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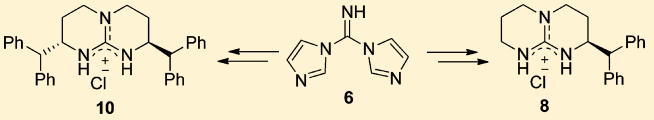
Synthesis of Chiral Bicyclic Guanidinium Salts using Di(imidazole-1-yl)methanimine

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

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 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]

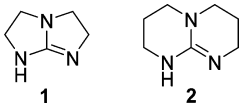


Figure 1. Simplest bicyclic guanidine bases 1,4,6-triazabicyclo[3.3.0]-oct-4-ene (TBO, **1**) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, **2**).

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 Schmidtchen[18] 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]

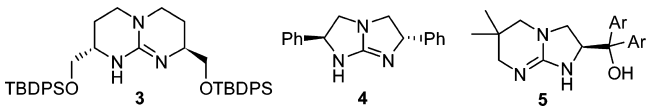


Figure 2. Bicyclic chiral guanidine bases used in molecular recognition and organocatalysis.

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

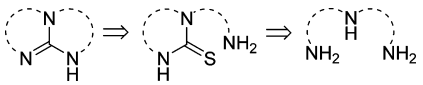


Figure 3. Retrosynthetic analysis of bicyclic guanidines via cyclic thiourea intermediates.

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,[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

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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

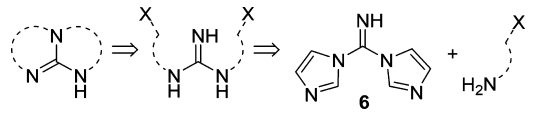


Figure 4. Retrosynthetic analysis of bicyclic guanidines by Schmidtchen approach.

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

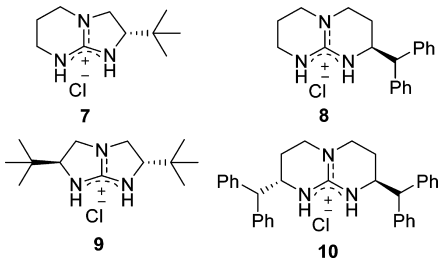


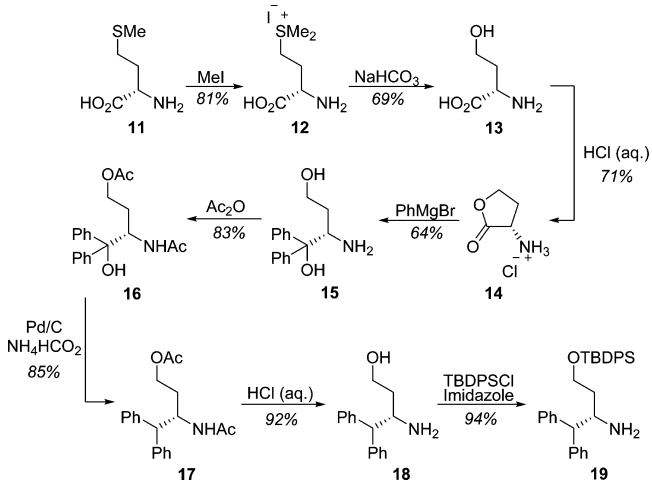
Figure 5. Target chiral bicyclic guanidinium salts.

guanidinium salts **7** and **8**, we also investigated the syntheses of TBO-derivative **9**[28] 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 C_2-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

Scheme 1. Synthesis of the Protected Aminoalcohol 19



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

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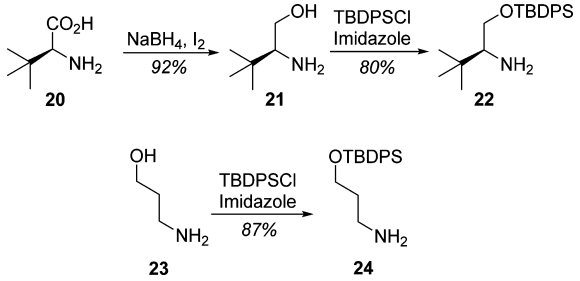
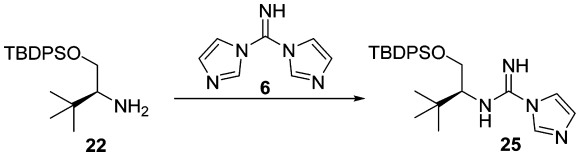
Scheme 2. Syntheses of the Protected Aminoalcohols 22 and 24



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



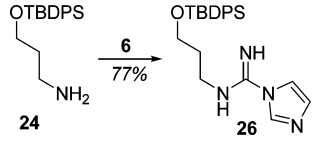
entry	solvent	yield of **25** (%)
1	THF	62[a]
2	THF	15[b]
3	THF	22[c]
4	neat	traces

[a]Reaction was carried out on 337 μmol scale in an open round-bottomed flask. [b]Reaction was carried out on 2.36 mmol scale in an open round-bottomed flask. [c]Reaction 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).

