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Synthesis of chiral diamines using novel 2-trichloromethyloxazolidin-4-one precursors derived from 5-*oxo*-proline and proline

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Abstract—Efficient syntheses of chiral vicinal diamines derived from (*S*)-*oxo*-proline and (*S*)-proline are described. The novel diastereomerically pure precursor (2*R*,5*S*)-2-trichloromethyl-1-aza-3-oxabicyclo-[3.3.0]-octan-4,8-dione **3** and its enantiomer are readily available by reaction of the inexpensive enantiomers of 5-*oxo*-proline with chloral. Compound **3** reacts with primary and secondary amines to afford the 5-*oxo*-prolylamides **4** in quantitative yield. In contrast, the (*S*)-proline-derived precursor (2*R*,5*S*)-2-trichloromethyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one **6** gave (*S*)-*N*-formylprolylamides **9** and/or (*S*)-prolylamides **8** depending on the reaction conditions. Upon reduction with $LiAlH_4$, amides **4** and **9** afforded the proline-derived (*S*)-2-(alkylaminomethyl)pyrrolidines **1** and (*S*)-*N*-methyl-2-(alkylaminomethyl)-pyrrolidines **5** in 70–90% yields.

1. Introduction

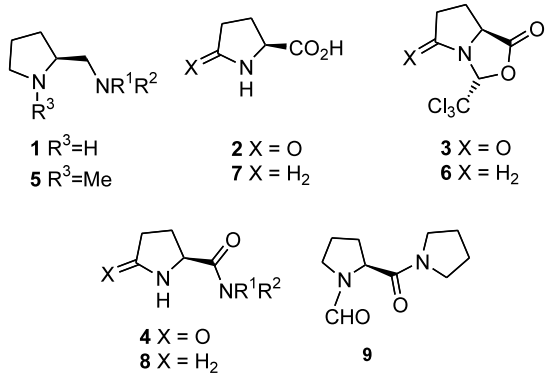
The growing utility of enantiomerically pure vicinal diamines and their derivatives as chiral auxiliaries and ligands in asymmetric synthesis demands the development of efficient methods for their preparation. Chiral diamines derived from proline, e.g. (*S*)-2-(alkylaminomethyl)pyrrolidines **1** have been found to be useful ligands for a number of enantioselective reactions.[1] For example, they are used as precursors of chiral lithium amides in enantioselective deprotonation reactions,[2] enantioselective alkylations of aldehydes[3] and aldol and Michael reactions.[4] Compounds **1** have also been used for the preparation of chiral phosphoramides for allylations and aldol addition reactions[5] and recently in the synthesis of diazaphospholidine precursors of chiral phosphapalladacycle catalysts.[6]

The conventional synthesis of these diamines starts from proline and uses a multistep approach involving *N*-protection, amide formation, deprotection and amide reduction and accompanying purifications. Alternative strategies have been reported aiming at shorter synthetic methods and minimization of racemization in the amide formation step.[7] Thus sulphamidates prepared from prolinol have been used as intermediates in the preparation of **1**.[8] These methods are either lengthy or are not applicable to the use of proline as the starting material. Recently, O'Brien has reported the preparation of (*R*)-**1** in 85% ee involving a (–)-sparteine-mediated asymmetric functionalization of *N*-Boc pyrrolidine.[9]

2. Result and discussion

2.1. Diamine synthesis

5-*oxo*-Proline **2** is commercially available in both enantiomeric forms at low cost, and we envisaged the preparation and use of (2*R*,5*S*)-2-trichloromethyl-1-aza-3-oxabicyclo-[3.3.0]-octan-4,8-dione **3** for preparing diamines **1** (Scheme 1). We reasoned that the straight



Scheme 1.

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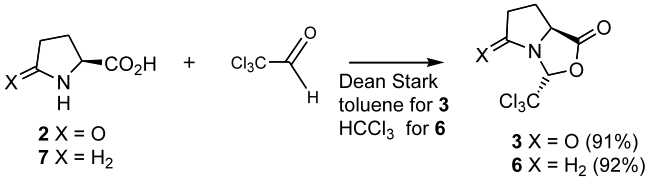
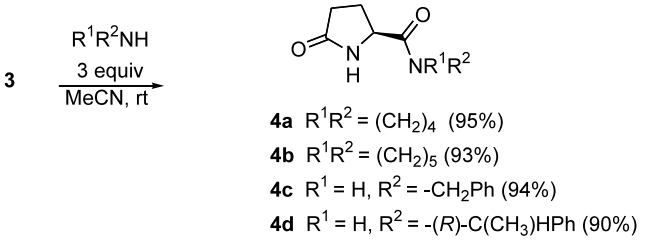
forward preparation of amides **4** from **3** could be an efficient approach to **1**. We report herein on the synthesis of **3** and the preparatively simple and stereoconservative route to the diamine derivatives **1** and the preparation of diamines **5** from **6** (Scheme 1).

