Modified Guanidines as Potential Chiral Superbases. 1. Preparation of 1,3-Disubstituted 2-Iminoimidazolidines and the Related Guanidines through Chloroamidine Derivatives

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Modified guanidines were explored as potential chiral superbases. Thus, chiral 1,3-dimethyl-2-iminoimidazolidines with or without 4,5-diphenyl groups, their guanidinium salts, and the 2-iminoimidazolidines with (*S*)-1-phenylethyl groups on the ring nitrogens were prepared by treatment of 2-chloroimidazolinium chlorides with appropriate amines. Bicyclic guanidines were also prepared from a prolinamide using a similar procedure.

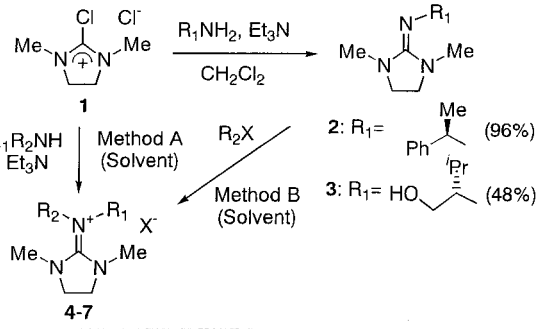
Introduction

Due to their strongly basic character,[1] guanidines can be considered as superbases[2] and, although chiral guanidines are expected to have potential as asymmetric reagents, their limited use[3] in asymmetric synthesis as chiral auxiliaries is due mainly to the absence of simple preparation methods. We[4] have reported the simple preparation of 1,3-dimethyl-2-iminoimidazolidine derivatives as monocyclic chiral guanidines from 2-chloro-1,3-dimethylimidazolinium chloride (DMC)[5] (**1**) and (4*S*,5*S*)-2-chloro-1,3-dimethyl-4,5-diphenylimidazolinium chloride (**8**) and their application to asymmetric alkylative esterification of benzoic acid with 1-phenylethyl bromide. In this paper we describe the preparation of different types of fully substituted chiral guanidines through chloroamidine intermediates in addition to further examples for the preparation of 1,3-dimethyl-2-iminoimidazolidine derivatives.[4]

Results and Discussion

Preparation of 2-Chloroimidazolinium-Derived Guanidines 2, 3, 9−21, and 27−31 and Guanidinium Salts 4−7, 22, and 23. According to the reported method[4] additional 1,3-dimethyl-2-iminoimidazolidines **2** and **3** were prepared by treatment of DMC (**1**) with appropriate primary amines (Scheme 1). Use of secondary amines in place of primary amines as nucleophiles directly afforded quaternary guanidinium chlorides, which were also obtainable by alkylation of the corresponding guanidines. Thus, four guanidinium salts **4**−**7** were prepared from **1** by either direct or indirect methods as shown in Scheme 1.

Scheme 1



Guanidinium Salts	R_1	R_2	Methods (Solvent)	Yield (%)
4 (X=Cl)	Me, Ph	Me	A (MeCN)	99
5 (X=Cl)	Me, Ph	$PhCH_2$	A (CH_2Cl_2)	75
6 (X=I)	Me, Ph	Me	B (MeCN)	83
7 (X=I)	Me, (1-Naphthyl)	Me	B (PhH)	46

The (4*S*,5*S*)-4,5-diphenyl analogue **8** was similarly led to the corresponding guanidines **9**−**21** (Table 1) and guanidinium salts **22** and **23** (Scheme 2). Even hydroxyethyl-substituted guanidines **16**−**20** and a complex guanidine **21** with a bulky 2-bornyl group could be obtained notably without protection of the hydroxy function in the former cases.

The related 2-iminoimidazolidines **27**−**31** with an (*S*)-1-phenylethyl group as a chiral substituent on the ring

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(1) Yamamoto, Y.; Kojima, S. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons Inc.: New York, 1991; Vol. 2, pp 485−526.
(2) Costa, M.; Chiusoli, G. P.; Taffurelli, D.; Dalmonego, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1541−1546.
(3) (a) For the nitroaldol (Henry) reaction, see Chinchilla, R.; Najera, C.; Sanchez-Agullo, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393−1402. (b) For the Strecker reaction, see Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910−4911. Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160. (c) For the Michael reaction, see Alcazar, V.; Moran, J. R.; deMendoza, J. *Tetrahedron Lett.* **1995**, *36*, 3941−3944. Ma, D.; Cheng, K. *Tetrahedron: Asymmetry* **1999**, *10*, 713−719. Howard-Jones, A.; Murphy, P. J.; Thomas, D. A. Caulkett, P. W. R. *J. Org. Chem.* **1999**, *64*, 1039−1041.
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(5) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 5832−5835. *Idem. Ibid.* **1999**, *64*, 6984−6988. *Idem. Ibid.* **1999**, *64*, 6989−6992.

