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Chiral 1,3-diamines from a lithiated isocyanide and chiral aziridines

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Abstract

Reaction of lithiated 4-methoxybenzylisocyanide with homochiral amino acid derived *N*-tosyl- and *N*-diphenylphosphinoylaziridines proceeds diastereoselectively to provide *N*-protected 3-isocyanoamines. Separation of the diastereomers of these adducts or the corresponding formamides, and subsequent transformations, lead to 1,3-diamines and their monoprotected and differentially bisprotected derivatives.

1. Introduction

Although the number of reports on the synthesis of 1,3-diamines[1] has grown over the last few years, this class of compounds is not receiving the attention which has been devoted to its 1,2-analogues.[2] In connection with our interest in the preparation and use of 1,3-diamines as ligands for cytostatic *cis*-platinum complexes,[3] we required a method for the preparation of diastereo- and enantiomerically pure 1,3-diamines. Our approach is based on the retrosynthetic cleavage of the target molecule to an α-amino carbanion and a 2-aminoethyl cation (Scheme 1). We anticipated that lithiated isocyanides and *N*-activated aziridines as synthetic equivalents for the above-mentioned synthons should provide diastereomeric *N*-protected 3-isocyanoamines, which, after separation of the diastereomers, should afford enantiomerically pure[4] 1,3-diamines in few steps. Lithiated isocyanides[5,6] as well as *N*-activated aziridines[7,8] have been widely employed as synthetic building blocks, but to the best of our knowledge, this approach to 1,3-diamines has not been explored up to now.

Homochiral-activated aziridines are easily prepared from chiral amino alcohols, which in turn are obtained by reduction of α-amino acids.[8] As aziridine activators, we chose the *p*-toluenesulfonyl group (Ts) and the more easily removed diphenylphosphinoyl group (Dpp).[9,10] Here, we report the results

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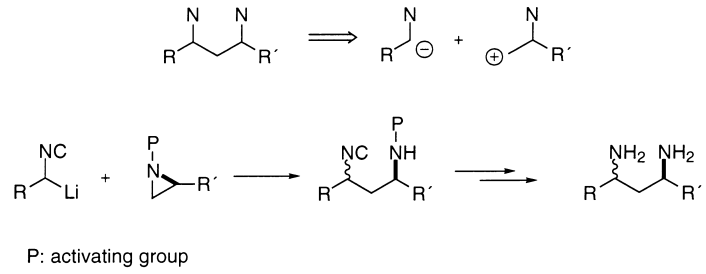
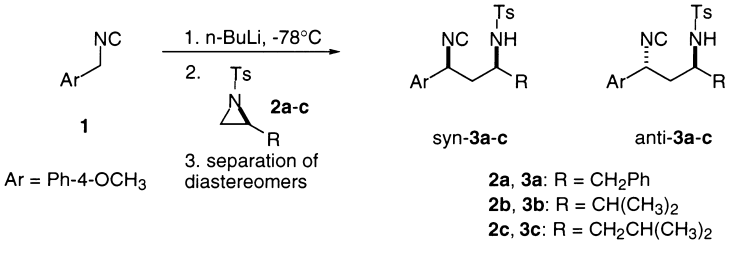


Scheme 1.

obtained with *N*-Ts and *N*-Dpp aziridines derived from L-phenylalanine, L-valine, L-leucine and lithiated 4-methoxybenzylisocyanide.

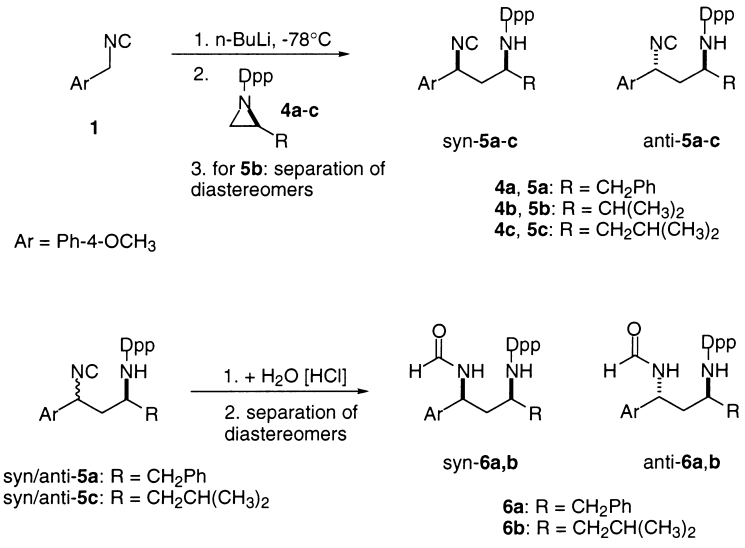
2. Results and discussion

We started with the L-phenylalanine derived *N*-tosylaziridine **2a** (Scheme 2). 4-Methoxybenzylisocyanide **1** was treated with *n*-BuLi at −78°C,[11] and the resulting anion was reacted with aziridine **2a** for 3 h at −78°C followed by aqueous work-up. ^{1}H NMR analysis of the crude material showed the presence of two diastereoisomers in a 60:40 *syn:anti* ratio. Chromatographic separation gave diastereomerically pure *syn*-**3a** and *anti*-**3a** in 38% and 17% yield, respectively, and 36% of a diastereomeric mixture. Use of aziridines **2b** and **c** resulted in the formation of diastereomeric mixtures with *syn:anti* ratios of 70:30 and 60:40, respectively, from which only the *syn*-isomers (*syn*-**3b**: 34%; *syn*-**3c**: 20%) could be isolated diastereomerically pure by column chromatography. The *anti*-isomers were obtained contaminated with *syn*-isomers (*anti*-**3b**: 12% chemical yield, d.e. 86%; *anti*-**3c**: 15% chemical yield, d.e. 82%). In addition, about 30% of diastereomeric mixtures were obtained.



Scheme 2.

The *N*-Dpp aziridines turned out to be less reactive towards the lithiated isocyanide **1** than their *N*-Ts counterparts. Applying the conditions found effective in the reaction with *N*-Ts aziridines, adduct **5a** was isolated in only 40% yield along with the starting aziridine **4a** (Scheme 3). The use of two equivalents of isocyanide **1** and modified temperature protocol was found essential for complete disappearance of the starting aziridine from the reaction mixture. Thus, **5a** was obtained in 81% yield after column chromatography as a diastereomeric mixture (*syn*:*anti*, 60:40) from which the *syn*-isomer could be isolated diastereomerically pure by recrystallization from CH_2Cl_2/petroleum ether in 30% yield. Under the same reaction conditions, L-valine derived aziridine **4b** gave the *syn*- and *anti*-diastereomer of **5b** as an 80:20 diastereomeric mixture. Column chromatography provided diastereomerically pure *syn*-**5b** and *anti*-**5b** in 30% and 10% yield, respectively, and 20% of a diastereomeric mixture. Reaction of lithiated isocyanide **1** with aziridine **4c** resulted in formation of a 1:1 diastereomeric mixture of *syn*-**5c** and *anti*-**5c**, inseparable by column chromatography or recrystallization.

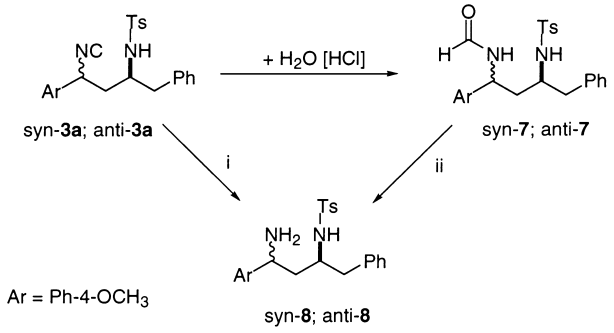


Scheme 3.

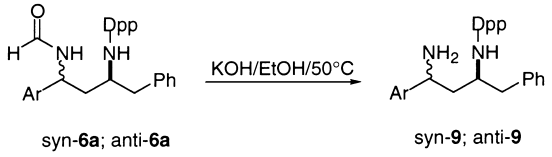
In the case of adducts **5a** and **c**, where pure diastereoisomers could not be obtained by column chromatography, we found that chromatographic separation worked very efficiently after conversion into 3-phosphinamido-formamides **6a** and **b** by short treatment of Et_2O/THF solutions of **5a** and **c**, respectively, with a small amount of conc. HCl[12] (Scheme 3). In this manner, *syn*-**6a** and *syn*-**6b** were obtained in 42% and 34% yield, and *anti*-**6a** and *anti*-**6b** in 35% and 34% yield, respectively.