The new oxazolidindione **3**, which has a second stereogenic center at C-2, was obtained on a multigram scale in 91% yield as a crystalline, air stable material by refluxing a toluene solution of (*S*)-*oxo*-proline **2** and an equivalent amount of chloral in the presence of catalytic amounts of *p*-toluenesulfonic acid (Scheme 2). NMR spectroscopy showed that the reaction had produced only the single diastereoisomer **3**. The oxazolidinone **6** was prepared by refluxing a chloroform solution of (*S*)-proline **7** with an equivalent amount of chloral in a Dean Stark apparatus and was crystallized from ethanol in a 92% yield (Scheme 2). This procedure is a modification of a published method.[10] Oxazolidinone **6** has previously been characterized by ^{1}H NMR and its structure has been determined by X-ray crystallography.[10]



Scheme 2.

Compounds **3** and **6** can be readily transformed into amides by nucleophilic ring opening with amines. This reaction is coupled with the deprotection of the amino group. The precursor **3** displayed high reactivity in acetonitrile, and in the presence of 3 equiv. of amine, amides **4** were obtained within 10 min in quantitative yields (Scheme 3). Amides **4** were conveniently isolated as precipitates and were crystallized from ethyl acetate.



Scheme 3.

Although the possible use of **6** for peptide synthesis has been described long ago,[11] no interest seems to have been paid to its use as a starting material for diamine synthesis. The reactivity of the oxazolidinone **6** towards amines was found to be different from that of **3** and the reaction showed a marked solvent effect. Depending on the reaction conditions, either amide **8** or **9**, which has an *N*-formyl group, was formed (Scheme 4). In the reaction of **6** with 1 equiv. of pyrrolidine in ethanol both the *N*-formylprolylamide **9a** and the prolylamide **8a** together with chloroform were formed, as shown by NMR and GC–MS. This result suggests that pyrrolidine first reacts with **6** to yield **9a** which then reacts at a comparable rate with another molecule of pyrrolidine, removing the formyl group, to yield **8a**. Reaction of **6** with 3 equiv. of pyrrolidine in methanol or ethanol afforded, after 10 min, a quantitative yield of **8** along with *N*-formylpyrrolidine. The latter compound could be removed under vacuum or by dry flash chromatography.

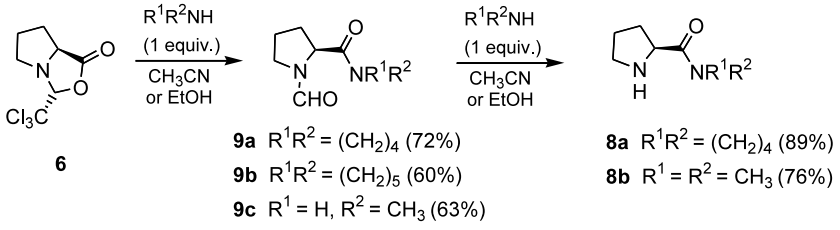
In acetonitrile the reaction of **6** with 1 equiv. pyrrolidine resulted almost exclusively in the product **9a**. Using an excess of the amine in acetonitrile with a prolonged reaction time of ca. 20 h gave **8a** under the same conditions. In contrast, piperidine reacted with **6** in acetonitrile to afford the piperidyl analogue **9b** only when the reaction was completed under reflux for 3 h. In ethanol this reaction takes place at room temperature with 1 equiv. piperidine and is completed within 10 min.

All isolated compounds were found to be pure by NMR and GC–MS, and the yields were over 95% for **8** and 70% for **9** after rapid dry flash chromatography.