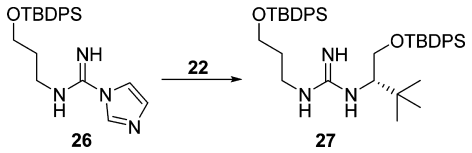
In an alternative approach, we reacted the protected aminoalcohol **24** with the reagent **6**. Without any steric hindrance from the bulky *tert*-butyl group, the displacement of imidazole took place significantly faster (23 h) and did not show the above-mentioned sensitivity to the concentrations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

Table 2. Synthesis of the Open-Chain Guanidine Intermediate 27



entry	solvent	T (°C)	yield of **27** (%)
1	1.4-dioxane	90	–
2	neat	110	–
3	neat	150	–
4	neat	200	–
5[a]	neat	115	55[b]

[a]1.0 equiv TFA was added. [b]Product 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/CH_2Cl_2 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 silyl 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

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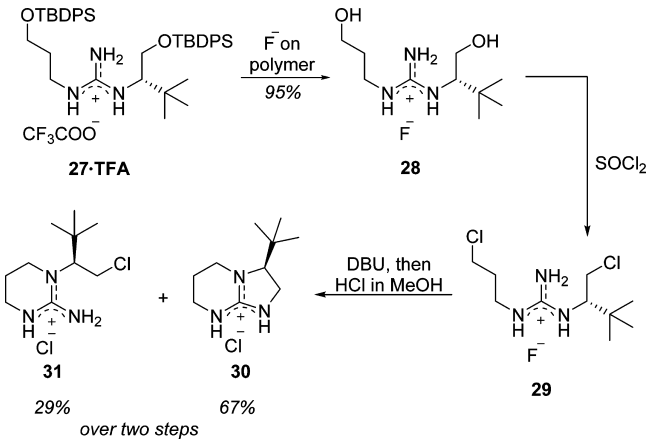
J. Org. Chem. 2016, 81, 4516–4529

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

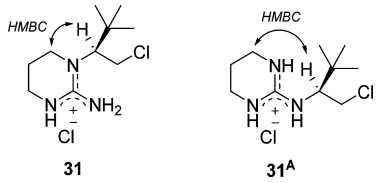


Figure 6. Key HMBC correlations for the intermediate **31**. Formation of the product with alternative structure **31**^{A} was ruled out due to unlikely correlation over five bonds through two nitrogen atoms.

possible bicycle possessing the structure **30**. Indeed, upon reacting the monocyclic guanidinium salt **31** with DBU at 75 °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 two-fold 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 alkyl-substituted 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

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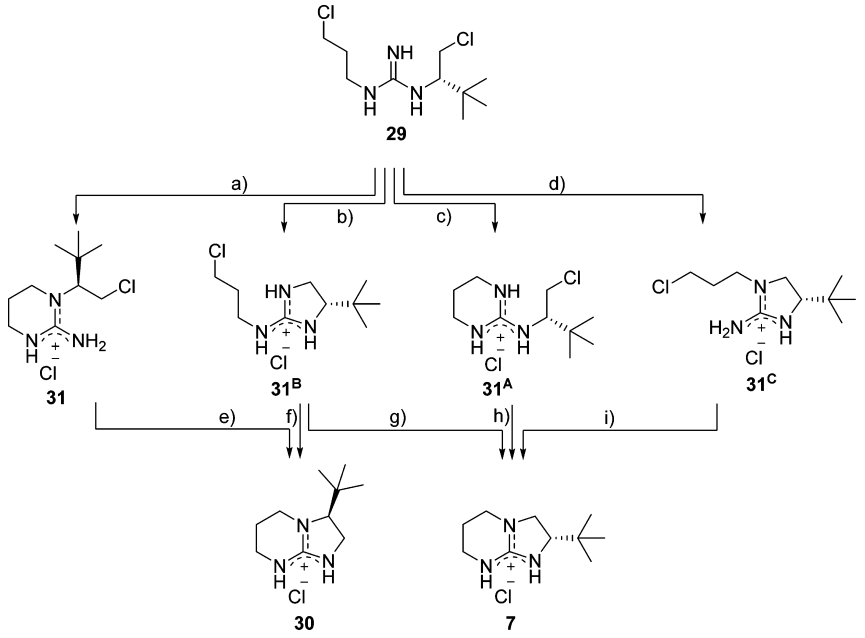
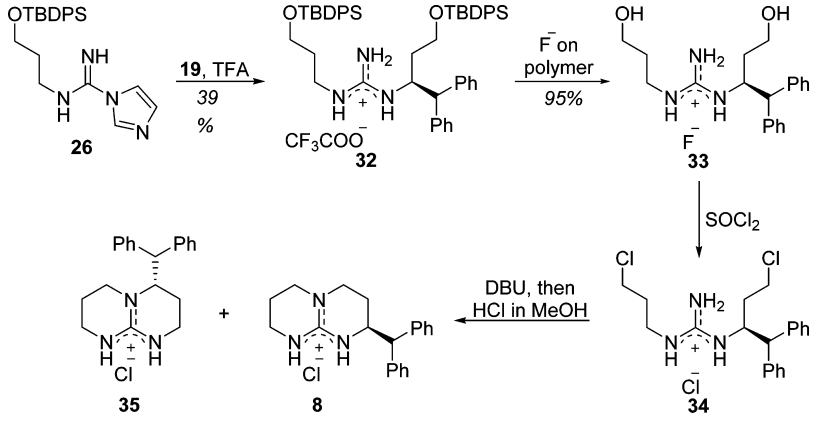
Scheme 5. Possible Cyclization Pathways of 29 Leading to Various Bicyclic Regioisomers



