z (%):** 65.1 (13.66), 91.0 (100), 160.2 (70.71), 161.2 (9.31). **HR-ESI-TOF** $[M+H]^+$ calculated for $C_{18}H_{21}N_4$: 293.1760; found: 293.1767, (error = 2.1376).

(2R,3R)-3-Azido-1-benzyl-2-phenyl piperidine, (R,R)-10. R_f 0.54 (hexane:AcOEt, 9:1), $[\alpha]_D^{25} -36.7$ (c 1.09, $CHCl_3$). δ_H ($CDCl_3$, 500 MHz): 1.47-1.54 (m, 1H, $CH_2CH_2CH_2$), 1.72 (tdd, 1H, $J = 13.39, 4.01, 3.22$ Hz, $-CH_2CH_2CHN_3$), 1.91 (tt, 1H, CH_2CH_2CH , $J = 12.82, 3.46$ Hz), 1.99 (ddd, 1H, $J = 12.17, 11.46, 2.46$ Hz, CH_2CH_2N), 2.11 (dddd, 1H, $J = 13.69, 6.17, 3.22, 1.63$ Hz, CH_2CH_2N), 2.88 (d, 1H, $J = 13.75$ Hz, NCH_2Ph), 3.03 (dtd, 1H, $J = 11.01, 3.03, 1.43$ Hz, CH_2CH_2N), 3.41 [d, 1H, $J = 2.43, NCH(Ph)CH(N_3)$], 3.62 [dd, 1H, $J = 5.87, 3.01$ Hz, $CH(Ph)CH(N_3)$], 13.88 (d, 1H, $J = 13.75$ Hz, NCH_2Ph), ArH: 7.18-7.23 (m, 1H), 7.24-7.31 (m, 5H), 7.33-7.39 (m, 2H), 7.47-7.54 (2H); δ_C ($CDCl_3$, 125 MHz): 20.48 ($CH_2-CH_2-CH_2-$), 29.83 ($CH_2CH_2CHN_3$), 52.95 (CH_2CH_2N), 59.48 (NCH_2Ph), 63.40 [$CH(Ph)CH(N_3)$], 70.75 [$NCH(Ph)CH(N_3)$], ArC: 126.71, 127.58, 128.10, 128.37, 128.56, 128.59, 138.63 (NCH_2Ph , *Cipso*), 140.43 [$CH(Ph)CH(N_3)$, *Cipso*]. **IR (ATR, cm^{-1}):** ν_{max} 3858.0, 3740, 3618, 3028, 2942, 2792, 2360, 2104 (N_3), 1700, 1650, 1494, 1452, 1332, 1268, 1132, 1070, 1032, 962, 898, 744, 702. **MS (EI) m/z (%):** 65.1 (24.31), 91.1 (100), 104.1 (13.76), 118.1 (25.34), 146.2 (10.39), 160.2 (29.13), 194.2 (10.24), 236.3 (9.67). **HR-ESI-TOF** $[M+H]^+$ calculated for $C_{18}H_{21}N_4$: 293.1760; found: 293.1762, (error = 0.4321).

General procedure for the catalytic hydrogenation of azido group. A determined amount of the

required azide **9** was dissolved in 50 mL of EtOH in a PYREX[®] heavy wall centrifuge bottle which was conditioned with inert atmosphere. Subsequently, 10 % w/w of palladium on charcoal (1 %) was added to the solution, the recipient was placed in the hydrogenator and then, the system was purged twice with hydrogen pressure. Finally 60-70 psi were charged leaving the reaction mixture under mechanical stirring during 2-5 h. The reaction was monitored by TLC and once the initial azide is depleted, the mixture is poured onto a celite pad to remove the catalyst and the filtrate was concentrated under vacuum. The crude was purified with column chromatography, using CH₂Cl₂:AcOEt (9:1) as eluent, obtaining the corresponding diamine.

