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Synthesis of hindered chiral guanidine bases starting from (*S*)-(*N*,*N*-dialkyl-aminomethyl)pyrrolidines and BrCN

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Abstract—An efficient method for the preparation of hindered chiral guanidines using cyanogen bromide is described. The reaction between BrCN and vicinal diamines derived from (*S*)-2-(*N*,*N*-dialkyl-aminomethyl)-pyrrolidines provides chiral substituted cyanamides. The cyanamide derivatives reacted with secondary amines in hexafluoroisopropanol at reflux to form chiral hindered guanidines, which were isolated in good to excellent yields (70–96%). The chiral guanidines were prepared in an effort to design sophisticated chiral guanidine catalysts for asymmetric synthesis.

1. Introduction

The guanidine functional group is an important compound in many biological, chemical and medicinal applications.[1] For instance,[2] guanidines received increasing interest as medicinal agents with antitumour, anti-hypertensive, anti-glaucoma and cardiotonic activities, as well as H_2 antagonism/agonism.

In some cases, due to their strongly basic character, guanidines can be as considered superbases that readily undergo protonation to generate resonance-stabilized guanidinium cations.[3] The wide range of biological activities and chemical applications found for guanidines has motivated the development of many reagents for their synthesis. Various methods achieve guanylation by the addition of a nucleophilic amine to a cyanamide,[4] or a carbodiimide.[5] Further guanylating methods involve the reaction between primary or secondary amines with heavy metals or carbodiimide promoted *N*,*N*-dialkylthioureas,[6] N-protected-*S*-alkylisothioureas,[7] or aminoiminosulfonic-acids.[8] Further methods, which would expand the range of substrates that could be converted into guanidine products, are based on the reaction of an electrophile with a nucleophilic guanidine to give higher substituted guanidine.[9] Additionally, the nucleophilic reaction of an amine to a reagent of the type $R_2N(Z)C{=}NR$ leads to a displacement of a leaving group Z, where Z can be the benzotriazole group of benzotriazole-1-carboxamidinium tosylate or di(benzotriazol-1-yl)methanimine, the pyrazole moiety of 1*H*-pyrazole-1-carboxamidine, or of its N,N′-diprotected derivatives.[10]

Chiral guanidines have potential as chiral auxiliaries in asymmetric synthesis, but obviously there is a lack of convenient preparation methods.[11] Previously, we reported the simple preparation of chiral guanidines as potential chiral superbases. These procedures have allowed the synthesis of enantiopure guanidines starting from *N*,*N*′-di-isopropylcarbodiimide and (*S*)-2-(*N*,*N*-dialkylamino-methyl)pyrrolidine.[5b] However, we could show that the diisopropyl groups are limited to the use of these guanidines in asymmetric synthesis.[12] For this reason, we have used an efficient synthesis, which allows access to sterically hindered chiral guanidine bases.

Herein, we report the preparation of sterically hindered ambitious chiral guanidines by a convenient method using chiral 1,2-diamines and cyanogen bromide. To the best of our knowledge, no attempt to synthesize chiral guanidines starting from (*S*)-2-(*N*,*N*-dialkylamino-methyl)pyrrolidines and cyanogen bromide has so far been published.

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2. Results and discussion

The starting chiral vicinal diamines **1a–c** were prepared, using a known three step procedure[13] in good to excellent yields by reaction in the first step of (*S*)-2-pyrrolidinone-5-carboxylic acid with anhydrous chloral to afford a diastereomerically pure oxazolidinone derivate precursor. This compound could be readily transformed into amides by nucleophilic ring opening with the corresponding amines. Finally, the amides were reduced with $LiAlH_4$ to the desired chiral vicinal diamines **1a–c**. Furthermore, the procedure could be extended to larger scales as described in the literature.[12]

Based on literature procedure for the formation of hindered guanidines,[14] we decided to prepare the cyanamides from the chiral *N*,*N*-(dialkylaminomethyl)-pyrrolidine derivates **1a–c**, and in a second step, we transformed the substituted cyanamide derivates with the corresponding amines into the desired guanidines. The reaction of **1a–c** with a small excess of cyanogen bromide and 1.3 equiv of triethylamines in THF afforded, after stirring at room temperature, the substituted crude cyanamides **2a–c** in quantitative yields (Scheme 1).

The purification of **2a–c** with bulb to bulb distillation gave yields in the range of 60–80% (isolated yields, Table 1). The molecular structures of compounds **2a–c** were established from their NMR (^1H, ^{13}C, DEPT 135, HMQC, HMBC) spectroscopic data. The ^{13}C NMR spectra of **2a–c** exhibited the requisite number of signals in small appearance, whereas the resonance signal of the significant cyano group was assigned to δ 117 ppm. In the ^1H NMR spectra, the methylene protons of **2a–c** are diastereotopic and appeared as complex multiplets in the range of δ 1.5–4.0 ppm. Furthermore, the IR spectra showed a strong band of the CN group at 2200 cm^{-1}.

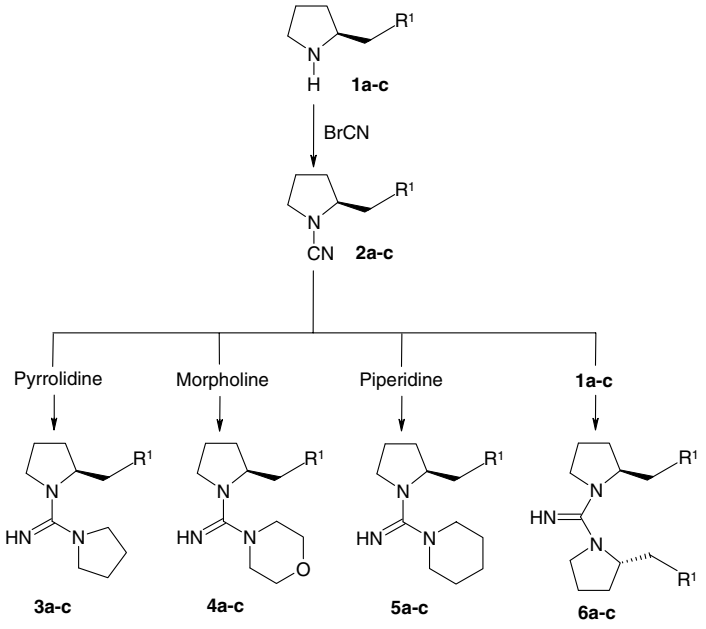
Table 1. Results for the preparation of **2a–c**

Cyanamide	R^1	Yield[a] (%)	$[\alpha]_D^{rt}$
2a	1-Pyrrolidinyl	64.0	−50.2
2b	4-Morpholinyl	80.0	−40.5
2c	1-Piperidinyl	77.6	−50.8

[a] Isolated yields.

