Synthesis of Chiral Bicyclic Guanidinium Salts using Di(imidazole-1yl)methanimine

Aleksej Turočkin,*,*,* Roman Honeker,*, William Raven,* and Philipp Selig*,*,+

[†]Institute of Organic Chemistry and [‡]Institute of Inorganic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany

S Supporting Information

ABSTRACT: A detailed account of the synthesis of chiral bicyclic guanidinium salts is presented. This work represents the first systematic investigation of an approach toward the challenging target molecules via a key guanylation step employing di(imidazole-1-yl)methanimine (6) followed by a



two-fold cyclization, which resulted in guanidinium salts 8 and 10. Factors governing the regioselectivity of the final cyclization step are discussed based on further data obtained in the course of the attempted syntheses of two additional bicyclic guanidinium salts.

INTRODUCTION

It is of common knowledge that guanidines belong to the strongest organic bases and are notable for their utility as catalysts and reagents in organic synthesis.¹ Among the great variety of members of the guanidine family, species containing all three nitrogen atoms embedded into a bicyclic molecular framework (e.g., compounds 1 and 2 being the simplest representatives, see Figure 1) deserve special attention: Not



Figure 1. Simplest bicyclic guanidine bases 1,4,6-triazabicyclo[3.3.0]-oct-4-ene (TBO, 1) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 2).

only do these molecules exhibit much stronger Brønsted basicities as compared to their acyclic counterparts,² but bicyclic guanidines have also been recognized as exceptionally strong nucleophiles.³ Furthermore, their ability to act as potentially bidentate hydrogen-bond donors has rendered these molecules into unique multifunctional organocatalysts.^{4,5}

Our first efforts in the field of guanidine organocatalysis consisted of systematic investigations with the commercially available base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 2) and provided ample precedence of the multifunctional nature of this reagent.^{6–8} These studies have led to the discoveries of TBD-mediated complex multistep reaction cascades and enabled new entries to highly substituted heterocycles. The next objective of our research was the development of asymmetric versions for those transformations by using chiral bicyclic guanidines.

Chiral bicyclic guanidines have been known for more than two decades and have found applications in the fields of molecular recognition^{9,10} and asymmetric organocatalysis.^{11–17} Among the structures of interest, one can easily recognize the striking prevalence of the C_2 -symmetric bicyclic systems such as compound 3 developed by Schmidtchen¹⁸ and TBO derivative 4 reported by Corey (Figure 2).¹⁹ Misaki–Sugimura catalyst (5), on the other hand, represents a rare exception, as it is the only successful non- C_2 -symmetric bicyclic guanidine organocatalyst known to date.^{20–22}



Figure 2. Bicyclic chiral guanidine bases used in molecular recognition and organocatalysis.

The vast majority of bicyclic guanidines have been synthesized according to the strategy presented in Figure 3.

$$(\underbrace{\mathsf{N}}_{\mathsf{N}} \underbrace{\mathsf{N}}_{\mathsf{H}}) \Rightarrow (\underbrace{\mathsf{N}}_{\mathsf{N}} \underbrace{\mathsf{N}}_{\mathsf{S}} \underbrace{\mathsf{N}}_{\mathsf{H}_2} \Rightarrow (\underbrace{\mathsf{N}}_{\mathsf{N}} \underbrace{\mathsf{N}}_{\mathsf{N}} \underbrace{\mathsf{N}} \underbrace{\mathsf{N}} \underbrace{\mathsf{N}}_{\mathsf{N}} \underbrace{\mathsf{N}}_{\mathsf{N}} \underbrace{\mathsf{N}} \underbrace{\mathsf$$

Figure 3. Retrosynthetic analysis of bicyclic guanidines via cyclic thiourea intermediates.

In every case, an acyclic triamine precursor was used as a key intermediate which was subsequently converted to a cyclic thiourea followed by a condensation reaction leading to the target structure. Special note should be taken of the fact that late cyclization stages included variations of the thiocarbonyl equivalent (e.g., $Cl_2CS_1^{23}$ Me $_2CS_3^{24}$ or Im $_2CS^{25}$) and were reported to proceed both as a multistep sequence or a one-pot reaction.

Among the studies dealing with the syntheses of bicyclic guanidines, the contributions of Franz Schmidtchen deserve special attention: In one of his very last published works,²⁶ he

Received: February 7, 2016

ACS Publications © XXXX American Chemical Society

used an approach which made use of guanylating reagent 6, which had previously been developed by Wu et al. in the laboratories of Guilford Pharmaceuticals Inc. (Figure 4).²⁷ The



Figure 4. Retrosynthetic analysis of bicyclic guanidines by Schmidtchen approach.

key step was the reaction between a primary amine and reagent 6: The imidazole leaving groups were displaced by 2 equiv of the amine, and an open-chain guanidinium salt was formed. Final steps included two-fold intramolecular nucleophilic substitution affording the desired structure. In contrast to the approach via triamine precursors, the significant advantage of this new strategy was the introduction of the critical guanylation reaction in the early stage of the synthesis. Subsequent end-game chemistry allowed for robust and reliable assembly of the final bicyclic guanidine scaffold. As a matter of fact, this approach was successfully applied to the synthesis of guanidine 3 (Figure 2). Despite the obvious elegance of this route, it has remained neglected and was never applied for the syntheses of other bicyclic guanidines.

In order to investigate the practical applicability and limitations of the guanylation approach reported by Schmidtchen, we set out to prepare guanidinium salts presented in Figure 5. Besides our efforts to access the hitherto unknown



Figure 5. Target chiral bicyclic guanidinium salts.

guanidinium salts 7 and 8, we also investigated the syntheses of TBO-derivative 9²⁸ and TBD-derivative 10.²⁴ With regard to the latter two structures, there is no doubt that the planned study was of special interest for the development of a new and convenient approach to C_2 -symmetric guanidinium salts. For instance, despite a brilliant and a very detailed report by Davis on guanidine 10^{24} it was evident that the synthesis was anything but simple, as it required careful choices of protecting groups and included several unstable intermediates. Since the only known entries to guanidines 9 and 10 had relied exclusively on the approach rationalized on Figure 3, we were eager to investigate the applicability of the Schmidtchen's strategy as a more robust alternative. We looked upon the syntheses of those structures as an exercise in guanidine chemistry allowing us to address the following synthetic questions: (a) applicability of the chosen approach to the modular syntheses of non C2-symmetric bicyclic guanidines; (b) syntheses of C_2 -symmetric guanidines; and (c) syntheses of [4.4.0]-, [3.3.0]-, and [4.3.0]-bicyclic systems.

RESULTS AND DISCUSSION

Preparation of Starting Materials. The protected chiral aminoalcohol **19** was an obvious choice as a key intermediate for the syntheses of guanidinium salts **8** and **10** and is readily available from L-methionine following the sequence described by Davis et al. (Scheme 1).²⁹ It is noteworthy that, after some





experimentation, the synthesis of this useful building block was easily scaled up, and we can now provide detailed experimental procedures for the preparation of gram quantities of chiral amine 19 (see Experimental Section). The first steps involved the transformation of L-methionine (11) into L-homoserine (13) by S-methylation followed by hydrolysis of the methylsylfonium salt 12 under basic conditions. In agreement with the work of Davis, precise pH control was vital for the success of the reaction, since racemization readily took place at pH values above 6. A further observation was attributed to the temperature control of the heating medium in the event that the use of heating mantles, despite their practical convenience, happened to cause the destruction of the reaction components affording homoserine as a dark brown solid. Due to insufficient transparency of the corresponding solutions of compound 13, using the material obtained this way was troublesome for the determination of its enantiopurity by polarimetry. We found that using an oil bath at 140 °C was absolutely sufficient to circumvent any destruction processes and to obtain enantiopure homoserine (13) in decagram quantities as a beautiful white solid. Subsequent cyclization under acidic conditions and lactone opening using excess of the phenyl Grignard reagent delivered the chiral aminodiol 15. Primary alcohol and amine functionalities were protected by acetylation in order to enable the removal of the tertiary hydroxyl group by transfer hydrogenolysis in the next step. After the subsequent hydrogenylitic reduction, hydrolysis, and TBDPS-protection, the key target intermediate 19 was obtained.

The *tert*-butyl-substituted protected aminoalcohol **22** was prepared from L-*tert*-leucine (**20**) in two steps by the reduction using $NaBH_4/I_2^{30}$ followed by O-silylation (Scheme 2). Substrate **24** was prepared from 3-amino-1-propanol using the same TBDPS-protection conditions.

Attempted Synthesis of the Chiral [4.3.0]-Bicyclic Guanidinium Chloride 7. The next objective of our study was the synthesis of the non- C_2 -symmetric bicyclic guanidinium

Scheme 2. Syntheses of the Protected Aminoalcohols 22 and 24



salt 7 from the aminoalcohols 22 and 24 and the guanylating reagent 6. We chose as a first step the reaction of compound 6 with the protected *tert*-leucinol 22, leading to the unsymmetric guanylating reagent 25 (Table 1). The desired intermediate was

Table 1. Synthesis of the Chiral Guanylating Reagent 25



"Reaction was carried out on 337 μ mol scale in an open roundbottomed flask. ^bReaction was carried out on 2.36 mmol scale in an open round-bottomed flask. ^cReaction was carried out in a closed round-bottomed flask.

isolated after reacting the starting materials at 40 °C in THF (Table 1, entry 1). Despite the synthetically useful yield of 62%, we faced significant obstacles at this stage of the synthesis. First, steric hindrance of tert-butyl group resulted in a rather low reactivity of compound 22, and, as follows, this step suffered from very long reaction times (120 h). Furthermore, concentration dependence of the one-fold guanylation represented another problem for the elaboration of the intermediate 25. This reaction was performed in an open reaction vessel enabling slow evaporation of the solvent and leading to gradual increase of the concentrations of the reaction components. However, we were not able to reproduce this initially promising result on a seven-fold scale (2.36 mmol aminoalcohol 22) and obtained the intermediate 25 in only 15% yield (Table 1, entry 2). Conversely, when the reaction was carried out in a closed round-bottom flask, the yield of the isolated product was 22% (Table 1, entry 3). As we attempted this transformation under solvent-free conditions, decomposition of the guanylating reagent 6 took place to a significant degree, so that only traces of compound 25 could be detected (Table 1, entry 4).

In an alternative approach, we reacted the protected aminoalcohol 24 with the reagent 6. Without any steric hindrance from the bulky *tert*-butyl group, the displacement of imidazole took place significantly faster (23 h) and did not show the above-mentioned sensitivity to the concentrations of the reacting components (Scheme 3).

Scheme 3. Synthesis of the Nonsymmetrical Guanylating Reagent 26



The subsequent step was the synthesis of the key chiral guanidine 27 by the attachment of the aminoalcohol 22 through the substitution of the second imidazole moiety (Table 2). No product was formed when we reacted the components



ΟΤΙ	BDPS	OTBDPS	
			OTBDPS
entry	solvent	T (°C)	yield of 2 7 (%)
1	1.4-dioxane	90	_
2	neat	110	-
3	neat	150	-
4	neat	200	-
5 ^a	neat	115	55 ^b
410 · T		1 1 . 1	

^a1.0 equiv TFA was added. ^bProduct isolated as a trifluoroacetate salt (27**·TFA**).

22 and 26 at 90 °C in dioxane (Table 2, entry 1). Even performing the reaction at elevated temperatures under solvent free conditions resulted in no conversion of starting materials (Table 2, entries 2-4). The elaboration of the guanidine intermediate 27 was finally possible by running this reaction at 115 °C in the presence of 1 equiv of TFA (Table 2, entry 5).²⁶ It should be noted that the key guanylation step was performed under solvent-free conditions and the use of stirring bars became impossible due to an extremely high viscosity of the reaction mixture. In search for a solution to this practical obstacle, we found that using a Kugelrohr oven as a reactor was a very convenient alternative to magnetic stirring and enabled even mixing of the highly viscous reaction mixture. At this point, we also faced a significant purification problem, as the guanidinium salt 27. TFA could not be sufficiently separated from the unreacted amine 22 using standard eluents (MeOH/ CH₂Cl₂ or MeOH/EtOAc) for column chromatography. We found that two chromatographic purifications were necessary to obtain the product 27. TFA in acceptable purity. For the first chromatography, we employed silica gel as a stationary phase and were able to separate the mixture of the product and amine 22 from more polar and apolar impurities, while the second chromatography was performed using neutral aluminum oxide to separate the guanidinium salt 27. TFA from the unreacted amine 22.

Cleavage of the silvl protecting groups was carried out to afford diol **28** at the next stage (Scheme 4). This deprotected guanidinium species possessed an extremely high polarity, and any conventional purification techniques such as extraction or column chromatography were not applicable at this stage. For that reason, fluoride on polymer carrier was used instead of TBAF for the deprotection step, since the latter would produce Scheme 4. Final Steps in the Attempted Synthesis of the Guanidinium Salt 7



an inseparable mixture with the desired intermediate. Indeed, the guanidinium salt 28 could be conveniently purified by simple filtration of the polymer beads and subsequent precipitation. The intermediate 29 was obtained by reacting the diol 28 with excess thionyl chloride at 60 °C (when this reaction was attempted at room temperature (rt) overnight, we observed incomplete conversion of the starting material). The final two-fold cyclization step was performed under conditions analogous to those reported by Schmidtchen et al.: Dichloride 29 was suspended in MeCN and, after addition of an excess DBU, complete conversion of the starting material was observed after 18 h.²⁶ Subsequent work up and chromatographic purification afforded guanidinium salts 30 and 31. The main bicyclic product was the undesired regioisomer and was isolated as an inseparable 92:8 mixture with another guanidine species.³¹ We assume, that the minor component of this mixture was the desired compound possessing structure 7.