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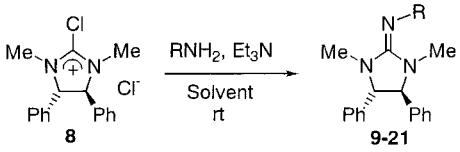
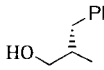
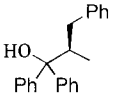
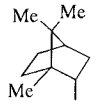
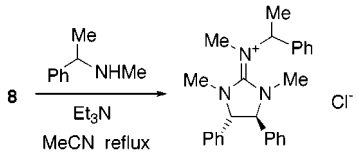
Table 1. Preparation of (4*S*,5*S*)-1,3-Dimethyl-4,5-diphenyl-2-iminoimidazolidines 9−21



Conditions		Guanidines		
Solvents[a]	Time (h)		R	Yield[b] (%)
A	1.5	**9**	$Ph(CH_2)_2$-	63
A	3	**10**	Ph	74
B	3	**11**	4-Pyridyl	64
B	1	**12**	2-Pyridyl	88
B	4	**13**	H	77
C	39	**14**	OH	88
B	0.3	**15**	$HO(CH_2)_2$-	91
B	0.3	**16**		84
B	0.5	**17**		85
B	0.8	**18**		91
B	0.5	**19**		94
A	1.2	**20**		78
A	0.6	**21**		88

[a] A = CH_2Cl_2, B = MeCN, C = DMF. [b] Isolated, nonoptimized yields.

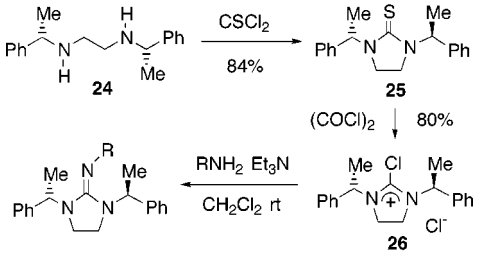
Scheme 2

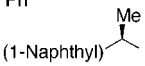
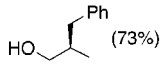


22: (*R*): 100% (15 h)
23: (*S*): 63% (6 h)

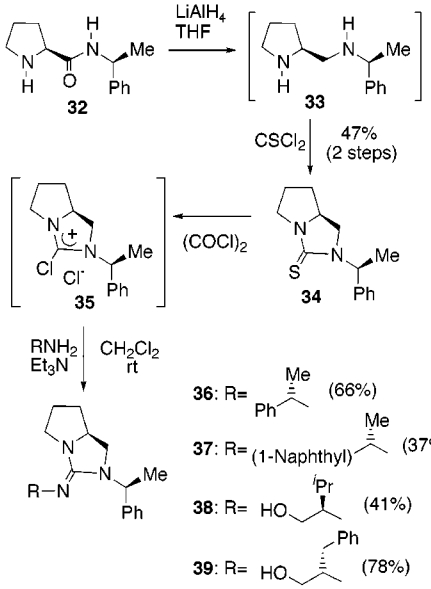
nitrogens were prepared from *N*,*N*′-bis[(*S*)-1-phenylethyl]-ethylenediamine[6] (**24**) through the 2-chloroimidazolinium chloride **26** as shown in Scheme 3. It is noteworthy that the thiourea precursor **25**, which was easily obtained by treatment of **24** with thiophosgen, was needed for the preparation of 1,3-bis[(*S*)-1-phenylethyl]-2-chloroimidazolinium chloride (**26**) due to lack of reactivity of the corresponding urea derivative. In contrast, ready preparation of chloroimidazolinium chlorides had been observed when dimethyl-substituted ureas were used as substrates.[4] It thus appears that the steric bulk of the phenylethyl group on the nitrogen atom causes lower reactivity of the urea.