Then we turned our attention to the transformation of the obtained diastereomerically pure compounds into monoprotected 1,3-diamines, thereby allowing further selective manipulation of the two amino groups. Reflux of the pure diastereoisomers of 3-isocyano-tosylamides **3a** in 2 N HCl/dioxane and subsequent evaporation of the reaction mixtures gave the hydrochloride salts of 3-amino-tosylamides *syn*-**8** and *anti*-**8** in high yields (95% and 93%), from which the free bases were liberated with an Na_2CO_3 solution (Scheme 4). Isolation of the hydrochloride salts was of no benefit for purification and characterization, since no solvent for recrystallization of the hydrochloride salts could be found, whereas crystalline free bases **8** could be recrystallized from toluene. Alternatively, monoprotected 1,3-diamines can be obtained by alkaline hydrolysis of 3-tosylamido-formamides, prepared by acid-catalyzed addition of water to the isocyano functionality. This was demonstrated by the conversion of *syn*-**7** to *syn*-**8** by treatment with ethanolic KOH (Scheme 4). This protocol also worked for the diastereomers of 3-phosphinamido-formamides **6a** providing the Dpp-monoprotected 1,3-diamine derivatives *syn*-**9** and *anti*-**9** in 68% and 63% yield, respectively.

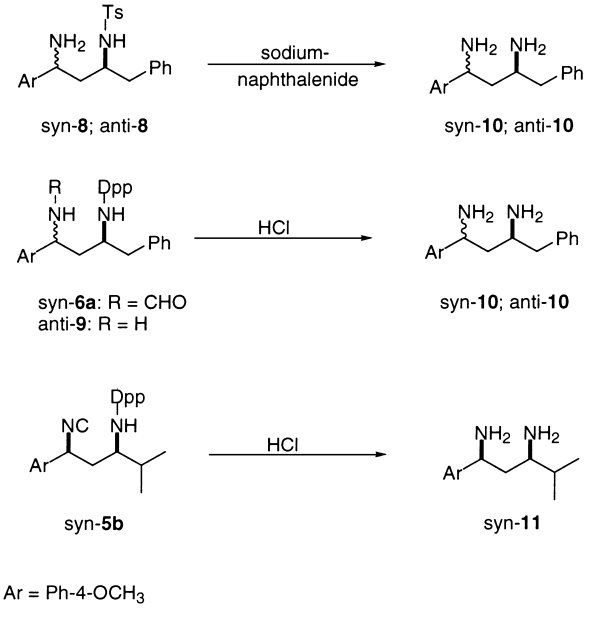
Reductive removal of the tosyl group from 3-amino-toluenesulfonamides **8** by exposure to sodium naphthalenide[13] gave diastereomeric 1,3-diamines only in modest yield (*syn*-**10**: 39%; *anti*-**10**: 35%; Scheme 5). Higher yields were achieved starting from Dpp-derivatives as shown by the one-step double deprotection of 3-phosphinamido-formamide *syn*-**6a** and by the deprotection of 3-amino-phosphinamide *anti*-**9**: treatment with conc. HCl gave the diastereomeric 1,3-diamines *syn*-**10** and *anti*-**10** in 60% and 91% yield, respectively. The conversion of 3-isocyano-phosphinamide *syn*-**5b** into the corresponding 1,3-diamine *syn*-**11** in a three-step one-pot process in 75% yield is worth noting. These examples demonstrate that our approach allows preparation of diastereo- and enantiomerically pure 1,3-diamines in only two (separation of diastereoisomers of 3-isocyano-phosphinamides) or three steps (separation of diastereoisomers of 3-isocyano-sulfonamides or of 3-phosphinamido-formamides) from easily available isocyanides and aziridines.



Reagents and conditions: i) 1. 2N HCl/dioxane/Δ; 2. Na_2CO_3; ii) for **syn-7** KOH/EtOH/50°C



Scheme 4.

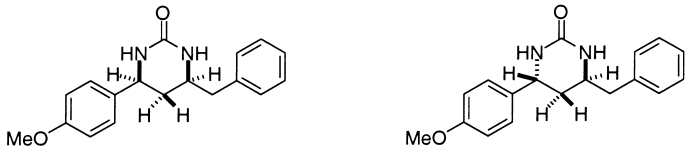


Scheme 5.

2.1. *Stereochemical assignment*

The relative stereochemistry of the phenylalanine derived products was determined from the ^{1}H NMR data of cyclic ureas **12** (Scheme 6), which were prepared by treatment of the diamines with carbonyldiimidazole.[14] Since the absolute configuration of the amino acid derived stereogenic center was known, assignment of the relative stereochemistry allowed determination of the absolute configuration of the newly created stereogenic center. The $\Delta\delta$ (^{1}H) values for diastereotopic protons 5-H_A and 5-

H_B and the differences between the vicinal coupling constants $J_{5\text{-}H(A),4\text{-}H}$ or $J_{5\text{-}H(A),6\text{-}H}$ on the one side and $J_{5\text{-}H(B),4\text{-}H}$ or $J_{5\text{-}H(B),6\text{-}H}$ on the other side are known to be small, if existing at all, in *anti*-perhydropyrimidine and *anti*-perhydro-1,3-oxazine systems and relatively large in the corresponding *syn*-systems.[14–17] Therefore, we assigned *cis*-configuration to the isomer of **12** with a shift difference of 0.41 ppm and the coupling constants of 11.4, 3.5 and 3.3 Hz and *trans*-configuration to the isomer of **12** with a shift difference of 0.05 ppm and the coupling constants of 6.9, 5.5, 5.2 and 5.0 Hz.



cis-**12** trans-**12**

Scheme 6.

The absolute and relative stereochemistries of L-valine- and L-leucine-derived products were established by comparing their ^{1}H NMR data with that of the L-phenylalanine derived products at the 3-isocyano- or 3-formamido adduct stage. Signals of the benzylic proton at the isocyanide-bearing carbon were observed at a higher field in the *syn*-isomers of 3-isocyano-amides **3** and **5** than in the *anti*-isomers. The coupling constants between these protons and the diastereotopic protons of the adjacent methylene group were identical (J=7.2 Hz) in the *syn*-diastereoisomers and different (J_1=10.7–11.0 Hz, J_2=2.3–3.3 Hz) in the *anti*-diastereoisomers.

3. Conclusion

This methodology is an easy way to prepare homochiral 1,3-diamines from readily available starting materials. Selective manipulation of the *N*-functionalities in the 3-isocyano-amides allows the synthesis of differentially bisprotected diamines as well as monoprotected derivatives. Also, since *R*-amino acids are commercially available, our approach allows for the preparation of all four stereoisomers of 1,3-diamines.

4. Experimental

4.1. General methods

Compounds **1**,[11] **2a–c**[18–20] and **4a–c**[9] were prepared according to literature procedures. Commercial reagent grade solvents and chemicals were used as obtained except as indicated below. THF was distilled from sodium benzophenone ketyl. Pyridine and Et_3N were stored over KOH pellets. Petroleum ether refers to the 40–60°C boiling fraction. Solvents used for column chromatography were distilled prior to use. All oxygen- or moisture-sensitive reactions were run in flame-dried glassware under nitrogen. Organic extracts were dried over anhydrous Na_2SO_4. For thin-layer chromatography (TLC) analysis, precoated TLC plates (Merck Kieselgel 60 F_{254} and Merck aluminum oxide 60 F_{254} neutral) were used, and column chromatography was performed using Merck Kieselgel 60. Spots were visualized with ultraviolet light (254 nm) or detected by exposure to iodine fumes. Infrared spectra were recorded with a FT-IR spectrometer; only representative bands are given. ^{1}H and ^{13}C NMR spectra were obtained at 250 and 62 MHz, respectively. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter with

a thermally jacketed 10 cm cell at 20°C (concentration *c* is given as g/100 ml). Diastereomeric ratios were established by the integration of well separated signals of the diastereomers in the crude reaction mixtures. Compounds which were not submitted for, or did not pass elemental analysis, were judged to be of >95% purity based on TLC homogenity and ^{1}H NMR analyses.