Scheme 6. Synthesis of the Bicyclic Guanidinium Salt 8



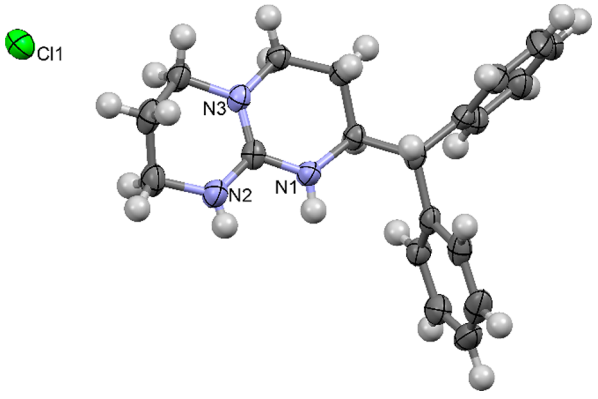
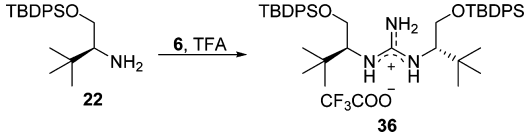


Figure 7. X-ray crystal structure of guanidinium salt **8**.[32] Ellipsoids are drawn at 80% probability. A water molecule has been omitted for clarity.

Table 3. Synthesis of the Open-Chain Guanidinium Salt 36



entry	*t* (h)	*T* (°C)	yield of **36** (%)
1	2	115	26
2	2	105	20
3	4	105	40

above-mentioned syntheses of the non C_2-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

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an acceptable yield of 40% after prolonged reaction time at 105 °C (Table 3, entries 2–3).

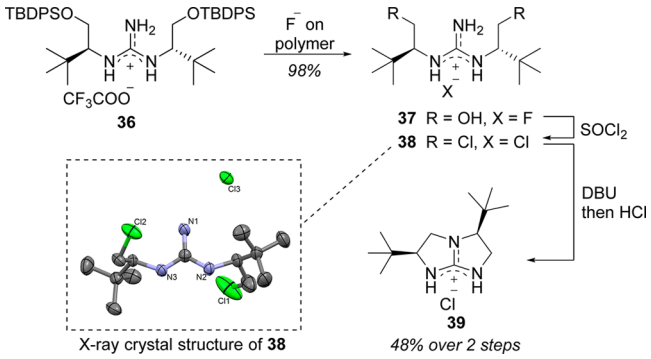
This key step suffered from the same purification problem described for related intermediates **27·TFA** and **32**, as the protected aminoalcohol **22** could not be separated from the product **36** by column chromatography when standard eluents consisting of CH_2Cl_2 and MeOH were used. Owing to the 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 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 **10**[32] 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

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



[a]Ellipsoids of **38** are drawn at 80% probability.

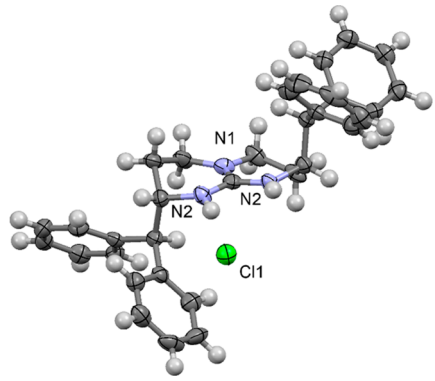
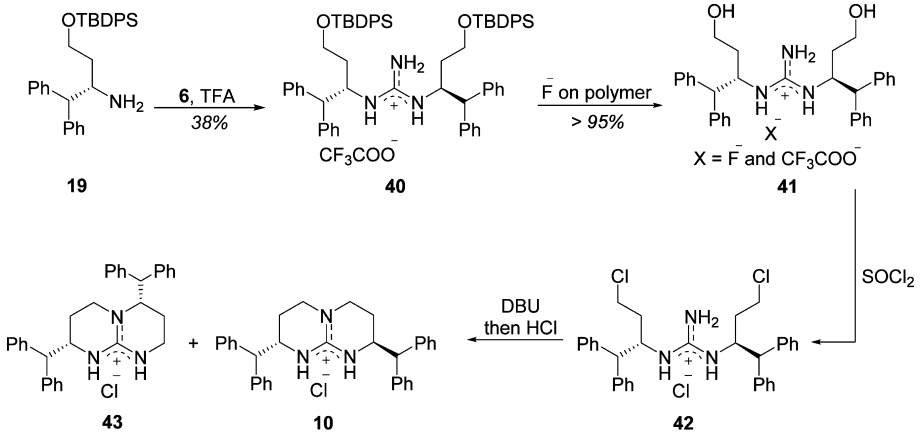