Chiral guanidines **3–6** were prepared following a modified procedure of Snider et al.[14] Treatment of 1 equiv of cyanamide **2a–c** with 1 equiv of secondary amine in hexafluoroisopropanol (HFIP) for 16 h, yielded the corresponding chiral guanidines **3–5** (Scheme 1). After simple purification of guanidines **3–5** by dissolution in aqueous citric acid (pH = 7) in order to extract the impurities, the aqueous solution was basified with 50% KOH solution and the guanidines extracted with CH_2Cl_2 to afforded the desired products in good to excellent yields (Table 2). As expected, the reaction of **2a–c** with the chiral 1,2-diamines **1a–c** as secondary amine led to comparable results and produced only the single diastereomer. Guanidines **6a–c** were easily purified by the above-mentioned procedure to give good yields in a purity of over 90% by ^1H NMR spectroscopy.

To elucidate the structures of **3–6**, 2D NMR experiments (HMQC, HMBC, COSY) were carried out at room temperature in addition to ^1H, ^{13}C and DEPT 135. In general, the NMR measurements of **3–6** were recorded in dichloromethane and benzene due to the strong basic character of these guanidines.[5b] As expected, the ^{13}C NMR spectra showed the requisite number of signals and the significant guanidine carbon atom appeared in the range of 161–165 ppm. In the ^1H NMR spectra of **3–6**, the methylene protons were observed as complex multiplets in the region of δ 1.1–4.5 ppm and the methine proton appeared as multiplet in the range



Scheme 1. Synthesis of chiral cyanamides **2a–c** and guanidines **3–6**; R^1 see Table 1.

Table 2. Prepared hindered guanidines **3**–**6**

Guanidines	R^1	Sec. amine	Yield[a] (%)	$[\alpha]_D^{rt}$
3a	1-Pyrrolidinyl	Pyrrolidine	98.5	−22.2
3b	4-Morpholinyl	Pyrrolidine	97.4	−18.9
3c	1-Piperidinyl	Pyrrolidine	79.4	−21.5
4a	1-Pyrrolidinyl	Morpholine	71.9	27.7
4b	4-Morpholinyl	Morpholine	75.1	26.2
4c	1-Piperidinyl	Morpholine	76.9	23.1
5a	1-Pyrrolidinyl	Piperidine	90.7	54.2
5b	4-Morpholinyl	Piperidine	96.7	51.7
5c	1-Piperidinyl	Piperidine	90.6	34.3
6a	1-Pyrrolidinyl	**1a**	75.1	−40.8
6b	4-Morpholinyl	**1b**	98.6	−49.3
6c	1-Piperidinyl	**1c**	75.1	−40.4

[a] Isolated yields.

of δ 3.7–4.5 ppm. The NH guanidine proton revealed as broad singlet at δ 4.9–6.1 ppm, but in some cases, no identification was possible. Positive EI mass spectrometry was used to confirm that all products had the expected molecular formulas.

Choosing **4a** as a representative for guanidines **3**–**6**, ^{1}H NMR investigations of **4a** were carried out in the presence of the shift reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol in order to assess the enantiomeric purity.[15] Additionally, the reliability of the shift reagent was tested with the racemate of **4a**. Figure 1 shows the ^{1}H NMR spectra of the racemic and enantiopure (*S*)-form of **4a**.

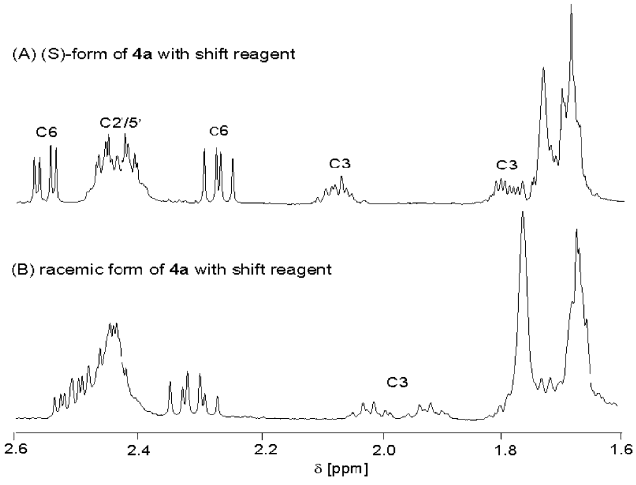


Figure 1. ^{1}H-spectra (400 MHz) of **4a** after addition of the chiral shift reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

When the chiral shift agent was added to a solution of racemic **4a** in THF-d_8 and immediately after that the ^{1}H NMR spectrum was measured at room temperature, one of the C3 methylene protons split into two multiplets of roughly equal intensity (Fig. 1B). In the case of the enantiomerically pure guanidine **4a**, no racemization was observed within the NMR accuracy (Fig. 1A). Thus, the enantiomeric purity of the isolated compound **4a** is higher than 95%.[5b]

To confirm the correct absolute configuration of chiral guanidines **3**–**6**, a zinc chloride complex[5a] of **4a** and a guanidine hydrochloride complex[5b] of **6a** were crystallized and investigated by X-ray crystallography. The X-ray analysis of **4a**·($ZnCl_2$) showed the expected (*S*)-configuration at C2-carbon (Fig. 2 and Table 3).

