Synthesis and Characterization of Chiral Guanidines und Guanidinium Salts Derived from 1-Phenylethylamine

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The synthesis of two new chiral guanidines **5** and **12** and derived guanidinium salts **6**, **11**, **13** – **15** with one and three *N*-(1-phenylethyl) substituents is described. In both cases, the well-precedented, reliable route *via* chloro-formamidines was taken. Since direct attachment of the *N*-methyl-*N*-(1-phenethyl)-amino group failed, the two-step protocol – introduction of the primary 1-phenethylamino group first followed by *N*-methylation – was employed. Crystal structures and NMR data reveal, that the sterically highly congested "*tris*" salt – with formal C_3 symmetry, albeit unsymmetrical in the crystal – constitutes an intriguing structure with two rotamers present in solution.

Key words: Chiral Guanidine, Chiral Guanidinium Salts, (*R*)- and (*S*)-1-Phenylethylamine, Quaternization, Crystal Structures

Introduction

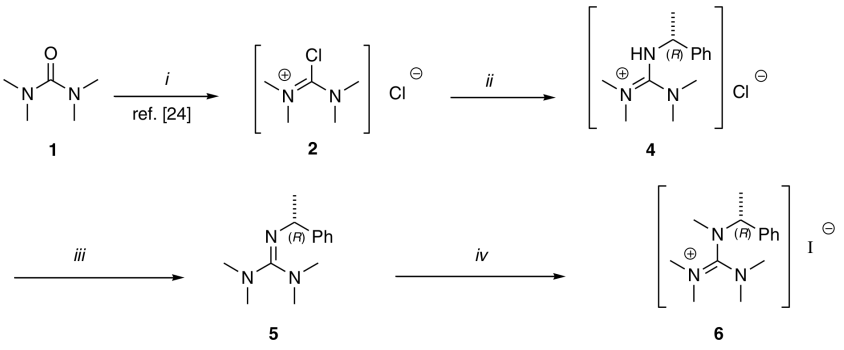
Guanidines and their derivatives have found many applications in Organic Synthesis, notably because they constitute strong neutral bases [1, 2]. Guanidines and guanidinium salts are also present in many natural products [3], for example in the essential amino acid L-arginine [4] or polycyclic marine alkaloids such as the crambescidins or ptilomycalin A [3 – 5]. Some guanidino-acetic acids have also been found to be highly potent sweeteners [6]. Apart from uses as neutral, non-nucleophilic bases ("superbases") [7, 8], guanidines show some potential as catalysts, in particular when chiral derivatives are at stake. Thus, additions, cycloadditions, and rearrangements with mostly useful enantioselectivities induced by chiral guanidine catalysts have been reported [9 – 15].

As for guanidinium salts, there has been modest, but recently increasing interest in uses both as r. t. ionic liquids [16 – 18] and further, with chiral derivatives, as catalysts for asymmetric transformations [19, 20]. In view of the few examples known of simple, chiral guanidines and guanidinium salts, we have embarked on syntheses of fully alkylated derivatives, where one or three N-substituents are derived from amply available (*R*)-or (*S*)-1-phenylethylamine [21 – 23]. For the synthesis of such penta-substituted guanidines and hexa-substituted guanidinium salts the protocol advanced by Kantlehner *et al.* [16, 24 – 26] seemed most appropriate. The starting material, or intermediate, is the respective tetraalkylurea, which is transformed into to the corresponding chloroamidinium salt. On treatment with an amine, the latter is converted to the pentaalkylguanidinium salt, which by deprotonation leads to the guanidine. The final alkylation would afford the hexaalkylguanidinium salt. Alternatively, the latter might be obtained directly from the chloroamidinium salt upon action of a secondary amine [*cf.* 10a]. Derivatives with low melting points or liquid at r. t. may result therefrom, or otherwise may become available by anion metathesis [27, 28, *cf.* 16 – 18].

Results and Discussion

Synthesis of guanidines and guanidinium salts

The synthesis of the *mono-N*-phenethyl-guanidine **4** and the guanidinium iodide **6** started with tetramethylurea (**1**) (Scheme 1). The action of phosgene as described [24] gave the tetramethyl-chloroformamidinium chloride (**2**) which on addition of (*R*)-1-phenylethylamine (**3**) and triethylamine in acetonitrile reacted exothermally to produce a mixture of the guanidinium chloride **4** and triethylammonium chloride. The guanidinium salt **4** was obtained by treatment with exactly one equivalent of sodium hydrox-



Scheme 1. Synthesis of the (*R*)-guanidine **5** and the (*R*)-pentamethyl-(1-phenylethyl)-guanidinium salt **6**. Reagents and conditions: (*i*) $COCl_2$, ref. [24]; (*ii*) 1) (*R*)-$H_2NCH(CH_3)Ph$ **3**, Et_3N, H_3CCN, 1 h, r. t.; 2) 1.0 NaOH·aq., 0 °C; 30 °C, 2 mbar (yield 81 %); (*iii*) 3.0 NaOH·aq., Et_2O, 0 °C, 20 min (yield 80 %); (*iv*) H_3C-I, H_3CCN, 82 °C, 2 h (yield 67 %).

ide. With an excess of base the guanidine **5** was liberated in 65 % overall yield. Since the ensuing *N*-methylation with trimethyloxonium tetrafluoroborate only led to impure material, this was carried out with methyl iodide and proceeded satisfactorily (Scheme 1). The pentamethyl-phenethylguanidinium iodide (**6**) was isolated in 67 % yield in the form of colorless crystals, suitable for crystal structure analysis [29]. It should be noted that the conversion of **2** to **6** by directly introducing the *N*-methyl-*N*-phenethylamino group had failed.