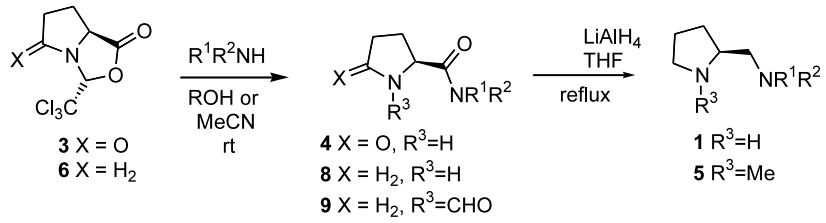
The prolylamides **4**, **8** and **9** can be converted into their corresponding diamines **1** and **5** on reduction with $LiAlH_4$ (Scheme 5 and Table 1).

2.2. Stereochemistry

No racemization at the stereogenic centers of the products obtained by reaction of **3** with amines were expected. This was confirmed by the observation that when **3** was reacted with (*R*)-phenylethylamine, a single product diastereoisomer was obtained as shown by NMR. Moreover, the enantiomeric purity of **1** has been verified by ^{31}P NMR spectroscopy using a chiral organophosphorus derivatizing agent **10** based on a method previously reported in the literature.[6b,c]



Scheme 4.



Scheme 5.

Table 1. Yields of diamines **1** and **5** obtained from **4** and **9** by reduction with $LiAlH_4$

Diamine	R^1	R^2	R^3	Yield (%)
1a		$-(CH_2)_4-$	H	90
1b		$-(CH_2)_5-$	H	88
1c	H	$-CH_2Ph$	H	82
1d	H	-(*R*)-$C(CH_3)HPh$	H	80
5a		$-(CH_2)_4-$	Me	77
5b		$-(CH_2)_5-$	Me	70

The chiral derivatizing agent **10** was easily prepared by reaction of tris(diethylamino)phosphine and L-ephedrine in refluxing toluene (Scheme 6) for 1 h. ^{31}P NMR spectroscopic analysis show the presence of only one diastereomer at δ 133.5 ppm. For easy handling CDA **10** was employed as a 0.25 M solution in toluene stored under nitrogen.

CDA **10** reacted with chiral amines **1** at 70°C for 30 min to form the diastereomeric adducts (*R*)-**11** and (*S*)-**11** (Scheme 6). The latter were directly analyzed by ^{31}P NMR spectroscopy and the results obtained with diamines **1** are summarized in Table 2. Thus, only one diastereomer was detected in comparison with authentic racemic material, indicating that no racemization at the stereogenic center occurred during the synthesis.

3. Conclusion

In summary compounds **3** and **6** have been shown to be useful synthetic precursors to various enantiomerically pure proline-derived diamines. Two distinct protocols for the addition reaction have been described. The inexpensive oxazolidinone **3** offers an easy access to diamines **1** in both enantiomeric forms. Further extension of this methodology to other amino acids is currently explored.

Table 2. ^{31}P NMR shift difference of diastereoisomers **10**

Diamine	^{31}P Derivatives	^{31}P (ppm) *R*/*S*	$\Delta\delta$ (ppm)
1a	**11a**	126.2/124.3	1.9
1b	**11b**	125.2/123.0	2.2
1c	**11c**	130.0/129.4	0.6

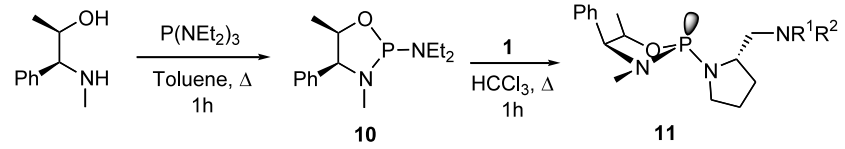
4. Experimental

4.1. General

Solvents were dried and purified according to standard techniques. ^1H NMR were recorded at 400 MHz (Varian 400 NMR). ^{13}C NMR were measured at 100.59 MHz with $CDCl_3$ as solvent. GC–MS were recorded on a Varian Saturn 2000. Melting points were determined on a Büchi B-545 apparatus and are uncorrected.