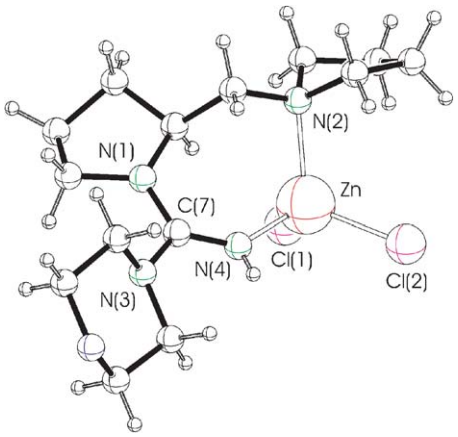


Figure 2. Crystal structure of **4a**·($ZnCl_2$).

Table 3. Selected bond lengths (Å) and bond angles (°) for the zinc(II) complex **4a**·($ZnCl_2$)

Bond lengths		Bond angles	
N(1)–C(7)	1.349(4)	N(1)–C(7)–N(3)	115.4(2)
N(3)–C(7)	1.386(4)	N(3)–C(7)–N(4)	123.9(3)
N(4)–C(10)	1.310(4)	N(1)–C(7)–N(4)	120.7(3)
N(2)–Zn	2.096(3)	N(2)–Zn–N(4)	103.87(11)
N(4)–Zn	2.000(3)	N(2)–Zn–Cl(1)	109.05(7)
Zn–Cl(1)	2.2487(8)	N(2)–Zn–Cl(2)	110.68(7)
Zn–Cl(2)	2.2487(8)	N(4)–Zn–C(10)	138.1(2)

For the hydrochloride complex **6a**·(HCl)[16] of the diastereomer **6a**, the absolute configuration for both stereogenic centres (C2, C3) was determined to be *S* (Fig. 3 and Table 4).

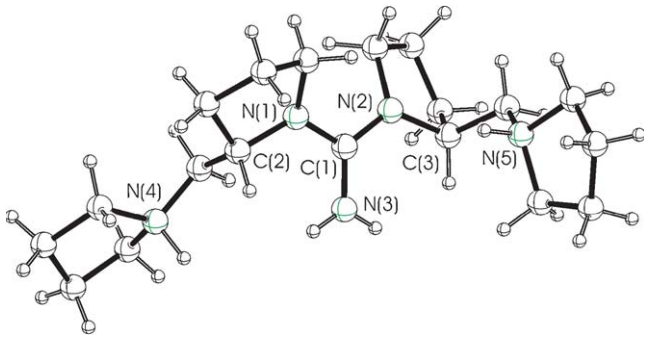


Figure 3. Crystal structure of diastereomeric hydrochloride complex **6a**·(HCl), chlorides are omitted for clarity.

Table 4. Selected bond lengths (Å) and bond angles (°) for the hydrochloride complex **6a**·(HCl)

Bond lengths		Bond angles	
N(1)–C(1)	1.337(6)	N(1)–C(1)–N(3)	122.7(4)
N(3)–C(1)	1.325(6)	N(3)–C(1)–N(2)	120.4(4)
N(2)–C(1)	1.358(6)	N(1)–C(1)–N(2)	116.8(4)
N(1)–C(2)	1.483(6)	C(1)–N(2)–C(3)	121.7(4)
N(2)–C(3)	1.487(6)	C(1)–N(1)–C(2)	123.8(4)

Finally, in preliminary tests we found that the new guanidines **3**–**6** possess strong basicity. The Henry reaction between 2-methylpropanal and nitromethane in CD_3CN promoted by **6a** provided the corresponding nitro-alcohol. This experiment demonstrates that **6a** has a pK_a value of at least 28 in MeCN, since the pK_a value of nitromethane in MeCN is approximately 28.[17] Potentiometric titrations are currently in progress and will be reported in due course.

3. Conclusion

An efficient method for the preparation of sterically hindered chiral guanidines **3**–**6** derived from (*S*)-2-(*N*,*N*-dialkylamino-methyl)pyrrolidines **1a**–**c** using cyanogen bromide has been reported. In the first step, the reaction of 1,2-diamines with BrCN produced substituted cyanamides **2a**–**c**, which were subsequently reacted with secondary amines in the presence of hexafluoroisopropanol to afford hindered chiral guanidines **3**–**6**. This protocol provides an alternative method for the preparation of chiral guanidines. An attractive feature of this methodology is that only a few byproducts are generated and at the end of the reaction, simple aqueous work-up gives high yields of the desired products.

We are currently seeking to extend the guanidine chemistry to investigate its application in asymmetric syntheses, for example, Henry reaction or Michael addition as chiral bases. Further work is currently in progress in order to determine the basicity of this new class of guanidines.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AC 250 MHz and AC 400 MHz using the residual solvent resonance as an internal standard. CD_2Cl_2 (H $\delta = 5.32$, C $\delta = 53.8$) and C_6D_6 (H $\delta = 7.15$, C $\delta = 128.0$) were used as solvents. The geminal protons are described as X/X. Optical rotations were recorded on a Polartronic E and are reported as $[\alpha]_D^{rt}$ (*c* in g/100 ml, solvent). Elemental analyses were conducted by the microanalytical service of our department. IR spectra were recorded on an ATR–BIORAD FTS-25. MS spectra were recorded on a Finnigan MAT SAQ 710 (EI) and on a Finnigan MAT SSQ (ESI). All compounds were fully characterized. The elemental compositions were determined by microanalytical data (±0.4%) or HRMS. Hexafluoro-isopropanol, (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol and cyanogen bromide were commercially available and used without further purification. Chiral 1,2-diamines **1a**–**c** are described in the literature.[13] Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone.