The synthesis of the *tris*-phenethyl compounds **11** – **14** was carried out similarly (Scheme 2). First, (*S*)-phenethylamine (**10**) by formylation [28] and reduction with lithium aluminium hydride was converted to (*S*)-*N*-methyl-*N*-(1-phenylethyl)-amine (**7**), a known compound [30, 31]. The (*S*,*S*)-*bis*-(methylphenethyl)-urea (**8**), a low melting solid, was formed with phosgene in toluene. Further treatment with excess phosgene in acetonitrile, according to the well-established, reliable procedure [24], afforded the chloro-formamidinium chloride **9** which was kept in solution for the next step. The third (*S*)-phenylethylamino substitutent was attached as above, by means of (*S*)-1-phenylethylamine (**10**) and triethylamine at r. t. (again, direct introduction of the secondary amino group with **7** had failed). The latter was removed on base treatment, and the remaining guanidinium salt **11** was finally purified by recrystallization from acetonitrile/diethyl ether/ethanol. Unexpectedly, this salt **11** crystallized with one equivalent of ethanol (!), as first suspected from the seemingly deviating elemental analysis and then unambiguously established by a crystal structure determination (Fig. 1, Table 1).

The solid pentaalkyl-guanidinium salt **11**·EtOH was deprotonated as above to yield the oily guanidine **12**, ready for the concluding *N*-methylation. This was first attempted with trimethyloxonium tetrafluoroborate, however, only an impure product was obtained:

Table 1. Crystal structure data and numbers pertinent to data collection and structure refinement of **11** · EtOH and **14**.

	11 · EtOH	**14**
Formula	$C_{29}H_{40}ClN_3O$	$C_{28}H_{36}F_6N_3P$
M_r	482.09	559.57
Crystal size, mm^3	$0.6 \times 0.6 \times 0.5$	$0.4 \times 0.3 \times 0.3$
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$
a, Å	9.6977(14)	9.1245(14)
b, Å	16.493(3)	14.596(3)
c, Å	17.866(2)	11.0278(15)
β, deg	90	102.355(11)
V, $Å^3$	2857.6(8)	1434.7(4)
Z	4	2
D_{calcd}, $g\,cm^{-3}$	1.12	1.30
μ, cm^{-1}	0.1 (CuK_α)	0.0 (MoK_α)
$F(000)$, e	1040	588
Radiation; λ, Å	CuK_α; 1.54178	MoK_α; 0.71073
hkl range	±10, $-17 \rightarrow +19$, $-18 \rightarrow +21$	$+12$, ±19, ±14
θ range, deg	5.19 – 66.00	1.89 – 28.00
Refl. measured / unique	4544 / 4023	7328 / 6916
R_{int}	0.0559	0.0430
Data / restraints / ref. param.	4023 / 0 / 319	6916 / 91 / 377
$R(F)$ / $wR(F^2)$[a,b] ($I \geq 2\sigma(I)$)	0.0637 / 0.1356	0.0783 / 0.1362
$R(F)$ / $wR(F^2)$[a,b] (all data)	0.01028, 0.1640	0.1561, 0.1597
GoF (F^2)[c]	−0.01(3)	1.036
x (Flack)	−0.01(3)	−0.17(19)
$\Delta\rho_{fin}$ (max / min), e $Å^{-3}$	0.166 / −0.273	0.222 / −0.214

[a] $R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; [b] $wR(F^2) = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$; [c] GoF $= [\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$.

Although a solid consisting mostly of the expected guanidinium salt according to NMR and HRMS data, purification could not be achieved [32]. On the other hand, with methyl iodide clean *N*-methylation of the guanidine **12** was registered, and the resulting "*tris*" salt **13** was isolated in pure form and good yield. This iodide **13** had a m. p. of 105 – 107 °C, therefore silver salt metathesis [16 – 18, 27, 28] was called upon to eventually get access to lower-melting derivatives