4.2. Preparation of oxazolidinones 3 and 6

4.2.1. (2*R*,5*S*)-2-Trichloromethyl-1-aza-3-oxabicyclo-[3,3,0]-octan-4,8-dione, 3. Anhydrous chloral (50 ml, 0.05 mol, 1.5 equiv.) was added to a stirred solution of (*S*)-*oxo*-proline **2** (12.9 g, 0.1 mol) in toluene (300 ml) and PTSA (0.5 g, 2.6 mmol). The reaction mixture was heated under reflux for 16 h in a Dean Stark equipment. The resulting brown solution was filtered immediately (hot) and the filtrate was evaporated under reduced pressure (care for crystals). The crystals that formed were collected by filtration and were washed with ethyl acetate (2×15 ml). The filtrate was evaporated under reduced pressure and the remaining solid was dissolved in 30 ml ethyl acetate and crystallized. The product was purified by recrystallisation from EtOAc to give **3** as white needles (23.6 g, 91%), mp: 229.2°C. $[\alpha]_D^{22} = +43.5$ (*c* 2, C_6H_6). ^1H NMR showed the existence of only one diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.30 (m, 1H), 2.50 (dd, 1H), 2.69 (m, 1H), 2.85 (m, 1H), 4.69 (t, 1H), 6.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 179.02, 172.07, 92.64, 74.13, 56.97, 32.13, 24.79. GC–MS, *m*/*z*: 258 (M^+).



Scheme 6.

4.2.2. (2*R*,5*S*)-2-Trichloromethyl-1-aza-3-oxabicyclo-[3,3,0]-octan-4-one, 6. Anhydrous chloral (22 g, 0.15 mol, 1.5 equiv.) was added to a stirred solution of (*S*)-proline **7** (11.5 g, 0.1 mol) in chloroform (150 ml) at 20°C. The reaction mixture was heated under reflux for 3 h in a Dean Stark equipment. After 3 h the amount of the collected water was measured (1.8 ml) and the reaction mixture was cooled to room temperature. The cooled mixture was washed with water (2×50 ml) and the resulting water layers were combined and extracted with CH_2Cl_2 (2×25 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by recrystallisation from EtOH to give **6** as white needles (22.4 g, 92%), mp: 107.6°C (from EtOH). $[\alpha]_D^{22}=+32.7$ (*c* 2, C_6H_6) (lit.[10b] $[\alpha]_D^{20}=+33$ (*c* 2, C_6H_6) and (lit.[10a] $[\alpha]_D^{20}=+32.5$, (*c* 2, C_6H_6)). ^{1}H NMR showed the existence of only one diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.76 (m, 1H), 1.93 (m, 1H), 2.12 (m, 1H), 2.21 (m, 1H), 3.12 (m, 1H), 3.41 (m, 1H), 4.12 (dd, 1H), 5.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 176.00, 103.66, 92.64, 77.40, 62.44, 57.94, 29.98, 25.38. GC–MS, *m*/*z*: 253 (M−1).

4.3. General procedure for preparation of compounds 4 from 3

Oxazolidindione **3** (2 mmol, 516 mg) was dissolved in acetonitrile (5 ml-gentle warming is required in some cases). Amine (6 mmol) was added dropwise and the mixture was stirred for 10 min, after which time the reaction was complete (NMR and GC–MS analysis). The solvent was evaporated under reduced pressure (care for crystals). The remaining white solid product was then recrystallized from AcOEt.

4.3.1. (5*S*)-(Pyrrolidine-1-carbonyl)-pyrrolidin-2-one, 4a. Prepared from pyrrolidine (for 5 mmol, 865 mg, 95%), mp: 114.3°C (from EtOAc). $[\alpha]_D^{20}=-43.6$ (*c* 2, H_2O) (lit.[12] $[\alpha]_D^{20}=-40.5$ (*c* 2, H_2O)). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.89 (q, 2H), 2.01 (q, 2H), 2.12 (m, 1H), 2.36–2.48 (m, 3H), 3.39 (m, 1H), 3.48–3.54 (m, 3H), 4.37 (dd, 1H), 6.18 (bs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 24.08, 25.03, 26.42, 29.69, 46.03, 46.53, 55.34, 169.99, 178.41. GC–MS, *m*/*z*: 183 (M^+).

4.3.2. (5*S*)-(Piperidine-1-carbonyl)-pyrrolidin-2-one, 4b. Prepared from piperidine (for 5 mmol, 910 mg, 93%), mp: 58°C (from EtOAc). $[\alpha]_D^{20}=-46.7$ (*c* 2, H_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.58 (m, 4H), 1.67 (m, 2H), 2.10 (m, 1H), 2.30–2.52 (m, 3H), 3.38 (m, 2H), 3.56 (m, 2H), 4.85 (dd, 1H), 6.23 (bs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 178.44, 169.80, 54.08, 45.96, 43.32, 29.53, 26.31, 25.40, 25.30, 24.33. GC–MS, *m*/*z*: 197 (M^+).