(R)-[(S)-1-Benzylpyrrolidin-2-yl](phenyl)methanamine, (S,R)-1. The general procedure described above was used with 2.48 g (9.31 mmol) of azide (*S,R*)-**9** and 0.25 g of Pd/C (1% w/w) suspended in 50 mL of EtOH under 60 psi of H₂ pressure during 3 h. The diamine (*S,R*)-**1** was obtained after chromatography with 90% yield as a yellow oil, improved purification could be achieved by Kugelrohr distillation (150 °C, 0.5-1 mmHg). R_f 0.63 (CH₂Cl₂:AcOEt, 9:1), $[\alpha]_D^{25} -44$ (*c* 1.05, CHCl₃), δ_H (CDCl₃, 500 MHz): 1.36 (ddd, 1H, *J* = 17.54, 12.9, 8.73 Hz, CH₂CH₂CH), 1.54-1.7 (m, 2H, CH₂CH₂CH), 1.70-1.84 (b, 2H, NH₂), 1.89 (dddd, 1H, *J* = 12.9, 9.1, 6.38, 4.1 Hz, one for CH₂CH₂CH), 2.20 (td, *J* = 9.52, 7.2 Hz, CH₂CH₂N), 2.77 (ddd, 1H, *J* = 9.24, 6.23, 3.44 Hz, NCHCH₂), 3.00 (ddd, 1H, *J* = 8.99, 6.84, 2.29 Hz, CH₂CH₂N), 3.38, 4.10 (d, 2 X 1H, *J* = 13.1 Hz, NCH₂Ph), 4.24 [d, 1H, *J* = 3.29 Hz, CHCH(Ph)NH₂], 7.19-7.27 (m, 2H, ArH), 7.29-7.37 (m, 6H, ArH), 7.38-7.42 (m, 2H, ArH). (CDCl₃, 125 MHz): 23.46 (CH₂-CH₂-CH₂-), 23.97 (CH₂CH₂CH), 54.77 [CHCH(Ph)NH₂], 55.06 (CH₂CH₂N), 59.02 (NCH₂Ph), 69.97 (NCHCH₂), ArC: 126.75, 126.81, 126.99, 128.27, 128.39, 128.75, 140.00 (NCH₂Ph, *Cipso*), 143.69 [CH(Ph)NH₂, *Cipso*]. IR (ATR, cm⁻¹): ν_{\max} 3025, 2961, 2871, 2787, 1681, 1602, 1494, 1451, 1373, 1290, 1207, 1118, 1071, 1028, 912, 873, 736, 697, 648. HR-ESI-TOF [M+H]⁺ calculated for C₁₈H₂₃N₂: 267.3881; found: 267.1855, (error = 0.8407).

(S)-[(S)-1-Benzylpyrrolidin-2-yl](phenyl)methanamine, (S,S)-1. The general procedure described above was used with 3.66 g (13.41 mmol) of azide (*S,S*)-**9** and 0.37 g of Pd/C (1% w/w) suspended in 100 mL of EtOH under 60 psi of H₂ pressure during 2 h. The diamine (*S,S*)-**1** was obtained after chromatography with 97% yield as a yellow oil. R_f 0.68 (CH₂Cl₂:AcOEt, 9:1), $[\alpha]_D^{25} +41$ (*c* 1.0, CHCl₃), δ_H (CDCl₃, 500 MHz): 1.54-1.7 (m, 3H, CH₂CH₂CH), 1.73-1.81 (m, 1H one for CH₂CH₂CH), 1.82-1.92 (b, 2H, NH₂), 2.31 (td, *J* = 9.16, 6.35 Hz, CH₂CH₂N), 2.92 (ddd, 1H, *J* = 9.99, 6.34, 3.62 Hz, NCHCH₂), 3.01 (ddd, 1H, *J* = 9.02, 6.45, 2.86 Hz, CH₂CH₂N), 3.44 (d, 1H, *J* = 13.32 Hz, NCH₂Ph), 3.84 [d, 1H, *J* = 6.59 Hz, CHCH(Ph)NH₂], 3.97 (d, 1H, *J* = 13.32 Hz, NCH₂Ph), 7.2-7.27 (m, 2H, ArH), 7.28-7.37 (m, 6H, ArH), 7.37-7.42 (m, 2H, ArH). (CDCl₃, 125 MHz): 24.33 (CH₂-CH₂-CH₂-), 28.62 (CH₂CH₂CH), 54.74 [CHCH(Ph)NH₂], 60.54 (CH₂CH₂N), 61.83 (NCH₂Ph), 70.35 (NCHCH₂), ArC: 126.71, 126.88, 127.42,

128.13, 128.19, 128.50, 140.37 (NCH₂Ph, *Cipso*), 144.55 [CH(Ph)NH₂, *Cipso*]. **IR (ATR, cm⁻¹):** ν_{\max} IR (cm⁻¹): 3060, 3025, 2964, 2870, 2787, 1663, 1601, 1493, 1451, 1352, 1122, 1069, 1028, 910, 870, 737, 697, 673, 597, 568. **HR-ESI-TOF [M+H]⁺** calculated for C₁₈H₂₃N₂: 267.3881; found: 267.1857, (error = 0.4665).