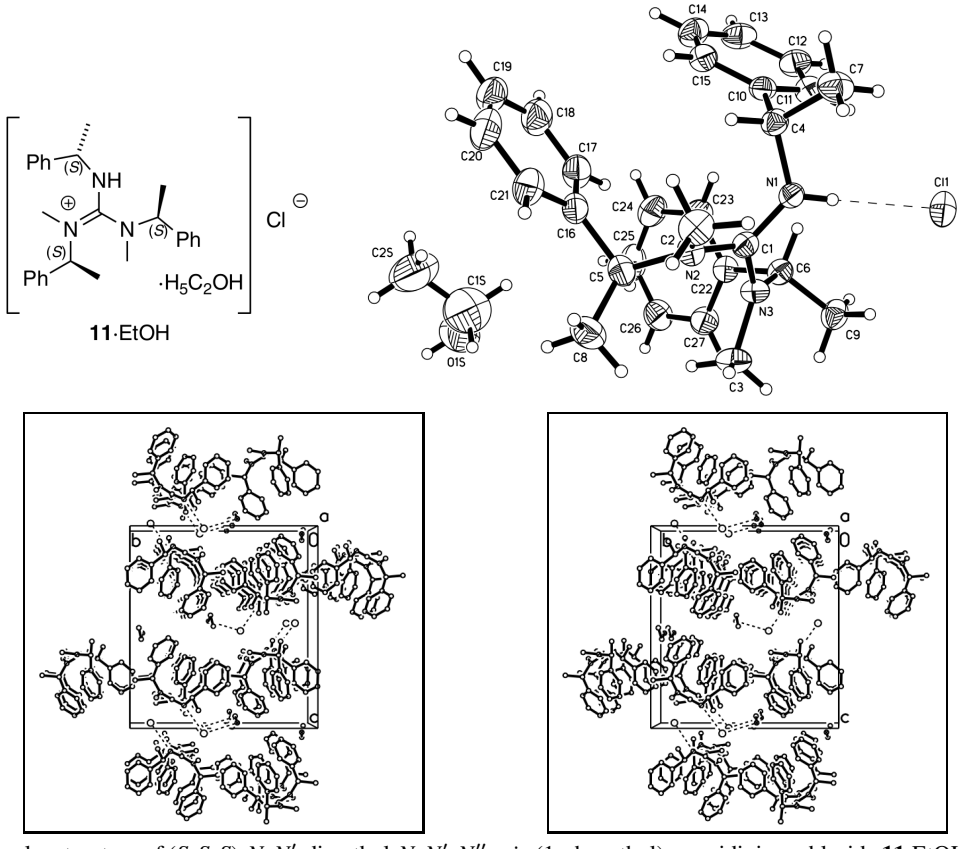


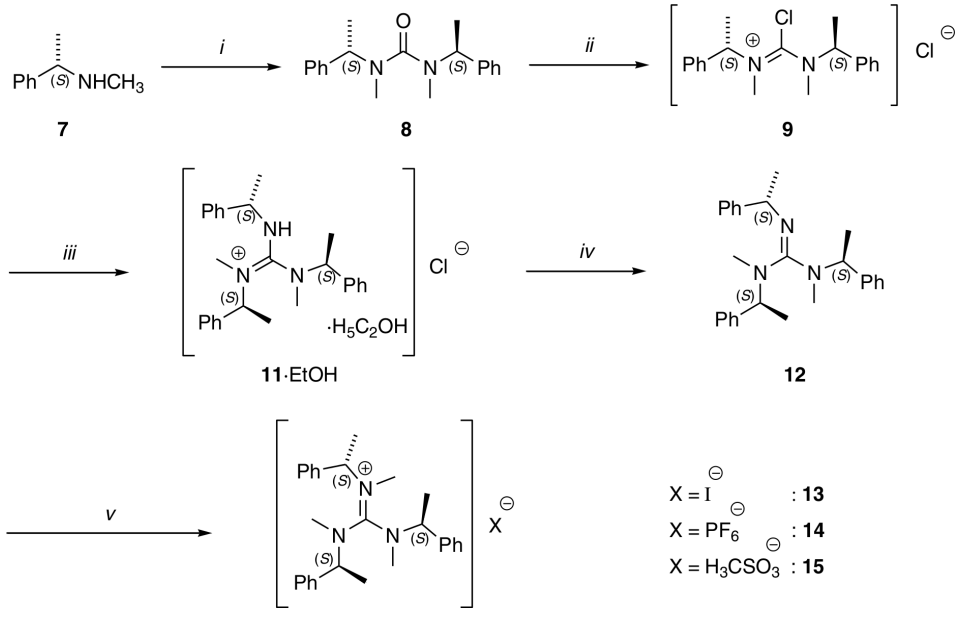
Fig. 1. Molecular structure of (*S*,*S*,*S*)-*N*,*N*′-dimethyl-*N*,*N*′,*N*″-*tris*-(1-phenethyl)-guanidinium chloride **11**·EtOH in the crystal and view of the unit cell along the crystallographic *a* axis (stereo view).

in view of obtaining new chiral ionic liquids. Thus, the iodide **13** was treated with silver hexafluorophosphate and methylsulfonate, respectively, in an acetonitrile/water mixture. However, the new hexafluorophosphate **14**, a pure solid (97 % yield), showed an even higher melting point of 175 – 177 °C, and the methylsulfonate, a viscous liquid, could not be secured in analytically pure form (Scheme 2). Crystals of the "*tris*" iodide **13** became amorphous after a short period of time, thus precluding crystal structure determination. This, however, was feasible with the hexafluorophosphate **14** as depicted below (Fig. 2, Table 1).

*Spectroscopic properties of the "tris" guanidinium hexafluorophosphate **14***

The NMR spectra of the pentaalkyl-substituted guanidinium salt **11** show more signals than expected from a single species and could not be analyzed satisfactorily, due to the complex situation with the lack of a symmetry element in any of the presumed rotamers and to the presence of ethanol. On the other hand, the "*tris*" salts **13** – **15** provide an intriguing case with the same kind and configuration of substituents at the three nitrogen atoms which – due to steric interactions – may have planar (sp^2) or pyramidal (sp^3) properties. With regard to the orientation of the phenyl groups, the simplest case would be presented with all three of them aligned in the same face of the plane defined by the CN_3 moiety, possessing a C_3 axis of symmetry. This would constitute a three-dimensional equivalent of a planar "triskele" as known, *f. e.*, from the flag of Sicily (Fig. 3).

The crystal structure of the "*tris*" hexafluorophosphate **14** clearly shows that one of the three phenyl groups is situated below the CN_3 plane. Further, the dialkylamino groups are twisted out-of-plane, and full resonance stabilization of the CN_3 part is not operative. While the crystal structure exhibits a single conformation, the NMR spectra reveal a more



Scheme 2. Synthesis of (*S*,*S*,*S*)-*tris*-(1-phenylethyl)-guanidine (**12**) and guanidinium salts **11**, **13** – **15**. Reagents and conditions: (*i*) $COCl_2$ (20 % solution in toluene), CH_2Cl_2, Et_3N, 0 °C for 3 h, then r. t. over night (yield 60 – 94 %); (*ii*) $COCl_2$, H_3CCN, (crude product); (*iii*) 1) (*S*)-$PhCH(NH_2)CH_3$ **10**, H_3CCN, Et_3N, r. t., 2 h; 2) 1.0 NaOH·aq., 0 °C (81 % of **11**·EtOH); (*iv*) Et_2O, NaOH·aq. (6 M), 0 °C, 1 h, (yield 78 %); (*v*) H_3C-I, H_3CCN, 50 °C, 12 h (yield of **13** 75 %); (*vi*) $AgPF_6$, H_2O/H_3CCN (1 : 1), r. t., 2 h (yield of **14** 97 %); (*vii*) $MeSO_3Ag$, H_2O/H_3CCN (1 : 1), r. t., 2 h (impure product **15**, 100 %).