Figure 8. X-ray crystal structure of guanidinium salt **10**.[32] Ellipsoids are drawn at 80% probability. Water molecules have been omitted for clarity.

Scheme 8. Synthesis of the Bicyclic Guanidinium Salt 10



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J. Org. Chem. 2016, 81, 4516–4529

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/CH_2Cl_2 and silica gel as stationary phase.

Analysis. Thin-layer chromatography was carried out with ready-to-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 $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.2 g $Ce(SO_4)_2\cdot 4H_2O$ in 200 mL of 10% H_2SO_4. The staining reagent $KMnO_4$ was prepared by dissolving 3 g $KMnO_4$ and 10 g K_2CO_3 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 $CDCl_3$, 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 CH_2Cl_2 (250 mL). Subsequently, a solution of bromocyanide (1.85 g, 17.5 mmol) in CH_2Cl_2 (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 CH_2Cl_2. 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 CH_2Cl_2 to give a second crop of the product. Combined solids weighed 1.92 g (11.9 mmol, 68%). R_f = 0.34 (CH_2Cl_2/MeOH = 9/1, [UV]). ^{1}H 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). ^{13}C NMR (101 MHz, DMSO-d_6): 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.[26,27]

*(S)-(3-Amino-3-carboxypropyl)dimethylsulfonium Iodide (**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/H_2O = 3/1/1, [ninhydrin]). Mp 163−166 °C (Lit.:[29] 163−165 C). ^{1}H 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). ^{13}C 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.[36]

*(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 $NaHCO_3$ 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, $NaHCO_3$ solution was added until the pH rose to ∼5.0. Reaction mixture was further refluxed until the pH

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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). ^{13}C NMR (151 MHz, D_2O): δ 174.3, 58.6, 53.3, 32.0. $[\alpha]_D^{21\ °C}$ = −8.3 (H_2O, c = 1) (Lit.:[37] − 8.0 [H_2O, 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.[29]

*(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 MHz, D_2O): δ 4.64 (td, J = 9.2, 1.0 Hz, 1H), 4.51−4.44 (m, 2H), 2.86−2.80 (m, 1H), 2.51−2.41 (m, 1H). ^{13}C NMR (151 MHz, D_2O): 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.[38]

*(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(3*H*)-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). ^{13}C NMR (151 MHz, DMSO-d_6) δ 147.3, 146.4, 128.0, 127.8, 126.02, 125.98, 125.8, 125.5, 80.0, 59.6, 55.0, 33.7. $[\alpha]_D^{22\ °C}$ = −28.1 (EtOH, c = 0.26) (Lit.:[29] −26.0 [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.[29]

*(3S)-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 CH_2Cl_2 (3 × 450 mL). The combined organic layers were dried over $MgSO_4$ 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, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 (3*S*)-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 × 100 mL), and dried over $MgSO_4$. 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, $CDCl_3$) 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). ^{13}C NMR (151 MHz, $CDCl_3$) 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.[29]

*(3S)-3-Amino-4,4-diphenyl-1-butanol (**18**).*[29] A suspension of (3*S*)-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 $MgSO_4$. 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 (CH_2Cl_2/MeOH = 9/1, [UV, ninhydrin]). ^1H NMR (600 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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. $[\alpha]_D^{21\ °C}$ = +15.5 (CH_2Cl_2, c = 1). This is a known compound. Spectroscopic data agree with those reported in the literature.[29]

*(2S)-4-[tert-Butyl(diphenyl)silyl]oxy-1,1-diphenyl-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, HPLC-garde). 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 → 98/2 → 97/3 → 95/5). The product **19** (7.41 g, 15.4 mmol, 94%) was obtained as brownish viscous oil. R_f = 0.42 (CH_2Cl_2/MeOH = 9/1, [UV, ninhydrin]). ^1H NMR (600 MHz, $CDCl_3$) 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). ^{13}C NMR (151 MHz, $CDCl_3$) 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. $[\alpha]_D^{21\ °C}$ = +3.9 ($CHCl_3$, c = 1). IR (ATR) $\tilde{\nu}$ = 3386 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