*4.2. 3-Isocyano-*p*-toluenesulfonamides **3a–c**. General procedure*

To a solution of isocyanide **1** (1.19 g, 8 mmol) in dry THF (30 ml), *n*-BuLi (1.6 M in hexane, 5.3 ml, 8.5 mmol) was added dropwise at −78°C under nitrogen. After stirring for 40 min at −78°C, a solution of aziridine **2a–c** (8 mmol) in dry THF (40 ml) was added, and stirring was continued for 3 h at −78°C. Half saturated NH_4Cl solution (40 ml) was added, the layers were separated, and the aqueous layer was extracted with Et_2O (2×100 ml). The combined organic layers were washed with brine (2×10 ml), dried and evaporated.

*4.2.1. (2*S*,4*S*)- and (2*S*,4*R*)-*N*-[4-Isocyano-4-(4-methoxyphenyl)-1-phenyl-2-butyl]-*p*-toluenesulfonamide (*syn-***3a***;* anti-***3a***)*

Colorless oil (diastereomeric mixture; *syn*:*anti*, 60:40). The diastereomers were separated by column chromatography (CH_2Cl_2:EtOAc, 95:5). In addition to 1.25 g (36%) of a pale yellow oil (diastereomeric mixture; *syn*:*anti*, 60:40), the following were obtained.

syn-**3a** (2*S*,4*S*): Colorless crystals (1.32 g, 38%); m.p. 107°C; IR (KBr): 3243 (NH), 2155 (NC), 1315, 1153 cm^{-1} (S=O). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.99–2.21 (m, 2H, CH_2), 2.43 (s, 3H, $ArCH_3$), 2.57, 2.70 (ABX, J_{AB}=13.8 Hz, J_{AX}=6.4 Hz, J_{BX}=6.4 Hz, 2H, $ArCH_2$), 3.30–3.43 (m, 1H, C*H*NHTs), 3.82 (s, 3H, OCH_3), 4.39 (d, J=8.0 Hz, 1H, NH, exchangeable), 4.71 (dd, J=7.2 Hz, 1H, C*H*NC), 6.86, 7.13 (AA′BB′, J=8.7 Hz, 4H, ArH), 6.82–6.89 (m, 2H, ArH), 7.09–7.22 (m, 3H, ArH), 7.24, 7.58 (AA′BB′, J=8.7 Hz, 4H, ArH). Anal. calcd for $C_{25}H_{26}N_2O_3S$ (434.5): C, 69.10; H, 6.03; N, 6.45. Found: C, 68.94; H, 6.12; N, 6.29. $[\alpha]_D^{20}$=−81.0 (*c*=0.51, MeOH).

anti-**3a** (2*S*,4*R*): Colorless crystals (0.59 g, 17%); m.p. 119°C; IR (KBr): 3228 (NH), 2135 (NC), 1321, 1157 cm^{-1} (S=O). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.62–1.77 (m, 1H, *H*CH), 1.98 (ddd, J=14.1, 11.0, 2.9 Hz, 1H, HC*H*) 2.44 (s, 3H, $ArCH_3$), 2.67 (d, J=6.2 Hz, 2H, $ArCH_2$), 3.70–3.85 (m, 1H, C*H*NHTs), 3.80 (s, 3H, OCH_3), 4.44 (d, J=8.9 Hz, 1H, NH, exchangeable), 4.79 (dd, J=10.9, 3.1 Hz, 1H, C*H*NC), 6.87, 7.15 (AA′BB′, J=8.7 Hz, 4H, ArH), 6.90–6.98 (m, 2H, ArH), 7.12–7.26 (m, 3H, ArH), 7.29, 7.74 (AA′BB′, J=8.2 Hz, 4H, ArH). Anal. calcd for $C_{25}H_{26}N_2O_3S$ (434.5): C, 69.10; H, 6.03; N, 6.45. Found: C, 68.81; H, 6.01; N, 6.34. $[\alpha]_D^{20}$=−12.1 (*c*=0.28, MeOH).

*4.2.2. (1*S*,3*R*)- and (1*R*,3*R*)-*N*-[1-Isocyano-1-(4-methoxyphenyl)-4-methyl-3-pentyl]-*p*-toluenesulfonamide (*syn-***3b***;* anti-***3b***)*

Pale yellow oil (diastereomeric mixture; *syn*:*anti*, 70:30). The diastereomers were separated by column chromatography (CH_2Cl_2:EtOAc, 95:5). In addition to 0.97 g (31%) of a colorless oil (diastereomeric mixture; *syn*:*anti*, 85:15), the following were obtained.

syn-**3b** (1*S*,3*R*): Colorless foam (1.07 g, 34%); IR (KBr): 3284 (NH), 2138 (NC), 1327, 1161 cm^{-1} (S=O). ^{1}H NMR ($CDCl_3$): δ (ppm)=0.64 (d, J=6.9 Hz, 3H, CH_3), 0.71 (d, J=6.9 Hz, 3H, CH_3), 1.59–1.71 (m, 1H, C*H*(CH_3)$_2$), 1.96 (dd, J=6.9 Hz, 2H, CH_2), 2.44 (s, 3H, $ArCH_3$), 3.00–3.10 (m, 1H, C*H*NH), 3.82 (s, 3H, OCH_3), 4.57 (d, J=9.3 Hz, 1H, NH, exchangeable), 4.66 (dd, J=7.2 Hz, 1H, C*H*NC), 6.88, 7.19 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.31, 7.74 (AA′BB′, J=8.2 Hz, 4H, ArH). Anal. calcd for $C_{21}H_{26}N_2O_3S$ (386.5): C, 65.26; H, 6.78; N, 7.25. Found: C, 65.17; H, 6.93; N, 7.12. $[\alpha]_D^{20}$=−49.0 (*c*=1.15, $CHCl_3$).

anti-**3b** (1*R*,3*R*): Colorless foam (0.38 g, 12%), contaminated with 7% of *syn*-**3b**; IR (KBr): 3286 (NH), 2138 (NC), 1326, 1160 cm^{-1} (S=O). ^1H NMR ($CDCl_3$): δ (ppm)=0.71 (d, J=6.8 Hz, 3H, CH_3), 0.80 (d, J=6.9 Hz, 3H, CH_3), 1.53–1.80 (m, 2H, *H*CH and C*H*(CH_3)$_2$), 1.91 (ddd, J=14.1, 11.5, 2.4 Hz, 1H, HC*H*), 2.44 (s, 3H, ArCH_3), 3.38–3.49 (m, 1H, C*H*NH), 3.81 (s, 3H, OCH_3), 4.70 (d, J=9.2 Hz, 1H, NH, exchangeable), 4.73 (dd, J=10.8, 2.8 Hz, 1H, C*H*NC), 6.88, 7.18 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.34, 7.84 (AA′BB′, J_{AB}=8.2 Hz, 4H, ArH). Anal. calcd for $C_{21}H_{26}N_2O_3S$ (386.5): C, 65.26; H, 6.78; N, 7.25. Found: C, 65.16; H, 6.99; N, 7.16. $[\alpha]_D^{20}$=−9.5 (*c*=1.05, $CHCl_3$).