4.3.3. 5-*oxo*-Pyrrolidine-(2*S*)-carboxylic acid benzylamide, 4c. Prepared from benzylamine (for 1 mmol, 205 mg, 94%), mp: 138.3°C (from EtOAc). $[\alpha]_D^{22}=-29.6$ (*c* 2, H_2O) (lit.[12] $[\alpha]_D^{27}=-29.8$, *c* 2, H_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.11 (m, 1H), 2.24 (m, 2H), 2.43 (m, 1H), 4.10 (dd, 1H, $J=4.81$ Hz), 4.40 (m, 1H, $J=6.88$ Hz), 6.95 (bs, 1H, NH), 7.02 (bs, 1H, NH), 7.21–7.31 (m, 5H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 179.77, 172.35, 138.00, 128.86, 127.96, 127.77, 57.32, 43.66, 29.45, 25.99. GC–MS, *m*/*z*: 218 (M^+).

4.3.4. 5-*oxo*-Pyrrolidine-(2*S*)-carboxylic acid-(*R*)-phenylethylamide, 4d. Prepared from (*R*)-phenylethylamine (for 1 mmol, 210 mg, 90%), mp: 153°C (from EtOAc). $[\alpha]_D^{20}=+103.5$ (*c* 1.7, H_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.49 (d, 3H), 2.09 (m, 1H), 2.25 (m, 2H), 2.45 (m, 1H), 4.14 (m, 1H), 5.11 (m, 1H), 6.82 (bs, 1H, NH), 7.15 (bs, 1H, NH), 7.23–7.32 (m, 5H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 179.71, 171.20, 143.04, 128.90, 127.63, 126.26, 57.34, 49.06, 29.55, 25.99, 21.85. GC–MS, *m*/*z*: 233 (M^+).

4.4. General procedure for preparation of compounds 8 and 9 from 6

Oxazolidinone **6** (2 mmol, 489 mg) was dissolved in ethanol (5 ml). Pyrrolidine (6 mmol) was added (dropwise) and the mixture was stirred for 10 min, after which time NMR and GC–MS analyses indicated that the reaction was complete. The solvent was then evaporated and the residual oil was purified by dry flash chromatography using CH_2Cl_2–MeOH (94:4) as eluent.

4.4.1. (*S*)-Prolylpyrrolidine, 8a. (89% yield). Crude **8a** was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.61–1.90 (m, 4H), 1.95 (m, 2H), 2.08 (m, 1H), 2.54 (bs, 1H), 2.80 (m, 1H), 3.17 (m, 1H), 3.35–3.56 (m, 4H), 3.75 (dd, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.74, 59.60, 47.82, 46.01, 30.94, 26.59, 26.09, 24.11. GC–MS, *m*/*z*: 169 (M^+).

4.4.2. (*S*)-Prolyldimethylamine, 8b. (76% yield). In the same way as for **8a**, compound **8b** was obtained from **6** and dimethylamine 33%/EtOH (6 mmol, 1.1 ml). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.65 (m, 2H), 1.80 (m, 1H), 2.10 (m, 1H), 2.44 (bs, 1H), 2.80 (m, 1H), 2.97 and 3.02 (2s, 6H), 3.17 (m, 1H), 3.88 (dd, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.09, 58.15, 47.72, 36.66, 35.95, 30.77, 26.59. GC–MS, *m*/*z*: 183 (M^+).

4.4.3. (*S*)-2-(Pyrrolidine-1-carbonyl)-pyrrolidine-1-carbaldehyde, 9a. (72% yield). In the same way as for **8a**, compound **9a** was obtained by reacting **6** (2 mmol, 489 mg) with pyrrolidine (2 mmol, 170 μl) in acetonitrile 1 h at rt. $[\alpha]_D^{21}=-79$ (*c* 2, EtOH). ^{1}H NMR ($CDCl_3$/TMS) (400 MHz) δ ppm: 1.86 (m, 2H) −2.01 (m, 4H), 2.17 (m, 2H), 3.42 (m, 2H), 3.58 (m, 2H), 3.71 (m, 1H), 3.85 (m, 1H), 4.55 (m, 1H), 8.15 and 8.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.20, 161.76, 65.74, 59.12, 47.54, 46.20, 28.47, 26.15, 25.09, 24.10. GC–MS *m*/*z*: 197 (M^+).