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(11) [M^+], 422.4 (76) [$(M - t\text{-Bu})^+$], 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 $NaBH_4$ (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 CH_2Cl_2 (4 × 250 mL). Combined organic layers were dried over Na_2SO_4 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]). ^{1}H NMR (600 MHz, $CDCl_3$): 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, 3.6 Hz, 1H), 2.30 (bs, 3H), 0.82 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 62.3, 61.6, 33.0, 26.2. $[\alpha]_D^{25\ °C}$ = +36.2 (CH_3Cl, c = 1) (Lit.:[39] $[\alpha]_D^{25\ °C}$ = +38.2 [CH_3Cl, c = 1]). This is a known compound. Spectroscopic data agree with those reported in the literature.[39]

*(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 → 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 CH_2Cl_2 (150 mL) and washed with saturated aq. $NaHCO_3$ (3 × 150 mL) solution. The combined aqueous phases were extracted with CH_2Cl_2 (50 mL). The combined organic phases were dried over $MgSO_4$, 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]). ^{1}H 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). ^{13}C NMR (151 MHz, $CDCl_3$) 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. $[\alpha]_D^{21\ °C}$ = +18.4 (CH_3Cl, c = 1). IR (ATR) $\tilde{\nu}$ = 3069 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) [$(M - t\text{-Bu})^+$], 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**).* TBDPSCl (7.57 mL, 8.0 g, 29.1 mmol) was added to a solution of 3-amino-1-propanol **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, CH_2Cl_2/MeOH = 9/1), affording the hydrochloride salt of the desired product as a yellowish solid. This material was dissolved in H_2O (200 mL), and the resulting solution titrated with aqueous NaOH (1 M) until pH > 10 was reached. This solution was extracted with CH_2Cl_2 (4 × 90 mL), and the combined organic layers were washed with H_2O (2 × 150 mL) and brine (150 mL). After drying over Na_2SO_4 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 (CH_2Cl_2/MeOH = 9/1, [UV, ninhydrin]). ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (101 MHz, $CDCl_3$): 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 $C_{19}H_{28}NOSi^+$ [$M + H^+$]: 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 μmol) 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 μnol, 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 ^{13}C NMR spectrum. ^{1}H NMR (600 MHz, CD_3OD) 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, CD_3OD) 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 $C_{26}H_{37}N_4OSi^+$ [$M + H^+$]: 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]). ^{1}H NMR (600 MHz, CD_3OD) 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 = 6.3 Hz, 2H), 1.91 (quint, J = 6.3 Hz, 2H), 1.05 (s, 9H). ^{13}C NMR (151 MHz, CD_3OD) 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 CH_2Cl_2, 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 μL, 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

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J. Org. Chem. 2016, 81, 4516−4529

gummy mass was purified by column chromatography (Si, 3.0 × 19 cm, CH_2Cl_2/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, CH_2Cl_2/MeOH = 97/3) to separate the final product from unreacted aminoalcohol **22**. The product **27·TFA** (687 mg, 850 μmol, 55%) was obtained as an off-white foam and contained residual CH_2Cl_2 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, CH_2Cl_2/MeOH = 97/3 [UV, bromocresol green]) R_f = 0.23 (Al, CH_2Cl_2/MeOH = 97/3 [UV, bromocresol green]) ^{1}H NMR (600 MHz, CD_3OD) 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). ^{13}C NMR (151 MHz, CD_3OD) 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. ^{19}F NMR (564 MHz, CD_3OD) δ −76.7 (s).

The optical rotation is given for the corresponding hydroxide salt of **27** (**27·H$_2$O**).[42] $[\alpha]_D^{29\ °C}$ = −46.7 (CH_3Cl, 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_3COO^-)$^+$], 616.38 [(M − CF_3COO^- − H^+ − Ph)$^+$]. HRMS (ESI, Orbitrap): calcd for $C_{42}H_{60}N_3O_2Si_2^+$ [(M − CF_3COO^-)$^+$]: 694.42186; found: 694.42377.