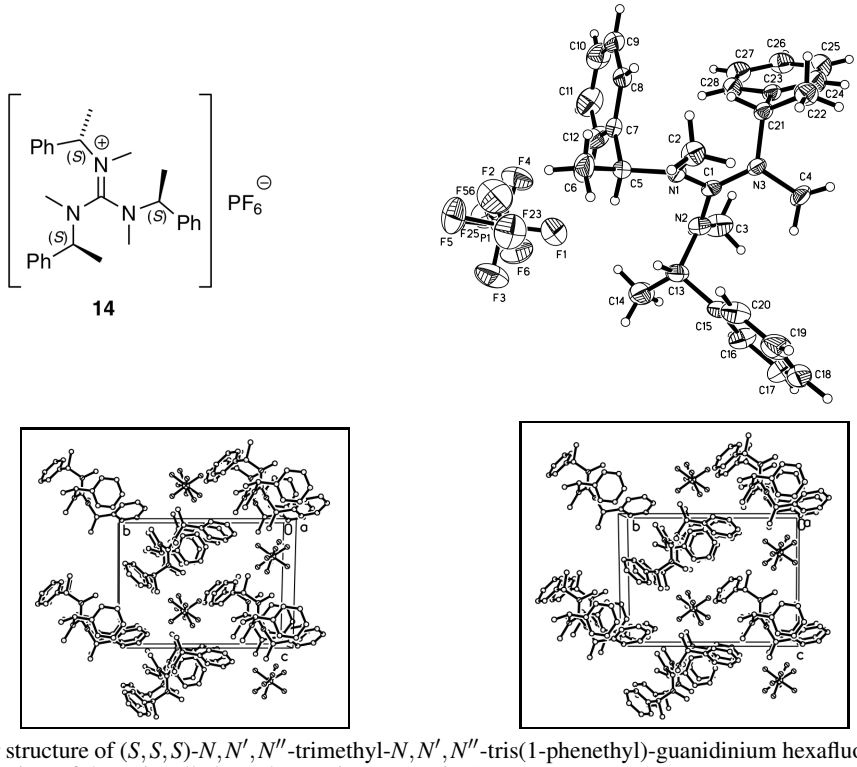
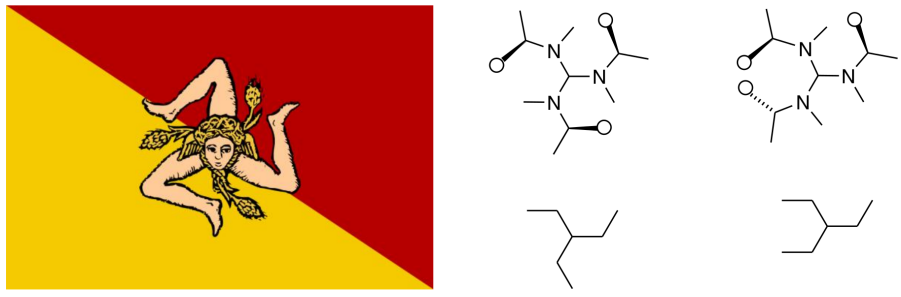


Fig. 2. Molecular structure of (*S*,*S*,*S*)-*N*,*N*′,*N*″-trimethyl-*N*,*N*′,*N*″-tris(1-phenethyl)-guanidinium hexafluorophosphate (**14**) in the crystal and view of the unit cell along the *a* axis (stereo view).



a) b) c)

Fig. 3. a) "Triskele", Flag of Sicily (http://de.wikipedia.org/wiki/Sizilien); b) "syn" arrangement of the three *N*-(1-phenethylamino) substituents in respective guanidinium salts **13** – **15**; c) "anti" arrangement.

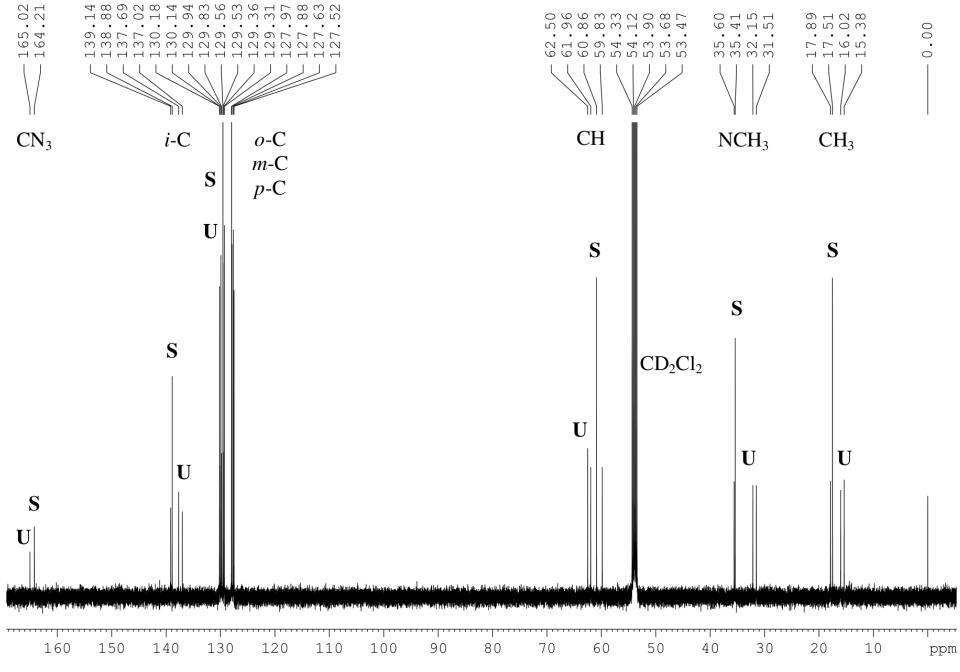


Fig. 4. ^{13}C NMR spectrum of the guanidinium iodide **13** in CD_2Cl_2 at 300 K; **S** and **U** for the "symmetric", respectively "unsymmetric" rotamer of **13**.

complex, "dynamic" picture (Fig. 4). In fact, three temperature-dependant processes leading to conformational changes may be operative: (*i*) rotation around the C1–N bonds regardless of the spatial arrangement around the nitrogen atom; (*ii*) inversion at the nitrogen atoms, since the crystal structure shows considerable pyramidalization for one of them; (*iii*) rotation around the *N*–CPh bonds which seems to be hindered due to heavy steric congestion as seen in the crystal structure. The NMR spectra of the three "*tris*" salts **13** – **15** were practically identical; the ^{13}C NMR spectrum of the iodide **13** is depicted in Fig. 4.