*4.2.3. (1*S,*3*S*)- and (1*R,*3*S*)*-N-*[1-Isocyano-1-(4-methoxyphenyl)-5-methyl-3-hexyl]*-p-*toluenesulfonamide (*syn-***3c***;* anti-***3c)***

Pale yellow oil (diastereomeric mixture; *syn*:*anti*, 60:40). The diastereomers were separated by column chromatography (CH_2Cl_2:EtOAc, 95:5). In addition to 0.97 g (30%) of a colorless oil (diastereomeric mixture; *syn*:*anti*, 65:35), the following were obtained.

syn-**3c** (1*S*,3*S*): Colorless foam (0.64 g, 20%); IR (KBr): 3280 (NH), 2138 (NC), 1333, 1161 cm^{-1} (S=O). ^1H NMR ($CDCl_3$): δ (ppm)=0.59 (d, J=6.4 Hz, 6H, 2CH_3), 1.04–1.18 and 1.20–1.49 (m, 3H, CH_2 and C*H*(CH_3)$_2$), 1.87–2.13 (m, 2H, C*H*$_2$CHNC), 2.43 (s, 3H, ArCH_3), 3.13–3.27 (m, 1H, C*H*NH), 3.82 (s, 3H, OCH_3), 4.44 (d, J=8.4 Hz, 1H, NH, exchangeable), 4.71 (dd, J=7.2 Hz, 1H, C*H*NC), 6.84, 7.22 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.31, 7.74 (AA′BB′, J=8.3 Hz, 4H, ArH). Anal. calcd for $C_{22}H_{28}N_2O_3S$ (400.5): C, 65.97; H, 7.05; N, 6.99. Found: C, 65.74; H, 7.04; N, 6.85. $[\alpha]_D^{20}$=−9.2 (*c*=0.76, $CHCl_3$).

anti-**3c** (1*R*,3*S*): Colorless foam (0.48 g, 15%), contaminated with 9% of *syn*-**3c**; IR (KBr): 3270 (NH), 2138 (NC), 1331, 1161 cm^{-1} (S=O). ^1H NMR ($CDCl_3$): δ (ppm)=0.65 (d, J=6.5 Hz, 3H, CH_3), 0.74 (d, J=6.5 Hz, 3H, CH_3), 1.10–1.30 (m, 2H, CH_2), 1.33–1.51 (m, 1H, C*H*(CH_3)$_2$), 1.60–1.77 (m, 1H, *H*CHCHNC), 1.97 (ddd, J=14.1, 11.0, 3.0 Hz, 1H, HC*H*CHNC), 2.44 (s, 3H, ArCH_3), 3.40–3.54 (m, 1H, C*H*NHTs), 3.81 (s, 3H, OCH_3), 4.38 (d, J=8.7 Hz, NH, exchangeable), 4.86 (dd, J=10.7, 3.3 Hz, 1H, C*H*NC), 6.88, 7.20 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.33, 7.81 (AA′BB′, J=8.0 Hz, 4H, ArH). Anal. calcd for $C_{22}H_{28}N_2O_3S$ (400.5): C, 65.97; H, 7.05; N, 6.99. Found: C, 65.89; H, 7.30; N, 6.74. $[\alpha]_D^{20}$=−71.1 (*c*=0.65, $CHCl_3$).

4.3. 3-Isocyano-phosphinamides ***5a–c****. General procedure*

To a solution of isocyanide **1** (1.48 g, 10 mmol) in dry THF (30 ml), *n*-BuLi (1.6 M in hexane, 6.6 ml, 10.5 mmol) was added dropwise at −78°C under nitrogen. After stirring for 40 min at −78°C, a solution of aziridine **4a–c** (5 mmol) in dry THF (40 ml) was added, and stirring was continued for 5 h at −78°C. The cooling bath was removed, and stirring was continued for 15 min. Half saturated NH_4Cl solution (40 ml) was added, the layers were separated, and the aqueous layer was extracted with EtOAc (2×60 ml). The combined organic layers were washed with brine (2×20 ml), dried and evaporated.

*4.3.1. (2*S,*4*S*)- and (2*S,*4*R*)*-N-*[4-Isocyano-4-(4-methoxyphenyl)-1-phenyl-2-butyl]-diphenylphosphinamide (*syn-***5a***;* anti-***5a)****. Diastereomeric mixture*

The crude product was purified by column chromatography (EtOAc): colorless crystals (1.96 g, 81%, diastereomeric mixture; *syn*:*anti*, 60:40); IR (KBr): 3434 (NH), 2138 (NC), 1179 cm^{-1} (P=O). ^1H NMR ($CDCl_3$): δ (ppm)=1.70–1.87 (m, 1H, *H*CH, *anti*-diastereomer), 2.00–2.28 (m, 3H, HC*H*, *anti*- and CH_2 *syn*-diastereomer), 2.71–3.03 (m, 3H, PhCH_2 and NH, exchangeable), 3.10–3.29 (m, CHN, 0.6H, *syn*-diastereomer), 3.48–3.66 (m, CHN, 0.4H, *anti*-diastereomer), 3.78 (s, 1.8H, OCH_3, *syn*-diastereomer), 3.79 (s, 1.2H, OCH_3, *anti*-diastereomer), 5.07 (dd, J=7.2 Hz, 0.6H, C*H*NC, *syn*-diastereomer), 5.43 (dd, J=10.9, 3.1 Hz, 0.4H, C*H*NC, *anti*-diastereomer), 6.78, 7.21 (AA′BB′, J=8.7 Hz, 2.4H, ArH, *syn*-

diastereomer), 6.85, 7.29 (AA′BB′, J=8.7 Hz, 1.6H, ArH, *anti*-diastereomer), 7.00–7.07 (m, 1H, ArH), 7.13–7.74 (m, 12H, ArH), 7.80–7.94 (m, 2H, ArH). Anal. calcd for $C_{30}H_{29}N_2O_2P$ (485.5): C, 74.98; H, 6.08; N, 5.83. Found: C, 74.57; H, 5.98; N, 5.97. Recrystallization from CH_2Cl_2/petroleum ether afforded pure *syn*-**5a** (2*S*,4*S*) (0.72 g, 30%) as colorless crystals: m.p. 188°C; IR (KBr): 3434, 3251 (NH), 2137 (NC), 1184 cm^{-1} (P=O). ^1H NMR ($CDCl_3$): δ (ppm)=2.19–2.25 (m, 2H, CH_2), 2.76–2.86 (m, 3H, $PhCH_2$ and NH, exchangeable), 3.10–3.25 (m, 1H, CHN), 3.78 (s, 3H, OCH_3), 5.07 (dd, J=7.2 Hz, 1H, C*H*NC), 6.78, 7.21 (AA′BB′, J=8.7 Hz, 4H, ArH), 6.98–7.07 (m, 2H, ArH), 7.15–7.70 (m, 11H, ArH), 7.80–7.91 (m, 2H, ArH). Anal. calcd for $C_{30}H_{29}N_2O_2P$ (485.5): C, 74.98; H, 6.08; N, 5.83. Found: C, 74.65; H, 5.81; N, 5.98. $[\alpha]_D^{20}=-23.7$ (*c*=0.12, EtOAc).

*4.3.2. (1*S,*3*R*)- and (1*R,*3*R*)*-N-*[1-Isocyano-1-(4-methoxyphenyl)-4-methyl-3-pentyl]-diphenylphosphinamide (*syn-***5b***;* anti-***5b**)*

Pale yellow oil (diastereomeric mixture; *syn*:*anti*, 80:20). The diastereomers were separated by column chromatography (EtOAc) and recrystallized from Et_2O. In addition to 0.42 g (20%) of a colorless oil (diastereomeric mixture; *syn*:*anti*, 70:30), the following were obtained.

syn-**5b** (1*S*,3*R*): Colorless crystals (0.64 g, 30%); m.p. 156°C; IR (KBr): 3434, 3174 (NH), 2132 (NC), 1185 cm^{-1} (P=O). ^1H NMR ($CDCl_3$): δ (ppm)=0.70 (d, J=6.9 Hz, 3H, CH_3), 0.88 (d, J=6.9 Hz, 3H, CH_3), 1.78–1.94 (m, 1H, C*H*(CH_3)$_2$), 2.06–2.18 (m, 2H, CH_2), 2.68–2.95 (m, 2H, C*H*NH and NH, exchangeable), 3.79 (s, 3H, OCH_3), 5.09 (dd, J=7.2 Hz, 1H, C*H*NC), 6.83, 7.30 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.38–7.60 (m, 6H, ArH), 7.80–8.00 (m, 4H, ArH). Anal. calcd for $C_{26}H_{29}N_2O_2P$ (432.5): C, 72.20; H, 6.76; N, 6.48. Found: C, 72.24; H, 6.78; N, 6.42. $[\alpha]_D^{20}=-30.8$ (*c*=1.13, $CHCl_3$).

anti-**5b** (1*R*,3*R*): Colorless crystals (0.21 g, 10%); m.p. 130°C; IR (KBr): 3425, 3160 (NH), 2138 (NC), 1187 cm^{-1} (P=O). ^1H NMR ($CDCl_3$): δ (ppm)=0.90 (d, J=6.6 Hz, 3H, CH_3), 0.92 (d, J=6.5 Hz, 3H, CH_3), 1.60–1.78 (m, 1H, C*H*(CH_3)$_2$), 1.83–2.07 (m, 2H, CH_2), 2.72–2.91 (m, 1H, NH, exchangeable), 3.10–3.25 (m, 1H, C*H*NH), 3.80 (s, 3H, OCH_3), 5.51 (dd, J=11.0, 2.3 Hz, 1H, C*H*NC), 6.88, 7.30 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.40–7.60 (m, 6H, ArH), 7.89–8.07 (m, 4H, ArH). Anal. calcd for $C_{26}H_{29}N_2O_2P$ (432.5): C, 72.20; H, 6.76; N, 6.48. Found: C, 72.00; H, 6.66; N, 6.35. $[\alpha]_D^{20}=-24.6$ (*c*=0.69, $CHCl_3$).