(2*R*,3*R*)-1-Benzyl-2-phenylpiperidin-3-amine, (*R,R*)-12. The general procedure described above was used with 4.67 g (15.8 mmol) of azide (*R,R*)-10 and 0.47 g of Pd/C (1% w/w) suspended in 100 mL of EtOH under 60 psi of H₂ pressure overnight. The diamine (*R,R*)-12 was obtained after chromatography with 97% yield as a yellow oil (15.3 mmol, 4.08 g). δ_{H} (CDCl₃, 500 MHz): 1.45-1.52 (m, 1H, CH₂CH₂CH₂CH), 1.58 (br, 2H, NH₂), 1.69-1.87 (m, 2H, CH₂CH₂CH), 1.90-2.02 (m, 2H, CH₂CH₂CH₂CH), 2.83-2.88 (m, 1H, CH₂CH₂CH), 2.85 (d, 1H, *J* = 13.92 Hz, NCH₂Ph), 3.00 (dt, 1H, *J* = 11.54, 4.00 Hz, CH₂CH₂CH₂CH), 3.40 (d, 1H, *J* = 2.32 Hz, CHCHNBn), 3.93 (d, 1H, *J* = 13.92 Hz, NCH₂Ph), 7.18-7.45 (m, 10H, ArH); δ_{C} (CDCl₃, 125 MHz): 19.95 (CH₂CH₂CH₂CH), 32.24 (CH₂CH₂CH₂CH), 51.98 (CH₂CH₂CHNH₂), 53.67 (CH₂CH₂CH₂CH), 59.68 (NCH₂Ph), 72.62 (CHCHNBn) ArC: 126.61, 126.97, 128.10, 128.17, 128.32, 128.38, 139.45 (NCH₂Ph, *Cipso*), 142.01 [CH(Ph)CH, *Cipso*]. **HR-ESI-TOF [M+H]⁺** calculated for C₁₈H₂₃N₂: 267.1855; found: 267.1856, (error = 0.0922).

General procedure for the acetylation reaction. A determined amount of the required diamine was dissolved with anhydrous THF in a round-bottomed flask equipped with magnetic stirring and conditioned with nitrogen atmosphere. Subsequently, 1.3 equivalents of Et₃N and 1.2 equivalents of MeCOCl were simultaneously added at 0 °C. Then, the reaction mixture was left stirring during 48 h at room temperature. After this time, the reaction was concentrated and the crude was extracted twice with brine and AcOEt. Subsequently, the organic layer was dried with Na₂SO₄, the solvent was evaporated under reduced pressure and the resultant concentrate is supported on silica and purified using CH₂Cl₂:AcOEt (9:1) as eluent in flash chromatography, obtaining the corresponding acetamides.

***N*-{(*R*)-[(*S*)-1-Benzylpyrrolidin-2-yl](phenyl)methyl}acetamide, (*S,R*)-11.** The general procedure which was described above was followed using 2.13 g (8 mmol) of (*S,R*)-1, 1.5 mL (1.05 g, 10.4 mmol) of Et₃N and 0.7 mL (0.75 g, 9.6 mmol) of MeCOCl and 30 mL of THF to obtain the acetamide (*S,R*)-11 in 62 % of isolated yield after recrystallization, as a white solid, mp 180-181 °C (AcOEt/hexane); R_f 0.48 (CH₂Cl₂/MeOH, 9:1); $[\alpha]_{\text{D}}^{25}$ -62 (*c* 1.0, CHCl₃), δ_{H} (CDCl₃, 500 MHz): 1.36-1.48 (m, 1H, CH₂CH₂CH), 1.48-1.62 (m, 3H, CH₂CH₂CH), 2.05 (s, 3H, CH₃CO), 2.23 (td, 1H, *J* = 9.04, 8.45 Hz, CH₂CH₂N), 2.88 (td, 1H, *J* = 7.59, 4.96 Hz, CH₂CHN), 2.94 (ddd, 1H, *J* = 9.54, 7.11, 2.63 Hz, CH₂CH₂N), 3.28 (d, 1H, *J* = 12.82 Hz, NCH₂Ph), 4.04 (d, 1H, *J* = 12.89 Hz, NCH₂Ph), 5.07 (t, 1H, *J* = 5.12 Hz, CHCHNHAc), 6.35 (d, 1H, *J* = 4.15 Hz, NH), 7.18-7.35 (m, 10H, ArH); δ_{C} (CDCl₃, 125 MHz): 21.78 (COCH₃), 23.41

(CH₂-CH₂-CH₂-), 26.00 (CH₂CH₂CH), 53.54 (CH₂CH₂N), 54.18 [CH(Ph)NHAc], 58.25 (NCH₂Ph), 67.26 (NCHCH₂), ArC: 126.29, 126.84, 127.03, 128.22, 128.30, 128.73, 139.04 (NCH₂Ph, *Cipso*), 140.24 [CH(Ph)NHAc, *Cipso*], 170.35 [NH(C=O)CH₃]. **IR (ATR, cm⁻¹):** ν_{\max} 3323, 2793, 1640, 1550, 1455, 1132, 1029, 978, 845, 739, 696, 644, 581. **MS (IE) m/z (%):** 91.1 (42), 160.05 (100), 161.05 (11). **HR-ESI-TOF [M+H]⁺ (m/z)** calculated for C₂₀H₂₅N₂O: 309.1961; found: 309.1968, (error = 2.1343).