4.2. Chiral diamines 1a–c

4.2.1. (*S*)-2-(Pyrrolidin-1-ylmethyl)-pyrrolidine 1a.[13] Yield 90.1%. HRMS *m*/*z* 155.1550 $(M+1)^+$. $C_9H_{19}N_2$ requires 155.1548. ^{1}H NMR ($CDCl_3$): δ 3.17 (m, 1H, CH), 2.91/2.76 (m, 2H, CH_2), 2.53/2.46 (m, 4H, $2\times CH_2$), 2.49/2.32 (m, 2H, CH_2), 2.06 (s, 1H, NH), 1.86/1.32 (m, 2H, CH_2), 1.73 (m, 6H, $3\times CH_2$). ^{13}C NMR ($CDCl_3$): δ 62.6 (CH_2), 57.8 (CH), 54.9 ($2\times CH_2$), 46.5 (CH_2), 30.6 (CH_2), 25.5 (CH_2), 23.8 ($2\times CH_2$). IR (ATR, ν/cm^{-1}): 3277 (ν_{NH}), 2959–2783 (ν_{CH}). EI-MS *m*/*z* 155 $(M+H)^+$. $[\alpha]_D^{20} = +10.8$ (*c* 2.59, EtOH).

4.2.2. (*S*)-2-(Morpholin-4-ylmethyl)-pyrrolidine 1b.[12] Yield 55.5%. HRMS *m*/*z* 171.1490 $(M+1)^+$. $C_9H_{19}N_2O$ requires 171.1497. ^{1}H NMR ($CDCl_3$): δ 3.66 (m, 4H, $2\times CH_2$), 3.23 (m, 1H, CH), 2.95/2.81 (m, 2H, CH_2), 2.51/2.38 (m, 4H, $2\times CH_2$) 2.26 (m, 2H, CH_2), 2.00 (s, 1H, NH), 1.84/1.29 (m, 2H, CH_2), 1.71 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 67.4 ($2\times CH_2$), 64.9 (CH_2), 55.3 (CH), 54.8 ($2\times CH_2$), 46.7 (CH_2), 30.9 (CH_2), 25.4 (CH_2). IR (ATR, ν/cm^{-1}): 3313 (ν_{NH}), 2954–2705 (ν_{CH}). EI-MS *m*/*z* 171 $(M+1)^+$. $[\alpha]_D^{20} = +11.3$ (*c* 2.40, EtOH).

4.2.3. (*S*)-2-(Piperidin-1-ylmethyl)-pyrrolidine 1c.[13] Yield 36.2%. HRMS *m*/*z* 169.1705 $(M+1)^+$. $C_{10}H_{21}N_2$ requires 169.1705. ^{1}H NMR ($CDCl_3$): δ 3.24 (m, 1H, CH), 2.97/2.81 (m, 2H, CH_2), 2.45/2.32 (m, 4H, $2\times CH_2$), 2.24 (m, 2H, CH_2), 1.84/1.30 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 1.55 (m, 4H, $2\times CH_2$), 1.42 (m, 2H, CH_2), NH at room temperature not detected. ^{13}C NMR ($CDCl_3$): δ 65.3 (CH_2), 56.0 ($2\times CH_2$), 55.5 (CH), 46.4 (CH_2), 30.5 (CH_2), 26.6 ($2\times CH_2$), 25.4 (CH_2), 24.9 (CH_2). IR (ATR, ν/cm^{-1}): 3313 (ν_{NH}), 2954–2705 (ν_{CH}). EI-MS *m*/*z* 169 $(M+H)^+$. $[\alpha]_D^{20} = +15.2$ (*c* 10.0, EtOH).

4.3. General procedure for preparation of chiral cyanamide derivates 2

To a solution of **1a**–**c** (6.5 mmol) and triethylamine (8.5 mmol) in 30 mL dry THF, 7.5 mmol of cyanogen bromide dissolved in 5 mL, THF was added while stirring. The reaction mixture was magnetically stirred for 30 min at room temperature. The white precipitate formed was filtered off and washed with THF. The solvent was evaporated under reduced pressure and the resulting yellow oily residue dissolved in 40 mL of water. The aqueous solution was adjusted with aqueous citric acid to pH 7. After extraction with ether (3×20 mL), the pH value of the aqueous solution was raised with concentrated KOH solution (50%) to pH 10. Following an extraction with CH_2Cl_2 (3×20 mL), the combined organic phases were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the resulting oily crude product purified by bulb to bulb distillation.

4.3.1. (*S*)-2-(Pyrrolidin-1-ylmethyl)-pyrrolidine-1-carbonitrile 2a. Yield 64.0%. (Found: C, 67.27; H, 9.45; N, 23.27. $C_{10}H_{17}N_3$ requires C, 67.00; H, 9.56; N, 23.44.) ^{1}H NMR ($CDCl_3$): δ 3.63 (m, 1H, CH), 3.35 (m, 2H, CH_2), 2.66/2.43 (m, 2H, CH_2), 2.50 (m, 4H, $2\times CH_2$), 1.96/1.67 (m, 2H, CH_2), 1.83 (m, 2H, $2\times CH_2$), 1.70 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 117.3 (CN), 61.0

(CH), 59.6 (CH_2), 54.6 ($2\times CH_2$), 50.9 (CH_2), 30.0 (CH_2), 24.5 (CH_2), 23.5 ($2\times CH_2$). IR (ATR, ν/cm^{-1}): 2959–2787 (ν_{CH}), 2203 (ν_{CN}). EI-MS, m/z 179 (M^+). $[\alpha]_D^{20} = -50.2$ (c 2.95, $CHCl_3$).

4.3.2. (*S*)-2-(Morpholin-4-ylmethyl)-pyrrolidine-1-carbonitrile 2b. Yield 80.0%. (Found: C, 61.26; H, 8.81; N, 21.01 $C_{10}H_{17}N_3O$ requires C, 61.51; H, 8.78; N, 21.52.) ^1H NMR ($CDCl_3$): δ 3.68 (m, 4H, $2\times CH_2$), 3.68 (m, 1H, CH), 3.41 (m, 2H, CH_2), 2.49/2.39 (m, 2H, CH_2), 2.45 (m, 4H, $2\times CH_2$), 1.98/1.66 (m, 2H, CH_2), 1.87 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 117.3 (CN), 66.9 ($2\times CH_2$), 62.3 (CH_2), 59.1 (CH), 54.3 ($2\times CH_2$), 51.1 (CH_2), 29.8 (CH_2), 24.7 (CH_2). IR (ATR, ν/cm^{-1}): 2953–2806 (ν_{CH}), 2202 (ν_{CN}). EI-MS, m/z 195 (M^+). $[\alpha]_D^{20} = -40.5$ (c 2.37, $CHCl_3$).