*(S)-((1-Hydroxy-3,3-dimethylbutan-2-yl)amino)((3-hydroxypropyl)amino)methaniminium Fluoride (**28**).*[43] To a flask containing a solution of protected guanidine **27·TFA** (685 mg, 848 μmol) 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 Et_2O to this solution, the product **28** precipitated as a heavy colorless oil. Addition of Et_2O (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 (CH_2Cl_2/MeOH = 9/1 [bromocresol green]). ^{1}H NMR (600 MHz, CD_3OD) 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). ^{13}C NMR (151 MHz, CD_3OD) δ 159.13, 64.3, 62.6, 59.5, 39.6, 35.0, 32.6, 27.0. ^{19}F NMR (564 MHz, CD_3OD) δ −139.6 (s, 1F). $[\alpha]_D^{29\ °C}$ = −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 μmol) in absolute MeCN (16 mL), thionyl chloride (374 μL, 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 (CH_2Cl_2/MeOH = 9/1 [bromocresol green, $KMnO_4$]) ^{1}H NMR (600 MHz, CD_3OD) 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). ^{13}C NMR (151 MHz, CD_3OD) δ 158.7, 63.8, 46.1, 42.5, 40.0, 36.6, 32.7, 26.6. ^{19}F NMR (564 MHz, CD_3OD) δ −154.2 (s, 1F). $[\alpha]_D^{29\ °C}$ = −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 $C_{10}H_{22}N_3Cl_2^+$ [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 μmol 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 μmol, 67% over 2 steps) which consisted of two regioisomers **30** and **7** (**30**/**7** = 92/8, determined by ^{1}H NMR). R_f = 0.18 (EtOAc/MeOH = 7/3 [bromocresol green, $KMnO_4$]). $[\alpha]_D^{29\ °C}$ = −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): ^{1}H NMR (600 MHz, CD_3OD) 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). ^{13}C NMR (151 MHz, CD_3OD) 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. ^{1}H NMR (600 MHz, CD_3OD) δ 1.02 (s, 9H). ^{13}C NMR (151 MHz, CD_3OD) δ 26.3.

*(S)-1-(1-Chloro-3,3-dimethylbutan-2-yl)tetrahydropyrimidin-2(1H)-iminium Chloride (**31**).* Monocyclized guanidinium salt **31** (63 mg, 248 μmol, *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, $KMnO_4$]). ^{1}H NMR (600 MHz, CD_3OD) δ 3.95 (dd, J = 10.7, 2.0 Hz, 1H, C*H*HCl), 3.60−3.51 (m, 2H, NC*H*tBu and CH*H*Cl), 3.40−3.37 (m, 4H, 2 × CH_2N), 1.99−1.93 (m, 2H, $CH_2CH_2CH_2$), 1.00 (s, 9H). ^{13}C NMR (151 MHz, CD_3OD) δ 155.5, 63.2 (CH), 46.2 (CH_2), 39.8 (CH_2), 36.6 (CH_2), 26.6, 21.3 (CH_2). 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 (^{37}Cl) − Cl^-], 218.14 [M (^{35}Cl) − Cl^-], 182.16 [(M − 2Cl^- − H^+)$^+$]. HRMS (ESI, Orbitrap): calcd for $C_{10}H_{21}N_3Cl^+$ [M (^{35}Cl) − Cl^-]: 218.14185; found: 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-trifluoroacetate (**32**).*[41] To a flask containing a solution of aminoalcohol **19** (470 mg, 980 μmol) in CH_2Cl_2 (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 × 18.5 cm, CH_2Cl_2/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 μmol, *39%*) was obtained as a white foam. R_f = 0.37 (Si, CH_2Cl_2/MeOH = 97/3 [UV, bromocresol green]) R_f = 0.43 (Al, CH_2Cl_2/MeOH = 97/3 [UV,

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J. Org. Chem. 2016, 81, 4516−4529

bromocresol green]). A significant signal broadening was observed in the ^{1}H NMR spectrum. A possible explanation for this effect is the aggregate formation or hindered rotation due to steric bulk of protecting groups. ^{1}H NMR (400 MHz, CD_3OD): 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). ^{13}C NMR (151 MHz, CD_3OD): 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. ^{19}F NMR (564 MHz, CD_3OD): δ −76.3 (s, 3F). $[\alpha]_D^{29\ °C}$ = +28.1 ($CHCl_3$, 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 − CF_3COO^-]. HRMS (ESI, Orbitrap): calcd for $C_{52}H_{64}N_3O_2Si_2^+$ [M − CF_3COO^-]: 818.45316; found: 818.44891.

*(S)-((4-Hydroxy-1,1-diphenylbutan-2-yl)amino)((3-hydroxypropyl)amino)methaniminium Fluoride (**33**).*[43] To a flask containing a solution of protected guanidine **32** (344 mg, 370 μmol) 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 Et_2O to this solution, the product **33** precipitated as a heavy colorless oil. Addition of Et_2O 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 μmol, *95%*). R_f = 0.00 (CH_2Cl_2/MeOH = 9/1 [UV, bromocresol green]). A significant signal broadening was observed in the ^{1}H NMR spectrum. A possible explanation for this effect is the aggregate formation or hindered rotation due to steric bulk of protecting groups. ^{1}H NMR (600 MHz, CD_3OD): 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). ^{13}C NMR (151 MHz, CD_3OD): 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. ^{19}F NMR (564 MHz, CD_3OD): δ −144.2 (s, 1F). $[\alpha]_D^{31\ °C}$ = +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 $CHCl_3$ (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 (CH_2Cl_2/MeOH = 9/1 [UV, bromocresol green]). ^{1}H NMR (400 MHz, CD_3OD): 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). ^{13}C NMR (101 MHz, CD_3OD): δ 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. $[\alpha]_D^{31\ °C}$ = +57.2 (MeOH, c = 2). IR: $\tilde{\nu}$ = 3162 (m), 2960 (w), 2876 (w), 1634 (vs), 1494 (m), 1449 (m), 1290 (m), 1123 (m), 750 (m), 700 (vs). MS (ESI): m/z = 382.14 [M (2 × ^{37}Cl) − Cl^-], 380.15 [M (^{35}Cl, ^{37}Cl) − Cl^-], 378.15 [M (2 × ^{35}Cl) − Cl^-]. HRMS (ESI, Orbitrap): calcd for $C_{20}H_{26}N_3Cl_2^+$ [M (2 × ^{35}Cl) − Cl^-]: 378.14983; found: 378.14871.