***N*-{(*S*)-[(*S*)-1-Benzylpyrrolidin-2-yl](phenyl)methyl}acetamide, (*S,S*)-11.** The general procedure which was described above was followed using 1.15 g (4.3 mmol) of (*S,R*)-1, 0.8 mL (0.57 g, 5.6 mmol) of Et₃N and 0.37 mL (0.41 g, 5.2 mmol) of MeCOCl and 15 mL of THF to obtain the acetamide (*S,R*)-11 in 90% of yield, as a white solid, mp 136 °C (AcOEt/hexane); R_f 0.53 (CH₂Cl₂/MeOH, 9:1); $[\alpha]_D^{25} +76$ (*c* 1.0, CHCl₃), **δ_{H} (CDCl₃, 500 MHz):** 1.58-1.72 (m, 2H, CH₂CH₂CH), 1.72-1.78 (m, 1H, CH₂CH₂CH), 2.07-2.13 (m, 1H, CH₂CH₂CH), 2.13 (s, 3H, CH₃CO), 2.24 (td, 1H, *J* = 9.85, 6.35 Hz, CH₂CH₂N), 2.90 (ddd, 1H, *J* = 9.20, 6.77, 2.36 Hz, CH₂CH₂N), 2.97 (d, 1H, *J* = 13.03 Hz, NCH₂Ph), 3.19 (ddd, 1H, *J* = 9.49, 4.77, 2.11 Hz, NCHCH₂), 3.26 (d, 1H, *J* = 12.89 Hz, NCH₂Ph), 5.06 (dd, 1H, *J* = 8.31, 2.0 Hz, CHCHNHCOCH₃), 6.85 (d, 1H, *J* = 8.02 Hz, NH), 7.09-7.39 (m, 10H, ArH); **δ_{C} (CDCl₃, 125 MHz):** 23.50 (COCH₃), 24.17 (CH₂-CH₂-CH₂-), 30.61 (CH₂CH₂CH), 55.25 (CH₂CH₂N), 55.74 [CH(Ph)NHCOCH₃], 60.52 (NCH₂Ph), 67.74 (NCHCH₂), ArC: 125.94, 126.82, 126.85, 128.16, 128.39, 128.56, 139.53 (NCH₂Ph, *Cipso*), 141.46 [CH(Ph)NHAc, *Cipso*], 169.84 [NH(C=O)CH₃]. **IR (ATR, cm⁻¹):** 3337, 2970, 2801, 1646, 1534, 1373, 1295, 1140, 1111, 744, 700, 627. **HR-ESI-TOF [M+H]⁺ (m/z)** calculated for C₂₀H₂₅N₂O: 309.1961; found: 309.1963, (error = 0.5172).

***N*-[(2*R*,3*R*)-1-Benzyl-2-phenylpiperidin-3-yl]acetamide, (*R,R*)-13.** The general procedure which was described above was followed using 4.1 g (15.3 mmol) of (*R,R*)-12, 2.8 mL (2.02 g, 20 mmol) of Et₃N and 1.3 mL (1.44 g, 18.4 mmol) of MeCOCl and 100 mL of THF to obtain the acetamide (*S,R*)-11 in 79% of isolated yield after recrystallization, as a white solid, mp 160-161 °C (AcOEt/hexane); R_f 0.61 (CH₂Cl₂/MeOH, 9:1); $[\alpha]_D^{25} +3.3$ (*c* 1.0, CHCl₃). **δ_{H} (CDCl₃, 500 MHz):** 1.51-1.58 (m, 1H, CH₂CH₂CH₂CH), 1.59-1.80 (m, 2H, CH₂CH₂CH), 1.86 (s, 3H, CH₃CO), 1.92-1.98 (m, 1H, CH₂CH₂CH), 2.02 (ddd, 1H, *J* = 11.89, 11.86, 2.94 Hz, CH₂CH₂CH₂), 2.87 (d, 1H, *J* = 13.89 Hz, NCH₂Ph), 3.02 (ddd, 1H, *J* = 11.81, 3.97, 3.94 Hz, CH₂CH₂CH₂), 3.46 (d, 1H, *J* = 2.58 Hz, CHCHNBn), 3.95 (d, 1H, *J* = 13.89 Hz, NCH₂Ph), 4.14 (dd, 1H, *J* = 8.88, 2.72 Hz, CH₂CHNHAc), 6.30 (d, 1H, *J* = 8.73 Hz, NH), 7.19-7.40 (m, 10H, ArH); **δ_{C} (CDCl₃, 125 MHz):** 20.60 (COCH₃), 23.28 (CH₂-CH₂-CH₂-), 29.77 (CH₂CH₂CH), 50.12 (CH₂CH₂N), 53.35 [CH(Ph)NHCOCH₃], 59.36 (NCH₂Ph), 70.45 (NCHCH₂), ArC: 126.87, 127.33, 127.80, 128.16, 128.24, 128.57, 138.59 (NCH₂Ph, *Cipso*), 140.34 [CH(Ph)NHAc, *Cipso*], 168.93 [NH(C=O)CH₃]. **IR (ATR, cm⁻¹):** 3244, 3060, 2944, 2793, 2359, 2162, 1978, 1651, 1625, 1538, 1495, 1449, 1370, 1288, 1225, 1203, 1134, 1105, 1030, 737, 701, 598. **HR-ESI-TOF [M+H]⁺ (m/z)** calculated

for C₂₀H₂₅N₂O: 309.1961; found: 309.1965, (error = 1.1640).