In the ^{1}H NMR spectrum four sets of signals are recognized for C-CH_3, N-CH and N-CH_3, in an approximate ratio of 1 : 1 : 1 : 1, with large shift differences of > 1 ppm for the two pairs each of the N-CH and N-CH_3. A like set of pairs is seen for the C-CH_3 absorptions, with $\Delta\delta$ of *ca.* 0.3 ppm. The ^{13}C NMR spectrum more clearly shows sets of four signals from the *C*-methyl and *N*-methyl carbon absorptions, the same for the tertiary carbon atom of CHNMe and for the *ipso*-carbon atoms of the phenyl rings, with somewhat different ratios. After peak assignments from HMBC measurements and C,H COSY, a preliminary conclu-

sion is that there are two species, *i. e.* two rotamers, present in CD_2Cl_2 solution, in a ratio of *ca.* 55 : 45. According to this, the ^{13}C NMR data point to the presence of a species in which all three substituted amino groups have identical environments on the ^{13}C NMR time scale at r. t. This would explain why all alkyl substitutents give rise to a single peak for the respective carbon atom absorptions, and this rotamer would represent the "symmetric one", **S**, with C_3 symmetry. The second species for each of the presumably equivalent groups gives rise to three signals of equal intensity and indicates that here no symmetry element is present, according to an "unsymmetric" species **U**. In order to fully rationalize this situation and the processes involved, however, more detailed NMR studies and the temperature-dependent behavior of absorptions are needed and, hopefully, will provide coalescence temperature(s) and heights of rotational barriers [33].

Conclusion

The known preparation of guanidines and guanidinium salts was applied to obtain new chiral derivatives based on optically active 1-phenylethylamines, of interest with regard to potential uses as chiral bases and catalysts or ionic liquids. Thus, the "*mono*" and the "*tris*" compounds (referring to the number of *N*-1-phenylethyl groups incorporated) were obtained, all of them being crystalline at r. t. The "*tris*" salts **13** – **15**, for the guanidinium part, show the presence of two rotamers in solution, a symmetric and an unsymmetric one, as deduced from NMR data. An unsymmetric rotamer of the "*tris*" hexafluorophosphate **14** is the species seen is the crystal structure [34]. So far, efforts to use the "*tris*" guanidine **12** and the "*tris*" iodide **13** as catalysts for asymmetric transformations (Morita-Baylis-Hillman reaction [35], Michael addition [36], epoxidation [37]) have not led to noteworthy stereoselectivities, requiring broader studies.

Experimental Section

^1H NMR spectra were recorded with Bruker ARX 300 and 500 (300.1 and 500.1 MHz) instruments, ^{13}C NMR spectra were recorded with the same instruments (75.5 and 125.8 MHz). NMR shifts δ (in ppm) are reported relative to tetramethylsilane as internal standard. FT-IR spectra were obtained on a Bruker (IFS 28) spectrometer. Melting points were measured with a Fischer-Johns heating apparatus and are uncorrected. Angles of rotation were measured with a polarimeter 241 MC of Perkin Elmer. The optical rotations were calculated from Na_D absorption. Elemental analyses were obtained in the laboratories at the Institut für Organische Chemie, Universität Stuttgart.

(S)-*N*-Methyl-*N*-(1-phenylethyl)-amine (**7**) was obtained from (*S*)-1-phenylethylamine (**10**) *via* its *N*-formyl derivative [30c] by $LiAlH_4$ reduction; colorless liquid, yield 54 – 81 %, $[\alpha]_D^{20} = -76$ ($c = 1.00$, EtOH), enantiomer $[\alpha]_D^{20} = 74.3$ ($c = 1.02$, $CHCl_3$); ref. [30b]: $[\alpha]_D^{20} = 74.9$ ($c = 1.02$, $CHCl_3$).

*(R)-N,N,N′,N′-Tetramethyl-N″-(1-phenylethyl)-guanidinium chloride (**4**)*

In analogy to the literature procedure given in [24] an equimolar mixture of (*R*)-phenylethylamine **3** (1.05 mL, 1.00 g, 8.25 mmol) and triethylamine (1.15 mL, 0.83 g, 8.25 mmol) at r. t. was added to a solution of (*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-chloroformamidinium chloride **2** [24d, e] (1.41 g, 8.25 mmol) in acetonitrile (8.80 mL; 0.94 mol/L) with vigorous stirring. The mixture warmed up almost to boiling; it was then stirred for 1 h at r. t. and concentrated to dryness *in vacuo* (2 mbar, 30 °C). The resulting mixture of salts at 0 °C was treated with aq. NaOH (0.33 g, 8.25 mmol in 1 mL of water), then triethylamine and water were distilled off (2 mbar, 30 °C). The residue, a yellow solid, was taken up with acetonitrile (1.65 mL) and heated to reflux for 15 min. The suspension was filtered, and the filtrate was concentrated to dryness (2 mbar, 25 °C), leaving the salt **4** as a pale-yellow solid (1.72 g, 81 %). M. p. 249 °C. – $[\alpha]_D^{20} = -10.5$ ($c = 1.00$, CH_3CN). The salt was used for the next step without further purification. – IR (film): ν = 3414 (NH), 3130, 2973, 1608 (C-NH), 1584, 1397, 706, 534 (CN_3^+) cm^{-1}. – ^1H NMR (250.1 MHz, $CDCl_3$): δ = 1.80 (d, 3 H, C*H*$_3$CH, ^3J = 6.6 Hz), 2.68 (s, 3 H, CH_3N), 2.80 (s, 1 H, NH), 2.88 (s, 3 H, CH_3N), 3.03 (1 s, 6 H, *C*H$_3$N), 4.47 (q, 1 H, CH_3CH, ^3J = 6.6 Hz), 7.27 – 7.44 (m, 5 H, C_6H_5). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.2 (*C*H$_3$CH), 39.8 – 40.7 (4 CH_3N), 56.5 (*C*HCH$_3$), 125.7 (*p*C of C_6H_5), 127.9 and 129.1 (*o*, *m*C of C_6H_5), 143.1 (*i*C of C_6H_5), 161.2 (CN_3^+).