*4.3.3. (1*S,*3*S*)- and (1*R,*3*S*)*-N-*[1-Isocyano-1-(4-methoxyphenyl)-5-methyl-3-hexyl]-diphenylphosphinamide (*syn-***5c***;* anti-***5c**). Diastereomeric mixture*

The crude product was purified by column chromatography (EtOAc): pale yellow foam (1.78 g, 80%, diastereomeric mixture *syn*:*anti*, 50:50); IR (KBr): 3425, 3149 (NH), 2138 (NC), 1178 cm^{-1} (P=O). ^1H NMR ($CDCl_3$): δ (ppm)=0.52 (d, J=6.5 Hz, 1.5H, CH_3), 0.69–0.82 (m, 4.5H, CH_3), 1.30–1.87 (m, 4H, C*H*$_2$CHCH_3)$_2$, C*H*(CH_3)$_2$ and *H*CH), 1.96–2.28 (m, 1H, HC*H*), 2.70–2.81 (m, 0.5H, NH, exchangeable), 2.85–3.08 (m, 0.5H, C*H*NH, *syn*-diastereomer), 3.17–3.38 (m, 0.5H, C*H*NH, *anti*-diastereomer), 3.78 and 3.80 (s, 3H, OCH_3, *syn*- and *anti*-diastereomer), 5.07 (dd, J=7.2 Hz, 0.5H, C*H*NC, *syn*-diastereomer), 5.41 (dd, J=10.6, 3.3 Hz, 0.5H, C*H*NC, *anti*-diastereomer), 6.83, 7.33 (AA′BB′, J=8.8 Hz, 2H, Ar*H*, *syn*-diastereomer), 6.87, 7.28 (AA′BB′, J=8.9 Hz, 2H, ArH, *anti*-diastereomer), 7.36–7.59 (m, 6H, ArH), 7.81–8.02 (m, 4H, ArH). Anal. calcd for $C_{27}H_{31}N_2O_2P$ (447.5): C, 72.63; H, 7.00; N, 6.27. Found: C, 72.66; H, 7.08; N, 6.19.

*4.4. 3-Phosphinamido-formamides **6**. General procedure*

At 0°C, to a stirred solution of 3-isocyano-phosphinamides **5a**,**c** (3 mmol) in Et_2O:THF 1:1 (80 ml) concd HCl (1 ml) was added. The cooling bath was removed, and stirring was continued for 3 min. The

mixture was shaken with saturated $NaHCO_3$ solution (25 ml), the layers were separated, and the aqueous layer was extracted with EtOAc (2×100 ml). The combined organic layers were washed with brine (2×15 ml), dried and evaporated.

*4.4.1. (1*S,*3*S*)- and (1*R,*3*S*)*-N-*[3-Diphenylphosphinamido-1-(4-methoxyphenyl)-4-phenyl-1-butyl]-formamide (*syn-**6a**; anti-**6a**)*

Pale yellow oil (diastereomeric mixture *syn*:*anti*, 60:40). The diastereomers were separated by column chromatography (CH_2Cl_2:MeOH, 95:5). *syn*-**6a** was recrystallized from toluene.

syn-**6a** (1*S*,3*S*): Pale yellow crystals (1.06 g, 42%); m.p. 95°C; IR (KBr): 3211 (NH), 1665 (C=O), 1179 cm^{-1} (P=O). ^1H NMR ($CDCl_3$): δ (ppm)=1.93 (ddd, J=14.2, 8.2, 4.1 Hz, 1H, *H*CH), 2.39 (ddd, J=14.2, 11.1, 3.7 Hz, 1H, HC*H*), 2.61 (s, 1H, NH, exchangeable), 2.62–2.80 [m, 1H, *H*CHPh, after H/D-exchange: 2.66 (dd, J=13.5, 8.2 Hz)], 2.93–3.06 (m, 1H, HC*H*Ph), 3.19–3.34 (m, 1H, C*H*NHPO), 3.75 (s, 3H, OCH_3), 4.96–5.05 [m, 1H, C*H*NHCHO, after H/D-exchange: 5.09 (dd, J=11.1, 3.7 Hz)], 6.78, 7.16 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.12–7.21 (m, 1H, ArH), 7.23–7.51 (m, 12H, ArH), 7.67–7.80 (m, 3H, N*H*CHO, exchangeable and 2H, ArH), 8.07 (s, 1H, NC*H*O). Anal. calcd for $C_{30}H_{31}N_2O_3P$ (503.5): C, 72.27; H, 6.27; N, 5.62. Found: C, 72.02; H, 6.47; N, 5.42. $[\alpha]_D^{20}$=−77.15 (*c*=0.15, $CHCl_3$).

anti-**6a** (1*R*,3*S*): Colorless crystals (0.88 g, 35%); m.p. 75°C; IR (KBr): 3210 (NH), 1665 (C=O), 1179 cm^{-1} (P=O). ^1H NMR ($CDCl_3$): δ (ppm)=1.91–2.07 (m, 1H, *H*CH), 2.25–2.49 (m, 1H, HC*H*), 2.78 (d, J=6.6 Hz, 2H, $PhCH_2$), 2.96–3.07 (m, 1H, NH, exchangeable), 3.14–3.31 (m, 1H, C*H*NHPO), 3.77 (s, 3H, OCH_3), 5.20–5.28 [m, 1H, C*H*NHCHO, after H/D-exchange: 5.23 (dd, J=7.0, 5.2 Hz)], 6.76, 7.16 (AA′BB′, J=8.7 Hz, 4H, ArH), 6.94–7.03 (m, 2H, ArH), 7.21–7.57 (m, 11H, ArH), 7.72–7.85 (m, 2H, ArH), 8.10 (d, J=7.7 Hz, 1H, N*H*CHO, exchangeable), 8.14 (s, 1H, NC*H*O). Anal. calcd for $C_{30}H_{31}N_2O_3P$ (503.5): C, 72.27; H, 6.27; N, 5.62. Found: C, 72.12; H, 6.49; N, 5.43. $[\alpha]_D^{20}$=−11.8 (*c*=0.45, $CHCl_3$).

*4.4.2. (1*S,*3*S*)- and (1*R,*3*S*)*-N-*[3-Diphenylphosphinamido-1-(4-methoxyphenyl)-5-methyl-1-hexyl]-formamide (*syn-**6b**; anti-**6b**)*

Pale yellow oil (diastereomeric mixture; *syn*:*anti*, 50:50). The diastereomers were separated by column chromatography (CH_2Cl_2:MeOH, 95:5). In addition to 0.13 g (9%) of a colorless oil (diastereomeric mixture; *syn*:*anti*, 50:50), the following were obtained.

syn-**6b** (1*S*,3*S*): Colorless foam (0.48 g, 34%); IR (KBr): 3433 (NH), 1665 (C=O), 1181 cm^{-1} (P=O). ^1H NMR ($CDCl_3$): δ (ppm)=0.69 (d, J=6.6 Hz, 3H, CH_3), 0.81 (d, J=6.6 Hz, 3H, CH_3), 1.41 (dd, J=7.0 Hz, 2H, CH_2CH(CH_3)$_2$), 1.67–1.97 (m, 2H, C*H*(CH_3)$_2$ and *H*CH), 2.40 (ddd, J=14.2, 10.8, 3.8 Hz, 1H, HC*H*), 2.78–2.89 (m, 1H, NH, exchangeable), 3.05–3.21 (m, 1H, C*H*NH), 3.76 (s, 3H, OCH_3), 4.90–5.01 [m, 1H, C*H*NHCHO, after H/D-exchange: 4.98 (dd, J=10.8, 4.0 Hz)], 6.80, 7.22 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.40–7.58 (m, 6H, ArH), 7.70 (d, J=7.6 Hz, NH, exchangeable), 7.77–7.99 (m, 4H, ArH), 8.14 (s, 1H, NC*H*O). Anal. calcd for $C_{27}H_{33}N_2O_3P$ (464.5): C, 69.81; H, 7.16; N, 6.03. Found: C, 69.76; H, 7.21; N, 5.99. $[\alpha]_D^{20}$=−98.0 (*c*=1.34, $CHCl_3$).