(2*R*,3*R*)-2-Phenylpiperidin-3-amine, (R,R)-14. 0.54 g (1.8 mmol) of diamine **(R,R)-12** was dissolved in 50 mL of EtOH acidified with 0.12 mL of AcOH (0.12 g, 2 mmol) under inert atmosphere in a quartz glass for hydrogenation reactor. Subsequently, 15% w/w Pd(OH)₂ (1%) was added to the solution and then, the recipient was placed inside a reactor with mechanical stirring. Afterwards, the system was purged twice with hydrogen pressure. Finally, the reactor was charged with 1000 psi of hydrogen pressure and heated at 60 °C during 72 h. After this period, temperature was automatically set to room temperature and the suspension is poured onto a celite pad to remove the catalyst and the filtrate was concentrated under vacuum. The crude was purified with column chromatography, using CH₂Cl₂:MeOH:NH₄OH_(conc) (90:9:1) as eluent, obtaining the corresponding diamine in 80% yield as a yellow oil. δ_{H} (CDCl₃, 500 MHz): 1.32-1.45 (m, 1H, CH₂CH₂CHNH₂), 1.63-1.79 (m, 2H, CH₂CH₂CHNH₂), 1.81-1.92 (m, 1H, CH₂CH₂CHNH₂), 2.68 (td, 1H, *J* = 11.77, 2.65 Hz, CH₂CH₂NH), 2.90 (d, 1H, *J* = 1.83 Hz, CH₂CH₂CHNH₂), 3.11 (dd, 1H, *J* = 10.39, 3.06 Hz, CH₂CH₂NH), 3.74 (d, 1H, *J* = 1.22 Hz, CHCHNH), 7.07-7.32 (m, 5H, ArH); δ_{C} (CDCl₃, 125 MHz): 19.48 (NHCH₂-CH₂-CH₂-), 31.94 (NHCH₂-CH₂-CH₂-), 47.28 (NHCH₂CH₂CH₂), 50.48 (CH₂CHNH₂), 64.60 [CH(Ph)NH], ArC: 126.30, 126.71, 128.07, 142.45 [CH(Ph), *Cipso*]. Chemical shifts and other spectroscopic data are in agreement with those reported in the literature.^{13a}

General procedure for the conversion of amino group into a thiourea functionality. A determined amount of the required diamine was dissolved with anhydrous THF in a round-bottomed flask equipped with magnetic stirring and conditioned with nitrogen atmosphere. Subsequently, 1.6 equivalents of Edman reagent were added at 0 °C. Then, the reaction mixture was left stirring during 48 h at room temperature. After this time, the reaction was concentrated and the crude was extracted twice with brine and AcOEt. Subsequently, the organic layer was dried with Na₂SO₄, the solvent was evaporated under reduced pressure and the resultant concentrate is supported on silica and purified by flash chromatography using hexane:AcOEt (8:2) as eluent, giving rise to a pure thiourea.

1-{(R)-[(S)-1-Benzylpyrrolidin-2-yl](phenyl)methyl}-3-phenylthiourea, (S,R)-15. The general procedure described above was followed with 1.4 g (5.3 mmol) of **(S,R)-1**, 1.6 mL (1.14 g, 8.4 mmol) of PhN=C=S and 50 mL of THF to afford 1.49 g of the desired thiourea **(S,R)-15** (3.7 mmol, 71% yield), as a pale yellow foam, R_f 0.34 (hexane/AcOEt, 7:3); $[\alpha]_{\text{D}}^{25}$ -45 (*c* 1.0, CHCl₃), δ_{H} (DMSO-*d*₆, 120 °C, 500 MHz): 1.48-1.68 (m, 5H), 2.21-2.28 (m, 1H), 2.76-2.88 (m, 2H), 3.31 (d, 1H, *J* = 12.8 Hz), 3.99 (d, 1H, *J* = 12.6 Hz), 5.69 (s, 1H), 7.05-7.40 (m, 15H). δ_{C} (DMSO-*d*₆, 120 °C, 125 MHz): 22.71, 26.88, 53.85, 58.48, 58.98, 68.06, 114.86, 123.88, 124.78, 124.85, 126.98, 127.21, 127.49, 128.53, 128.96, 129.16, 129.25, 140.19, 182.22. IR (ATR, cm⁻¹): ν_{max} 2966, 2798, 1597, 1521, 1494, 1451, 732, 695.

HR-ESI-TOF [M+H]⁺ calculated for C₂₅H₂₈N₃S: 402.1998; found: 402.2002 (error = 0.8792).