*(R)-N,N,N′,N′-Tetramethyl-N″-(1-phenylethyl)-guanidine (**5**)*

According to reference [24] the guanidinium salt **4** (1.25 g, 4.89 mmol) was covered with diethyl ether (7 mL), and aq. NaOH (0.75 g, 18.72 mmol in 3 mL of water) was added with vigorous stirring. After 20 min the ethereal phase was separated, and the residue was stirred with another portion of ether (3 mL). The combined ether phases were dried (K_2CO_3), and the filtrate was rota-evaporated (2 mbar) leaving **5** as a yellow liquid (0.855 g, 80 %). – $[\alpha]_D^{20}$ = 31.4 (c = 1.00, CH_3CN). – IR (film): ν = 3080, 1610 (C=N), 1581, 1236 (C-N), 1133, 699 cm^{-1}. – ^1H NMR (250.1 MHz, $CDCl_3$): δ = 1.39 (d, 3 H, C*H*$_3$CH, ^3J = 6.5 Hz); 2.61, 2.71 (2 s, 12 H, CH_3N); 4.51 (q, 1 H, CH_3CH, ^3J = 6.5 Hz), 7.09 –

7.38 (m, 5 H, C_6H_5). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 27.2 (*C*H_3CH), 38.7 – 39.8 (4 CH_3N), 56.7 (*C*HCH$_3$), 125.7 (*p*C of C_6H_5), 126.2 and 128.0 (*o*-,*m*-C of C_6H_5), 149.7 (*i*-C of C_6H_5), 159.4 (CN_3^+). – Anal. for $C_{13}H_{21}N_3$ (219.3): calcd. C 71.19, H 9.65, N 19.16; found C 70.57, H 9.59, N 18.75.

*(R)-N,N,N′,N′,N″-Pentamethyl-N″-(1-phenylethyl)-guanidinium iodide (**6**)*

In analogy to a procedure given in ref. [24] the guanidine **5** (693 mg, 3.16 mmol) was dissolved in acetonitrile (10 mL). Methyl iodide (448 mg, 3.16 mmol) in acetonitrile (0.5 mL) was added. The mixture became warm and then was heated to reflux for 2 h under exclusion of moisture. Acetonitrile was distilled off (2 mbar), and the residue was treated with diethyl ether (abs., 4 mL) causing precipitation of a solid. The product was several times extracted with boiling ether (2 mL each) to leave colorless crystals suitable for crystal structure analysis [29] (766 mg, 67 %). M. p. 145 – 146 °C. – $[\alpha]_D^{20}$ = 14.3 (*c* = 1.00, CH_3CN). – IR (film): ν = 3425, 2982, 1604 (C-NH), 1558 (C=N), 1491, 1470, 1450, 1402, 1363, 1299, 1192, 1065, 1053, 980, 772, 707 cm^{-1}. – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 1.73 (d, 3 H, C*H*$_3$CH, ^3J = 6.9 Hz), 2.63 (s, 3 H, CH_3N), 2.87 (s, 3 H, CH_3N), 3.06 (s, 3 H, CH_3N), 3.13 (s, 3 H, CH_3N), 3.25 (s, 3 H, CH_3N), 4.77 (q, 1 H, CH_3C*H*, ^3J = 6.9 Hz), 7.24 – 7.44 (m, 5 H, C_6H_5). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.5 (*C*H_3CH), 34.0 (CH_3N); 41.2, 42.0 (CH_3N); 60.0 (*C*HCH$_3$), 126.7 (*p*C of C_6H_5), 128.9 and 129.3 (*o*, *m*C of C_6H_5), 138.5 (*i*C of C_6H_5), 163.6 (CN_3^+).

*(S,S)-N,N′-Dimethyl-N,N′-bis-(1-phenylethyl)-urea (**8**)*

Caution! Phosgene is highly toxic. Exposure to vapors or solutions containing phosgene must strictly be avoided. All operations should be conducted in a well-ventilated hood.

To an ice-cooled mixture of (*S*)-methyl-1-phenylethylamine **7** (13.0 mL, 12.1 g, 0.1 mol) and triethylamine (14.0 mL, 10.1 g, 0.1 mol) in methylene chloride (250 mL) a solution of phosgene in toluene (20 %, 26 mL, 0.05 mol) was slowly introduced. The mixture was stirred in an ice bath for 3 h, then left at r. t. over night. The mixture was concentrated to dryness *in vacuo* (2 mbar, 60 °C) leaving a solid residue. The residue was dissolved in methylene chloride (150 mL), and the resulting solution was washed with aq. HCl (100 mL), then with water (3 × 100 mL). The organic layer was separated and concentrated *in vacuo* (2 mbar, 65 °C) to give a thick oil that solidified to yield a colorless product (12.7 g, 86 %). M. p. 32 °C. – $[\alpha]_D^{20}$ = −136 (*c* = 1.00, EtOH). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 1.57 (d, 6 H, C*H*$_3$CH, ^3J = 7.0 Hz), 2.55 (s, 6 H, CH_3N), 5.20 (q, 2 H, CH_3C*H*, ^3J = 7.0 Hz), 7.32 – 7.34 (m, 10 H, 2 C_6H_5). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.2 (*C*H_3CH), 31.2 (CH_3N), 54.8 (*C*H-CH$_3$), 126.9 (*p*C of C_6H_5), 127.2 and 128.3 (*o*-,*m*-C of C_6H_5), 141.5 (*i*C of C_6H_5), 165.4 (C=O). – Anal. for $C_{19}H_{24}N_2O$ (296.2): calcd. C 76.99, H 8.16, N 9.45; found C 77.05, H 8.08, N 9.50.

*(S,S)-N,N′-Dimethyl-N,N′-bis-(1-phenylethyl)-chloroformamidinium chloride (**9**)*

To an ice-cooled solution of the urea derivative **8** (11 g, 39 mmol) in acetonitrile a solution of phosgene (40 g, 0.4 mol, 198 g or 211 mL of 20 % in toluene) was slowly introduced over a period of 25 min. The mixture was stirred at r. t. over night, and the excess of phosgene was removed *in vacuo* (20 °C, 200 mbar) together with 30 mL of acetonitrile. The colorless solution of **9** was stored at 5 °C and used directly for the next step.