anti-**6b** (1*R*,3*S*): Colorless foam (0.48 g, 34%); IR (KBr): 3205 (NH), 1669 (C=O), 1181 cm^{-1} (P=O). ^1H NMR ($CDCl_3$): δ (ppm)=0.60–0.69 (m, 6H, 2CH_3), 1.23–1.70 (m, 3H, CH_2CH(CH_3)$_2$ and C*H*(CH_3)$_2$), 1.88 (ddd, J=14.6, 5.0, 4.9 Hz, 1H, *H*CH), 2.32 (ddd, J=14.6, 8.4, 4.7 Hz, 1H, HC*H*), 2.90–3.08 (m, 2H, C*H*NH and NH, exchangeable), 3.77 (s, 3H, OCH_3), 5.13–5.21 [m, 1H, C*H*NHCHO, after H/D-exchange: 5.16 (dd, J=8.4, 4.7 Hz)], 6.80, 7.25 (AA′BB′, J_{AB}=8.7 Hz, 4H, ArH), 7.38–7.60 (m, 6H, ArH), 7.79–7.99 (m, 4H, ArH), 8.14 (s, 1H, NC*H*O), 8.35 (d, J=7.9 Hz, 1H, NH, exchangeable). Anal. calcd for $C_{27}H_{33}N_2O_3P$ (464.5): C, 69.81; H, 7.16; N, 6.03. Found: C, 69.80; H, 7.33; N, 5.97. $[\alpha]_D^{20}$=−30.3 (*c*=1.14, $CHCl_3$).

4.5. (1S,3S)- and (1R,3S)-N-[1-(4-Methoxyphenyl)-4-phenyl-3-p-toluenesulfonamido-1-butyl]formamide (syn-7; anti-7)

syn-**7** (1*S*,3*S*): At 0°C, to a stirred solution of 3-isocyano-*p*-toluenesulfonamide *syn*-**3a** (0.22 g, 0.5 mmol) in Et_2O (100 ml), concd HCl (1.1 ml) was added. The cooling bath was removed, and stirring was continued for 5 min. The mixture was shaken with saturated $NaHCO_3$ solution (30 ml), the layers were separated, and the aqueous layer was extracted with Et_2O (2×30 ml). The combined organic layers were washed with brine (2×15 ml), dried and evaporated. Recrystallization from CH_2Cl_2/petroleum ether afforded *syn*-**7** (0.19 g, 84%) as colorless crystals: m.p. 72°C; IR (KBr): 3344 (NH), 1665 (C=O), 1315, 1153 cm^{-1} (S=O). ^1H NMR ($CDCl_3$): δ (ppm)=1.90–2.02 (m, 1H, *H*CH), 2.09–2.23 (m, 1H, HC*H*), 2.41 (s, 3H, CH_3), 2.64, 2.89 (ABX, J_{AB}=13.7 Hz, J_{AX}=6.3 Hz, J_{BX}=6.7 Hz, 2H, $PhCH_2$), 3.25–3.40 (m, 1H, C*H*NHTs), 3.79 (s, 3H, OCH_3), 4.77 (d, J=7.0 Hz, 1H, N*H*Ts, exchangeable), 4.93 (dd, J=7.2 Hz, 1H, ArCHN), 5.83 (d, J=7.8 Hz, 1H N*H*CHO, exchangeable), 6.78, 6.93 (AA′BB′, J=8.7 Hz, 4H, ArH), 6.90–7.04 (m, 2H, ArH), 7.10–7.28 (m, 5H, ArH), 7.49–7.60 (m, 2H, ArH), 8.16 (s, 1H, NC*H*O). Anal. calcd for $C_{25}H_{28}N_2O_4S$ (452.6): C, 66.35; H, 6.24; N, 6.19. Found: C, 66.13; H, 6.31; N, 6.30. $[\alpha]_D^{20}$=−4.1 (*c*=0.32, EtOH).

anti-**7** (1*R*,3*S*): Starting from *anti*-**3a** (0.22 g, 0.5 mmol), and following the procedure described for the preparation of *syn*-**7**, using half amounts of Et_2O (50 ml) and concd HCl (0.55 ml); *anti*-**7** (0.20 g, 88%) was obtained after recrystallization from CH_2Cl_2/petroleum ether as colorless crystals: m.p. 70°C; IR (KBr): 3377 (NH), 1670 (C=O), 1324, 1156 cm^{-1} (S=O). ^1H NMR ($CDCl_3$): δ (ppm)=1.74–1.86 (m, 1H, *H*CH), 2.04–2.29 (m, 1H, HC*H*), 2.39 (s, 3H, CH_3), 2.59, 2.76 (ABX, J_{AB}=13.9 Hz, J_{AX}=6.1 Hz, J_{BX}=7.3 Hz, 2H, $PhCH_2$), 3.20–3.32 (m, 1H, C*H*NHTs), 3.82 (s, 3H, OCH_3), 4.64 (d, J=7.0 Hz, 1H, NHTs, exchangeable), 5.09 (dd, J=7.2 Hz, 1H, ArCHN), 6.07 (d, J=7.8 Hz, 1H N*H*CHO, exchangeable), 6.88, 7.18 (AA′BB′, J=8.7 Hz, 4H, ArH), 6.79–6.93 (m, 2H, ArH), 7.05–7.34 (m, 5H, ArH), 7.36–7.48 (m, 2H, ArH), 8.14 (s, 1H, NCHO). Anal. calcd for $C_{25}H_{28}N_2O_4S$ (452.6): C, 66.35; H, 6.24; N, 6.19. Found: C, 66.14; H, 6.39; N, 6.26. $[\alpha]_D^{20}$=+5.8 (*c*=0.38, EtOH).

4.6. (2S,4S)- and (2S,4R)-N-[4-Amino-4-(4-methoxyphenyl-1-phenyl-2-butyl]-p-toluenesulfonamide hydrochloride (syn-8·HCl; anti-8·HCl)

syn-**8**·HCl (2*S*,4*S*): A solution of *syn*-**3a** (1.52 g, 3.5 mmol) in 2 N HCl (70 ml) and dioxane (140 ml) was stirred for 1 h at room temperature and then refluxed for 6 h. The mixture was evaporated in vacuo to dryness, and the residue was triturated with Et_2O to afford *syn*-**8**·HCl (1.54 g, 95%) as colorless crystals: m.p. 236°C; IR (KBr): 3423 (NH), 1325, 1148 cm^{-1} (S=O). ^1H NMR ($CDCl_3$): δ (ppm)=2.28–2.70 [m, 4H, $PhCH_2$ and CH_2CHNHTs, after H/D-exchange: 2.48 (d, J=7.2 Hz, $PhCH_2$)], 2.33 (s, 3H, CH_3), 3.10–3.28 (m, 1H, C*H*NHTs), 3.71 (s, 3H, OCH_3), 4.60 [m, 1H, C*H*NH_3^+, after H/D-exchange: 4.52 (dd, J=8.7, 4.6 Hz)], 6.65–6.73 (m, 2H, ArH), 6.77, 7.28 (AA′BB′, J=8.7 Hz, 4H, ArH), 6.91–7.03 (m, 3H, ArH), 7.09, 7.53 (AA′BB′, J=8.2 Hz, 4H, ArH), 7.43 (d, J=7.9 Hz, 1H, NHTs, exchangeable), 8.34 (s, 3H, NH_3^+, exchangeable). $[\alpha]_D^{20}$=−70.2 (*c*=0.50, $CHCl_3$).

anti-**8**·HCl (2*S*,4*R*): The same procedure as described above for the preparation of *syn*-**8**·HCl was used to afford *anti*-**8**·HCl (1.51 g, 93%) as colorless crystals: m.p. 222°C; IR (KBr): 3423 (NH), 1304, 1156 cm^{-1} (S=O). ^1H NMR ($CDCl_3$): δ (ppm)=2.29–2.79 (m, 4H, $PhCH_2$ and CH_2CHNHTs), 2.33 (s, 3H, CH_3), 3.35–3.51 (m, 1H, C*H*NHTs), 3.73 (s, 3H, OCH_3), 4.58 [m, 1H, C*H*NH_3^+, after H/D-exchange: 4.55 (dd, J=8.1, 6.5 Hz)], 6.23 (d, J=7.9 Hz, 1H, NHTs, exchangeable), 6.71–6.80 (m, 2H, ArH), 6.83, 7.44 (AA′BB′, J=8.6 Hz, 4H, ArH), 6.90–7.08 (m, 5H, ArH), 7.30–7.41 (m, 2H, ArH), 8.63 (s, 3H, NH_3^+, exchangeable). $[\alpha]_D^{20}$=−73.7 (*c*=0.70, $CHCl_3$).