The structure determination of the obtained bicyclic product 30 deserves special comment. It should first be noted that the standard two-dimensional NMR experiments (NOESY, HSQC, HMBC) did not provide any conclusion whether the isolated compound possessed structure 30 or 7. Attempts to obtain crystalline material suitable for an X-ray study were fruitless. First, the usual aggregate state of the main product was an oil. Second, we did observe formation of beautiful clear prisms in acetonitrile after storing the corresponding solution of the compound 30 for several days at rt. Nevertheless, after we removed the acetonitrile supernatant, crystalline material "melted" to a colorless oil within several minutes. Significant information regarding the real structure of the product 30 was obtained after studying the monocyclic guanidinium salt 31. HMBC spectra of this species showed a clear three-bond through-nitrogen correlation between the methine proton and a methylene carbon attached to one of the nitrogen atoms (Figure 6). This observation enabled us to assume that the isolated compound indeed possessed the structure 31 rather than the alternative connectivity 31^A: Whereas the long-range correlation between the nuclei of the compound 31 is transferred over three bonds, the latter structure would require a very unlikely correlation across five bonds including two heteroatoms. After having determined the structure of monocyclic guanidinium salt 31, we were now able to deduce the connectivity of the species 30. We envisioned that cyclization of the guanidinium salt 31 would lead to only one



Figure 6. Key HMBC correlations for the intermediate 31. Formation of the product with alternative structure 31^A was ruled out due to unlikely correlation over five bonds through two nitrogen atoms.

possible bicycle possessing the structure **30**. Indeed, upon reacting the monocyclic guanidinium salt **31** with DBU at 75 $^{\circ}$ C, a bicyclic product **30** was obtained, which was spectroscopically identical to the main product of the two-fold cyclization of the intermediate **29**.

Regioselectivities of the Final Cyclization Steps. A possible mechanistic rationale for the formation of compound 30 is presented in Scheme 5 and can be generalized to explain the formation of undesired regioisomers of other target guanidines mentioned in this manuscript. We initially expected that the desired guanidinium salt 7 would be formed by a twofold intramolecular cyclization at the less substituted nitrogen atom (Pathways $c \rightarrow h$ and $b \rightarrow g$). These reaction pathways were supposed to be the preferred ones, because alkylsubstituted nitrogen atoms were sterically more hindered, especially those containing the bulky tert-butyl group. After the isolation of the species 31 and 30, it became obvious that we were dealing with the alternative reaction pathway: The reactivity was governed by electronic rather than steric factors, resulting in preferential nucleophilic attack by a secondary nitrogen atom (Pathway $a \rightarrow e$). Thus, we suggest that a strong electron-donating effect of the tert-butyl group led to enhanced nucleophilicity of the neighboring nitrogen atom resulting in the observed regioselectivity. As a result, it is likely that the first cyclization preferentially took place on the more nucleophilic nitrogen atom leading to the intermediate 31. Subsequently, the second nucleophilic substitution led to the bicyclic guanidinium salt 30.

Synthesis of the Chiral [4.4.0] Bicyclic Guanidinium Chloride 8. We now turned to the synthesis of the chiral benzhydryl-substituted guanidinium chloride 8 (Scheme 6). The nonsymmetric guanylating reagent 26 was reacted with the aminoalcohol 19 under the same conditions we applied for the synthesis of the compound 27. TFA. The key guanidinium salt 32 was isolated in 39% yield after two consecutive chromatographic purifications over silica gel and aluminum oxide. After deprotection of the alcohol functionalities, the guanidinium diol 33 was chlorinated with thionyl chloride to afford dichloride 34. After the final cyclization step and chromatographic purification, we were able to obtain the target guanidinium salt 8 in 44% yield. The structure of this compound was established by X-ray crystallography and is presented in Figure $7.^{32}$ In addition, we isolated a fraction consisting of the desired product 8 and regioisomer 35 (34% total yield). Thus, by contrast with the attempted cyclization toward guanidium salt 7, the total yield of bicycle 8 was 69% and clearly prevailed over the undesired side product 35.

Attempted Synthesis of the C_2 -Symmetric Chiral [3.3.0]-Bicyclic Guanidinium Chloride 9 (Tan's Guanidine). Protected aminoalcohol 22 was used in the key guanylation step leading to chiral acyclic guanidinium salt 36 (Table 3). Initial reaction conditions were adopted from the



Scheme 6. Synthesis of the Bicyclic Guanidinium Salt 8



8+35: 78% over 2 steps (total yield) 8:35 = 89:11



Figure 7. X-ray crystal structure of guanidinium salt 8.³² Ellipsoids are drawn at 80% probability. A water molecule has been omitted for clarity.



	NH ₂ <u>6, TF</u> 22		NH ₂ + + N + N - - - - - - - - - - - - -
entry	<i>t</i> (h)	T (°C)	yield of 36 (%)
1	2	115	26
2	2	105	20
3	4	105	40

above-mentioned syntheses of the non C2-symmetric guanidinium salts: We ran the two-fold substitution at 115 °C for 2 h in the presence of 1 equiv of TFA. Due to the fact that this initial attempt afforded the desired product in only 26% yield (Table 3, entry 1), the reaction temperature was reduced to avoid eventual decomposition of the guanylating reagent 6.33 As a result, we obtained the guanidinium trifluoroacetate 36 in

an acceptable yield of 40% after prolonged reaction time at 105 $^{\circ}$ C (Table 3, entries 2–3).

This key step suffered from the same purification problem described for related intermediates 27. TFA and 32, as the protected aminoalcohol 22 could not be separated from the product 36 by column chromatography when standard eluents consisting of CH₂Cl₂ and MeOH were used. Owing to the fact that our synthetic studies also revealed a great sensitivity of this problematic separation to the activity grade of aluminum oxide, we also faced problems with the reproducibility of our own purification procedures. In search for more reliable separation methods, it was found that guanidinium salt 36 could be easily separated from unreacted aminoalcohol 22 by a single column chromatography over silica gel when a small amount of AcOH or formic acid was added to the eluent. We assume that using acidic additives led to the formation of the ammonium salt of the compound 22, which was significantly more polar than the guanidinium salt 36. As a result, the desired key intermediate 36 could be isolated as a less polar fraction in acceptable purity free of any starting amine.

After subsequent desilylation and chlorination steps, guanidinium salt 38^{32} was isolated as a crude mixture and subjected to the final cyclization step without additional purification (Scheme 7). Guanidinium salt **39** was obtained as

Scheme 7. Final Steps in the Attempted Synthesis of the Guanidinium Salt 9^a



^aEllipsoids of **38** are drawn at 80% probability.

Scheme 8. Synthesis of the Bicyclic Guanidinium Salt 10

the final product. Interestingly, no traces of the desired regioisomer 9 were found in the reaction mixture, as species 39 was the only isolated bicyclic product.

Synthesis of the C_2 -Symmetric Chiral [4.4.0]-Bicyclic Guanidinium Chloride 10 (Davis's Guanidine). Our final endeavor was targeted toward the synthesis of the chiral TBD derivative 10 first described by Davis et al.²⁴ The guanylation step was performed under the same reaction conditions we used for the synthesis of the compound 36, and the open-chain guanidinium trifluoroacetate 40 was obtained in 38% yield (Scheme 8). At the next stage, cleavage of the silyl groups was carried out to give diol 41, which was isolated as a mixture of guanidinium fluoride and trifluoroacetate salts. Subsequent reactions with thionyl chloride and DBU-mediated double cyclization afforded the desired guanidinium salt 10 in 14% yield along with its regioisomer 43, which was formed in 49% yield. After column chromatographic purification, product 10 was isolated in 8% yield in pure form.

An X-ray crystallographic study on the bicyclic salt 10³² delivered a very surprising structural insight contradicting the computational data obtained by Davis et al. In contrast to the initially proposed preference to equatorial positioning of the benzhydryl groups,³⁴ we could clearly observe that the bulky residues occupy the axial positions (Figure 8)! Moreover, the



Figure 8. X-ray crystal structure of guanidinium salt **10**.³² Ellipsoids are drawn at 80% probability. Water molecules have been omitted for clarity.



10: 8% over 2 steps (isolated) **10+43:** 63% over 2 steps (total yield) **10:43 =** 22:78

orientation of the two benzhydryl groups around the guanidinium active center creates a well-defined groove for substrate binding which could indeed make compound **10** a viable chiral organocatalyst. Although we are aware that X-ray crystallography does not always represent the real conformation present in the solution, we do hope that this observation provides a useful foundation for further studies on Davis's guanidine **10**.

CONCLUSION

We have carried out the first systematic study toward chiral bicyclic guanidinium salts using guanylating reagent 6 with subsequent two-fold intramolecular nucleophilic substitution. In course of this work, we have demonstrated the broad robustness and utility of the key guanylation step, as it was applicable to the syntheses of both symmetrically and nonsymmetrically substituted open-chain guanidinium salts. Most importantly, this approach demonstrated a high tolerance toward steric bulk of alkylated amines, so that even the strongly hindered tert-leucinol 22 was a viable substrate for the key transformation. A special feature of this work is also the strategic employment of TBDPS protecting groups enabling convenient purification of guanidinium intermediates. Although we have demonstrated the applicability of the selected approach to the modular syntheses of [4.4.0]-, [4.3.0]-, and [3.3.0]bicyclic guanidinium salts, regioselectivity in the final cyclization step remains a yet to be solved problem. Our data strongly suggest that the preference for the observed reaction pathways is governed by electronic rather than steric factors. Our further synthetic studies dealing with chiral bicyclic guanidinium salts will be reported elsewhere in due course.

EXPERIMENTAL SECTION

General Experimental Methods. Solvents for column chromatography and TLC (EtOAc, MeOH, CH_2Cl_2 , pentane, Et_2O) were of technical grade. EtOAc, MeOH, and CH_2Cl_2 were distilled before use. THF was of technical grade, purified by distillation and stored over KOH. Afterward, it was distilled over SOLVONA and stored over molecular sieves (4 Å). Dry CH_2Cl_2 was distilled over SOLVONA and stored over molecular sieves (4 Å). MeCN (HPLC grade or extra dry) and DMF (HPLC grade) were obtained commercially and used without further purification.

Working Techniques. Reactions with moisture- or air-sensitive compounds were carried out using the standard Schlenk technique. If the reactions were carried out below rt, the following cooling baths were employed: Dry ice/acetone (-20 to -30 °C), crushed ice/water (0 to 2 °C). Glass stoppers and PTFE sleeves were used to seal reaction vessels. The temperature of each reaction indicates the temperature of the cooling or heating medium. Yields of the reactions were calculated from the mass of purified and dried products. In the cases of problematic purifications, yields and purities of intermediates were estimated. For column chromatography, silica gel 60 (230–400 mesh) and neutral aluminum oxide 90 (70–230 mesh, activity stage I) were used. In the advanced phase of our study, we found that chromatographic purifications using aluminum oxide were not necessary when we used eluents consisting of AcOH/MeOH/ CH₂Cl₂ and silica gel as stationary phase.

Analysis. Thin-layer chromatography was carried out with readyto-use glass plates coated with silica gel from a commerical source. Detection was done both by irradiation of the plate with UV-light at 254 nm and by application of specific staining reagents. The ceric ammonium molybdate stain (CAM) was prepared by dissolving 10 g $(NH_4)_6Mo_7O_{24}$ ·4H₂O and 0.2 g Ce(SO₄)₂·4H₂O in 200 mL of 10% H₂SO₄. The staining reagent KMnO₄ was prepared by dissolving 3 g KMnO₄ and 10 g K₂CO₃ in 300 mL water followed by addition of 5 mL 5% aqueous NaOH. The staining reagent bromocresol green was prepared by adding 0.04 g bromocresol green to 100 mL EtOH. Then a 0.1 M NaOH solution was slowly dripped in until the solution just turned pale blue.³⁵ The staining reagent ninhydrin was prepared by dissolving 1.5 g ninhydrin and 3 mL acetic acid in 100 mL butanol.

NMR spectra were recorded using 300, 400, and 600 MHz NMR spectrometers. Chemical shifts δ are given in ppm. Calibration of the spectra was based on solvent residual peaks for the samples recorded in CDCl₃, methanol- d_4 , DMSO- d_6 . Coupling constants J are given in Hz. The following abbreviations are used to describe the signals in the NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; and m, complex multiplet. The abbreviation "virt x" is used to show that the detected signal seemed to look like x (e.g., "virt t" stands for "virtual triplet"). Signal and structure assignments for the compound **31** were performed using 2D NMR methods (HSQC and HMBC). The representative 2D NMR spectra can be found in the Supporting Information. HRMS were measured with an LTQ Orbitrap XL spectrometer.

Di(1H-imidazol-1-yl)methanimine (6).^{26,27} The following procedure was performed under exclusion of moisture. Due to high toxicity and volatility of bromocyanide, all operations should be performed in a properly functioning fume hood. Imidazole (3.2 g, 50 mmol, 3.0 equiv) was dissolved in dry CH₂Cl₂ (250 mL). Subsequently, a solution of bromocyanide (1.85 g, 17.5 mmol) in CH₂Cl₂ (10 mL) was added by syringe, and the solution heated to reflux for 45 min. After cooling to rt, the white precipitate was collected by decanting the supernatant and washing with the cold CH₂Cl₂. Mother liquor was then concentrated to ca. 20 mL and cooled to -20 °C for 4 d. Precipitated solid was filtered and washed with cold CH₂Cl₂ to give a second crop of the product. Combined solids weighed 1.92 g (11.9 mmol, 68%). R_f = 0.34 (CH₂Cl₂/MeOH = 9/1, [UV]). ¹H NMR (400 MHz, DMSO d_6): δ 10.20 (s, 1H), 8.11/8.05 (bs, 2H), 7.60/7.53 (bs, 2H), 7.13/ 7.11 (bs, 2H). ¹³C NMR (101 MHz, DMSO-d₆): δ 140.9, 137.4, 129.85/129.62, 118.95/118.92. This is a known compound. Spectroscopic data agree with those reported in the literature.²

(S)-(3-Amino-3-carboxypropyl)dimethylsulfonium lodide (12).29 To a flask containing a suspension of methionine (11, 60 g, 402 mmol) in distilled water (390 mL), iodomethane (64.0 mL, 145.9 g, 1.03 mol, 2.55 equiv) was added all at once. The resulting mixture was vigorously stirred at 35-40 °C overnight. After 21.5 h, no more solid material was left, and the biphasic mixture was evaporated under reduced pressure to afford a yellow oil. This material was dissolved in distilled water (160 mL). Addition of EtOH (580 mL) and a gentle mixing resulted in a rapid formation of a white precipitate. This suspension was allowed to stand overnight at rt, and the solid was collected by filtration. After removing solvent residues under reduced pressure, the product 12 was obtained as white solid (95.48 g, 327 mmol, 81%). It is recommended to store the obtained product in darkness, as it develops a brownish color upon exposure to the light. R_f = 0.19 (EtOH/AcOH/H₂O = 3/1/1, [ninhydrin]). Mp 163–166 °C (Lit.:²⁹ 163–165 C). ¹H NMR (600 MHz, D_2O): δ 3.92 (t, J = 6.5 Hz, 1H), 3.59-3.53 (m, 1H), 3.50-3.44 (m, 1H), 2.99 (s, 6H), 2.43-2.38 (m, 2H). ¹³C NMR (151 MHz, D_2O): δ 172.4, 52.7, 39.4, 25.0, 24.8, 24.7. Mp 163-166 °C (Lit.:²⁹ 163-165 C). This is a known compound. Spectroscopic data agree with those reported in the literature.30