*(S,S,S)-N-N′-Dimethyl-N,N′,N″-tris-(1-phenylethyl)-guanidinium chloride·ethanol (**11**·EtOH)*

In analogy to the procedure given in ref. [24] to a mixture of the chloroformamidinium chloride **9** (18.18 g, *c* = 0.55 mol kg^{-1}, 10 mmol) and (*S*)-phenylethylamine (**10**) (1.3 mL, 10 mmol) in acetonitrile was added dropwise 1.4 mL of triethylamine (10 mmol) at r. t. After 2 h reaction time, the solvent was removed *in vacuo* (40 °C, 20 mbar), and the residue was cooled to 0 °C. Under vigorous stirring, 1 mL of a 10 M solution of NaOH (10 mmol) was added. The mixture was evaporated *in vacuo* (40 °C, 20 mbar), and the residue was dissolved in hot acetronitrile. The resulting solution was filtered through a paper filter, and the solvent was removed *in vacuo* (40 °C, 20 mbar). The yellowish oil obtained was triturated with diethyl ether, and the resulting powder was recrystallized from a mixture of acetonitrile/diethyl ether/ethanol affording colorless crystals of the title compound **11**·EtOH (3.88 g, 8.05 mmol, 81 %), suitable for X-ray analysis. M. p. 171 – 172 °C. – $[\alpha]_D^{20}$ = −43 (*c* = 0.50, CH_3CN). – IR (film): ν = 3340 (O-H), 3318, 2979, 2868 (N-H), 1573, 1529 (C=N), 1454, 1400, 1205, 1087, 1058, 705 cm^{-1}. – Anal. for $C_{27}H_{34}N_3Cl\cdot(C_2H_6O)$ (482.1): calcd. C 72.25, H 8.36, N 8.72, Cl 7.35; found C 71.42, H 8.20, N 8.85, Cl 7.57. – ^{1}H NMR (500.1 MHz, CD_3CN, at 300 K, two rotamers, ratio *ca.* 56:44): major rotamer: δ = 1.66, 1.72, 1.81 (3 d, 3 H each, C*H*$_3$CH, ^3J = 7.5 Hz); 2.91, 2.95 (2 s, 3 H each, CH_3N), 3.95, 4.92, 5.01 (3 q, 1 H each, CH_3C*H*, ^3J = 7.5 Hz), 6.57 – 7.59 (m, 15 H, 3 C_6H_5), 9.71 (s, 1 H, NH^+); minor rotamer: δ = 1.57, 1.72, 1.78 (3 d, 3 H each, C*H*$_3$CH, ^3J = 7.5 Hz); 2.22, 2.46 (2 s, 3 H each, CH_3N); 4.07, 4.56, 4.96 (3 "t", 1 H each, CH_3C*H*, ^3J = 7.5, *J* = 9.0 Hz), 9.41 (d, 1 H, *J* = 9.0, NH^+); other H signals of C_6H_5 overlapping with those of the major rotamer. – ^{13}C NMR (125.8 MHz, CD_3CN, at 300 K, two rotamers, ratio *ca.* 60 : 40): major rotamer: δ = 17.8, 22.3, 22.4 (3 *C*H_3CH), 33.6 (2 CH_3N), 57.4, 59.9, 61.3 (3 *C*HCH$_3$), 127.9 – 130.0 (9 d of *o*-, *m*-, *p* – *C*H of 3 C_6H_5), 144.5 (*i*-C of C_6H_5), 162.6 (CN_3^+); minor rotamer:

δ = 16.5, 16.5, 16.8 (3 *C*H_3CH); 33.5. 57.8 (2 CH_3N); 57.4, 57.8, 60.1 (3 *C*HCH$_3$), 140.2 (*i*-C of C_6H_5), 162.6 (CN_3^+); other C signals of C_6H_5 overlapping with those of the major rotamer.

*(S,S,S)-N,N′-Dimethyl-N,N′,N″-tris-(1-phenylethyl)-guanidine (**12**)*

In analogy to the literature procedure [24], to an ice-cooled solution of the guanidinium chloride **11** (1.5 g, 3.44 mmol) in diethyl ether (9 mL) 3.6 mL (0.02 mol) of a 6 M solution of NaOH was added dropwise. After 1 h of reaction at 0 °C, the organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 × 5 mL). The combined organic phases were dried over $NaSO_4$ over night, and the solvent was removed *in vacuo* (30 °C, 15 mbar). High vacuum distillation (180 – 190 °C at *ca.* 10^{-6} mbar) of the crude product afforded 1.07 g (2.68 mmol, 78 %) of an analytically pure, viscous yellowish oil. – $[\alpha]_D^{20}$ = −32 (*c* = 1.3, CH_3CN). – IR (film): ν = 3060, 2922, 1597 (C=N), 1580, 1490, 1294 (C-N), 1077, 1025, 759, 696, 542 cm^{-1}. – Anal. for $C_{27}H_{33}N_3$ (399.6): calcd. C 81.16, H 8.32, N 10.52; found C 81.06, H 8.40, N 10.61. – ^{1}H NMR (500.1 MHz, CD_3CN): δ = 1.32 (d, C*H*$_3$CH, ^3J = 6.4 Hz); 1.43, 1.54 (2 d, 3 H each, 2 C*H*$_3$CH, ^3J = 6.9 Hz); 2.42, 2.59 (2 s, 3 H each, 2 CH_3N); 4.47, 4.58 (2 q, 1 H each, 2 CH_3C*H*, ^3J = 6.9 Hz), 5.31 (q, 1 H, CH_3C*H*, ^3J = 6.4 Hz), 7.20 – 7.50 (m, 15 H, 3 C_6H_5). – ^{13}C NMR (125.8 MHz, CD_3CN): δ = 16.1, 19.8, 27.3 (3 *C*H_3CH), 30.9, 35.4 (2 CH_3N), 55.6, 57.4, 59.8 (3 *C*HCH$_3$), 126.6 – 129.3 (15 d of *C*H of 3 C_6H_5); 143.7, 144.4, 150.2 (3 *i*-C of 3 C_6H_5), 158.1 (CN_3).