4.3.3. (*S*)-2-(Piperidin-1-ylmethyl)-pyrrolidine-1-carbonitrile 2c. Yield 77.6%. (Found: C, 68.16; H, 9.72; N, 21.62. $C_{11}H_{19}N_3$ requires C, 68.35; H, 9.91; N, 21.74.) ^1H NMR ($CDCl_3$): δ 3.66 (m, 1H, CH), 3.36 (m, 2H, CH_2), 2.44/2.26 (m, 2H, CH_2), 2.37 (m, 4H, $2\times CH_2$), 1.97/1.65 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 1.52 (m, 4H, $2\times CH_2$), 1.36 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 117.4 (CN), 62.5 (CH_2), 59.6 (CH), 55.1 ($2\times CH_2$), 51.0 (CH_2), 30.0 (CH_2), 25.9 ($2\times CH_2$), 24.4 (CH_2), 24.2 (CH_2). IR (ATR, ν/cm^{-1}): 2933–2776 (ν_{CH}), 2204 (ν_{CN}). EI-MS, m/z 193 (M^+). $[\alpha]_D^{20} = -50.8$ (c 2.71, CH_2Cl_2).

4.4. General procedure for preparation of chiral guanidine derivates 3–6

To a solution of **2** (3 mmol) in hexafluoroisopropanol (3 mL) was added the corresponding secondary amine (3 mmol, pyrrolidine, morpholine, piperidine or **1a**–**c**). The reaction mixture was refluxed for 16 h. Under vigorous stirring, the brown solution was then diluted with water (40 mL) and adjusted with aqueous citric acid to pH 7. After extraction of the impurities with ether (3×20 mL), the aqueous solution was alkalinized with concentrated KOH solution (50%) to pH 14 and the guanidines **3**–**6** were extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. Guanidines **3**–**6** are over 90% pure by ^1H NMR spectroscopy. Additionally, the resulting oily crude product can be purified by bulb to bulb distillation.

4.4.1. *C*-Pyrrolidin-1-yl-*C*-(2-(pyrrolidin-1-ylmethyl)-pyrrolidin-1-yl)-methylenamine 3a. Yield 98.5%. HRMS m/z 251.2235 $(M+1)^+$. $C_{14}H_{27}N_4$ requires 251.2236. ^1H NMR (C_6D_6): δ 6.06 (s, 1H, NH), 4.39 (m, 1H, CH), 3.18/3.05 (m, 2H, CH_2), 3.05 (m, 4H, $2\times CH_2$), 2.84/2.42 (m, 2H, CH_2), 2.51 (m, 4H, $2\times CH_2$), 2.06/1.68 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.55–1.27 (m, 6H, $3\times CH_2$). ^{13}C NMR (C_6D_6): δ 160.7 (CN_3), 60.0 (CH_2), 57.9 (CH), 54.8 ($2\times CH_2$), 50.2 ($2\times CH_2$), 48.3 (CH_2), 30.9 (CH_2), 25.3 (CH_2), 24.8 ($2\times CH_2$), 23.8 ($2\times CH_2$). IR (ATR, ν/cm^{-1}): 2961–2781 (ν_{CH}), 1570 ($\nu_{C=N}$). EI-MS m/z 250 (M^+). $[\alpha]_D^{20} = -22.2$ (c 2.47, CH_2Cl_2).

4.4.2. *C*-(2-(Morpholin-4-ylmethyl)-pyrrolidin-1-yl)-*C*-pyrrolidin-1-yl-methylenamine 3b. Yield 97.4%. HRMS m/z 267.2186 $(M+1)^+$. $C_{14}H_{27}N_4O$ requires 267.2185. ^1H NMR (C_6D_6): δ 5.00 (s, 1H, NH), 4.33 (m, 1H, CH), 3.60 (m, 4H, $2\times CH_2$), 3.04/2.97 (m, 2H, CH_2), 3.01 (m, 4H, $2\times CH_2$), 2.71/2.09 (m, 2H, CH_2), 2.43/2.32 (m, 4H, $2\times CH_2$), 1.99/1.55 (m, 2H, CH_2), 1.50/1.36 (m, 4H, $2\times CH_2$), 1.50 (m, 2H, CH_2). ^{13}C NMR (C_6D_6): δ 161.2 (CN_3), 67.1 ($2\times CH_2$), 63.2 (CH_2), 56.2 (CH), 54.8 ($2\times CH_2$), 50.2 (CH_2), 48.1 ($2\times CH_2$), 31.1 (CH_2), 25.3 ($2\times CH_2$), 24.8 (CH_2). IR (ATR, ν/cm^{-1}): 2956–2867 (ν_{CH}), 1567 ($\nu_{C=N}$), 1115 (ν_{COC}). EI-MS m/z 266 (M^+). $[\alpha]_D^{20} = -18.9$ (c 3.49, CH_2Cl_2).

4.4.3. *C*-(2-(Piperidin-1-ylmethyl)-pyrrolidin-1-yl)-*C*-pyrrolidin-1-yl-methylenamine 3c. Yield 79.4%. HRMS m/z 265.2394 $(M+1)^+$. $C_{15}H_{29}N_4$ requires 265.2392. ^1H NMR (C_6D_6): δ 5.17 (s, 1H, NH), 4.25 (m, 1H, CH), 3.05 (m, 6H, $3\times CH_2$), 2.76/2.17 (m, 2H, CH_2), 2.49/2.33 (m, 4H, $2\times CH_2$), 2.05/1.64 (m, 2H, CH_2), 1.62–1.40 (m, 12H, $6\times CH_2$). ^{13}C NMR (C_6D_6): δ 161.7 (CN_3), 63.9 (CH_2), 56.9 (CH), 55.3 ($2\times CH_2$), 50.4 ($2\times CH_2$), 48.3 (CH_2), 31.6 (CH_2), 26.6 ($2\times CH_2$), 25.5 ($2\times CH_2$), 25.0 (CH_2), 24.9 (CH_2). IR (ATR, ν/cm^{-1}): 2931–2866 (ν_{CH}), 1573 ($\nu_{C=N}$). EI-MS m/z 264 (M^+). $[\alpha]_D^{20} = -21.5$ (c 3.08, CH_2Cl_2).