1-[(S)-[(S)-1-Benzylpyrrolidin-2-yl](phenyl)methyl]-3-phenylthiourea, (S,S)-15. The general procedure described above was followed with 1.25 g (4.7 mmol) of (S,S)-**1**, 1.43 mL (1.02 g, 7.5 mmol) of PhN=C=S and 40 mL of THF to afford 1.31 g of the desired thiourea (S,S)-**15** (3.3 mmol, 69% isolated yield), as a white solid, mp 155-156 °C; R_f 0.38 (hexane/AcOEt, 7:3); $[\alpha]_D^{25}$ -212 (c 1.02, CHCl₃), δ_H (DMSO-*d*₆, 120 °C, 500 MHz): 1.61 (s, 2H), 1.85 (br, 1H), 2.04 (br, 1H), 2.17 (br, 1H), 2.55 (br, 1H), 2.83 (br, 1H), 3.12 (br, 1H), 3.21 (br, 1H), 5.53 (br, 1H), 6.71 (br, 1H), 7.14-7.46 (m, 15H). δ_C (DMSO-*d*₆, 120 °C, 125 MHz): 24.14, 31.22, 55.11, 60.36, 61.77, 68.49, 125.68, 126.32, 126.69, 127.01, 127.93, 128.16, 128.73, 130.32, 136.29, 139.50, 141.34, 150.00, 181.08. **IR (ATR, cm⁻¹):** ν_{\max} 3140, 2956, 1595, 1491, 1449, 1243, 1067, 794, 750, 668, 696. **HR-ESI-TOF [M+H]⁺** calculated for C₂₅H₂₈N₃S: 402.1998; found: 402.1997 (error = -0.3639). **Anal. Calcd** for C₂₅H₂₇N₃S: C, 74.77; H, 6.78; N, 10.46. Found: C, 74.98; H, 7.02; N, 10.66.

General procedure for the conversion of amino group into a sulfonamide functionality. A determined amount of the required diamine was dissolved with anhydrous THF in a round-bottomed flask equipped with magnetic stirring and conditioned with nitrogen atmosphere. Subsequently, 1.1 equiv of Et₃N were added at room temperature. Afterwards, 1.05 equiv. of the required 4-substituted benzenesulfonyl chloride, dissolved in dry THF, was slowly added to the mixture at 0 °C and stirred during 1-2 h at this temperature. Then, the reaction was left stirring overnight at room temperature and later, the solution was concentrated and the crude was extracted twice with brine and CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure. The resultant concentrate is supported on silica and purified by flash chromatography using Hexane:AcOEt (8:2) as eluent, giving rise to the corresponding sulfonamide.

N-[(R)-[(S)-1-Benzylpyrrolidin-2-yl](phenyl)methyl]-4-nitrobenzenesulfonamide, (S,R)-16. The general procedure described above was followed with 1.4 g (5.3 mmol) of (S,R)-**1**, 0.81 mL (0.59 g, 5.8 mmol) of Et₃N, 1.22 g (5.5 mmol) of 4-nitrobenzenesulfonyl chloride and 50 mL of THF; obtaining after recrystallization, 1.6 g of sulfonamide (S,R)-**16** (3.54 mmol, 67% isolated yield) as pale yellow crystals, mp 162-163 °C (AcOEt/hexane); R_f 0.26 (hexane/AcOEt, 7:3); $[\alpha]_D^{25}$ -92 (c 1.0, CHCl₃), δ_H (CDCl₃, 500 MHz): 1.32-1.35 (m, 1H), 1.56-1.60 (m, 2H), 1.75-1.77 (m, 1H), 2.22 (dd, 1H, *J* = 8.6, 17.95 Hz), 2.75 (ddd, 1H, *J* = 7.95, 4.5, 8.0 Hz), 3.03-3.04 (m, 1H), 3.18 (d, 1H, *J* = 13.4 Hz), 3.76 (d, 1H, *J* = 13.35 Hz), 4.53 (d, 1H, *J* = 4.5 Hz), 7.25 (m, 10H); 7.74 (d, 2H, *J* = 8.95 Hz), 7.99 (d, 2H, *J* = 8.95 Hz). δ_C (CDCl₃, 125 MHz): 21.72, 25.31, 53.97, 57.15, 57.21, 67.68, 123.80, 127.37, 127.40, 127.81, 128.26, 128.30, 128.62, 128.71, 137.71, 138.15, 145.37, 149.78. **IR (ATR, cm⁻¹):** ν_{\max} 3172, 2880, 1527, 1338, 1309, 1172, 1127, 1090, 858, 735, 687. **HR-ESI-TOF [M+H]⁺** calculated for C₂₄H₂₆N₃O₄S: 452.1638;

found: 452.1638 (error = -0.1212). **Anal. Calcd** for $C_{24}H_{25}N_3O_4S$: C, 63.84; H, 5.58; N, 9.31; S, 7.10. Found: C, 63.98; H, 5.63; N, 9.13; S, 6.86.