(*S*)-Homoserine (13).²⁹ We recommend using an oil bath as a heating medium in order to avoid extensive overheating of the reaction mixture. We found an optimal temperature of the oil bath to be 140 °C. Our initial attempts to use a heating mantle without well-defined temperature control led to dissatisfactory results: The reaction mixture quickly developed a dark brown color, and the final product could not be obtained in pure form. (*S*)-(3-Amino-3-carboxypropyl)dimethyl sulfonium iodide (12, 51.4 g, 176 mmol) dissolved in distilled water (81 mL) was heated to gentle reflux (140 °C) for 30 min. Within this time, the pH dropped from 5.8 to 3.8, and dropwise addition of NaHCO₃ in distilled water (152 mL) was started. Addition was performed under constant control of the pH value with the appropriate pH indicator test paper (pH range 3.8 to 5.8). In order to avoid the racemization, NaHCO₃ solution was added until the pH rose to ~5.0. Reaction mixture was further refluxed until the pH

dropped to values 3.5-4.5, whereupon the base was added dropwise again. Once the reaction was finished, water was removed under reduced pressure to give an oil which solidified upon standing at rt. The solid was dissolved in distilled water (45 mL) by gentle mixing and careful heating with a heat gun. When acetone (103 mL) and EtOH (1.28 L) were added to this solution, a white solid precipitated. After removing all solvents under reduced pressure, the solid was suspended in EtOH (500 mL), and after refluxing for 10 min filtered off again. The precipitate was washed with cold EtOH (100 mL) and dried in vacuo to give homoserine (13, 14.4 g, 121 mmol, 69%) as a white solid. The product contained an unidentified impurity. $R_f = 0.67$ $(EtOH/AcOH/H_2O = 3/1/1, [ninhydrin])$. ¹H NMR (600 MHz, D_2O): δ 3.85 (dd, J = 7.5, 4.8 Hz, 1H), 3.81–3.74 (m, 2H), 2.19–2.12 (m, 1H), 2.06–1.99 (m, 1H). ¹³C NMR (151 MHz, D₂O): δ 174.3, 58.6, 53.3, 32.0. [α]_D^{21 oC} = -8.3 (H₂O, c = 1) (Lit.:³⁷ – 8.0 [H₂O, c = 1]). Mp 195 °C (dec) (Lit.:²⁹ 201–202 °C [dec]). This is a known compound. Spectroscopic data agree with those reported in the literature.²

(S)-2-Oxotetrahydrofuran-3-aminium Chloride (14).²⁹ Homoserine (13, 14.4 g, 121 mmol) was refluxed in an aqueous HCl (2 M, 235 mL) for 3 h (temperature of oil bath was kept at ca. 140 °C). The mixture was stirred for further 17 h at rt. Subsequently, water was removed by azeotropic distillation with ethanol. Boiling temperature of the azeotrope was constantly kept below 79 °C by adding ethanol to the mixture. After approximately 4-5 L of EtOH were distilled off and the volume of the remaining brown solution was approximately 100 mL, it was cooled to rt and left to stand overnight. Filtration of the brown precipitate and subsequent washing with ethanol afforded the product 14 (11.83 g, 86 mmol, 71%) as a white powder. ¹H NMR $(600 \text{ MHz}, D_2 \text{O}): \delta 4.64 \text{ (td}, J = 9.2, 1.0 \text{ Hz}, 1\text{H}), 4.51-4.44 \text{ (m, 2H)},$ 2.86-2.80 (m, 1H), 2.51-2.41 (m, 1H). ¹³C NMR (151 MHz, D₂O): δ 174.4, 67.3, 48.5, 26.7. Mp 227 °C (dec) (Lit.:³⁸ 210–212 °C). This is a known compound. Spectroscopic data agree with those reported in the literature.

(S)-2-Amino-1,1-diphenylbutane-1,4-diol (15).²⁹ Magnesium turnings (4.34 g, 179 mmol, 4.9 equiv) were suspended in dry THF (70 mL) under Ar. To this suspension, a solution of bromobenzene (25.0 g, 159 mmol, 4.4 equiv) in dry THF (70 mL) was added dropwise within 40 min. The reaction mixture was subsequently heated to reflux for 1 h and then cooled to 2 °C. (S)-3-Aminodihydrofurane-2(3H)-on hydrochloride (14, 5.0 g, 36.6 mmol) was added in small portions over 12 min. The mixture was stirred for another 18 min at the same temperature and was then warmed to rt. After 19 h, the excess of Grignard reagent was destroyed by the careful addition of ice. The resulting mixture was cooled to 2 °C and aqueous HCl (2 M, 350 mL) was carefully added. Subsequently, the solution was stirred at rt for 1 h. After addition of aqueous ammonia (25%, 150 mL), the resulting suspension was stirred for another 1 h at rt. Precipiate was filtered off and washed with precooled EtOH (-20 °C) to afford the desired product (5.97 g, 23.2 mmol, 64%) as an off-white solid. ¹H NMR (300 MHz, DMSO- d_6) δ 7.58 (d, J = 7.4 Hz, 2H), 7.49 (d, J = 7.4 Hz, 2H), 7.37–7.06 (m, 6H), 5.33 (bs, 1H), 3.89 (dd, J = 9.3, 2.9 Hz, 1H), 3.64–3.43 (m, 2H), 1.77–1.03 (m, 3H). ¹³C NMR (151 MHz, DMSO-d₆) & 147.3, 146.4, 128.0, 127.8, 126.02, 125.98, 125.8, 125.5, 80.0, 59.6, 55.0, 33.7. $[\alpha]_D^{22 \text{ oC}} = -28.1 \text{ (EtOH, } c = 0.26 \text{) (Lit.:}^{29} -26.0 \text{)}$ [EtOH, c = 0.26]). Mp 198–199 °C (Lit.:²⁹ 200 °C). This is a known compound. Spectroscopic data agree with those reported in the literature.²

(35)-3-(Acetylamino)-4-hydroxy-4,4-diphenylbutyl Acetate (16).²⁹ Acetic anhydride (15.3 g, 14.2 mL, 149.9 mmol, 4.3 equiv) was slowly added to a suspension containing the diol 15 (8.88 g, 34.5 mmol) and pyridine (69.7 g, 71 mL, 881.4 mmol, 25.5 equiv), and the resulting solution was stirred at rt for 23 h. The reaction mixture was poured into a separatory funnel containing aqueous HCl (2 M, 560 mL), and the resulting emulsion was extracted with CH₂Cl₂ (3 × 450 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The resulting crude product was suspended in hexane (132 mL) and heated to reflux. EtOAc (ca. 70 mL) was added in small portions until the solid material dissolved. After the solution was slowly cooled to rt, it was stored at +7 °C for 8

d and at -20 °C for 2 d. The formed precipitate was collected by filtration and washed with hexane (20 mL). After drying under reduced pressure, the final product (9.84 g, 28.8 mmol, 83%) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.44 (m, 4H), 7.32–7.14 (m, 6H), 6.00 (br d, *J* = 8.0 Hz, 1H), 5.00–4.94 (m, 1H), 4.09 (virt t, *J* = 6.4 Hz, 2H), 2.02 (s, 3H), 1.85–1.79 (m, 2 H), 1.76 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.3, 170.9, 145.3, 144.8, 128.7, 128.5, 127.3, 127.2, 125.7, 125.6, 81.0, 61.9, 53.5, 29.5, 23.3, 21.2. This is a known compound. Spectroscopic data agree with those reported in the literature.²⁹

(3S)-3-(Acetylamino)-4,4-diphenylbutyl Acetate (17).²⁹ To a solution containing (3S)-3-(acetylamino)-4-hydroxy-4,4-diphenylbutyl acetate (16) (9.84 g, 28.8 mmol) in glacial acetic acid (99 mL), palladium on charcoal (10%, 1.33 g) and ammonium formate (9.18 g, 146 mmol, 5.0 equiv) were added. The resulting mixture was stirred at 110 °C for 32 h. It is highly recommended to monitor the reaction progress by NMR spectroscopy, since complete conversion of the starting material could not be sufficiently detected using TLC. The reaction mixture was cooled to rt and filtered through a plug of Celite which was additionally washed with a portion of CH_2Cl_2 (150 mL). The solution was washed with saturated aqueous Na_2CO_3 (3 × 600 mL), brine (1 \times 100 mL), and dried over MgSO₄. After evaporation of the solvents under reduced pressure, the product 17 (8.0 g, 24.6 mmol, 85%) was obtained as a yellow solid and used for subsequent reactions without additional purification. $R_f = 0.40$ (Pentante/EtOAc = 1/1, [UV, CAM]). ¹H NMR (600 MHz, CDCl₂) δ 7.26–7.22 (m, 8H), 7.19–7.12 (m, 2H), 5.26 (br d, J = 9.0 Hz, 1H), 4.89 (virt qd, J = 9.0, 3.0 Hz, 1H), 4.11-4.02 (m, 2H), 3.95 (d, J = 10.2 Hz, 1H), 1.99 (s, 3H) 1.92–1.86 (m, 1 H), 1.74 (s, 3H), 1.63–1.56 (m, 1 H). ¹³C NMR (151 MHz, CDCl₃) δ 171.2, 170.0, 142.0, 141.8, 129.0, 128.8, 128.32, 128.28, 127.1, 126.9, 61.7, 56.9, 49.2, 32.9, 23.4, 21.2. This is a known compound. Spectroscopic data agree with those reported in the literature.²

(3S)-3-Amino-4,4-diphenyl-1-butanol (18).²⁹ A suspension of (3S)-3-(acetylamino)-4,4-diphenylbutyl acetate (17) (2.65 g, 8.14 mmol) in aqueous HCl (33 mL, 1.4 M) was stirred at 100 °C for 7 h. The resulting solution was then cooled to rt and basified with solid NaOH until pH 14 was reached. Upon addition of NaOH, an oily precipitate was formed. The resulting emulsion was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organic layers were dried over MgSO₄. The solvent was removed under reduced pressure, and the product 18 (1.81 g, 7.5 mmol, 92%) was obtained as brownish oil which solidified upon standing at rt. $R_f = 0.28$ (CH₂Cl₂/MeOH = 9/1, [UV, ninhydrin]). ¹H NMR (600 MHz, CDCl₃) δ 7.36–7.30 (m, 4H), 7.28-7.25 (m, 4H), 7.22-7.15 (m, 2H), 3.82-3.69 (m, 4 H), 2.55 (s br, 3 H), 1.71–1.67 (m, 1 H), 1.49–1.43 (m, 1 H). ¹³C NMR (101 MHz, CDCl₃) δ 142.7, 142.0, 129.3, 129.0, 128.4, 128.1, 127.2, 126.9, 62.7, 60.9, 56.0, 35.4. $[\alpha]_D^{21 \circ C} = +15.5$ (CH₂Cl₂, c = 1). This is a known compound. Spectroscopic data agree with those reported in the literature.²

(2S)-4-[tert-Butvl(diphenvl)silvl]oxv-1,1-diphenvl-2-butanamine (19). Aminoalcohol 18 (4.42 g, 16.4 mmol) and imidazole (3.74 g, 54.9 mmol, 3.3 equiv) were dissolved in MeCN (93 mL, HPLCgarde). After addition of TBDPSCl (9.6 mL, 10.1 g, 37 mmol, 2.2 equiv), the resulting solution was stirred at rt under Ar for 2.5 h. The solvent was removed under reduced pressure, and the crude product (gummy mass) was purified by flash column chromatography (Si, 7.0 × 24 cm, $CH_2Cl_2/MeOH = 99/1 \rightarrow 98/2 \rightarrow 97/3 \rightarrow 95/5$). The product 19 (7.41 g, 15.4 mmol, 94%) was obtained as brownish viscous oil. $R_f = 0.42$ (CH₂Cl₂/MeOH = 9/1, [UV, ninhydrin]). ¹H NMR (600 MHz, CDCl₃) δ 7.68 (dd, J = 8.4, 1.2 Hz, 2H), 7.64 (dd, J= 8.4, 1.2 Hz, 2H), 7.45–7.41 (m, 2H), 7.40–7.35 (m, 6H), 7.33–7.24 (m, 6H), 7.21–7.16 (m, 2H), 3.89–3.83 (m, 2 H), 3.78–3.75 (m, 1H), 3.72 (d, J = 10.2 Hz, 1H), 1.83-31.78 (m, 1H), 1.55 (br s, 2H), 1.44–1.37 (m, 1H), 1.08 (s, 9H). ¹³C NMR (151 MHz, CDCl₃) δ 143.3, 143.1, 135.78, 135.76, 133.9, 133.8, 129.84, 129.80, 128.9, 128.8, 128.5, 128.4, 127.9, 127.8, 126.7, 126.5, 62.3, 60.3, 52.1, 37.8, 27.1, 19.4. $[\alpha]_{D}^{21 \text{ oC}} = +3.9 \text{ (CHCl}_{3}, c = 1). \text{ IR (ATR)} \tilde{\nu} = 3386 \text{ cm}^{-1}$ (w), 3065 (w), 2931 (m), 1593 (w), 1491 (w), 1427 (w), 1256 (w), 1104 (s), 936 (w), 722 (s), 740 (s). MS (EI, 70 eV) m/z (%) 480.6

(11) $[M^+]$, 422.4 (76) $[(M - t \cdot Bu)^+]$, 312.4 (82) $[(M - CHPh_2)^+]$, 234.3 (100), 198.2 (54), 167.2 (43) $[CHPh_2^+]$, 135.2 (40). MS (ESI, Orbitrap) m/z 502.2 (M + Na⁺), 480.3 (M + H⁺). HRMS (ESI, Orbitrap) calcd for $C_{32}H_{38}NOSi^+$ (M + H⁺): 480.27171; found: 480.27063.