4.4.4. (*S*)-2-(Piperidine-1-carbonyl)-pyrrolidine-1-carbaldehyde, 9b. (60% yield). In the same way as for **9a**, **9b** was obtained by reacting **6** (2 mmol, 489 mg) with pyrrolidine (2 mmol, 200 μl) in ethanol 10 min at rt. $[\alpha]_D^{21} = -69.5$ (*c* 1.05, EtOH). ^{1}H NMR ($CDCl_3$/TMS), (400 MHz) δ ppm: 1.55 (m, 4H), 1.68 (m, 2H), 1.90 (m, 2H), 2.08 (m, 1H), 2.22 (m, 1H), 3.48 (m, 3H), 3.70 (m, 3H), 4.64–4.84 (dd, 1H), 8.27 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.20, 160.50, 60.74, 54.20, 46.75, 43.44, 29.52, 26.49, 25.60, 24.61, 24.47. GC–MS *m*/*z*: 211 (M^+).

4.4.5. (*S*)-2-(*N*-Methyl-1-carbonyl)-pyrrolidine-1-carbaldehyde, 9c. (63% yield). In the same way as for **9a**, **9c** was obtained by reacting **6** (2 mmol, 489 mg) with ethylamine 33%/EtOH (2 mmol, 250 μl) in acetonitrile 10 min at rt. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.85–2.10 (m, 3H), 2.50 (m, 1H), 2.78 (d, 3H), 3.58 (m, 2H), 4.50 (dd, 1H), 8.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.22, 162.36, 61.47, 57.93, 47.11, 27.50, 24.30.

4.5. General procedure for preparation of diamines 1 and 5 from 4 and 9

Preparation of **1b** from **4b** illustrates a typical procedure: $LiAlH_4$ (1.140 g, 30 mmol) in dry THF (10 ml) at 20°C was stirred for few minutes under a nitrogen atmosphere. The mixture was cooled to 0°C and **4b** (980 mg, 5 mmol) in dry THF (20 ml) was added dropwise over 30 min. The mixture was heated under reflux for 4 h and then cooled in an ice bath. Aqueous NaOH (2 M) was added dropwise until a white precipitate of inorganic salts had formed. The inorganic salts were removed by filtration and washed with (3×30 ml) of THF. The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure. Distillation of the residue under reduced pressure gave **1b** as a colorless oil (740 mg, 88%). Amines **1a**–**1d** and **5a**, **5b** were prepared analogously.

4.5.1. (*S*)-(1-Pyrrolidinylmethyl)pyrrolidine, 1a. Colorless oil (693 mg, 90%), bp: 30°C/7.6×10^{-2} mmHg. $[\alpha]_D^{20} = +8.9$ (*c* 2.4, EtOH) (lit.[2] $[\alpha]_D^{20} = 8.2$, (*c* 2.4, EtOH)). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.34 (m, 1H), 1.65–1.80 (m, 6H), 1.87 (m, 1H), 2.05 (bs, 1H), 2.33 (dd, 1H), 2.45–2.60 (m, 5H), 2.85 (m, 1H), 2.97 (m, 1H), 3.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 62.33, 57.59, 54.78, 46.30, 30.33, 25.24, 23.62. GC–MS, *m*/*z*: 155 (M^+).

4.5.2. (*S*)-2-(1-Piperidinylmethyl)pyrrolidine, 1b. Colorless oil (740 mg, 88%), kugelrohr distillation, 110°C/7.6 mmHg. $[\alpha]_D^{21} = +15$ (*c* 7.75, EtOH) (lit.[2] $[\alpha]_D^{25} = +14$, *c* 10, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.28 (m, 1H), 1.42 (m, 2H), 1.58 (m, 4H), 1.72 (m, 2H), 1.86 (m, 1H), 2.24–2.36 (m, 6H), 2.83 (m, 1H), 2.99 (m, 1H), 3.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 65.23, 55.50, 51.51, 46.09, 30.46, 26.20, 25.30, 24.44. GC–MS, *m*/*z*: 17 (M^++1).