4.4.4. *C*-Morpholin-4-yl-*C*-(2-(pyrrolidin-1-ylmethyl)-pyrrolidin-1-yl)-methylenamine 4a. Yield 71.9%. HRMS m/z 267.2182 $(M+1)^+$. $C_{14}H_{27}N_4O$ requires 267.2185. ^1H NMR (CD_2Cl_2): δ 3.86 (m, 1H, CH), 3.64 (m, 4H, $2\times CH_2$), 3.35/3.23 (m, 2H, CH_2), 3.06/2.96 (m, 4H, $2\times CH_2$), 2.59/2.34 (m, 2H, CH_2), 2.50 (m, 4H, $2\times CH_2$), 2.10/1.76 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 1.72 (m, 4H, $2\times CH_2$), NH not detected at room temperature. ^{13}C NMR (CD_2Cl_2): δ 164.3 (CN_3), 67.1 ($2\times CH_2$), 59.6 (CH_2), 57.7 (CH), 55.0 ($2\times CH_2$), 49.4 (CH_2), 49.2 ($2\times CH_2$), 31.0 (CH_2), 24.6 (CH_2), 23.9 ($2\times CH_2$). IR (ATR, ν/cm^{-1}): 2957–2766 (ν_{CH}), 1587 ($\nu_{C=N}$). EI-MS m/z 266 (M^+). $[\alpha]_D^{20} = +27.7$ (c 2.60, CH_2Cl_2).

4.4.5. *C*-Morpholin-4-yl-*C*-(2-(morpholin-4-ylmethyl)-pyrrolidin-1-yl)-methylenamine 4b. Yield 75.1%. (Found: C, 59.23; H, 9.58; N, 19.44. $C_{14}H_{26}N_4O_2$ requires C, 59.55; H, 9.28; N, 19.44.) ^1H NMR (CD_2Cl_2): δ 4.90 (s, 1H, NH), 3.93 (m, 1H, CH), 3.65 (m, 8H, $4\times CH_2$), 3.34/3.24 (m, 2H, CH_2), 3.09/2.97 (m, 4H, $2\times CH_2$), 2.46 (m, 4H, $2\times CH_2$), 2.41/2.19 (m, 2H, CH_2), 2.13/1.69 (m, 2H, CH_2), 1.77 (m, 2H, CH_2). ^{13}C NMR (CD_2Cl_2): δ 164.3 (CN_3), 67.3 ($2\times CH_2$), 67.1 ($2\times CH_2$), 62.3 (CH_2), 56.3 (CH), 54.8 ($2\times CH_2$), 49.4 (CH_2), 49.2 ($2\times CH_2$), 31.0 (CH_2), 24.5 (CH_2). IR (ATR, ν/cm^{-1}): 2955–2848 (ν_{CH}), 1586 ($\nu_{C=N}$), 1113 (ν_{COC}). EI-MS m/z 282 (M^+). $[\alpha]_D^{20} = +26.2$ (c 2.60, CH_2Cl_2).

4.4.6. *C*-Morpholin-4-yl-*C*-(2-(piperidin-1-ylmethyl)-pyrrolidin-1-yl)-methylenamine 4c. Yield 76.0%. (Found: C, 64.16; H, 10.14; N, 19.70. $C_{15}H_{28}N_4O$ requires C, 64.25; H, 10.06; N, 19.98.) ^1H NMR (C_6D_6):

δ 4.08 (m, 1H, CH), 3.60 (m, 4H, $2\times CH_2$), 3.23/3.04 (m, 2H, CH_2), 3.04/2.93 (m, 4H, $2\times CH_2$), 2.66/2.18 (m, 2H, CH_2), 2.54/2.40 (m, 4H, $2\times CH_2$), 1.98/1.74 (m, 2H, CH_2), 1.61/1.54 (m, 2H, CH_2), 1.61 (m, 4H, $2\times CH_2$), 1.40 (m, 2H, CH_2), NH not detected at room temperature. ^{13}C NMR (C_6D_6): δ 163.6 (CN_3), 66.6 ($2\times CH_2$), 62.5 (CH_2), 56.3 (CH), 55.6 ($2\times CH_2$), 48.9 ($3\times CH_2$), 30.8 (CH_2), 26.4 ($2\times CH_2$), 24.6 (CH_2), 24.2 (CH_2). IR (ATR, ν/cm^{-1}): 2930–2848 (ν_{CH}), 1588 ($\nu_{C=N}$), 1116 (ν_{COC}). EI-MS m/z 280 (M^+). $[\alpha]_D^{20}$ = +23.1 (c 2.60, CH_2Cl_2).

4.4.7. *C*-Piperidin-1-yl-*C*-(2-(pyrrolidin-1-ylmethyl)-pyrrolidin-1-yl)-methylenamine 5a. Yield 90.7%. HRMS m/z 265.2391 $(M+1)^+$. $C_{15}H_{29}N_4$ requires 265.2392. ^{1}H NMR (C_6D_6): δ 4.25 (m, 1H, CH), 3.33/3.16 (m, 2H, CH_2), 3.03 (m, 4H, $2\times CH_2$), 2.87/2.54 (m, 2H, CH_2), 2.61 (m, 4H, $2\times CH_2$), 2.03/1.90 (m, 2H, CH_2), 1.76 (m, 12H, $6\times CH_2$) NH not detected at room temperature. ^{13}C NMR (C_6D_6): δ 164.6 (CN_3), 59.6 (CH_2), 57.5 (CH), 54.9 ($2\times CH_2$), 49.5 ($2\times CH_2$), 49.2 (CH_2), 30.7 (CH_2), 26.2 ($2\times CH_2$), 25.2 (CH_2), 24.4 (CH_2) 24.0 ($2\times CH_2$). IR (ATR, ν/cm^{-1}): 2930–2790 (ν_{CH}), 1584 ($\nu_{C=N}$). EI-MS m/z 264 (M^+). $[\alpha]_D^{20}$ = +54.2 (c 2.40, CH_2Cl_2).