(S)-tert-Leucinol (21).³⁰ A 2 L three-necked flask was charged with dry THF (400 mL) and NaBH₄ (19.0 g, 502.4 mmol, 2.5 equiv). Subsequently, L-tert-leucine (20, 27.4 g, 209 mmol) was added in small portions, and weak gas evolution was observed. After cooling the resulting suspension in an ice/ H_2O bath, a solution of iodine (53.0 g, 209 mmol, 1.0 equiv) in dry THF (100 mL) was added dropwise resulting in vigorous gas evolution. When the addition of iodine was complete, the resulting white suspension was stirred at 100 °C for 19 h (overnight). Afterward, the reaction mixture was cooled to rt, and MeOH was added dropwise until no more gas evolution was observed and clear solution was obtained. All solvents were removed under reduced pressure to afford a white paste. The resulting crude material was taken up with 20% aqueous KOH solution (415 mL) and stirred at rt for 4 h. This mixture was subsequently extracted with CH₂Cl₂ (4 \times 250 mL). Combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting oily residue was purified by Kugelrohr distillation affording the final product 21 (22.57 g, 193 mmol, 92%) as a colorless jelly-like substance solidifying at +7 °C. The product contained an unknown impurity. $R_f = 0.28 (CH_2Cl_2/$ MeOH = 9/1, [ninhydrin]). ¹H NMR (600 MHz, CDCl₃): δ 3.64 (dd, J = 10.5, 3.6 Hz, 1H, 3.16 (dd, J = 10.5, 9.8 Hz, 1H), 2.45 (dd, J = 9.8, 10.5 Hz), 2.45 (dd, J = 10.5, 9.8 Hz), 2.45 (dd, J = 10.5, 10.5 \text{ Hz}), 2.45 (dd, J = 10.5, 10.5 \text{ Hz})), 2.45 (dd, J = 10.5, 10.5 \text{ Hz} 3.6 Hz, 1H), 2.30 (bs, 3H), 0.82 (s, 9H). ¹³C NMR (151 MHz, CDCl₃): δ 62.3, 61.6, 33.0, 26.2. $[\alpha]_{D}^{25 \circ C} = +36.2$ (CH₃Cl, c = 1) $\alpha_D^{25 \circ C} = +38.2$ [CH₃Cl, c = 1]). This is a known compound. (Lit.³ Spectroscopic data agree with those reported in the literature.

(2S)-1-[tert-Butyl(diphenyl)silyl]oxy-3,3-dimethyl-2-butanamine (22). Aminoalcohol 21 (3.05 g, 26 mmol) and imidazole (5.31 g, 78 mmol, 3.0 equiv) were dissolved in MeCN (109 mL, HPLC-grade). After addition of TBDPSCl (13.5 mL, 14.3 g, 52 mmol, 2.0 equiv), the resulting solution was stirred at rt under Ar for 2 h. The solvent was removed under reduced pressure, and the crude product (gummy mass) was purified by flash column chromatography (Si, 5.0×20 cm, $CH_2Cl_2/MeOH = 97/3 \rightarrow 95/5$). The final product 22 (4.08 g, 11.5 mmol, 44%) was obtained as a colorless oil. The corresponding hydrochloride salt was isolated as a slightly more polar fraction. This HCl salt was dissolved in CH₂Cl₂ (150 mL) and washed with saturated aq. NaHCO₃ (3×150 mL) solution. The combined aqueous phases were extracted with CH₂Cl₂ (50 mL). The combined organic phases were dried over MgSO4, and the solvent was removed under reduced pressure to give an additional portion of the product 22 (3.29 g, 9.2 mmol, 36%). The total yield of 22 was 80% (7.37 g, 20.7 mmol). $R_f =$ $0.5 (CH_2Cl_2/MeOH = 9/1, [UV, ninhydrin]).$ ¹H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4H), 7.44–7.35 (m, 6H), 3.79 (dd, J = 9.6, 3.2 Hz, 1H), 3.45 (virt t, J = 9.6 Hz, 1H), 2.63 (dd, J = 8.8, 2.8 Hz, 1H), 1.53 (br s, 2H), 1.06 (s, 9H), 0.82 (s, 9H). ¹³C NMR (151 MHz, CDCl₃) δ 135.74, 135.72, 133.8, 133.7, 129.83, 129.80, 127.85, 127.83, 66.0, 61.8, 33.0, 27.0, 26.7, 19.4. $[\alpha]_{\rm D}^{21} \,^{\circ \rm C} = +18.4$ (CH₃Cl, c = 1). IR (ATR) $\tilde{\nu} = 3069 \text{ cm}^{-1}$ (w), 2952 (s), 2861 (s), 2329 (w), 2111 (w), 1588 (w), 1470 (s), 1427 (m), 1391 (m), 1361 (m), 1189 (w), 1106 (s), 1171 (s), 999 (m), 938 (w), 820 (s), 735 (s), 700 (s). MS (EI, 70 eV) m/z (%) 356.4 (30) [M⁺], 298.3 (100) [(M - t-Bu)⁺], 198.2 (77), 178.2 (12), 135.1 (15), 86.2 (52), 57.3 (23). MS (ESI, Orbitrap) m/z 733.4 [2M + Na⁺], 711.5 [2M + H⁺], 378.2 [M + Na⁺], 356.2 [M + H^+], 278.2 [(M – Ph)⁺]. HRMS (ESI, Orbitrap) calcd for $C_{22}H_{34}NOSi^+$ [M + H⁺]: 356.24042; found: 356.24023.

3-((tert-Butyldiphenylsilyl)oxy)propan-1-amine (24). TBDPSCI (7.57 mL, 8.0 g, 29.1 mmol) was added to a solution of 3-amino-1propanol 23 (2.66 mL, 2.62 g, 34.9 mmol, 1.2 equiv) in MeCN (HPLC-Grade, 160 mL), and the resulting solution was stirred under Ar for 45 h. The solvent was removed in vacuo and the resulting crude mixture purified by flash column chromatography (Si, 7.5 × 16 cm, CH₂Cl₂/MeOH = 9/1), affording the hydrochloride salt of the desired product as a yellowish solid. This material was dissolved in H₂O (200 mL), and the resulting solution titrated with aqueous NaOH (1 M) until pH > 10 was reached. This solution was extracted with CH₂Cl₂ (4 × 90 mL), and the combined organic layers were washed with H₂O (2 × 150 mL) and brine (150 mL). After drying over Na₂SO₄ and evaporation of the solvent under reduced pressure, the desired product **24** (7.93 g, 25.3 mmol, 87%) was obtained as yellowish oil. $R_f = 0.26$ (CH₂Cl₂/MeOH = 9/1, [UV, ninhydrin]). ¹H NMR (400 MHz, CDCl₃): δ 7.69–7.64 (m, 4H), 7.45–7.35 (m, 6H), 3.75 (t, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 6.7 Hz, 2H), 1.74–1.66 (m, 2H), 1.30 (bs, 2H), 1.05 (s, 9H). ¹³C NMR (101 MHz, CDCl₃): δ 135.5, 133.8, 129.6, 127.6, 61.9, 39.3, 36.2, 26.9, 19.1.IR: $\tilde{\nu}$ = 3059 (m), 2937 (vs), 2864 (s), 1589 (w), 1468 (m), 1429 (m), 1385 (m), 1102 (vs), 818 (m), 704 (s), 612 (m), 503 (s). MS (ESI): *m*/*z* = 314.19 [M + H⁺], 236.15 [(M – Ph)⁺]. HRMS (ESI, Orbitrap): calcd for C₁₉H₂₈NOSi⁺ [M + H⁺]: 314.19347; found: 314.19357. Spectroscopic data do not agree with those reported in the literature.⁴⁰ We assume that the compound reported in the literature is the hydrochloride salt of amine **24**.

(S)-N-(1-((tert-butyldiphenylsilyl)oxy)-3,3-dimethylbutan-2-yl)-1H-imidazole-1-carboximidamide (25). Guanylating reagent 6 (45.3 mg, 281 μ mol) was added to a flask containing a solution of aminoalcohol 22 (120 mg, 337 µmol, 1.2 equiv) in THF (reagent grade, 1.8 mL). The reaction mixture was stirred at 40 °C for 120 h in an open flask, so that a slow evaporation of the solvent and concentration of reaction mixture was achieved. Afterward, the remaining solvent was removed in vacuo, and the crude product was purified by flash column chromatography (Si, 1.8×19 cm, pentane/ EtOAc = 1/4) affording the product 25 (78.8 mg, 175 μ nol, 62%) as a white foam. The final product contained the residual ethyl acetate and some unidentified impurities (estimated purity ca. 90%). $R_f = 0.45$ (P/ EtOAc = 1/4 [UV, bromocresol green]). Due to the very low concentration of the sample, some signals cannot be seen in the ¹³C NMR spectrum. ¹H NMR (600 MHz, CD₃OD) δ 8.16 (bs, 1H), 7.69 (dd, J = 8.0, 1.4 Hz, 2H), 7.67 (dd, J = 8.0, 1.4 Hz, 2H), 7.58 (bs, 1H), 7.45-7.32 (m, 6H), 7.05 (bs, 1H), 3.99 (dd, J = 10.0, 2.9 Hz, 1H), 3.69-3.63 (bm, 1H), 3.49-3.37 (bm, 1H), 1.01 (s, 9H), 0.89 (s, 9H). ^{13}C NMR (151 MHz, CD₃OD) δ 136.72, 136.70, 130.9, 130.8, 128.8, 128.7, 118.8, 35.2, 27.3, 19.9. MS (ESI): $m/z = 471.25 [M + Na^+]$, 449.27 [M + H⁺], 371.22 [(M – Ph)⁺]. HRMS (ESI, Orbitrap): calcd for C₂₆H₃₇N₄OSi⁺ [M + H⁺]: 449.27311; found: 449.27155. Due to the fact that this intermediate was not used for the synthesis of the target guanidine, IR spectroscopic data and optical rotation were not collected

N-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-1H-imidazole-1-carboximidamide (26). Guanylating reagent 6 (1.27 g, 7.87 mmol) was added to a flask containing a solution of aminoalcohol 24 (2.96 g, 9.44 mmol, 1.2 equiv) in THF (reagent grade, 36 mL). The reaction mixture was stirred at 40 °C for 23 h in an open flask to allow a slow evaporation of the solvent and concentration of the reaction mixture. Afterward, the remaining solvent was removed in vacuo, and the crude product was purified by column chromatography (Si, 4.8 × 18.5 cm, $CH_2Cl_2/MeOH = 92/8$) affording the desired product (2.46 g, 6.05) mmol, 77%) as a white foam. The final product contained some unidentified impurities (estimated purity ca. 95%). $R_f = 0.37 (CH_2Cl_2/$ MeOH = 9/1 [UV, bromocresol green]). ¹H NMR (600 MHz, CD₃OD) δ 8.08 (bs, 1H), 7.71-7.64 (m, 4H), 7.49 (bs, 1H), 7.40-7.30 (m, 6H), 7.01 (bs, 1H), 3.81 (t, J = 6.3 Hz, 2H), 3.38 (t, J = 6.3Hz, 2H), 1.91 (quint, J = 6.3 Hz, 2H), 1.05 (s, 9H). ¹³C NMR (151 MHz, CD₃OD) δ 149.3, 136.7, 136.6, 134.7, 130.8, 129.3, 128.7, 118.5, 62.4, 41.9, 33.4, 27.5, 20.0. IR: $\tilde{\nu} = 3015$ (m), 2968 (m), 2168 (w), 1979 (w), 1739 (vs), 1437 (m), 1366 (s), 1217 (s), 1097 (m), 909 (w), 739 (w), 696 (w). MS (ESI): $m/z = 407.22 [M + H^+]$, 329.18 $[(M - Ph)^+]$. HRMS (ESI, Orbitrap): calcd for $C_{23}H_{31}N_4OSi^+$ [M + H⁺]: 407.22616; found: 407.22485.

(S)-6-(tert-Butyl)-2,2,15,15-tetramethyl-3,3,14,14-tetraphenyl-4,13-dioxa-7,9-diaza-3,14-disilahexadecan-8-iminium Trifluoroacetate/Hydroxide (**27·TFA/27·H**₂**O**).⁴¹ To a flask containing a solution of aminoalcohol **22** (550 mg, 1.54 mmol) in 20 mL CH₂Cl₂, the unsymmetrical guanylating reagent **26** (1.26 g, 3.09 mmol, 2.0 equiv) was added. After stirring the resulting mixture for 5 min, the solvent was removed under reduced pressure, and TFA (115 μ L, 176 mg, 1.54 mmol, 1.0 equiv) was added. The resulting mass was mixed in a Kugelrohr oven at 115 °C for 2 h under Ar. The resulting crude gummy mass was purified by column chromatography (Si, 3.0×19 cm, CH₂Cl₂/MeOH = 97/3) to remove the impurities which were more polar than the obtained product. This prepurified mixture was subjected to another chromatographic purification (Al neutral, 3.0×19 cm, CH₂Cl₂/MeOH = 97/3) to separate the final product from unreacted aminoalcohol **22**. The product **27**•**TFA** (687 mg, 850 μ mol, 55%) was obtained as an off-white foam and contained residual CH₂Cl₂ and some unidentified impurities (estimated purity ca. 95%).

The following analytical data are given for the trifluoroacetate salt **27·TFA.** $R_f = 0.18$ (Si, CH₂Cl₂/MeOH = 97/3 [UV, bromocresol green]) $R_f = 0.23$ (Al, CH₂Cl₂/MeOH = 97/3 [UV, bromocresol green]) ¹H NMR (600 MHz, CD₃OD) δ 7.71–7.64 (m, 8H), 7.45–7.36 (m, 12H), 3.92 (dd, J = 10.2, 2.7 Hz, 1H), 3.76 (t, J = 5.7 Hz, 2H), 3.63–3.59 (m, 1H), 3.58–3.55 (m, 1H), 3.45–3.36 (m, 2H), 1.85 (m, 2H), 1.05 (s, 9H), 1.04 (s, 9H), 0.92 (s, 9H). ¹³C NMR (151 MHz, CD₃OD) δ 158.7, 136.63, 136.61, 136.57, 134.5, 133.98, 133.95, 131.1, 131.0, 128.99, 128.95, 128.87, 64.8, 63.8, 62.0, 39.7, 34.7, 32.9, 27.4, 27.3, 26.9, 20.0, 19.9. ¹⁹F NMR (564 MHz, CD₃OD) δ –76.7 (s).