*(S,S,S)-N,N′,N″-Trimethyl-N,N′,N″-tris(1-phenylethyl)-guanidinium iodide (**13**)*

In analogy to the literature procedure [24], into a two-necked round-bottomed flask equipped with a condenser and a $CaCl_2$ drying tower the guanidine **12** (360 mg, 0.90 mmol) and 5 mL of dried acetonitrile were introduced. A solution of methyl iodide (0.08 ml, 1.35 mmol) in 2.5 mL abs. CH_3CN was added dropwise, and the reaction mixture was heated to 50 °C for 12 h. The solvent was removed *in vacuo* (40 °C, 200 mbar), and the brownish crude oil was triturated in hexane until the precipitation of a fine colorless powder. The solid residue was filtered off and was taken up in 1 mL of MeOH. Addition of 60 mL of hexane and a few drops of diethyl ether initiated a slow crystallization that furnished 238 mg (0.40 mmol, 75 %) of **13** as a colorless solid. M. p. 105 – 107 °C. – $[\alpha]_D^{20}$ = −36.4 (*c* = 1.04, CH_3CN). – IR (film): ν = 3325, 2965, 1572, 1530 (C=N), 1454, 1399, 1086, 1053, 705 cm^{-1}. – Anal. for $C_{28}H_{36}N_3I$ (541.2): calcd. C 62.10, H 6.65, N 7.76, I 23.47; found C 61.86, H 6.74, N 7.67, I 23.27. – Two rotamers of **13** in CD_2Cl_2 (ratio *ca.* 55 : 45) at 300 K. – ^{1}H NMR (500.1 MHz, CD_2Cl_2): major rotamer **U**: δ = 1.55, 1.85, 1.87 (3 d, 3 H each, C*H*$_3$CH, ^3J = 7.1 Hz); 2.04, 2.30, 3.20 (3 s, 3 H each, CH_3N); 3.98, 5.00, 5.05 (3 q, 1 H each, CH_3C*H*, ^3J = 7.1 Hz), 6.64, 7.36, 7.58 (3 m, 2 H each, 3 *o*-C_6H_5); 7.25, 7.36, 7.52 (3 m, *p*-H of 3 C_6H_5); 7.25, 7.52, 7.58 (3 m, *m*-H of C_6H_5); minor rotamer **S**: δ = 1.58 (d, 9 H, C*H*$_3$CH, ^3J = 7.1 Hz); 3.09 (s, 9 H, CH_3N); 3.90 (q, 3 H, CH_3C*H*, ^3J = 7.1 Hz); absorptions of C_6H_5 overlapped by those of the major rotamer. – ^{13}C NMR (125.8 MHz, CD_2Cl_2, at 300 K): major rotamer **U**: δ = 15.4, 16.0, 17.9 (3 *C*H_3CH), 31.5, 32.1, 35.6 (3 CH_3N), 59.8, 62.0, 62.5 (3 *C*HCH$_3$); 127.6, 127.5, 127.9 (*i*-C of 3 C_6H_5), 129.4, 129.8, 130.1, 129.3, 129.9, 130.2 (*o*-, *m*-, *p*-C of 3 C_6H_5); 137.0, 137.7, 139.1 (*i*-C of 3 C_6H_5), 165.0 (CN_3^+); minor rotamer **S**: δ = 17.5 (3 *C*H_3CH), 35.4 (3 CH_3N), 60.9 (*C*HCH$_3$), 128.0, 129.53, 129.56 (*o*-, *m*-, *p*-C of 3 C_6H_5, in part overlapping with signals of **U**), 138.87 (*i*-C of C_6H_5), 164.2 (CN_3^+).

*(S,S,S)-N,N′,N″-Trimethyl-N,N′,N″-tris-(1-phenylethyl)-guanidinium hexafluorophosphate (**14**)*

Under exclusion of light, 233 mg (0.92 mmol) of $AgPF_6$ was added to a solution of the guanidinium iodide **13** (500 mg, 0.92 mmol) in 1.6 mL of a H_2O-CH_3CN (1 : 1) mixture. The suspension was allowed to react at r. t. for 2 h, then the golden-yellow precipitate of AgI was filtered off through a small cotton pad. The filtrate was concentrated *in vacuo* (40 °C, 200 mbar), and the residue was recrystallized from acetone-CH_3CN-Et_2O affording 500 mg (0.89 mmol, 97 %) of the guanidinium salt **14** as analytically pure, colorless crystals, suitable for X-ray analysis. M. p. 175 – 177 °C. – $[\alpha]_D^{20}$ = −36.2 (*c* = 1.02, $(CH_3)_2CO$). – IR (film): ν = 2992, 1524 (C=N), 1454, 1403, 1088, 1058, 702 cm^{-1}. – Anal. for $C_{28}H_{36}N_3PF_6$ (559.6): calcd. C 60.10, H 6.48, N 7.51, P 5.54; found C 60.18, H 6.49, N 7.49, P 5.56. – NMR data identical to those given for **13**.

*(S,S,S)-N,N′,N″-Trimethyl-N,N′,N″-tris(1-phenyl-ethyl)-guanidinium methylsulfonate (**15**)*

Under exclusion of light 112 mg (0.54 mmol) of $AgMeSO_3$ was added to a solution of the guanidinium iodide **13** (300 mg, 0.54 mmol) in 1 mL of a H_2O/CH_3CN (1 : 1) mixture. The suspension was allowed to warm to r. t. for 2 h, and the golden-yellow precipitate of AgI was filtered off through a small cotton pad. The filtrate was concentrated *in vacuo* (20 °C, 200 mbar), and the residue was taken up in ethanol. The solution was filtered again, and the filtrate was concentrated *in vacuo* (20 °C, 200 mbar) to furnish 284 g (0.55 mmol, '100 %') of the guanidinium salt **15** as a colorless, viscous oil with deviating values of elemental analysis. – Anal. for $C_{28}H_{39}N_3SO_3$ (509.7): calcd. C 68.34, H 7.71, N 8.24, S 6.29; found C 65.60, H 7.85, N 7.68, S 10.12. – NMR data identical to those given for **13**.

Crystal structure determinations

For the X-ray crystal structure analyses a Nicolet P3 diffractometer equipped with a graphite monochromator was used. The measurements were done with CuK_α (compound **11**·EtOH) or MoK_α radiation (compound **14**). Crystal data and numbers pertinent to data collection and structure refinement of **11**·EtOH and **14** are given in Table 1. Programs used: SHELXS-97 [38], SHELXL-97 [39], and SHELXTL-PLUS [40].

CCDC 870852 (**11**·EtOH) and CCDC 870853 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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