4.4.8. *C*-(2-(Morpholin-4-ylmethyl)-pyrrolidin-1-yl)-*C*-piperidin-1-yl-methylenamine 5b. Yield 96.7%. HRMS m/z 281.2348 $(M+1)^+$. $C_{15}H_{29}N_4O$ requires 281.2341. ^{1}H NMR (C_6D_6): δ 4.91 (m, 1H, NH), 4.24 (m, 1H, CH), 3.71 (m, 4H, $2\times CH_2$), 3.30/3.13 (m, 2H, CH_2), 3.00/2.93 (m, 4H, $2\times CH_2$), 2.70/2.18 (m, 2H, CH_2), 2.52/2.41 (m, 4H, $2\times CH_2$), 1.91/1.71 (m, 2H, CH_2), 1.67–1.34 (m, 8H, $4\times CH_2$). ^{13}C NMR (C_6D_6): δ 164.5 (CN_3), 67.3 ($2\times CH_2$), 62.5 (CH_2), 55.8 (CH), 55.0 ($2\times CH_2$), 49.4 ($2\times CH_2$), 49.3 (CH_2), 30.8 (CH_2), 26.1 ($2\times CH_2$), 25.1 (CH_2), 24.4 (CH_2). IR (ATR, ν/cm^{-1}): 2929–2804 (ν_{CH}), 1582 ($\nu_{C=N}$). EI-MS m/z 280 (M^+). $[\alpha]_D^{20}$ = +51.7 (c 2.32, CH_2Cl_2).

4.4.9. *C*-Piperidin-1-yl-*C*-(2-(piperidin-1-ylmethyl)-pyrrolidin-1-yl)-methylenamine 5c. Yield 90.6%. HRMS m/z 279.2553 $(M+1)^+$. $C_{16}H_{31}N_4$ requires 279.2549. ^{1}H NMR (C_6D_6): δ 5.24 (s, 1H, NH), 4.10 (m, 1H, CH), 3.19/3.03 (m, 2H, CH_2), 2.91/2.86 (m, 4H, $2\times CH_2$), 2.61/2.10 (m, 2H, CH_2), 2.46/2.30 (m, 4H, $2\times CH_2$), 1.87/1.69 (m, 2H, CH_2), 1.55–1.23 (m, 14H, $7\times CH_2$). ^{13}C NMR (C_6D_6): δ 164.3 (CN_3), 62.5 (CH_2), 56.2 (CH), 55.6 ($2\times CH_2$), 49.3 ($2\times CH_2$), 49.0 (CH_2), 30.8 (CH_2), 26.5, 26.0, 25.0, 24.7, 24.2 ($6\times CH_2$), 24.2 (CH_2). IR (ATR, ν/cm^{-1}): 3427 (ν_{NH}) 2923, 2852 (ν_{CH}), 1589 ($\nu_{C=N}$). EI-MS m/z 278 (M^+). $[\alpha]_D^{20}$ = +34.3 (c 3.45, CH_2Cl_2).

4.4.10. *C*-[Bis-(2-(pyrrolidin-1-ylmethyl)-pyrrolidin-1-yl)]-methylenamine 6a. Yield 75.1%. HRMS m/z 334.2967 $(M+1)^+$. $C_{19}H_{36}N_5$ requires 344.2971. ^{1}H NMR (C_6D_6): δ 5.30 (s, 1H, NH) 4.31 (m, 2H, $2\times CH$), 3.19 (m, 4H, $2\times CH_2$), 2.94/2.49 (m, 4H, $2\times CH_2$), 2.60 (m, 8H, $4\times CH_2$), 2.13/1.80 (m, 4H, $2\times CH_2$), 1.70 (m, 8H, $4\times CH_2$), 1.61 (m, 4H, $2\times CH_2$). ^{13}C NMR (C_6D_6): δ 160.8 (CN_3), 60.1 ($2\times CH_2$), 57.7 ($2\times CH$), 54.9 ($4\times CH_2$), 50.1 ($2\times CH_2$), 31.3 ($2\times CH_2$), 24.8 ($2\times CH_2$), 24.0 ($4\times CH_2$). IR (ATR, ν/cm^{-1}): 2959, 2871, 2781 (ν_{CH}), 1577 ($\nu_{C=N}$). EI-MS m/z 333 (M^+). $[\alpha]_D^{20}$ = −40.8 (c 3.19, CH_2Cl_2).

4.4.11. *C*-[Bis-(2-(morpholin-4-ylmethyl)-pyrrolidin-1-yl)]-methylenamine 6b. Yield 98.6%. HRMS m/z 366.2872 $(M+1)^+$. $C_{19}H_{36}N_5O_2$ requires 366.2869. ^{1}H NMR (C_6D_6): δ 5.21 (s, 1H, NH), 4.24 (m, 2H, $2\times CH$), 3.71 (m, 8H, $4\times CH_2$), 3.14 (m, 4H, $2\times CH_2$), 2.74/2.16 (m, 4H, $2\times CH_2$), 2.50/2.43 (m, 8H, $4\times CH_2$), 2.06/1.66 (m, 4H, $2\times CH_2$), 1.62 (m, 4H, $2\times CH_2$). ^{13}C NMR (C_6D_6): δ 160.9 (CN_3), 67.2 ($4\times CH_2$), 63.1 ($2\times CH_2$), 56.1 ($2\times CH$), 54.9 ($4\times CH_2$), 50.0 ($2\times CH_2$), 31.3 ($2\times CH_2$), 24.8 ($2\times CH_2$). IR (ATR, ν/cm^{-1}): 2954, 2851, 2804 (ν_{CH}), 1573 ($\nu_{C=N}$), 1115 (ν_{COC}). EI-MS m/z 365 (M^+). $[\alpha]_D^{20}$ = −49.3 (c 2.23, CH_2Cl_2).