Scheme 3



27: R=  (77%)
28: R=  (82%)
29: R=  (73%)
30: R= $CH_2CO_2{}^tBu$ (92%)
31: R= 4-Pyridyl [65% (in $CHCl_3$)]

Scheme 4



36: R= (66%)
37: R= (37%)
38: R= (41%)
39: R= (78%)

Preparation of the Proline-Derived Bicyclic Guanidines 36−39. The proline-derived bicyclic guanidines could be similarly synthesized through a bicyclic chloroamidinium chloride. Thus, a prolinamide[7] **32** was converted into bicyclic thiourea **34** in 47% yield by successive reduction and thiocarbonylation. Chlorination of **34** followed by treatment with chiral primary amines without purification of the intermediate chloroamidinium chloride **35** afforded bicyclic guanidines **36**−**39** (Scheme 4) in moderate to good yields.

In these guanidine systems two geometrical isomers are possible on the exocyclic double bond because of unsymmetrical substituents on the ring nitrogens. In the ^1H NMR spectrum of **36**, an NOE enhancement of a signal at δ 3.28, assigned to one of the methylene protons adjacent to the ring nitrogen originated from a proline unit, was observed on irradiation of the methyl signal in the 2-phenylethylimino group at δ 1.49, indicating that they were located close to each other. Therefore, the proline-derived bicyclic guanidines obtained here appear to exist in the (*E*)-configuration.

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Conclusions

In summary, fully substituted chiral guanidines and guanidinium salts with a imidazolidine ring system were simply prepared by the reaction of chloroamidine derivatives with primary and secondary amines, respectively. Chiral guanidinium salts had been prepared by reaction of symmetrical phosgeniminium salts and chiral secondary amines,[8] in which the phosgeniminium salts leading to 2-iminium groups in the guanidinium systems were used as electrophiles. Thus, our preparation method for chiral guanidinium salts through chloroamidines are complementary to the reported method.[8] Although only limited examples are shown in this paper, these methods are applicable to preparation of similar types of modified guanidines.

Experimental Section

General. Melting points are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ with TMS as an internal reference unless otherwise stated. UV spectra were measured in MeOH. Organic extract was dried over $MgSO_4$ or Na_2SO_4 and evaporated under reduced pressure. Columns for chromatography contained silica gel 60 (SiO_2) (70−230 mesh ASTM; Merck).

A Typical Procedure for Preparation of 1,3-Dimethyl-2-iminoimidazolidines 2, 3, and 9−21: (4*S*,5*S*)-1,3-Dimethyl-4,5-diphenyl-2-[(*R*)-1-hydroxymethyl-2-methylpropylimino]imidazolidine (16). According to the reported method,[4] to a solution of (*R*)-1-hydroxymethyl-2-methylpropylamine (1.00 g, 9.69 mmol) and Et_3N (1.89 g, 18.7 mmol) in MeCN (100 mL) was added **8** (3.00 g, 9.35 mmol) at room temperature. The whole was stirred at room temperature for 0.3 h, poured into 5% HCl solution, and extracted with CH_2Cl_2. The residue obtained from the organic extract was dissolved in water and washed with toluene. The aqueous solution was made alkaline with 5% NaOH aqueous solution and extracted with toluene. The residue obtained from the organic extract was given as a colorless viscous oil, which was slowly solidified to colorless prisms, mp 66−69 °C; IR (neat) ν_{max} 1655 cm^{-1}; UV λ_{max} 207.2 (ϵ 32900) nm; $[\alpha]^{23}_D$ +83.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 0.99 (s, 6H), 1.78−1.89 (m. 1H), 2.64 (br s, 3H), 2.82 (br s, 3H), 3.59−3.65 (m, 1H), 3.69−3.79 (m, 2H), 3.85−3.90 (m, 2H), 6.91−7.35 (m, 10H); ^{13}C NMR δ 19.1, 19.3, 31.8, 33.6, 37.7, 60.8, 64.4, 72.7, 75.1, 127.5, 128.1, 128.6, 138.7, 157.8. Anal. Calcd for $C_{22}H_{29}N_3O$: C, 75.17; H, 8.32; N, 11.96. Found: C, 75.02; H, 8.38; N, 11.84.