*4.7. (2S,4S)- and (2S,4R)-*N*-[4-Amino-4-(4-methoxyphenyl)-1-phenyl-2-butyl]-*p*-toluenesulfonamide (*syn-***8***;* anti-***8****)*

syn-**8** (2*S*,4*S*): To *syn*-**8**·HCl (1.38 g, 3 mmol) a saturated Na_2CO_3 solution was added and the resulting mixture was extracted with CH_2Cl_2 (3×100 ml). The combined CH_2Cl_2 layers were dried and evaporated. Recrystallization from toluene gave *syn*-**8** (1.12 g, 87%) as colorless crystals: m.p. 106°C; IR (KBr): 3367, 3297 (NH), 1324, 1157 cm^{-1} (S=O). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.46–1.75 (m, 5H, C*H*$_2$CHNH, NHTs and NH_2, exchangeable), 2.44 (s, 3H, CH_3), 2.66, 2.98 (ABX, J_{AB}=13.5 Hz, J_{AX}=3.9 Hz, J_{BX}=8.3 Hz, 2H, $PhCH_2$), 3.33–3.50 (m, 2H, C*H*NHTs and C*H*NH_2), 3.76 (s, 3H, OCH_3), 6.77, 6.89 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.00–7.10 (m, 2H, ArH), 7.12–7.19 (m, 3H, ArH), 7.32, 7.80 (AA′BB′, J=8.1 Hz, 4H, ArH). Anal. calcd for $C_{24}H_{28}N_2O_3S$ (424.57): C, 67.90; H, 6.65; N, 6.60. Found: C, 67.91; H, 6.56; N, 6.48. $[\alpha]_D^{20}$=+37.5 (*c*=0.48, $CHCl_3$).

anti-**8** (2*S*,4*R*): Starting from *anti*-**8a**·HCl and following the same procedure as described above for the preparation of *syn*-**8**, *anti*-**8** (1.01 g, 79%) was obtained as colorless crystals: m.p. 108°C; IR (KBr): 3450, 3340, 3301 (NH), 1306, 1148 cm^{-1} (S=O). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.51–1.80 (m, 5H, C*H*$_2$, NHTs and NH_2, exchangeable), 2.41 (s, 3H, CH_3), 2.60–2.71 (m, 2H, $PhCH_2$), 3.60–3.71 (m, 1H, C*H*NHTs), 3.78 (s, 3H, OCH_3), 4.06 (dd, J=9.3, 4.3 Hz, 1H, C*H*NH_2), 6.82, 7.08 (AA′BB′, J=8.7 Hz, 4H, ArH), 6.90–7.00 (m, 2H, ArH), 7.12–7.20 (m, 3H, ArH), 7.24, 7.68 (AA′BB′, J=8.1 Hz, 4H, ArH). Anal. calcd for $C_{24}H_{28}N_2O_3S$ (424.57): C, 67.90; H, 6.65; N, 6.60. Found: C, 67.83; H, 6.66; N, 6.53. $[\alpha]_D^{20}$=+15.2 (*c*=0.54, $CHCl_3$).

4.7.1. syn-***8*** *From 3-toluenesulfonamido-formamide* syn-***7***

A solution of *syn*-**7** (0.45 g, 1 mmol) in 10% ethanolic KOH (50 ml) was stirred overnight at 50°C. EtOH was removed in vacuo, water (30 ml) was added, and the mixture was extracted with EtOAc (3×50 ml). The combined organic layers were washed with brine, dried and evaporated. Column chromatography (EtOAc:MeOH, 9:1) and recrystallization from toluene afforded *syn*-**8** (0.31 g, 74%).

*4.8. (2S,4S)- and (2S,4R)-*N*-[4-Amino-4-(4-methoxyphenyl)-1-phenyl-2-butyl]-diphenylphosphinamide (*syn-***9***;* anti-***9****)*

syn-**9** (2*S*,4*S*): A solution of *syn*-**6a** (0.75 g, 1.5 mmol) in 10% ethanolic KOH (80 ml) was stirred for 6.5 h at 50°C. EtOH was removed in vacuo, water (80 ml) was added, and the mixture was extracted with EtOAc (3×100 ml). The combined organic layers were washed with brine (2×15 ml), dried and evaporated. Column chromatography (CH_2Cl_2:MeOH, 9:1) and recrystallization from toluene afforded *syn*-**9** (0.48 g, 68%) as colorless crystals: m.p. 131°C; IR (KBr): 3386 (NH and NH_2), 1180 cm^{-1} (P=O). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.67 (s, 2H, NH_2, exchangeable), 1.85 (dd, J=6.7 Hz, 2H, CH_2), 2.70–2.90 (m, 2H, $PhCH_2$), 3.25–3.94 (m, 2H, CHN and NH, exchangeable), 3.77 (s, 3H, OCH_3), 4.10 (dd, J=7.0 Hz, 1H, C*H*NH_2), 6.76, 7.09 (AA′BB′, J=8.7 Hz, 4H, ArH), 6.97–7.04 (m, 4H, ArH), 7.15–7.53 (m, 7H, ArH), 7.61–7.90 (m, 4H, ArH). Anal. calcd for $C_{29}H_{31}N_2O_2P$ (470.5): C, 74.02; H, 6.64; N, 5.95. Found: C, 73.86; H, 6.70; N, 6.02. $[\alpha]_D^{20}$=−23.75 (*c*=0.56, $CHCl_3$).

anti-**9** (2*S*,4*R*): Starting from *anti*-**6a**, and following the procedure described for the preparation of *syn*-**9**, *anti*-**9** (0.44 g, 63%) was obtained as colorless crystals: m.p. 163°C; IR (KBr): 3423 (NH and NH_2), 1179 cm^{-1} (P=O). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.69–1.81 (m, 1H, *H*CH), 1.83–2.03 (m, 3H, HC*H* and NH_2, exchangeable), 2.86 (d, J=6.3 Hz, 2H, $PhCH_2$), 3.32–3.51 (m, 1H, CHN), 3.64–3.72 (m, 1H, NH, exchangeable), 3.77 (s, 3H, OCH_3), 4.18 (dd, J=9.5, 4.7 Hz, 1H, C*H*NH_2), 6.80, 7.16 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.00–7.56 (m, 11H, ArH), 7.60–7.72 (m, 2H, ArH), 7.80–7.91 (m, 2H, ArH). Anal. calcd

for $C_{29}H_{31}N_2O_2P$ (470.5): C, 74.02; H, 6.64; N, 5.95. Found: C, 73.72; H, 6.81; N, 5.94. $[\alpha]_D^{20}=-10.7$ (c=0.88, $CHCl_3$).