The optical rotation is given for the corresponding hydroxide salt of **27** (**27**·**H**₂**O**).⁴² $[\alpha]_{D}^{29 \circ C} = -46.7$ (CH₃Cl, c = 1). IR: $\tilde{\nu} = 3060$ (w), 2948 (m), 2864 (m), 1739 (m), 1640 (m), 1468 (m), 1427 (m), 1366 (m), 1202 (m), 1102 (vs), 1001 (m), 818 (m), 697 (vs). MS (ESI): $m/z = 694.42 [(M - CF_{3}COO^{-})^{+}], 616.38 [(M - CF_{3}COO^{-} - H^{+} - Ph)^{+}].$ HRMS (ESI, Orbitrap): calcd for C₄₂H₆₀N₃O₂Si₂⁺ [(M - CF_{3}COO^{-})^{+}]; 694.42186; found: 694.42377.

(S)-((1-Hydroxy-3,3-dimethylbutan-2-yl)amino)((3-hydroxy-propyl)amino)methaniminium Fluoride (**28**).⁴³ To a flask containing a solution of protected guanidine 27. TFA (685 mg, 848 μ mol) in absolute MeCN (16 mL), fluoride on polymer (848 mg, 2.54 mmol, 3 equiv; 3.0 mmol/g loading on Amberlite IRA-900 resin; obtained from a commerical source) was added, and the resulting mixture was stirred under an Ar atmosphere at rt overnight. During the course of this reaction, temporary clotting of the polymer beads was observed. Subsequently, fluoride on polymer beads were filtered off and washed with MeOH, and all solvents were removed under reduced pressure. The residue was dissolved in MeOH (3 mL). Upon dropwise addition of Et₂O to this solution, the product 28 precipitated as a heavy colorless oil. Addition of Et₂O (ca. 3-4 mL) was continued until no more oil formation was observed. The resulting mixture was gently mixed on rotary evaporator for 1 h resulting in even distribution of the precipitate on the wall of the flask. After subsequent decantation of the solvent, washing of the oily residue with Et_2O (4 × 20 mL) and drying under reduced pressure, the guanidinium salt 28 was obtained as a colorless syrup (191 mg, 805 µmol, 95%). Isolated product was obtained in ca. 95% purity and contained traces of solvents and small amounts of the starting material 27. TFA or the corresponding monodeprotected intermediates. $R_f = 0.00$ (CH₂Cl₂/MeOH = 9/1 [bromocresol green]). ¹H NMR (600 MHz, CD₃OD) δ 3.86 (dd, J = 11.2, 3.1 Hz, 1H), 3.67–3.63 (m, 2H), 3.47 (dd, J = 11.2, 9.1 Hz, 1H), 3.38-3.33 (m, 3H), 1.83-1.77 (m, 2H), 0.98 (s, 9H). ¹³C NMR (151 MHz, CD₃OD) δ 159.13, 64.3, 62.6, 59.5, 39.6, 35.0, 32.6, 27.0. ¹⁹F NMR (564 MHz, CD₃OD) δ -139.6 (s, 1F). $[\alpha]_{D}^{29 \circ C} = -46.7$ (MeOH, c = 1). IR: $\tilde{\nu} = 3432$ (b, vs), 2922 (s), 2856 (m), 1640 (s), 1448 (vs), 1384 (vs), 1234 (m), 1059 (s), 875 (w), 668 (m). MS (ESI): $m/z = 240.17 [(M - F^{-} - H^{+} + Na^{+})^{+}], 218.19 [(M - F^{-})^{+}].$ HRMS (ESI, Orbitrap): calcd for $C_{10}H_{24}N_3O_2^+$ [(M - F⁻)⁺]: 218.18630: found: 218.18666.

(S)-((1-Chloro-3-methylbutan-2-yl)amino)((3-chloropropyl)amino)methaniminium Fluoride (29).⁴⁴ To a flask containing a solution of guanidinium salt 28 (203 mg, 855 μ mol) in absolute MeCN (16 mL), thionyl chloride (374 μ L, 611 mg, 5.1 mmol, 6 equiv) was added. The solution was stirred at 60 °C for 21 h. After addition of MeOH (20 mL), the resulting mixture was stirred for 40 min at rt. The solvents were removed under reduced pressure to give the crude product 29 as a yellowish solid. The crude product contained unknown impurities. It was characterized and subjected to the next reaction step without purification. The two-step yield was determined after the subsequent cyclization step. $R_f = 0.18$ (CH₂Cl₂/ MeOH = 9/1 [bromocresol green, KMnO₄]) ¹H NMR (600 MHz, CD₃OD) δ = 3.97 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.72 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.67 (t, *J* = 6.3 Hz, 2H), 3.59 (dd, *J* = 11.0 Hz, 1H), 3.47–3.39 (m, 2H), 2.07 (quint, *J* = 6.3 Hz, 2H), 1.01 (s, 9H). ¹³C NMR (151 MHz, CD₃OD) δ 158.7, 63.8, 46.1, 42.5, 40.0, 36.6, 32.7, 26.6. ¹⁹F NMR (564 MHz, CD₃OD) δ -154.2 (s, 1F). $[\alpha]_{D}^{29 \circ C} = -9.2$ (MeOH, *c* = 1). IR: $\tilde{\nu}$ = 2963 (m), 1633 (vs), 1446 (m), 1372 (m), 1284 (w), 1219 (w), 1001 (w), 728 (m). MS (ESI): *m*/*z* = 254.12 [M - F⁻]. HRMS (ESI, Orbitrap): calcd for C₁₀H₂₂N₃Cl₂⁺ [M - F⁻]: 254.11853; found: 254.11768.

(S)-3-(tert-Butyl)-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyrimidin-8-ium Chloride (**30**).⁴⁵ To a flask containing a suspension of crude guanidinium salt 29 (855 μ mol considering quantitative yield of the previous step) in dry MeCN (9.8 mL), DBU (511 µL, 521 mg, 3.4 mmol, 4 equiv) was added. The resulting dark brown solution was stirred under Ar at rt overnight. The reaction mixture was acidified with HCl solution (1.25 M in MeOH) to pH 1-2, and the solvents were removed under reduced pressure. The resulting crude product was purified by column chromatography (Si, 3×16.5 cm, EtOAc/ MeOH = 7/3). The isolated material (product contaminated with silica particles) was suspended in MeCN, and the silica was filtered off. Solvent was evaporated to give a yellowish oil (125 mg, 574 μ mol, 67% over 2 steps) which consisted of two regioisomers 30 and 7 (30/7 =92/8, determined by ¹H NMR). $R_f = 0.18$ (EtOAc/MeOH = 7/3 [bromocresol green, KMnO₄]). $[\alpha]_D^{29 \circ C} = -12.6$ (MeOH, c = 0.27). IR: $\tilde{\nu} = 2953$ (m), 1668 (vs), 1612 (vs), 1472 (m), 1373 (w), 1323 (w), 1285 (w), 1190 (w). MS (ESI): $m/z = 182.16 [M - Cl^{-}]$, 124.09 $[(M - Cl^{-} - C(CH_3)_3)^+]$. HRMS (ESI, Orbitrap): calcd for $C_{10}H_{20}N_3^+$ $[M - Cl^{-}]$: 182.16517; found: 182.16415.

NMR data of the regioisomer **30** (major isomer): ¹H NMR (600 MHz, CD₃OD) δ 3.78–3.68 (m, 2H), 3.51 (dd, *J* = 9.2, 6.7 Hz, 1H), 3.36–3.33 (m, 4H), 2.09–1.97 (m, 2H), 0.92 (s, 9H). ¹³C NMR (151 MHz, CD₃OD) δ 156.8, 63.9, 51.1, 42.8, 39.2, 34.4, 25.3, 21.4.

NMR data of the minor regioisomer, which is supposed to be the salt 7, is presented. This regioisomer was not isolated in pure form, and therefore only characteristic signals of the *t*-butyl rest are given. ¹H NMR (600 MHz, CD₃OD) δ 1.02 (s, 9H). ¹³C NMR (151 MHz, CD₃OD) δ 26.3.

(Š)-1-(1-Chloro-3,3-dimethylbutan-2-yl)tetrahydropyrimidin-2(1H)-iminium Chloride (**31**). Monocyclized guanidinium salt **31** (63 mg, 248 μ mol, 29% over 2 steps) was isolated as a minor reaction product as an off-white solid. The structure and relevant signal assignments were performed using HSQC and HMBC (see Supporting Information). $R_f = 0.37$ (EtOAc/MeOH = 7/3 [bromocresol green, KMnO₄]). ¹H NMR (600 MHz, CD₃OD) δ 3.95 (dd, J = 10.7, 2.0 Hz, 1H, CHHCl), 3.60–3.51 (m, 2H, NCHtBu and CHHCl), 3.40–3.37 (m, 4H, 2 × CH₂N), 1.99–1.93 (m, 2H, CH₂CH₂CH₂), 1.00 (s, 9H). ¹³C NMR (151 MHz, CD₃OD) δ 155.5, 63.2 (CH), 46.2 (CH₂), 39.8 (CH₂), 36.6 (CH₂), 26.6, 21.3 (CH₂). IR: $\tilde{\nu} = 2952$ (m), 2865 (m), 1644 (vs), 1460 (m), 1376 (w), 1318 (w), 1203 (m), 1118 (w), 725 (m). MS (ESI): m/z = 220.14 [M (³⁷Cl) - Cl⁻], 218.14 [M (³⁵Cl) - Cl⁻], 182.16 [(M - 2Cl⁻ - H⁺)⁺]. HRMS (ESI, Orbitrap): calcd for C₁₀H₂₁N₃Cl⁺ [M (³⁵Cl) - Cl⁻]: 218.14130.

(S)-7-Benzhydryl-2,2,16,16-tetramethyl-3,3,15,15-tetraphenyl-4,14-dioxa-8,10-diaza-3,15-disilaheptadecan-9-iminium 2,2,2-tri*fluoroacetate* (**32**).⁴⁷ To a flask containing a solution of aminoalcohol 19 (470 mg, 980 μ mol) in CH₂Cl₂ (20 mL), the unsymmetrical guanylating reagent 26 (797 mg, 1.96 mmol, 2.0 equiv) was added. After stirring the resulting mixture for 5 min, the solvent was removed under reduced pressure, and TFA (72.8 µL, 112 mg, 980 µmol, 1.0 equiv) was added. The resulting mass was mixed in a Kugelrohr oven at 115 °C for 2 h under Ar. The resulting crude gummy mass was purified by column chromatography (Si, 3.0 \times 18.5 cm, CH₂Cl₂/ MeOH = 97/3) to remove the impurities, which were more polar than the obtained product. This prepurified mixture was subjected to another chromatographic purification (Al neutral, 3.0×19.5 cm, $CH_2Cl_2/MeOH = 97/3$) to separate the final product from unreacted aminoalcohol 19. The product 32 (355 mg, 381 μ mol, 39%) was obtained as a white foam. $R_f = 0.37$ (Si, CH₂Cl₂/MeOH = 97/3 [UV, bromocresol green]) $R_f = 0.43$ (Al, $CH_2Cl_2/MeOH = 97/3$ [UV,

bromocresol green]). A significant signal broadening was observed in the ¹H NMR spectrum. A possible explanation for this effect is the aggregate formation or hindered rotation due to steric bulk of protecting groups. ¹H NMR (400 MHz, CD₃OD): δ 7.75–7.02 (m, 30H), 4.61–4.50 (bm, 1H), 4.07 (bd, *J* = 10.8 Hz, 1H), 3.83–3.73 (bm, 1H), 3.72–3.64 (bm, 1H), 3.59–3.51 (bm, 2H), 3.17–2.97 (bm, 2H), 1.90–1.78 (bm, 1H), 1.65–1.42 (bm, 3H), 1.03 (bs, 18H). ¹³C NMR (151 MHz, CD₃OD): δ 157.7, 143.1, 142.7, 136.5, 136.44, 136.36, 134.4, 133.9, 133.8, 131.0, 130.9, 130.0, 129.6, 129.14, 129.09, 128.9, 128.83, 128.81, 128.0, 127.8, 62.6, 61.8, 58.6, 54.3, 39.2, 37.2, 32.4, 27.5, 27.4, 19.92, 19.87. ¹⁹F NMR (564 MHz, CD₃OD): δ –76.3 (s, 3F). [*α*]_D^{29 °C} = +28.1 (CHCl₃, *c* = 2.5). IR: $\tilde{\nu}$ = 3058 (w), 2938 (m), 2863 (m), 1677 (m), 1593 (m), 1465 (m), 1427 (m), 1379 (w), 1189 (m), 1100 (vs), 999 (m), 820 (m), 697 (m). MS (ESI): *m*/*z* = 818.45 [M - CF₃COO⁻]. HRMS (ESI, Orbitrap): calcd for C₅₂H₆₄N₃O₂Si₂⁺ [M - CF₃COO⁻]: 818.45316; found: 818.44891.

(S)-((4-Hydroxy-1,1-diphenylbutan-2-yl)amino)((3-hydroxy-propyl)amino)methaniminium Fluoride (**33**).⁴³ To a flask containing a solution of protected guanidine 32 (344 mg, 370 μ mol) in absolute MeCN (7.2 mL), fluoride on polymer (370 mg, 1.11 mmol, 3 equiv; 3.0 mmol/g loading on Amberlite IRA-900 resin; obtained from a commerical source) was added, and the resulting mixture was stirred under an Ar atmosphere at rt overnight. During the course of this reaction, temporary clotting of the polymer beads was observed. Subsequently, fluoride on polymer beads was filtered off and washed with MeOH (10 mL), and all solvents were removed under reduced pressure. The residue was dissolved in 1.5 mL MeOH (1.5 mL). Upon dropwise addition of Et₂O to this solution, the product 33 precipitated as a heavy colorless oil. Addition of Et₂O was continued until no more oil formation was observed. The resulting mixture was gently mixed on rotary evaporator for 1 h resulting in even distribution of the precipitate on the wall of the flask. After subsequent decantation of the solvent, washing of the oily residue with Et_2O (3 × 15 mL) and drying under reduced pressure, the guanidinium salt 33 was obtained as a white foam (132 mg). Isolated product was obtained in ca. 95% purity and contained traces of solvents and small amounts of the starting material 32 or the corresponding monodeprotected intermediates. Taking this into account, the estimated amount of the product was approximately 125 mg (347 μ mol, 95%). $R_f = 0.00 (CH_2Cl_2/MeOH =$ 9/1 [UV, bromocresol green]). A significant signal broadening was observed in the ¹H NMR spectrum. A possible explanation for this effect is the aggregate formation or hindered rotation due to steric bulk of protecting groups. ¹H NMR (600 MHz, CD₃OD): δ 7.40 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 4.63-4.54 (bm, 1H), 4.03 (bd, J = 9.7 Hz, 1H), 3.65-3.59 (bm, 1H), 3.55 (td, J = 10.6, 4.3 Hz, 1H), 3.52–3.41 (bm, 2H), 3.19–2.87 (bm, 2H), 1.90-1.82 (m, 1H), 1.62-1.40 (bm, 3H). ¹³C NMR (151 MHz, CD₃OD): δ 158.1, 143.6, 143.0, 129.9, 129.6, 129.2, 127.9, 127.8, 59.5, 59.3, 58.7, 54.0, 39.3, 37.2, 32.3. ¹⁹F NMR (564 MHz, CD₃OD): δ -144.2 (s, 1F). $[\alpha]_D^{31} \sim^{C} = +53.2$ (MeOH, c = 2). IR: $\tilde{\nu} = 3060$ (w), 3029 (w), 2946 (w), 1635 (vs), 1492 (m), 1451 (m), 1367 (w), 1063 (s), 749 (s), 698 (vs). MS (ESI): $m/z = 364.20 [M - F^{-} - H^{+} + Na^{+}]$, 342.22 $[M - F^-]$. HRMS (ESI, Orbitrap): calcd for $C_{20}H_{28}N_3O_2^+$ [M- F⁻]: 342.21760; found: 342.21649.