***N*-{(*S*)-[(*S*)-1-Benzylpyrrolidin-2-yl](phenyl)methyl}-4-nitrobenzenesulfonamide, (*S,S*)-16.** The general procedure described above was followed with 1.48 g (5.6 mmol) of (*S,S*)-1, 0.85 mL (0.62 g, 6.1 mmol) of Et_3N , 1.34 g (6 mmol) of 4-nitrobenzenesulfonyl chloride and 50 mL of THF to obtain 1.71 g of sulfonamide (*S,S*)-16 (3.79 mmol, 68%) as a yellow resin-like oil; R_f 0.54 (hexane/AcOEt, 7:3); $[\alpha]_D^{25} +94$ (c 1.05, $CHCl_3$), δ_H ($CDCl_3$, 500 MHz): 1.22-1.28 (m, 1H), 1.60-1.66 (m, 1H), 1.70-1.80 (m, 2H), 1.89-1.98 (m, 1H), 2.39-2.46 (m, 1H), 2.93-2.99 (m, 1H), 3.04-3.10 (m, 1H), 3.30 (d, 1H, $J = 12.95$ Hz), 3.41 (d, 1H, $J = 12.95$ Hz), 4.26 (d, 1H, $J = 5.1$ Hz), 6.99 (m, 2H), 7.08 (m, 3H), 7.20 (m, 2H), 7.29 (m, 3H), 7.67 (d, 2H, $J = 9.1$ Hz), 8.07 (d, 2H, $J = 9.05$ Hz). δ_C ($CDCl_3$, 125 MHz): 24.20, 29.26, 54.66, 61.07, 61.20, 68.67, 123.69, 127.25, 127.39, 127.65, 128.25, 128.37, 128.62, 128.87, 139.05, 139.14, 146.88, 149.52. **IR (ATR, cm^{-1}):** ν_{max} 3292, 2962, 2800, 1606, 1527, 1494, 1347, 1309, 1106, 1091, 853, 926, 735, 699, 605. **HR-ESI-TOF $[M+H]^+$** calculated for $C_{24}H_{26}N_3O_4S$: 452.1638; found: 452.1647 (error = 1.8691).

***N*-{(*R*)-[(*S*)-1-Benzylpyrrolidin-2-yl](phenyl)methyl}-4-methylbenzenesulfonamide, (*S,R*)-17.** The general procedure for sulfonamide synthesis was followed with 1.4 g (5.3 mmol) of (*S,R*)-1, 0.81 mL (0.59 g, 5.8 mmol) of Et_3N , 1.06 g (5.6 mmol) of 4-methylbenzene-1-sulfonyl chloride and 50 mL of THF; obtaining after recrystallization, 1.5 g of sulfonamide (*S,R*)-17 (3.57 mmol, 67% isolated yield) as white crystals, mp 140 °C; R_f 0.49 (hexane/AcOEt, 7:3); $[\alpha]_D^{25} -104$ (c 1.0, $CHCl_3$), δ_H ($CDCl_3$, 500 MHz): 1.21-1.31 (m, 1H, CH_2CH_2CH-), 1.45-1.68 (m, 2H, CH_2CH_2CH-), 1.81 (dddd, 1H, $J = 13.35, 10.27, 8.16, 5.51$ Hz, CH_2CH_2CH-), 2.13 (td, 1H, $J = 9.16, 8.45$ Hz, $CHNCH_2CH_2$), 2.27 (s, 3H, $C_6H_5CH_3$), 2.64 (td, 1H, $J = 8.16, 4.41$ Hz, $NCHCHPh$), 2.97 (ddd, 1H, $J = 9.45, 7.59, 2.58$ Hz, $CHNCH_2CH_2$), 3.00, 3.57 (d, 2 x 1H, $J = 13.25$ Hz, NCH_2Ph), 4.37 (d, 1H, $J = 4.41$ Hz, $NCHCHPh$), 5.5-6.0 (br, 1H, NH), 6.98-7.02 (m, 2H, ArH), 7.14-7.18 (m, 2H, ArH), 7.19-7.3 (m, 6H, ArH), 7.3-7.35 (m, 2H, ArH), 7.53-7.57 (m, 2H, ArH). δ_C ($CDCl_3$, 125 MHz): 21.41 ($-C_6H_4CH_3$), 21.48 ($-CH_2CH_2CH-$), 24.89 (CH_2CH_2CH-), 53.72 ($CHNCH_2CH_2$), 56.58 ($NCHCHPh$), 56.77 (NCH_2Ph), 67.92 ($NCHCHPh$), ArC: 126.99, 127.16, 127.26, 127.44, 127.98, 128.25, 128.31, 129.26, 135.92 (NCH_2Ph , *Cipso*), 138.22 ($SO_2C_6H_4$, *Cipso*), 138.63 ($NCHCHPh$, *Cipso*), 143.25 ($C_6H_4-CH_3$, *Cipso*). **IR (ATR, cm^{-1}):** ν_{max} 3303, 2926, 2801, 1599, 1423, 1321, 1152, 1054, 839, 807, 755, 697, 670, 590. **MS (IE) m/z (%):** 160.1 (100), 161.1 (12.96). **HR-ESI-TOF $[M+H]^+$** calculated for $C_{25}H_{29}N_2O_2S$: 421.1944; found: 421.1943 (error = -0.3007).