A Typical Procedure for Preparation of Guanidinium Salts 4, 5, 22, and 23 by Reaction of Chloroimidazolinium Chlorides with Secondary Amines: *N*-[(*S*)-1-Phenylethyl]-*N*,*N*′,*N*″-trimethyl-*N*′,*N*″-ethyleneguanidinium Chloride (4). A solution of *N*-methyl-*N*-[(*S*)-1-phenylethyl]amine (2.88 g, 21.3 mmol) and Et_3N (2.15 g, 21.3 mmol) in MeCN (20 mL) was added to a solution of **1** (3.60 g, 21.3 mmol) in MeCN (20 mL). The whole was refluxed for 3 h, cooled, and evaporated. The residue was purified by column chromatography ($CHCl_3$−MeOH = 10:1) to give **4** (5.62 g, 99%) as a colorless oil; IR (neat) ν_{max} 1600, 1565 cm^{-1}; UV λ_{max} 209.2 (ϵ 12900), 229.2 (12000) nm; $[\alpha]^{21}_D$ −5.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.76 (d, *J* = 7.0 Hz, 3H), 2.90 (s, 3H), 3.06 (s, 6H), 3.90−4.01 (m, 2H), 4.06−4.16 (m, 2H), 4.85 (q, *J* = 7.0 Hz, 1H); ^{13}C NMR δ 17.2, 32.3, 36.2, 49.7, 59.1, 126.6, 128.4, 128.9, 138.1, 163.9; FABMS *m*/*z* 232 (M^+). **The Hexafluorophosphate.** The guanidinium chloride **4** was treated with an equimolar amount of an aqueous solution of ammonium hexafluorophosphate at room temperature for 1 h and extracted with CH_2Cl_2. Recrystallization of the residue, quantitatively obtained from the organic extract, from toluene gave the hexafluorophosphate as colorless fine prisms, mp 132−133 °C; IR (KBr) ν_{max} 1610, 1570, 830 cm^{-1}; UV λ_{max} 209.6 (ϵ 13900), 228.8 (12900) nm; $[\alpha]^{22}_D$ −3.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.73 (d, *J* = 7.0 Hz, 3H), 2.81 (s, 3H), 2.95 (s, 6H), 3.67−3.81 (m, 2H), 3.86−3.97 (m, 2H), 7.29−7.44 (m, 5H); ^{13}C NMR δ 17.2, 32.1, 36.0, 49.5, 59.3, 126.8, 128.7, 129.2, 138.4, 164.1. Anal. Calcd for $C_{14}H_{24}N_3PF_6$: C, 44.57; H, 5.88; N, 11.14. Found: C, 44.91; H, 5.89; N, 10.93.

A Typical Procedure for Preparation of Guanidinium Salts 6 and 7 by Methylation of 2-Iminoimidazolidines: *N*-[(*S*)-1-(1-Naphthyl)ethyl]-*N*,*N*′,*N*″-trimethyl-*N*′,*N*″-ethyleneguanidinium Iodide (7). A solution of 1,3-dimethyl-2-[(*S*)-1-(1-naphthyl)ethyl]iminoimidazolidine[4] (1.68 g, 6.30 mmol) and methyl iodide (1.07 g, 7.56 mmol) in benzene (50 mL) was stirred at room temperature for 5 days. The precipitates were collected by filtration and recrystallized from $CHCl_3$−toluene to give **7** as colorless fine prisms (1.19 g, 46%), mp 191−193 °C (decomp); IR (KBr) ν_{max} 1595, 1560 cm^{-1}; UV λ_{max} 222.4 (ϵ 101800), 284.0 (9200) nm; $[\alpha]^{23}_D$ +179.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.95 (d, *J* = 7.0 Hz, 3H), 2.83 (s, 6H), 2.87 (s, 3H), 3.66−3.80 (m, 2H), 4.15−4.29 (m, 2H), 5.59 (q, *J* = 7.0 Hz, 1H), 7.50−7.94 (m, 7H); ^{13}C NMR δ 17.0, 33.2, 36.9, 50.2, 54.9, 121.6, 124.4, 125.0, 126.3, 127.2, 129.6, 129.7, 130.3, 133.8, 134.4, 165.0. Anal. Calcd for $C_{18}H_{24}N_3I$: C, 52.82; H, 5.91; N, 10.27. Found: C, 52.75; H, 5.90; N, 10.17.