*4.9. (1S,3S)- and (1R,3S)-1-(4-Methoxyphenyl)-4-phenyl-1,3-diaminobutane (*syn-***10***; *anti-***10***)*

*4.9.1. From 3-amino-*p*-toluenesulfonamides* ***8***

syn-**10** (1*S*,3*S*): To a solution of *syn*-**8** (0.78 g, 1.83 mmol) in dry THF (20 ml) a solution of sodium naphthalenide [31 ml; prepared by stirring naphthalene (3.96 g, 31.2 mmol) and small pieces of sodium (1.92 g, 83.8 mmol) in dry THF (120 ml) for 3 h at room temperature under nitrogen] was added over 10 min at −78°C. After 6.5 h at −78°C, water (5 ml) was added, and THF was removed under reduced pressure. The mixture was diluted with water (10 ml) and extracted with EtOAc (3×30 ml). The combined EtOAc layers were washed with brine (2×20 ml), dried and evaporated. Column chromatography (CH_2Cl_2:MeOH, 90:10) afforded *syn*-**10** (0.17 g, 39%) as a colorless oil: IR (NaCl): 3357 cm^{-1} (NH). ^1H NMR ($CDCl_3$): δ (ppm)=1.76–2.05 (m, 2H, CH_2), 2.80 [d, J=6.9 Hz, 2H, $PhCH_2$, after H/D-exchange: 2.52, 2.75 (ABX, J_{AB}=13.3 Hz, J_{AX}=5.1 Hz, J_{BX}=8.3 Hz)], 3.10–3.26 (m, 1H, C*H*CH_2Ph, after H/D-exchange: 2.89–3.00), 3.72 (s, 3H, OCH_3), 4.00 [dd, J=9.4, 4.5 Hz, 1H, ArC*H*CH_2, after H/D-exchange: 4.01 (dd, J=7.1 Hz)], 4.22 (s, 4H, 2 NH_2, exchangeable), 6.85, 7.12 (AA′BB′, J=8.3 Hz, 4H, ArH), 7.15–7.22 (m, 5H, ArH). $[\alpha]_D^{20}=+14.15$ (c=0.53, $CHCl_3$).

anti-**10** (1*R*,3*S*): Starting from *anti*-**8**, and following the procedure described for the preparation of *syn*-**10**, *anti*-**10** (0.15 g, 35%) was obtained as a colorless oil: IR (NaCl): 3357 cm^{-1} (NH). ^1H NMR ($CDCl_3$): δ (ppm)=1.68–1.95 (m, 2H, CH_2), 2.37 (s, 4H, $2NH_2$, exchangeable), 2.61, 2.83 (ABX, J_{AB}=13.4 Hz, J_{AX}=5.3 Hz, J_{BX}=8.4 Hz, 2H, $PhCH_2$), 3.10–3.22 (m, 1H, C*H*CH_2Ph), 3.79 (s, 3H, OCH_3), 4.23 [dd, J=8.2, 5.1 Hz, 1H, ArC*H*NH_2, after H/D-exchange: 4.10 (dd, J=8.5, 5.5 Hz)], 6.86, 7.14 (AA′BB′, J=8.4 Hz, 4H, ArH), 7.18–7.31 (m, 5H, ArH). $[\alpha]_D^{20}=+4.0$ (c=0.15, $CHCl_3$).

4.9.2. From 3-phosphinamido-formamide syn-***6a***

syn-**10** (1*S*,3*S*): *syn*-**6a** (0.50 g, 1 mmol) was stirred with concd HCl (12 ml) for 15 min at room temperature and for 4 h at 50°C. The suspension was allowed to cool to room temperature and filtered. The filter cake was washed with 2 N HCl (2×10 ml), the combined filtrates were basified with 6 N NaOH and extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were dried and evaporated. Column chromatography (CH_2Cl_2:MeOH, 90:10) afforded *syn*-**10** (0.16 g, 60%) as a colorless oil.

4.9.3. From 3-amino-phosphinamide anti-***9***

anti-**10** (1*R*,3*S*): Starting from *anti*-**9** (1.88 g, 4.0 mmol), and following the procedure described for the preparation of *syn*-**10**, using 20 ml of concd HCl and a reaction time of 2.5 h at 50°C, *anti*-**10** (0.99 g, 91%) was obtained as a colorless oil.

*4.10. (1S,3R)-1-(4-Methoxyphenyl)-4-methyl-1,3-diaminopentane (*syn-***11***)*

Starting from *syn*-**5b** (0.37 g, 0.8 mmol), and following the procedure described for the preparation of *syn*-**10**, using 4 ml of concd HCl, *syn*-**11** (0.13 g, 75%) was obtained as a colorless oil: IR (NaCl): 3359 cm^{-1} (NH). ^1H NMR ($CDCl_3$): δ (ppm)=0.82 (d, J=6.8 Hz, 3H, CH_3), 0.85 (d, J=6.8 Hz, 3H, CH_3), 1.49–1.82 (m, 7H, CH_2, C*H*$(CH_3)_2$ and $2NH_2$, exchangeable), 2.40–2.50 (m, 1H, C*H*NH_2), 3.80 (s, 3H, OCH_3), 4.03 (dd, J=7.0 Hz, 1H, ArC*H*CH_2), 6.87, 7.25 (AA′BB′, J=8.3 Hz, 4H, ArH). $[\alpha]_D^{20}=+8.9$ (c=0.12, $CHCl_3$).

*4.11. (4S,6S)- and (4R,6S)-4-(4-Methoxyphenyl)-6-(phenylmethyl)hexahydropyrimidin-2-one (*cis-***12***;* trans-***12****)*

cis-**12** (4*S*,6*S*): To a stirred solution of *syn*-**10** (0.27 g, 1 mmol) in CH_2Cl_2 (15 ml), carbonyldiimidazole (0.20 g, 1.1 mmol) was added, and stirring was continued for 0.5 h. The solution was washed with 2 N HCl (10 ml), saturated $NaHCO_3$ solution (2×10 ml) and brine (2×10 ml), dried and evaporated. The crude product was purified by column chromatography (CH_2Cl_2:MeOH, 95:5): Colorless crystals (0.12 g, 40%); m.p. 149°C (toluene); IR (KBr): 3425, 3236 (NH), 1677 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ (ppm)=1.64 (dd, J=13.1, 11.4 Hz, 1H, *H*CH), 2.00–2.11 [m, 1H, HC*H*, after H/D-exchange: 2.04 (ddd, J=13.1, 3.5, 3.3 Hz)], 2.69, 2.83 (ABX, J_{AB}=13.4 Hz, J_{AX}=7.9 Hz, J_{BX}=6.2 Hz, 2H, $PhCH_2$), 3.70–3.76 [m, 1H, CHBn, after H/D-exchange: 3.75 (dddd, J=11.3, 7.9, 6.2, 3.3 Hz)], 3.80 (s, 3H, OCH_3), 4.43 (dd, J=11.4, 3.5 Hz, CHPh-4-OMe), 4.93 (s, 1H, NH, exchangeable), 5.01 (s, 1H, NH, exchangeable), 6.88, 7.21 (AA′BB′, J=8.8 Hz, 4H, ArH), 7.11–7.39 (m, 5H, ArH). Anal. calcd for $C_{18}H_{20}N_2O_2$ (296.4): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.39; H, 6.81; N, 9.20. $[\alpha]_D^{20}$=−36.25 (*c*=0.24, $CHCl_3$).

trans-**12** (4*R*,6*S*): Starting from *anti*-**10**, and following the procedure described for the preparation of *cis*-**12**, *trans*-**12** (0.13 g, 43%) was obtained as colorless crystals: m.p. 192°C (EtOH); IR (KBr): 3255 (NH), 1682 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ (ppm)=1.94–2.05 [m, 2H, CH_2, after H/D-exchange: 1.97 (ddd, J=13.2, 5.5, 5.2 Hz, *H*CH)], 2.03 (ddd, J=13.2, 6.9, 5.0 Hz, HC*H*)], 2.69, 2.83 (ABX, J_{AB}=13.4 Hz, J_{AX}=9.0 Hz, J_{BX}=5.1 Hz, 2H, $PhCH_2$), 3.42–3.59 [m, 1H, CHBn, after H/D-exchange: 3.49 (dddd, J=9.0, 6.9, 5.2, 5.1 Hz)], 3.81 (s, 3H, OCH_3), 4.60–4.73 [m, 2H, CHPh-4-OMe and NH, exchangeable, after H/D-exchange: 4.64 (dd, J=5.5, 5.0 Hz)], 4.93 (s, 1H, NH, exchangeable), 6.89, 7.20 (AA′BB′, J=8.7 Hz, 4H, ArH), 7.10–7.34 (m, 5H, ArH). Anal. calcd for $C_{18}H_{20}N_2O_2$ (296.4): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.53; H, 7.07; N, 9.39. $[\alpha]_D^{20}$=−11.7 (*c*=0.29, $CHCl_3$).

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