*(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 CH_2Cl_2 (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 μmol, 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, $KMnO_4$]). ^{1}H NMR (600 MHz, CD_3OD): δ 7.47 (d, J = 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). ^{13}C NMR (151 MHz, CD_3OD): 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. $[\alpha]_D^{21\ °C}$ = +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^- − $CHPh_2$)$^+$]. 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 ^{1}H 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, $KMnO_4$]) ^{1}H NMR (600 MHz, CD_3OD): 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). ^{13}C NMR (151 MHz, CD_3OD): 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 CH_2Cl_2 (1 mL) was added, and the resulting mixture was concentrated using a rotary evaporator under reduced pressure at rt. Upon removal of CH_2Cl_2, 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, CH_2Cl_2/MeOH/AcOH = 100/1/0.5 → 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 ^{1}H 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 (CH_2Cl_2/MeOH/AcOH = 100/8/0.5, [UV, bromocresol green]). ^{1}H NMR (600 MHz, $CDCl_3$) 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). ^{13}C NMR (151 MHz, $CDCl_3$) 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. ^{19}F NMR (564 MHz, $CDCl_3$) δ −75.7 (s, CF_3). $[\alpha]_D^{21\ °C}$ = −80.2 ($CHCl_3$, c = 1). IR (ATR) $\tilde{\nu}$ = 3317 cm^{-1} (w), 2956 (m), 2170 (w), 1897 (w),

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J. Org. Chem. 2016, 81, 4516−4529

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[(1S)-1-(hydroxymethyl)-2,2-dimethylpropyl]aminomethaniminium 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 × 5 mL), the product **37** was obtained as a white solid (261 mg, 934 μmol, 98%: estimated value due to impurities in the starting material). R_f = 0.0 (CH_2Cl_2/MeOH = 9/1, [bromocresol green]). ^{1}H NMR (400 MHz, CD_3OD) δ 3.91 (dd, J = 10.8, 2.8 Hz, 2H), 3.51 (dd, J = 9.2, 10.8 Hz, 2H), 3.35 (dd, J = 8.8, 2.8 Hz, 2H), 1.01 (s, 18H). ^{13}C NMR (151 MHz, CD_3OD) δ 160.4, 65.1, 63.3, 35.0, 27.2. ^{19}F NMR (376 MHz, CD_3OD) δ −150.6 (s, F^-). $[\alpha]_D^{21\ °C}$ = −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[(1S)-1-(chloromethyl)-2,2-dimethylpropyl]aminomethaniminium Chloride (**38**).*[44] To a flask containing a suspension of guanidinium salt **37** (110 mg, 394 μmol) in MeCN (HPLC grade, 12 mL), thionyl chloride (343 μL, 563 mg, 4.7 mmol, 12 equiv) was added. Upon addition of $SOCl_2$, 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 $KMnO_4$ 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, CH_2Cl_2/MeOH = 98/2 → 95/5) to give a sample for spectrosopic analyses (66 mg, 198 μmol) 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 (CH_2Cl_2/MeOH = 9/1, [$KMnO_4$, bromocresol green]) ^{1}H NMR (600 MHz, CD_3OD) 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). ^{13}C NMR (151 MHz, CD_3OD) δ 159.6, 63.9, 46.3, 36.9, 26.7. $[\alpha]_D^{21\ °C}$ = +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 $C_{13}H_{28}Cl_2N_3^+$ [(M − Cl^-)$^+$]: 296.16548; found: 296.16486.