(S)-((4-Chloro-1,1-diphenylbutan-2-yl)amino)((3-chloropropyl)amino)methaniminium Chloride (34).⁴⁴ To a flask containing a mixture of guanidinium salt 33 (133 mg, 368 µmol) in CHCl₃ (6.9 mL, HPLC grade), thionyl chloride (161 µL, 263 mg, 2.2 mmol, 6.0 equiv) was added. The mixture was stirred at 60 °C for 2.5 h. After cooling to rt and addition of MeOH (12 mL), the resulting mixture was stirred for 25 min at rt. The solvents were removed under reduced pressure to give the intermediate 34 as a yellowish foam (150 mg). This crude material was characterized and used in the next step without additional purification. $R_f = 0.30$ (CH₂Cl₂/MeOH = 9/1 [UV, bromocresol green]). ¹H NMR (400 MHz, CD₃OD): δ 7.47 (d, J = 7.4 Hz, 2H), 7.41 (d, J = 7.4 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.31– 7.16 (m, 4H), 4.70–4.59 (m, 1H), 4.03 (d, J = 10.9 Hz, 1H), 3.68– 3.54 (m, 2H), 3.45 (t, J = 5.7 Hz, 2H), 3.16 (t, J = 6.6 Hz, 2H), 2.12– 2.00 (m, 1H), 1.99–1.87 (m, 1H), 1.84–1.70 (bm, 2H). ¹³C NMR $\begin{array}{l} (101 \text{ MHz}, \text{CD}_3\text{OD}): \delta \ 157.4, 143.0, 142.4, 130.1, 129.6, 129.5, 129.2, \\ 128.2, 128.1, 59.4, 54.8, 42.4, 42.0, 39.6, 37.8, 32.6. <math display="inline">[\alpha]_D^{31 \text{ oC}} = +57.2 \\ (\text{MeOH}, \ c = 2). \ \text{IR}: \ \tilde{\nu} = 3162 \ (\text{m}), 2960 \ (\text{w}), 2876 \ (\text{w}), 1634 \ (\text{vs}), \\ 1494 \ (\text{m}), 1449 \ (\text{m}), 1290 \ (\text{m}), 1123 \ (\text{m}), 750 \ (\text{m}), 700 \ (\text{vs}). \ \text{MS} \\ (\text{ESI}): \ m/z = 382.14 \ [\text{M} \ (2 \times {}^{37}\text{Cl}) - \text{Cl}^-], 380.15 \ [\text{M} \ ({}^{35}\text{Cl}, {}^{37}\text{Cl}) - \\ \text{Cl}^-], 378.15 \ [\text{M} \ (2 \times {}^{35}\text{Cl}) - \ \text{Cl}^-]. \ \text{HRMS} \ (\text{ESI, Orbitrap}): \ \text{calcd for} \\ \ C_{20}H_{26}N_3\text{Cl}_2^+ \ [\text{M} \ (2 \times {}^{35}\text{Cl}) - \ \text{Cl}^-]: \ 378.14983; \ \text{found:} \ 378.14871. \end{array}$

(S)-2-Benzhydryl-2,3,4,6,7,8-hexahydro-1H-pyrimido[1,2-a]-pyrimidin-9-ium Chloride (8).⁴⁵ To a flask containing a solution of crude dichloride intermediate (61 mg, ca. 147 µmol) in dry CH₂Cl₂ (4.7 mL), DBU (91.3 µL, 93.1 mg, 612 µmol, 4.2 equiv) was added. The resulting solution was stirred at rt for 3 h. The reaction mixture was acidified with HCl solution (1.25 M in MeOH), and the solvents were removed under reduced pressure. The resulting crude product was purified by column chromatography (Si, 1.8 cm × 14.5 cm, EtOAc/MeOH = 7/3). After evaporation of solvents, the isolated material (product containing silica particles) was suspended in MeCN, and silica was filtered off. Solvent was evaporated to give the bicyclic guanidinium salt 8 (22 mg, 64 μ mol, 44%) as a white foam. Crystals suitable for X-ray analysis were obtained by dissolving this material in MeCN followed by slow evaporation at rt over several days.³² $R_f = 0.32$ (EtOAc/MeOH = 7/3 [UV, bromocresol green, KMnO₄]). ¹H NMR (600 MHz, CD₃OD): δ 7.47 (d, I = 7.3 Hz, 2H), 7.39–7.34 (m, 4H), 7.31 (t, J = 7.7 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 4.38 (ddd, J = 11.2, 7.8, 3.6 Hz, 1H), 3.96 (d, J = 11.2 Hz, 1H), 3.39-3.36 (m, 4H), 3.29-3.21 (m, 2H), 2.03-1.96 (m, 2H), 1.89-1.83 (m, 1H), 1.79–1.72 (m, 1H). ¹³C NMR (151 MHz, CD₃OD): δ 152.3, 142.5, 141.9, 130.2, 130.0, 129.4, 129.0, 128.4, 128.2, 58.0, 52.6, 47.7, 46.6, 39.0, 26.3, 21.5. $[\alpha]_D^{\text{21-C}} = +5.5$ (MeOH, c = 0.47). IR: $\tilde{\nu} =$ 3029 (s), 2943 (s), 1630 (vs), 1520 (m), 1495 (m), 1449 (m), 1320 (m), 1082 (m), 755 (m), 704 (s). MS (ESI): m/z = 306.20 [M - Cl^{-}], 138.10 [(M – H⁺ – Cl⁻ – CHPh₂)⁺]. HRMS (ESI, Orbitrap): calcd for $C_{20}H_{24}N_3^+$ [M - Cl⁻]: 306.19647; found: 306.19604.

Additionally, a mixture consisting of the desired product 8 and regioisomer **35** (8/**35** = 3/1 based on ¹H NMR analysis) was isolated. Compound **35** could not be obtained in pure form, and thus only partial assignment of its signals in NMR spectra was possible. $R_f = 0.40$ (EtOAc/MeOH = 7/3 [UV, bromocresol green, KMnO₄]) ¹H NMR (600 MHz, CD₃OD): δ 4.19 (d, J = 11.5 Hz, 1H), 3.19–3.13 (m, 2H), 3.03–2.97 (m, 1H), 2.26 (ddd, J = 12.2, 7.5, 11.5 Hz, 1H), 1.63–1.56 (m, 1H), 1.40–1.32 (m, 1H). ¹³C NMR (151 MHz, CD₃OD): δ 152.2, 143.0, 141.9, 130.2, 130.0, 129.9, 129.2, 128.5, 128.3, 61.8, 55.1, 49.5, 39.3, 36.0, 24.0, 21.7.

(6S,10S)-6,10-Di(tert-butyl)-2,2,14,14-tetramethyl-3,3,13,13-tetraphenyl-4,12-dioxa-7,9-diaza-3,13-disilapentadecan-8-iminium 2,2,2-trifluoroacetate (**36**).⁴¹ To a flask containing protected aminoalcohol 22 (2.01 g, 5.65 mmol, 2.0 equiv) and guanylating reagent 6 (456 mg, 2.83 mmol) of CH₂Cl₂ (1 mL) was added, and the resulting mixture was concentrated using a rotary evaporator under reduced pressure at rt. Upon removal of CH₂Cl₂, a suspension containing finely distributed guanylating reagent 6 was obtained. After the addition of TFA (217 µL, 323 mg, 2.83 mmol), the resulting suspension was mixed in a Kugelrohr oven at 105 °C for 4 h. Upon heating, the heterogeneous mixture became a very viscous brownish solution. The resulting crude product was purified by column chromatography (Si, 30×5 cm, CH₂Cl₂/MeOH/AcOH = 100/1/ $0.5 \rightarrow 98/2/0.5$) to give the symmetrically substituted guanidinium salt 36 (1.2 g) as an off-white foam. Isolated product contained approximately 10 to 20 mol % of unknown impurities, which were visible in the ¹H NMR spectrum. Taking this into account, the estimated amount of the pure product was approximately 980 mg (1.13 mmol, 40%). $R_f = 0.31$ (CH₂Cl₂/MeOH/AcOH = 100/8/0.5, [UV, bromocresol green]). ¹H NMR (600 MHz, CDCl₃) δ 9.16 (br s, 2H), 7.61 (d, J = 6.6 Hz, 4H), 7.58 (d, J = 6.6 Hz, 4H), 7.46-7.34 (m, 12H), 6.55 (br s, 2H), 3.94 (d, J = 10.2, 2H), 3.68 (virt t, J = 10.2 Hz, 2H), 3.20 (virt t, J = 8.4 Hz, 2H), 1.05 (s, 18H), 1.01 (s, 18H). ¹³C NMR (151 MHz, CDCl₃) δ 159.6, 135.51, 135.46, 132.1, 131.8, 130.49, 130.45, 128.33, 128.26, 66.8, 60.6, 34.0, 27.13, 27.06, 19.2. ¹⁹F NMR (564 MHz, CDCl₃) δ -75.7 (s, CF₃). $[\alpha]_{D}^{21 \text{ oC}} = -80.2$ (CHCl₃, c = 1). IR (ATR) $\tilde{\nu} = 3317 \text{ cm}^{-1}$ (w), 2956 (m), 2170 (w), 1897 (w),

1640 (s), 1471 (m), 1427 (m), 1367 (w), 1309 (w), 1245 (w), 1197 (m), 1107 (s), 1000 (m), 938 (w), 819 (s), 738 (s), 700 (s). MS (EI, 70 eV) m/z (%) 736.9 (2) $[(M - CF_3COO^{-})^+]$, 678.7 $[(M - CF_3COO^{-} - t-Bu)^+]$ (45), 466.5 (100), 340.3 (12), 224.1 (27), 135.1 (33). MS (ESI, Orbitrap) m/z 736.5 $[(M - CF_3COO^{-})^+]$. HRMS (ESI, Orbitrap) calcd for $C_{45}H_{66}N_3O_2Si_2^+$ $[(M - CF_3COO^{-})^+]$: 736.46881; found: 736.46930.

Bis[(15)-1-(hydroxymethyl)-2,2-dimethylpropyl]aminometh-animinium Fluoride (**37**).⁴³ To a flask containing a solution of protected guanidine 36 (844 mg; due to impurities, estimated amount of the starting material ca. 950 µmol) in MeCN (HPLC-grade, 19 mL), fluoride on polymer (1.2 g, 3.58 mmol, 4 equiv; 3.0 mmol/g loading on Amberlyst A-26 resin; obtained from a commerical source) was added, and the resulting mixture was stirred under Ar atmosphere at rt. During this time, a white precipitate was formed. After 25 h, MeOH was added to the resulting suspension until the formed precipitate completely dissolved. Fluoride on polymer beads were filtered off and washed with additional MeOH (10 mL), and the solvents were removed under reduced pressure. When the resulting crude product (oily mass) was washed with an Et_2O /pentane = 1/5 mixture $(3 \times 5 \text{ mL})$, the product 37 was obtained as a white solid (261 mg, 934 μ mol, 98%: estimated value due to impurities in the starting material). $R_f = 0.0 (CH_2Cl_2/MeOH = 9/1, [bromocresol green]).$ ¹H NMR (400 MHz, CD₃OD) δ 3.91 (dd, J = 10.8, 2.8 Hz, 2H), 3.51 (dd, I = 9.2, 10.8 Hz, 2H, 3.35 (dd, I = 8.8, 2.8 Hz, 2H), 1.01 (s, 18H). ¹³C NMR (151 MHz, CD₃OD) δ 160.4, 65.1, 63.3, 35.0, 27.2. ¹⁹F NMR (376 MHz, CD₃OD) δ –150.6 (s, F⁻). $[a]_{D}^{21 \circ C} = -97.3$ (MeOH, c = 1). Mp 161–164 °C. IR (ATR) $\tilde{\nu} = 3386$ cm⁻¹ (s), 3230 (s), 2956 (s), 2869 (s), 2325 (w), 2103 (w), 1689 (s), 1630 (s), 1523 (m), 1470 (s), 1362 (m), 1303 (m), 1251 (m), 1090 (m), 1056 (s), 1015 (m), 930 (m), 857 (m), 738 (m), 673 (m). MS (EI, 70 eV) m/z (%) 260.4 (100) $[(M - F^{-})^{+}]$, 228.3 (34), 202.3 (25) $[(M - F^{-} - t-Bu)^{+}]$, 57.3 (12) [t-Bu⁺]. MS (ESI, Orbitrap) m/z 260.2 [(M - F⁻)⁺]. HRMS (ESI, Orbitrap) calcd for $C_{13}H_{30}N_3O_2^+$ [(M - F⁻)⁺]: 260.23325; found: 260.23312.

Bis[(15)-1-(chloromethyl)-2,2-dimethylpropyl]aminomethaniminium Chloride (38).⁴⁴ To a flask containing a suspension of guanidinium salt 37 (110 mg, 394 μ mol) in MeCN (HPLC grade, 12 mL), thionyl chloride (343 μ L, 563 mg, 4.7 mmol, 12 equiv) was added. Upon addition of SOCl₂, all solids immediately dissolved, and the resulting mixture was stirred under an Ar atmosphere at 65–70 °C for 24 h. It is highly recommended to monitor the reaction progress by TLC using KMnO₄ staining reagent (a very characteristic and intensive staining of the product), since starting material and product are not UV active and using bromocresol green gave a very weak staining. After addition of MeOH (15 mL), the resulting mixture was stirred for 1 h at rt. The solvents were removed under reduced pressure to give the crude product as a yellow solid. The crude product was used without further purification.