1,3-Bis[(*S*)-1-phenylethyl]-2-thioxoimidazolidine (25). A solution of thiophosgene (4.63 g, 40.3 mmol) in CH_2Cl_2 (20 mL) was slowly added to a mixture of *N*,*N*′-bis[(*S*)-1-phenylethyl]ethylenediamine[6] (**24**) (10.8 g, 40.3 mmol) and Et_3N (8.1 g, 80.5 mmol) in CH_2Cl_2 (110 mL) at 0 °C. The whole was stirred at room temperature for 3 h, diluted with CH_2Cl_2, and washed with water. The residue obtained from the organic extract was purified by column chromatography (hexane−EtOAc = 1:1) to give **25** (10.5 g, 84%) as colorless prisms, mp 147 °C, which were recrystallized from MeOH; IR (KBr) ν_{max} 1325, 1300, 1275 cm^{-1}; UV λ_{max} 205.6 (ϵ 25200), 244.0 (23400) nm; $[\alpha]^{23}_D$ −188.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.53 (d, *J* = 7.0 Hz, 6H), 3.01−3.11 (m, 2H), 3.26−3.39 (m, 2H), 6.18 (q, *J* = 7.0 Hz, 2H), 7.23−7.40 (m, 10H); ^{13}C NMR δ 15.2, 40.8, 53.3, 127.2, 127.4, 128.4, 140.0, 181.4; FABMS *m*/*z* 311 $(M + H)^+$

1,3-Bis[(*S*)-1-phenylethyl]-2-chloroimidazolinium Chloride (26). A mixture of **25** (5.7 g, 18.4 mmol) and oxalyl chloride (2.8 g, 22 mmol) in anhydrous toluene (114 mL) was heated at 70 °C for 24 h. After cooling, precipitates were collected by filtration under protection of moisture to afford **26** (5.1 g, 80%) as a colorless hygroscopic solid; IR (KBr) ν_{max} 1595 cm^{-1}; $[\alpha]^{24}_D$ +6.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.77 (d, *J* = 7.0 Hz, 6H), 3.89−3.97 (m, 2H), 4.27−4.35 (m, 2H), 5.33 (q, *J* = 7.0 Hz, 2H), 7.31−7.45 (m, 10H); ^{13}C NMR δ 17.6, 44.8, 57.2, 127.0, 129.1, 129.3, 136.0, 153.5; HRFABMS *m*/*z* 313.1471 (M + H^+, $C_{19}H_{22}ClN_2$ requires *m*/*z* 313.1472), 315.1451 (M + 2 + H^+, $C_{19}H_{22}ClN_2$ requires *m*/*z* 315.1448).

A Typical Procedure for Preparation of 1,3-Bis[(*S*)-1-phenylethyl]-2-iminoimidazolidines 27−31: 1,3-Bis[(*S*)-1-phenylethyl]-2-[(*R*)-1-(1-naphthyl)ethylimino]imidazolidine (28). According to the above preparation method of 1,3-dimethyl-2-iminoimidazolidines treatment of **26** (2.06 g, 5.90 mmol) with (*R*)-1-(1-naphthyl)ethylamine (1.01 g, 5.90 mmol) and Et_3N (1.19 g, 11.8 mmol) in CH_2Cl_2 (30 mL) at room temperature for 1 h afforded **28** (2.16 g, 82%) as colorless prisms (recrystallized from hexane), mp 115 °C; IR (KBr) ν_{max} 1650 cm^{-1}; UV λ_{max} 225.6 (ϵ 94800), 283.2 (8000) nm; $[\alpha]^{26}_D$ −312.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.43 (d, *J* = 7.1 Hz, 6H), 1.60 (d, *J* = 6.2 Hz, 3H), 2.63−2.99 (m, 4H), 5.67 (q, *J* = 6.2 Hz, 1H), 7.17−7.22 (m, 10H), 7.37−7.51 (m, 3H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 8.04 (d, *J* = 7.1 Hz, 1H), 8.22 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 16.1, 27.7, 40.3, 52.6, 123.2, 123.4, 124.9, 125.4, 125.9, 126.5, 126.8, 127.3, 128.0, 128.8, 130.4, 133.9, 144.8, 153.4. Anal. Calcd for $C_{31}H_{33}N_3$:C, 83.18; H, 7.43; N, 9.39. Found: C, 82.85; H, 7.40; N, 9.37.