4.4.12. *C*-[Bis-(2-(piperidin-1-ylmethyl)-pyrrolidin-1-yl)]-methylenamine 6c. Yield 75.1%. HRMS m/z 362.3290 $(M+1)^+$. $C_{21}H_{40}N_5$ requires 362.3283. ^{1}H NMR (CD_2Cl_2): δ 3.98 (m, 1H, $2\times CH$), 3.29 (m, 4H, $2\times CH_2$), 2.51/2.15 (m, 4H, $2\times CH_2$), 2.41 (m, 8H, $4\times CH_2$), 2.09/1.70 (m, 4H, $2\times CH_2$), 1.82 (m, 4H, $2\times CH_2$), 1.53 (m, 8H, $2\times CH_2$), 1.41 (m, 4H, $2\times CH_2$), NH not detected at room temperature. ^{13}C NMR (CD_2Cl_2): δ 160.4 (CN_3), 63.6 ($2\times CH_2$), 58.0 ($2\times CH$), 55.5 ($4\times CH_2$), 50.1 ($2\times CH_2$), 31.6 ($2\times CH_2$), 26.6 ($4\times CH_2$), 25.0 ($2\times CH_2$), 24.6 ($2\times CH_2$). IR (ATR, ν/cm^{-1}): 2930, 2852, 2779 (ν_{CH}), 1577 ($\nu_{C=N}$). EI-MS m/z 361 (M^+). $[\alpha]_D^{20}$ = −40.4 (c 3.66, CH_2Cl_2).

4.5. Synthesis of zinc guanidine complex 4a·($ZnCl_2$)

A solution of **4a** (1.4 mmol) in 5 mL dry acetonitrile was added to a suspension of dehydrated $ZnCl_2$ (1.5 mmol) in 5 mL dry acetonitrile under argon. The resulting mixture was stirred for 20 min, filtered warm through Celite and concentrated to a volume of approximately 1 mL. The zinc complex **4a**·($ZnCl_2$) was precipitated upon addition of dry diethyl ether (5 mL). The suspension was filtered, washed with absolute diethyl ether (10 mL) and dried in vacuum to afford the solid. Single crystals suitable for X-ray analysis were obtained from pyridine by concentration and cooling.

4.6. X-ray crystallography

The intensity data for the compounds were collected on a Nonius Kappa CCD diffractometer, using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[18,19] The structures were solved by direct methods (SHELXS[20]) and refined by full-matrix least squares techniques against Fo^2 (SHELXL-97[21]). The hydrogen atoms for the imino-group and for the pyridine molecule were located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.[21] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

4.6.1. Crystal data for 4a·($ZnCl_2$).[22] $C_{14}H_{26}Cl_2N_4OZn\cdot C_5H_5N$, $M_r = 481.76\ g\ mol^{-1}$, colourless prism, size $0.04 \times 0.04 \times 0.04\ mm^3$, orthorhombic, space group $P2_12_12_1$, $a = 8.0709(2)$, $b = 10.4601(3)$, $c = 26.4511(8)$ Å, $V = 2233.07(11)$ Å^3, $T = -90$ °C, $Z = 4$, $\rho_{calcd} = 1.433\ g\ cm^{-3}$, μ (Mo-K$_\alpha$) $= 13.59\ cm^{-1}$, $F(000) = 1008$, 13,448 reflections in $h(-8/10)$, $k(-11/13)$, $l(-34/34)$, measured in the range $2.64° \leqslant \Theta \leqslant 27.46°$, completeness $\Theta_{max} = 98.6\%$, 4988 independent reflections, $R_{int} = 0.053$, 3840 reflections with $F_o > 4\sigma(F_o)$, 276 parameters, 0 restraints, $R1_{obs} = 0.038$, $wR^2_{obsd} = 0.073$, $R1_{all} = 0.066$, $wR^2_{all} = 0.082$, GOOF = 0.960, Flack-parameter −0.004(12), largest difference peak and hole: 0.325/−0.409 e Å^{-3}.

4.6.2. Crystal data for 6·(HCl).[22] $[C_{19}H_{38}Cl_4N_5]^{3+}\ 3Cl^-\cdot HCl$, $M_r = 479.35\ g\ mol^{-1}$, colourless prism, size $0.05 \times 0.05 \times 0.04\ mm^3$, orthorhombic, space group $P2_12_12_1$, $a = 22.3618(9)$, $b = 9.0905(3)$, $c = 12.1901(5)$ Å, $V = 2478.00(16)$ Å^3, $T = -90$ °C, $Z = 4$, $\rho_{calcd} = 1.285\ g\ cm^{-3}$, μ (Mo-K$_\alpha$) $= 4.93\ cm^{-1}$, $F(000) = 1024$, 15,865 reflections in $h(-28/28)$, $k(-11/11)$, $l(-14/15)$, measured in the range $1.82° \leqslant \Theta \leqslant 27.45°$, completeness $\Theta_{max} = 99.3\%$, 5602 independent reflections, $R_{int} = 0.086$, 4653 reflections with $F_o > 4\sigma(F_o)$, 258 parameters, 0 restraints, $R1_{obsd} = 0.080$, $wR^2_{obsd} = 0.206$, $R1_{all} = 0.099$, $wR^2_{all} = 0.219$, GOOF = 1.090, Flack-parameter 0.04(12), largest difference peak and hole: 1.076/−0.515 e Å^{-3}.

4.7. Chiral shift investigations

Compound **4a** (0.01 g, 0.038 mmol) was dissolved in THF-d_8 (ca. 0.5 mL) and examined by ^{1}H NMR spectroscopy. (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (0.01 g, 0.038 mmol) was added to the NMR tube, and the solution was reexamined. Additional shift reagent (3 equiv total) was added, and the solution was reexamined.

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