***N*-{(*S*)-[(*S*)-1-Benzylpyrrolidin-2-yl](phenyl)methyl}-4-methylbenzenesulfonamide, (*S,S*)-17.** The general procedure for sulfonamide synthesis was followed with 1.4 g (4.24 mmol) of (*S,S*)-1, 0.65 mL

(0.47 g, 4.7 mmol) of Et₃N, 0.88 g (4.6 mmol) of 4-methylbenzenesulfonyl chloride and 40 mL of THF; obtaining after recrystallization, 1.38 g of sulfonamide (*S,S*)-**17** (3.28 mmol, 77% isolated yield) as white crystals, mp 137-138 °C (AcOEt/hexane); R_f 0.54 (hexane/AcOEt, 7:3); $[\alpha]_D^{25} +127$ (c 0.98, CHCl₃), δ_H (CDCl₃, 500 MHz): δ_H (CDCl₃, 500 MHz): 1.49-1.71 (m, 3H, -CH₂CH₂CH-), 1.89 (ddd, 1H, *J* = 17.61, 12.39, 8.95 Hz, -CH₂CH₂CH-), 2.28 (ddd, 1H, *J* = 9.74, 9.09, 6.8 Hz, CHNCH₂CH₂), 2.35 (s, 3H, C₆H₅CH₃), 2.82 (ddd, 1H, *J* = 9.88, 6.52, 3.44 Hz, CHNCH₂CH₂), 3.04 (dt, 1H, *J* = 9.16, 4.03 Hz, NCHCHPh), 3.13, 3.38 (d, 2 x 1H, *J* = 12.96 Hz, NCH₂Ph), 4.28 (d, 1H, *J* = 4.03, NCHCHPh), 7.08-7.19 (m, 9H, ArH), 7.21-7.33 (m, 3H, ArH), 7.54-7.58 (m, 2H, ArH). δ_C (CDCl₃, 125 MHz): 21.41 (-C₆H₄CH₃), 23.91 (-CH₂CH₂CH-), 29.34 (-CH₂CH₂CH-), 54.32 (CHNCH₂CH₂), 60.33 (NCHCHPh), 60.68 (NCH₂Ph), 68.80 (NCHCHPh), ArC: 126.82, 126.96, 127.03, 128.09, 128.30, 128.62, 129.14, 137.75 (NCH₂Ph, *Cipso*), 139.06 (SO₂C₆H₄-, *Cipso*), 140.31 (NCHCHPh, *Cipso*), 142.75 (C₆H₄-CH₃, *Cipso*). IR (ATR, cm⁻¹): ν_{max} 3303, 2926, 2801, 1599, 1423, 1321, 1152, 1054, 839, 807, 755, 697, 670, 590. HR-ESI-TOF [M+H]⁺ calculated for C₂₅H₂₉N₂O₂S: 421.1944; found: 421.1949 (error = 1.1237). Anal. Calcd for C₂₅H₂₈N₂O₂S C, 71.40; H, 6.71; N, 6.66. Found: C, 71.04; H, 6.89; N, 6.98.

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23. Crystal data for (*S,R*)-**11**: C₂₀H₂₄N₂O, orthorhombic, space group P2₁2₁2₁, a = 8.4980(0) Å, b = 9.8990(0) Å, c = 21.46999(0) Å, α = 90 °, β = 90 °, γ = 90 °, V = 1806.09 Å³, crystal size: 0.425 x 0.375 x 0.125 mm³, R₁ = 0.0730, (wR₂ = 0.2048). CCDC 898457 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.
24. Crystal data for (*R,R*)-**13**: C₂₀H₂₄N₂O, orthorhombic, space group P3₁, a = 20.573(0) Å, b = 20.573(0) Å, c = 11.2766(0) Å, α = 90 °, β = 90 °, γ = 120 °, V = 4129.48 Å³, crystal size: 0.25 x 0.25 x 0.15 mm³, R₁ = 0.0774, (wR₂ = 0.1998). CCDC 898456 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.
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9.7000(0) Å, $c = 11.6750(0)$ Å, $\alpha = 90^\circ$, $\beta = 101.2099^\circ$, $\gamma = 90^\circ$, $V = 1136.75 \text{ \AA}^3$, crystal size: 0.45 x 0.3 x 0.125 mm³, $R_1 = 0.0432$, ($wR_2 = 0.1117$). CCDC 898458 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.

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