4.5.3. (*S*)-2-(1-Benzylmethyl)pyrrolidine, 1c. Colorless oil (770 mg, 80%), kugelrohr distillation, bp: 120°C/5×10^{-2} mmHg. $[\alpha]_D^{20} = +15.6$ (*c* 1.01, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.33 (m, 1H), 1.70 (m, 2H), 1.86 (m, 1H), 1.90 (bs, 2H, NH), 2.50–2.66 (AB system, 2H), 2.89 (m, 2H), 3.25 (m, 1H), 7.24–7.33 (m, 5H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 140.64, 128.45, 128.22, 126.95, 58.45, 54.80, 54.32, 46.65, 30.46, 29.83, 25.88. GC–MS, *m*/*z*: 191 (M^+).

4.5.4. (*S*)-2-((1*R*)-Phenylethylmethyl)pyrrolidine, 1d. Colorless oil (795 mg, 80%), kugelrohr distillation, bp: 113°C/7.6 10^{-2} mmHg. $[\alpha]_D^{20} = +54.4$ (*c* 1.02, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.28 (m, 1H), 1.37 (d, 3H, $J = 6.7$ Hz), 1.68 (m, 2H), 1.82 (m, 1H), 2.00 (bs, 2H, NH), 2.31 (dd, 1H), 2.54 (dd, 1H), 2.86 (t, 2H, $J = 7.21$ Hz), 3.21 (m, 1H, $J = 7.10$ Hz), 3.77 (q, 1H, $J = 6.78$ Hz), 7.23–7.33 (m, 5H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.01, 128.53, 126.92, 126.67, 58.50, 52.79, 46.52, 30.48, 29.77, 25.78, 24.64. GC–MS, *m*/*z*: 205 (M^+).

4.5.5. (*S*)-*N*-Methyl-2-(1-pyrrolidinomethyl)pyrrolidine, 5a. Colorless oil (638 mg, 77%) bp: 50°C/0.7 mmHg. $[\alpha]_D^{20} = -83.6$ (*c* 0.63, EtOH) (lit.[13] $[\alpha]_D = -84.5$ (*c* 0.5, EtOH)). ^{1}H NMR ($CDCl_3$/TMS), (400 MHz) δ ppm: 1.58 (m, 1H), 1.60–1.76 (m, 6H), 2.00 (m, 1H), 2.13 (m, 1H), 2.23 (m, 1H), 2.32 (m, 1H), 3.37 (s, 3H), 2.45–2.51 (m, 4H), 2.64 (dd, 1H), 3.03 (t, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 64.96, 61.71, 57.65, 55.04, 41.45, 31.14, 23.52, 22.64. GC–MS, *m*/*z*: 169 (M^+).

4.5.6. (*S*)-*N*-Methyl-2-(1-piperidinylmethyl)pyrrolidine, 5b. Colorless oil (630 mg, 70%) bp: 55°C/0.6 mmHg. $[\alpha]_D^{20} = -65.1$ (*c* 0.55, EtOH) (lit. $[\alpha]_D^{20} = -65.6$ (*c* 0.56, EtOH). ^{1}H NMR ($CDCl_3$/TMS), (400 MHz) δ ppm: 1.39 (m, 2H), 1.50–1.55 (m, 4H), 1.66–1.78 (m, 4H), 1.96 (m, 1H), 2.10–2.20 (m, 2H), 2.27 (m, 1H), 2.35 (m, 2H), 3.38 (s, 3H), 2.47 (dd, 1H), 3.02 (t, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 65.07, 63.12, 57.92, 55.52, 41.64, 31.43, 26.19, 24.63, 22.83. GC–MS, *m*/*z*: 183 (M^+).

4.6. General procedure for determination of enantiomeric composition of diamines 1

To a 50 ml two-necked round bottomed flask under a nitrogen atmosphere containing a solution of L-ephedrine (0.83 g, 5 mmol) in dry toluene (20 ml) was added dropwise tris(diethylamino)phosphine (1.24 g, 5 mmol). The mixture was then heated under reflux and monitored by ^{31}P NMR spectroscopy. After 1 h, 1 ml (0.25 mmol) was reacted in a 2 ml round flask under a nitrogen atmosphere with 1 equiv. of the desired racemic or chiral diamine **1** at 70°C for 30 min. The solvent was then removed under vaccum. The residue was transferred under nitrogen into a 5 mm NMR tube and $CDCl_3$ was added.

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