A small amount of the crude product (ca. 120 mg) was purified by column chromatography (Si, 2.0×20 cm, CH₂Cl₂/MeOH = $98/2 \rightarrow 95/5$) to give a sample for spectrosopic analyses (66 mg, 198 μ mol) as a yellowish solid. This sample still contained unidentified impurities.

Crystals suitable for X-ray analysis were obtained by dissolving this material in MeOH followed by slow evaporation at rt over several days.³² $R_f = 0.33$ (CH₂Cl₂/MeOH = 9/1, [KMnO₄, bromocresol green]) ¹H NMR (600 MHz, CD₃OD) δ 3.95 (dd, J = 12.0, 3.0 Hz, 2H), 3.79–3.69 (br m, 2H), 3.64–3.55 (br m, 2H), 1.03 (s, 18H). ¹³C NMR (151 MHz, CD₃OD) δ 159.6, 63.9, 46.3, 36.9, 26.7. $[\alpha]_D^{21 \circ C} =$ +0.5 (MeOH, c = 1). Mp decomposes above 220 °C IR (ATR) $\tilde{\nu} =$ 3156 cm⁻¹ (s), 2963 (s), 2411 (m), 2326 (m), 1661 (s), 1620 (s), 1473 (s), 1439 (m), 1368 (m), 1270 (m), 1213 (m), 1095 (m), 1053 (m), 1016 (m), 915 (m), 852 (w), 791 (w), 734 (s). MS (EI, 70 eV) m/z (%) 297.4 (2) [(M – Cl⁻)⁺], 236.1 (100), 200.6 (50). MS (ESI, Orbitrap) m/z 296.2 [(M – Cl⁻)⁺]. HRMS (ESI, Orbitrap) calcd for C₁₃H₂₈Cl₂N₃⁺ [(M – Cl⁻)⁺]: 296.16548; found: 296.16486.

(25,55)-2,5-Di(tert-butyl)-1H,2H,3H,5H,6H,7H-imidazo[1,2-a]imidazol-4-ium Chloride (**39**).⁴⁵ To a flask containing a suspension of crude guanidinium salt **38** (769 μ mol considering quantitative yield of the previous reaction) in MeCN (HPLC grade, 13 mL), DBU (460 μ L, 469 mg, 3.1 mmol, 4 equiv) was added. After addition of DBU, all solids slowly dissolved, and the resulting brown solution was stirred under an Ar atmosphere at rt for 28 h. The reaction mixture was acidified with HCl solution (1 M in MeOH) to pH 1-2, and the solvents were removed under reduced pressure. The resulting crude product (brown sticky mass) was purified by column chromatography (Si, 23 \times 3 cm, EtOAc/MeOH = 20/1 \rightarrow 7/1 \rightarrow 7/3). After evaporation of solvents, the isolated material (product containing silica particles) was suspended in MeCN, and silica was filtered off. Solvent was evaporated to give the final product as a yellowish solid (97 mg, 373 μ mol, 48%). $R_f = 0.41$ (EtOAc/MeOH = 8/2, [bromocresol green]) ¹H NMR (600 MHz, CD₃OD) δ 4.13 (dd, J = 9.6, 3.6 Hz, 1H), 3.96 (virt t, J = 9.6 Hz, 1H), 3.79 (virt t, J = 9.6 Hz, 1H), 3.64 (virt t, J = 9.6 Hz, 1H), 3.62 (dd, J = 9.6, 3.6 Hz, 1H), 3.56 (virt t, J = 9.6, Hz, 1H), 0.99 (s, 9H), 0.96 (s, 9H). ¹³C NMR (101 MHz, CD₃OD) δ 167.4, 73.0, 69.8, 51.8, 49.8, 35.3, 34.0, 26.4, 25.5. ¹H NMR (400 MHz, CDCl₃) δ 9.14 (br s, 1H), 8.85 (br s, 1H), 4.06 (dd, I = 10.0, 3.6 Hz, 1H), 3.93 (virt t, I = 10.0 Hz, 1H), 3.72 (virt t, I =10.0 Hz, 1H), 3.44 (virt t, J = 9.6 Hz, 1H), 3.43 (dd, J = 9.6, 3.6 Hz, 1H), 3.38 (virt t, J = 9.6, Hz, 1H), 0.92 (s, 9H), 0.91 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 166.2, 71.7, 69.1, 50.9, 49.0, 34.5, 33.3, 26.2, 25.3. $[\alpha]_{D}^{21 \circ C} = -18.5$ (MeOH, c = 0.1). Mp decomposes above 200 °C. IR (ATR) $\tilde{\nu} = 2957 \text{ cm}^{-1}$ (s), 1699 (s), 1559 (s), 1471 (s), 1399 (m), 1366 (m), 1272 (s), 1136 (m), 1067 (m), 1024 (m), 934 (w), 843 (m), 714 (m). MS (EI, 70 eV) m/z (%) 224.3 (4) [(M - $Cl^{-})^{+}$], 166.2 (100) [(M - HCl - t-Bu)^{+}], 96.1 (39), 57.2 (28). MS (ESI, Orbitrap) m/z 224.2 [(M - Cl⁻)⁺]. HRMS (ESI, Orbitrap) calcd for $C_{13}H_{26}N_3^+$ [(M - Cl⁻)⁺]: 224.21212; found: 224.21201.

(7S,11S)-7,11-Dibenzhydryl-2,2,16,16-tetramethyl-3,3,15,15-tetraphenyl-4,14-dioxa-8,10-diaza-3,15-disilaheptadecan-9-iminium 2,2,2-trifluoroacetate (**40**).⁴¹ To a flask containing TBDPS-protected aminoalcohol 19 (1.8 g, 3.75 mmol, 2.0 equiv), guanylating reagent 6 (303 mg, 1.88 mmol) and CH₂Cl₂ (1 mL) were added, and the resulting mixture was concentrated on a rotary evaporator under reduced pressure at rt. Upon removal of CH₂Cl₂, a suspension containing finely distributed guanylating reagent 6 was obtained. After the addition of TFA (144 μ L, 214 mg, 1.88 mmol), the resulting suspension was mixed in a Kugelrohr oven at 105 °C for 4 h. Upon heating, the heterogeneous mixture became a very viscous brownish solution. The resulting crude product was purified by column chromatography (Si, 30×5 cm, CH₂Cl₂/MeOH/AcOH = 100/2/ $0.5 \rightarrow 97/3/0.5$) to give the symmetrically substituted guanidinium salt 40 (758 mg, 690 μ mol, 38%) as a brownish oil. $R_f = 0.56$ $(CH_2Cl_2/MeOH/AcOH = 100/8/0.5, [UV, bromocresol green]).$ ¹H NMR (600 MHz, CDCl₃) δ 9.39 (br s, 2H), 7.62 (d, J = 6.6 Hz, 4H), 7.47 (t, J = 7.2 Hz, 8H), 7.41–7.38 (m, 2H), 7.36 (d, J = 7.8 Hz, 4H), 7.33-7.28 (m, 10H), 7.27-7.25 (m, 8H), 7.19 (t, J = 7.2 Hz, 4H), 7.04 (t, J = 7.2 Hz, 2H), 6.25 (br s, 2H), 4.47 (virt q, J = 10.8 Hz, 2H), 4.05 (d, J = 11.4 Hz, 2H), 3.52 (dd, J = 4.2, 10.8 Hz, 2H), 3.34 (virt t, J = 11.4 Hz, 2H), 1.67–1.62 (m, 2H), 1.18–1.12 (m, 2H), 1.03 (s, 9H). $^{13}\mathrm{C}$ NMR (151 MHz, CDCl₃) δ 158.1, 142.2, 141.6, 135.5, 135.4, 133.0, 132.1, 130.47, 130.46, 129.1, 128.8, 128.2, 128.1, 127.9, 127.1, 126.9, 60.3, 56.8, 53.7, 35.1, 27.3, 19.4. ¹⁹F NMR (282 MHz, CDCl₃) δ -75.6 (s, CF₃). $[\alpha]_{D}^{21 \circ C} = +2.5$ (CHCl₃, c = 1). IR (ATR) $\tilde{\nu} = 3335$ cm⁻¹ (w), 3187 (w), 3065 (w), 2935 (w), 2860 (w), 1805 (w), 1685 (s), 1428 (m), 1379 (w), 1305 (w), 1250 (w), 1194 (s), 1107 (s), 936 (m), 823 (m), 747 (s), 698 (s). MS (EI, 70 eV) m/z (%) 984.1 (1) $[(M - CF_{3}COO^{-})^{+}], 816.9 (29) [(M - CF_{3}COO^{-} - CHPh_{2})^{+}],$ 465.4 (35), 422.4 (80), 405.3 (100), 312.3 (71), 234.3 (49), 224.2 (37), 199.2 (43), 167.2 (37) [CHPh₂⁺]. MS (ESI, Orbitrap) m/z984.5 $[(M - CF_3COO^-)^+]$. HRMS (ESI, Orbitrap) calcd for $C_{65}H_{74}N_3O_2Si_2^+$ [(M - CF₃COO⁻)⁺]: 984.53141; found: 984.52673. Bis[(15)-1-benzhydryl-3-hydroxypropyl]aminomethaniminium Fluoride and Trifluoroacetate (41).⁴³ To a flask containing a solution of protected guanidinium salt 40 (1.33 g, 1.21 mmol) in MeCN (HPLC-grade, 80 mL), fluoride on polymer (2.0 g, 6.0 mmol, 5.0 equiv; 3.0 mmol/g loading on Amberlyst A-26 resin; obtained from a commerical source) was added, and the resulting mixture was stirred under Ar at rt. During this time, a white precipitate was formed. After 43 h, MeOH (ca. 30 mL) was added to the resulting suspension until

the formed precipitate completely dissolved. Fluoride on polymer beads were filtered off and washed with additional MeOH (10 mL), and the solvents were removed under reduced pressure. When the resulting crude product (oily mass) was washed with an Et₂O/pentane = 1/1 mixture (20 mL), a precipitate was formed. It was washed with pentane (10 mL) and dried under reduced pressure, and the product **41** (640 mg) was obtained as an off-white solid. The isolated product contained unidentified impurities and residual Et₂O. Quantitative yield was assumed.

Severe signal broadening was observed in NMR spectra, probably, due to aggregate formation. For this reason, only approximate chemical shifts and integral values are presented. $R_f = 0.0 (CH_2Cl_2/$ MeOH = 9/1, [UV, bromocresol green]). ¹H NMR (600 MHz, CD₃OD) 7.75-6.40 (m, 22 H), 4.75-3.80 (br m, 4H), 3.60-3.10 (br m, 2H), 2.00–1.55 (br m, 2H), 1.50–1.20 (br m, 2H). ¹³C NMR (151 MHz, CD₃OD) δ 158.3, 143.7, 143.1, 129.9, 129.7, 129.1, 129.0, 128.7, 127.9, 59.3, 53.6, 41.8, 37.7. One signal was not included due to overlaps resulting from low resolution.¹⁹F NMR (282 MHz, CD₃OD) , • °C = δ -76.9 (s, CF₃, minor signal), -150.5 (s, F⁻, major signal). $[\alpha]_{D}^{24}$ -4.7 (MeOH, c = 1). Mp 115–118 °C IR (ATR) $\tilde{\nu} = 3309$ cm⁻¹ (w), 3176 (w), 3060 (w), 3029 (w), 2929 (w), 1780 (w), 1646 (s), 1551 (w), 1493 (m), 1330 (w), 1251 (w), 1184 (w), 1106 (m), 1044 (m), 912 (w), 822 (m), 747 (s), 698 (s). MS (EI, 70 eV) m/z (%) 508.1 (1) $[(M - F^{-})^{+}]$, 340.5 (6) $[(M - CF_{3}COO^{-} - CHPh_{2})^{+}]$, 167.2 (100) [CHPh₂⁺], 152.2 (32), 99.2 (8). MS (ESI, Orbitrap) m/z 508.3 $[(M - F^{-})^{+}]$. HRMS (ESI, Orbitrap) calcd for $C_{33}H_{38}N_{3}O_{2}^{+}[(M - F^{-})^{+}]$. F⁻)⁺]: 508.29585; found: 508.29373.

Bis[(1S)-1-benzhydryl-3-chloropropyl]aminomethaniminium *Chloride* (42).⁴⁴ To a flask containing a suspension of guanidinium salt 41 (914 mg, 1.7 mmol) in MeCN (HPLC grade, 106 mL), thionyl chloride (1.3 mL, 2.1 g, 17.6 mmol, 12 equiv) was added. Upon addition of SOCl₂, all solids immediately dissolved, and the resulting mixture was stirred under Ar at rt for 24 h. After addition of MeOH (20 mL), the resulting mixture was stirred for 1 h at rt. The solvents were removed under reduced pressure to give the crude product 42 (1.41 g) as a yellowish solid. The crude product was used without further purification. A small amount of the crude product (ca. 100 mg) was purified by column chromatography (Si, 2.0×20 cm, CH₂Cl₂/ MeOH = $99/1 \rightarrow 97/3$) to give an analytically pure sample for spectrosopic analyses as an off-white solid. $R_f = 0.71$ (CH₂Cl₂/MeOH = 9/1, [bromocresol green]). ¹H NMR (300 MHz, CD₃OD) 7.41-7.18 (m, 20H), 4.45 (virt t, J = 9.6 Hz, 2H), 3.87 (br d, J = 10.8 Hz, 2H), 3.24-3.12 (br m, 2H), 3.09-2.94 (br m, 2H), 1.95-1.80 (br m, 2H), 1.74–1.57 (br m, 2H). ¹³C NMR (151 MHz, CD₃OD) & 157.0, 143.2, 142.5, 130.2, 129.7, 129.6, 129.2, 128.3, 128.2, 59.7, 54.5, 41.8, 37.9. $\left[\alpha\right]_{D}^{21 \circ C} = +61.6 \text{ (MeOH, } c = 1\text{). Mp } 133-136 \circ C \text{ IR (ATR)} \tilde{\nu} =$ 3633 cm⁻¹ (w), 3031 (m), 2317 (m), 2087 (w), 1961 (w), 1716 (w), 1582 (s), 1493 (m), 1449 (m), 1361 (m), 1251 (w), 1169 (w), 1083 (m), 1039 (m), 918 (w), 814 (w), 749 (s), 699 (s). MS (EI, 70 eV) m/z (%) 471.6 (4), 304.4 (100), 137.3 (7). MS (ESI, Orbitrap) m/z 544.2 $[(M - Cl^{-})^{+}]$. HRMS (ESI, Orbitrap) calcd for $C_{33}H_{36}Cl_2N_3^{+}$ $[(M - Cl^{-})^{+}]$: 544.22808; found: 544.22595.