*(2S,5S)-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 μmol considering quantitative yield of the previous reaction) in MeCN (HPLC grade, 13 mL), DBU (460 μL, 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 × 3 cm, EtOAc/MeOH = 20/1 → 7/1 → 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 μmol, 48%). R_f = 0.41 (EtOAc/MeOH = 8/2, [bromocresol green]) ^{1}H NMR (600 MHz, CD_3OD) 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). ^{13}C NMR (101 MHz, CD_3OD) δ 167.4, 73.0, 69.8, 51.8, 49.8, 35.3, 34.0, 26.4, 25.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (br s, 1H), 8.85 (br s, 1H), 4.06 (dd, J = 10.0, 3.6 Hz, 1H), 3.93 (virt t, J = 10.0 Hz, 1H), 3.72 (virt t, J = 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). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 71.7, 69.1, 50.9, 49.0, 34.5, 33.3, 26.2, 25.3. $[\alpha]_D^{21\ °C}$ = −18.5 (MeOH, c = 0.1). Mp decomposes above 200 °C. IR (ATR) $\tilde{\nu}$ = 2957 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 CH_2Cl_2 (1 mL) were added, and the resulting mixture was concentrated on a rotary evaporator under reduced pressure at rt. Upon removal of CH_2Cl_2, a suspension containing finely distributed guanylating reagent **6** was obtained. After the addition of TFA (144 μL, 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, CH_2Cl_2/MeOH/AcOH = 100/2/0.5 → 97/3/0.5) to give the symmetrically substituted guanidinium salt **40** (758 mg, 690 μmol, 38%) as a brownish oil. R_f = 0.56 (CH_2Cl_2/MeOH/AcOH = 100/8/0.5, [UV, bromocresol green]). ^{1}H NMR (600 MHz, $CDCl_3$) 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}C NMR (151 MHz, $CDCl_3$) 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. ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.6 (s, CF_3). $[\alpha]_D^{21\ °C}$ = +2.5 ($CHCl_3$, 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_3COO^-)$^+$], 816.9 (29) [(M − CF_3COO^- − $CHPh_2$)$^+$], 465.4 (35), 422.4 (80), 405.3 (100), 312.3 (71), 234.3 (49), 224.2 (37), 199.2 (43), 167.2 (37) [$CHPh_2^+$]. MS (ESI, Orbitrap) m/z 984.5 [(M − CF_3COO^-)$^+$]. HRMS (ESI, Orbitrap) calcd for $C_{65}H_{74}N_3O_2Si_2^+$ [(M − CF_3COO^-)$^+$]: 984.53141; found: 984.52673.

*Bis[(1S)-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

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J. Org. Chem. 2016, 81, 4516−4529

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 = 1/1 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 Et_2O. 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]). ^{1}H NMR (600 MHz, CD_3OD) 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). ^{13}C NMR (151 MHz, CD_3OD) 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. ^{19}F NMR (282 MHz, CD_3OD) δ −76.9 (s, CF_3, minor signal), −150.5 (s, F^-, major signal). $[\alpha]_D^{24\ °C}$ = −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) [$(M - CF_3COO^- - CHPh_2)^+$], 167.2 (100) [$CHPh_2^+$], 152.2 (32), 99.2 (8). MS (ESI, Orbitrap) m/z 508.3 [$(M - F^-)^+$]. HRMS (ESI, Orbitrap) calcd for $C_{33}H_{38}N_3O_2^+$ [$(M - F^-)^+$]: 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 $SOCl_2$, 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, CH_2Cl_2/MeOH = 99/1 → 97/3) to give an analytically pure sample for spectrosopic analyses as an off-white solid. R_f = 0.71 (CH_2Cl_2/MeOH = 9/1, [bromocresol green]). ^{1}H NMR (300 MHz, CD_3OD) 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). ^{13}C NMR (151 MHz, CD_3OD) δ 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. $[\alpha]_D^{21\ °C}$ = +61.6 (MeOH, c = 1). Mp 133−136 °C 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 → 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 × 2.0 cm, toluene/CH_2Cl_2/MeOH = 1/98/1 → 1/97/2 → 1/96/3 → 1/95/4→ CH_2Cl_2/MeOH = 96/4). The desired regioisomer **10** (69 mg, 136 μmol, 8%) was obtained as yellowish foam.[46]

Crystals suitable for X-ray analysis were obtained by dissolving this material in MeOH/$CHCl_3$ followed by slow evaporation at rt over several days.[32] R_f = 0.46 (CH_2Cl_2/MeOH = 9/1, [UV, bromocresol green]). ^{1}H NMR (600 MHz, CD_3OD) 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). ^{13}C NMR (151 MHz, CD_3OD) 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. $[\alpha]_D^{21\ °C}$ = −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 [$(M - Cl^-)^+$]. HRMS (ESI, Orbitrap) calcd for $C_{33}H_{34}N_3^+$ [$(M - Cl^-)^+$]: 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 μmol, 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 (CH_2Cl_2/MeOH = 9/1, [UV, bromocresol green]). ^{1}H NMR (400 MHz, CD_3OD) 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, CD_3OD) 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. $[\alpha]_D^{21\ °C}$ = +111.2 (MeOH, c = 1). IR (ATR) $\tilde{\nu}$ = 3636 cm^{-1} (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 $C_{33}H_{34}N_3^+$ [$(M - CF_3COO^-)^+$]: 472.27472; found: 472.27481.

■ ASSOCIATED CONTENT

Ⓢ 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

§Laboratorium für Organische Chemie, ETH Zürich, HCI E306, Vladimir-Prelog-Weg 3, 8093 Zurich, Switzerland
∥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.

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