(5*S*)-3-[(*S*)-1-Phenylethyl]-2-thioxo-1,3-diazabicyclo-[3.3.0]octane (34). A solution of *N*-[(*S*)-1-phenylethyl]-(*S*)-prolinamide[7] (**32**) (9.0 g, 41.4 mmol) in THF (30 mL) was slowly added to a suspension of $LiAlH_4$ (4.7 g, 124 mmol) in THF (200 mL) at room temperature, and the whole was heated at 60 °C for 14 h. After addition of saturated Na_2SO_4 aqueous solution

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to the mixture under ice-cooling, the resulting precipitates were filtered off and washed with THF. The filtrate and washings were combined, poured into water, and extracted with CH_2Cl_2. The residual red-brown viscous oil (9.6 g) obtained from the organic extract was dissolved in CH_2Cl_2 (100 mL), and then to the solution was added Et_3N (9.5 g, 94 mmol) followed by thiophosgene (5.4 g, 47 mmol). The mixture was stirred at room temperature for 5 h. After a similar workup to the method for **25** a residue obtained from the organic extract was purified by column chromatography (hexane−EtOAc = 2:1) to give **34** as a colorless viscous oil (4.7 g, 47% in two steps); IR (neat) ν_{max} 1435 cm^{-1}; UV λ_{max} 206.8 (ϵ 16500), 246.8 (18500) nm; $[\alpha]^{23}_D$ −314.8 (*c* 1.00, $CHCl_3$); ^1H NMR δ 1.03−1.07 (m, 1H), 1.55 (d, *J* = 7.1 Hz, 3H), 1.80−1.99 (m, 3H), 2.98 (dd, *J* = 10.2, 3.5 Hz, 1H), 3.28−3.36 (m, 1H), 3.61 (t, *J* = 10.2 Hz, 1H), 3.80−3.86 (m, 1H), 4.10−4.19 (m, 1H), 6.07 (q, *J* = 7.1 Hz, 1H), 7.25−7.35 (m, 5H); ^{13}C NMR δ 14.9, 24.0, 30.2, 45.7, 47.8, 53.0, 59.1, 76.6, 77.0, 77.4, 126.5, 127.1, 128.1, 139.3, 185.1; FABMS *m*/*z* 247 ($M + H^+$).

A Typical Procedure for Preparation of the Proline-Derived Bicyclic Guanidines 36−39: (5*S*)-3-[(*S*)-1-Phenylethyl]-2-[(*S*)-1-phenylethylimino]-1,3-diazabicyclo-[3.3.0]octane (36). A solution of **34** (2.41 g, 9.8 mmol) and oxalyl chloride (1.5 g, 11.8 mmol) in anhydrous toluene (50 mL) was stirred at 60 °C for 8 h, and evaporation of the solvent gave a crude **35**, which was dissolved in CH_2Cl_2 (20 mL) without purification. The solution was added to a solution of (*S*)-1-phenylethylamine (1.42 g, 11.7 mmol) and Et_3N (1.98 g, 19.6 mmol) in CH_2Cl_2 (50 mL), and the whole was stirred at room temperature for 1 h. A similar workup to the preparation method of 1,3-dimethyl-2-iminoimidazolidines afforded **36** as a colorless oil without any purification; IR (neat) ν_{max} 1640 cm^{-1}; UV λ_{max} 208.0 (ϵ 30800) nm; $[\alpha]^{23}_D$ −73.6 (*c* 1.00, $CHCl_3$); ^1H NMR δ 1.24−1.31 (m, 1H), 1.38 (d, *J* = 6.4 Hz, 1H), 1.49 (d, *J* = 7.0 Hz, 3H), 1.60−1.67 (m, 1H), 1.73−1.79 (m, 1H), 2.64 (dd, *J* = 8.2, 4.0 Hz, 1H), 2.82−2.90 (m, 1H), 3.18−3.23 (m, 1H), 3.28 (t, *J* = 8.2 Hz, 1H), 3.63−3.72 (m, 1H), 4.79 (q, *J* = 6.4 Hz, 1H), 5.55 (q, *J* = 7.0 Hz, 1H), 7.12−7.46 (m, 10H); ^{13}C NMR δ 14.5, 26.3, 27.9, 30.9, 44.5, 50.4, 52.0, 56.6, 59.1, 76.6, 77.0, 77.4, 125.5, 126.1, 126.5, 127.2, 127.8, 128.0, 142.1, 149.5, 157.1; HRFABMS *m*/*z* 334.2272 ($M + H^+$, $C_{12}H_{28}N_3$ requires *m*/*z* 334.2282).

Supporting Information Available: Characterization data of **2**, **3**, **5**, **6**, **9-15**, **17-23**, **27**, **29-31**, and **37−39**, ^1H and ^{13}C NMR charts of **25**, **26**, **34**, and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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