(2S,8S)-2,8-Dibenzhydryl-1H,2H,3H,4H,6H,7H,8H,9H-pyrimido-[1,2-a]pyrimidin-5-ium Chloride (10).⁴⁵ To a flask containing a suspension of crude guanidinium salt 42 (1.6 mmol assuming quantitative yield of the previous reaction) in dry MeCN (30 mL), DBU (955 µL, 974 mg, 6.4 mmol, 4.0 equiv) was added. The resulting brown suspension was stirred under Ar at rt for 4 h. After addition of one more portion of DBU (470 µL, 479 mg, 3.2 mmol, 2.0 equiv), the mixture was stirred at rt for another 16 h. The reaction mixture was acidified with HCl (1 M in MeOH) to pH 1-2, and the solvents were removed under reduced pressure. The resulting crude product (brown sticky mass) was purified by column chromatography (Si, 26×3.5 cm, $CH_2Cl_2/MeOH = 97/3 \rightarrow 92/8$). Due to the very similar polarities of the formed regioisomers 10 and 43, one more chromatographic purification was necessary to afford separation (Si, 20 \times 2.0 cm, toluene/CH₂Cl₂/MeOH = $1/98/1 \rightarrow 1/97/2 \rightarrow 1/96/3 \rightarrow 1/95/4 \rightarrow$ $CH_2Cl_2/MeOH = 96/4$). The desired regioisomer 10 (69 mg, 136 μ mol, 8%) was obtained as yellowish foam.⁴⁶

Crystals suitable for X-ray analysis were obtained by dissolving this material in MeOH/CHCl₃ followed by slow evaporation at rt over several days.³² $R_f = 0.46$ (CH₂Cl₂/MeOH = 9/1, [UV, bromocresol green]). ¹H NMR (600 MHz, CD₃OD) 7.41 (d, J = 7.2 Hz, 4H), 7.32–7.27 (m, 12H), 7.22–7.17 (m, 4H), 4.33 (ddd, J = 9.0, 10.8, 3.6 Hz, 2H), 3.87 (br d, J = 10.8 Hz, 2H), 3.42–3.35 (m, 4H), 1.83–1.79 (m, 2H), 1.74–1.67 (m, 2H). ¹³C NMR (151 MHz, CD₃OD) δ 152.3, 142.6, 141.8, 130.3, 130.1, 129.4, 129.1, 128.6, 128.3, 58.4, 52.7, 46.9, 26.7. $[\alpha]_D^{21 \circ C} = -23.0$ (MeOH, c = 1). IR (ATR) $\tilde{\nu} = 3645$ cm⁻¹ (w), 3263 (w), 3138 (w), 2938 (w), 2873 (w), 2081 (w), 1620 (s), 1526 (w), 1493 (m), 1448 (m), 1360 (m), 1314 (s), 1106 (m), 1029 (w), 919 (s), 898 (s). MS (EI, 70 eV) m/z (%) 472.6 (1) [(M – Cl⁻)⁺], 304.4 (100), 137.2 (7). MS (ESI, Orbitrap) m/z 472.3 [(M – Cl⁻)⁺]: 472.27472; found: 472.27390.

(2S,6S)-2,6-Dibenzhydryl-1H,2H,3H,4H,6H,7H,8H,9H-pyrimido-[1,2-a]pyrimidin-5-ium Chloride (43). The undesired regioisomer 43 (250 mg, 492 μ mol, 31%) was the main reaction product and obtained as a slightly less polar fraction (white foam). Furthermore, a mixture containing both regioisomers isomers (10/43 = 1/3) was obtained in a total yield of 24%. The total yield of the desired guanidinium salt 10 is therefore ca. 14%. $R_f = 0.46$ (CH₂Cl₂/MeOH = 9/1, [UV, bromocresol green]). ¹H NMR (400 MHz, CD₃OD) 7.59 (d, J = 7.2 Hz, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.49–7.35 (m, 9H), 7.29–7.22 (m, 4H), 7.18-7.14 (m, 1H), 7.06 (d, J = 7.2 Hz, 2H), 4.50 (d, J =11.6 Hz, 1H), 4.30–4.25 (m, 1H), 4.22 (d, J = 11.6 Hz, 1H), 3.52 (d, J = 11.2 Hz, 1H), 3.44-3.36 (m, 1H), 3.27-3.16 (m, 2H), 2.54-2.47 (m, 1H), 2.03–1.93 (m, 1H), 1.87 (dd, J = 14.0, 5.6 Hz, 1H), 1.61– 1.53 (m, 1H), 1.18–1.11 (m, 1H). 13 C NMR (101 MHz, CD₃OD) δ 151.8, 143.5, 142.4, 142.3, 142.2, 130.5, 130.3, 130.2, 130.0, 129.4, 129.2, 128.9, 128.5, 128.4, 128.3, 62.0, 57.1, 55.4, 52.5, 47.5, 36.1, 25.3, 24.0. $[\alpha]_{D}^{21 \text{ oC}} = +111.2 \text{ (MeOH, } c = 1\text{). IR (ATR)} \tilde{\nu} = 3636 \text{ cm}^{-1} \text{ (w)},$ 3278 (w), 3028 (w), 2945 (w), 2884 (w), 2059 (w), 1630 (s), 1527 (w), 1493 (m), 1449 (m), 1363 (m), 1316 (s), 1205 (w), 1101 (m), 1027 (m), 749 (s), 699 (s). MS (EI, 70 eV) m/z (%) 472.6 (5) [(M - $Cl^{-})^{+}$], 304.4 (100), 137.1 (19). MS (ESI, Orbitrap) m/z 472.3 [(M - $CF_3COO^{-})^+$]. HRMS (ESI, Orbitrap) calcd for $C_{33}H_{34}N_3^+$ [(M – CF₃COO⁻)⁺]: 472.27472; found: 472.27481.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00283.

Crystallographic data for compounds 8, 10 and 38 (CIF) NMR spectra of all intermediates and final products. Relevant HSQC and HMBC correlations of the compound 31 (PDF)

AUTHOR INFORMATION

Corresponding Authors

- *E-mail: aleksej.turockin@org.chem.ethz.ch.
- *E-mail: philipp.selig@patheon.com.

Present Addresses

⁸Laboratorium für Organische Chemie, ETH Zürich, HCI E306, Vladimir-Prelog-Weg 3, 8093 Zurich, Switzerland
 ^{II}Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, 48149 Münster, Germany

[⊥]Patheon, St.-Peter-Str. 25, 4020 Linz, Austria

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Generous financial support by the Fonds der Chemischen Industrie (Liebig-Scholarship to P.S. no. Li 186/09, PhD scholarship to A.T. no. Do-L 190/06) and Evonik Industries AG (Germany Grant to R.H.) is gratefully acknowledged. We thank Prof. Dr. U. Englert (Institute of Inorganic Chemistry, RWTH Aachen University) for X-ray structure determinations. Special thanks go to Prof. Dr. D. Enders, Institute of Organic Chemistry, RWTH Aachen University, for the generous provision of laboratory space and chemicals.

REFERENCES

(1) Ishikawa, T. In *Superbases for Organic Synthesis*; Ishikawa, T., Ed.; John Wiley & Sons Ltd.: Chichester, 2009; p 93.

(2) For instance, $pK_a[80\% DMSO]$ of guanidinium hydrochloride is 13.6; see: Baldini, L.; Cacciapaglia, R.; Casnati, A.; Mandolini, L.; Salvio, R.; Sansone, F.; Ungaro, R. *J. Org. Chem.* **2012**, *77*, 3381. Whereas $pK_a[MeCN]$ of protonated TBD (**2**) is 28.0; see: Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.

(3) Maji, B.; Stephenson, D. S.; Mayr, H. ChemCatChem 2012, 4, 993.

(4) Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. J. Am. Chem. Soc. 2006, 128, 4556.

(5) Kiesewetter, M. K.; Scholten, M. D.; Kirn, N.; Weber, R. L.; Hedrick, J. L.; Waymouth, R. M. J. Org. Chem. **2009**, 74, 9490.

(6) Selig, P.; Turočkin, A.; Raven, W. Synlett 2013, 24, 2535.

(7) Selig, P.; Turočkin, A.; Raven, W. Chem. Commun. 2013, 49,

2930.
(8) Selig, P.; Turočkin, A.; Raven, W. Adv. Synth. Catal. 2013, 355, 297.

(9) Blondeau, P.; Segura, M.; Pérez-Fernández, R.; de Mendoza, J. Chem. Soc. Rev. 2007, 36, 198.

(10) Dieng, P. S.; Sirlin, C. Int. J. Mol. Sci. 2010, 11, 3334.

(11) Fu, X.; Tan, C.-H. Chem. Commun. 2011, 47, 8210.

(12) Selig, P. Synthesis 2013, 45, 703.

(13) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. Chem. Soc. Rev. 2012, 41, 2109.

(14) Leow, D.; Tan, C.-H. Chem. - Asian J. 2009, 4, 488.

(15) Terada, M. Yuki Gosei Kagaku Kyokaishi 2010, 68, 1159.

(16) Ishikawa, T. Chem. Pharm. Bull. 2010, 58, 1555.

(17) Shubina, T. E.; Freund, M.; Schenker, S.; Clark, T.; Tsogoeva, S. B. *Beilstein J. Org. Chem.* **2012**, *8*, 1485.

(18) Gleich, A.; Schmidtchen, F. Chem. Ber. 1990, 123, 907.

(19) Corey, E. J.; Grogan, M. J. Org. Lett. 1999, 1, 157.

(20) Misaki, T.; Takimoto, G.; Sugimura, T. J. Am. Chem. Soc. 2010, 132, 6286.

(21) Misaki, T.; Kawano, K.; Sugimura, T. J. Am. Chem. Soc. 2011, 133, 5695.

(22) Dai, Q.; Huang, H.; Zhao, J. C.-G. J. Org. Chem. 2013, 78, 4153.

(23) Corey, E. J.; Ohtani, M. Tetrahedron Lett. 1989, 30, 5227.

(24) Davis, A. P.; Dempsey, K. J. Tetrahedron: Asymmetry **1995**, 6, 2829.

(25) Echavarren, A.; Galán, A.; de Mendoza, J.; Salmerón, A.; Lehn, J.-M. Helv. Chim. Acta 1988, 71, 685.

(26) Jadhav, V. D.; Schmidtchen, F. P. J. Org. Chem. 2008, 73, 1077. (27) Wu, Y.-Q.; Hamilton, S. K.; Wilkinson, D. E.; Hamilton, G. S. J. Org. Chem. 2002, 67, 7553.

(28) For detailed account on applications of Tan's guanidine, see: Leow, D.; Tan, C.-H. Synlett **2010**, 11, 1589.

(29) Boyle, P. H.; Davis, A. P.; Dempsey, K. J.; Hosken, G. L. Tetrahedron: Asymmetry 1995, 6, 2819.

(30) McKennon, M. J.; Meyers, A. I. J. Org. Chem. 1993, 58, 3568.

(31) This ratio was determined using NMR spectroscopy by integration of the signals corresponding to *tert*-butyl groups (see Experimental Section). However, precise structure assignment of the minor species was not possible due to its extremely low quantity and our inability to isolate it in pure form.

(32) See the Supporting Information for the X-ray crystal structures of 8, 10, and 38. CCDC-1449940 (8)/1449941 (10)/1449942 (38) 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.

(33) At elevated temperatures, the reagent 6 is known to decompose to the corresponding cyanamide by elimination of imidazole: McCallum, P. B. W.; Grimmett, M. R.; Blackman, A. G.; Weavers, R. T. Aust. J. Chem. 1999, 52, 159.

(34) Boyle, P. H.; Davis, A. P.; Dempsey, K. J.; Hosken, G. D. J. Chem. Soc., Chem. Commun. **1994**, 1875.

(35) Bromocresol green staining reagent has become for us one of the most valuable qualitative tools for convenient detection of guanidines. In course of this work, we have noticed that developing of TLC plates containing guanidines and guanidinium intermediates with bromocresol green showed a very specific turquoise color clearly distinct from the blue staining of amines.

(36) Sciuto, S.; Piatelli, M.; Chillemi, R. *Phytochemistry* **1982**, *21*, 227. (37) Staron, T.; Allard, C.; Xuong, N. D.; Chambre, M.-M.; Grabowski, H. C. R. Acad. Sci. **1964**, 259, 3114.

(38) Kumaraswamy, G.; Jayaprakash, N. *Tetrahedron Lett.* **2010**, *51*, 6500.

(39) Cariou, C. A. M.; Kariuki, B. M.; Snaith, J. S. Org. Biomol. Chem. 2008, 6, 3337.

(40) Baliani, A.; Peal, V.; Gros, L.; Brun, R.; Kaiser, M.; Barrett, M. P.; Gilbert, I. H. Org. Biomol. Chem. **2009**, *7*, 1154.

(41) This procedure was based on the guanylation protocol described by Schmidtchen in ref 26.

(42) $27 \cdot H_2O$ was obtained after additional column chromatography of $27 \cdot TFA$ over activated alumina as stationary phase. We assume that anion exchange occurred due to different activity grade of that batch of aluminium oxide compared to the one used for the first chromatographic purification.

(43) This deprotection was based in the procedure described by Schmidtchen in ref 26.

(44) This chlorination procedure was based on the protocol described by: McKay, A. F.; Kreling, M.-E. Can. J. Chem. 1957, 35, 1438.

(45) The final cyclization protocol was based on the procedure described by Schmidtchen in ref 26.

(46) The corresponding hydroiodide salt of this guanidine was reported by Davis et al. (see ref 24). Our spectroscopic data essentially match those reported by Davis. The only disagreement is that we observed eight aromatic signals in the ¹³C NMR spectrum, whereas Davis reported 10 carbon signals in the aromatic region.