Modified Guanidines as Potential Chiral Superbases. 2. Preparation of 1,3-Unsubstituted and 1-Substituted 2-Iminoimidazolidine Derivatives and a Related Guanidine by the 2-Chloro-1,3-dimethylimidazolinium Chloride-Induced Cyclization of Thioureas

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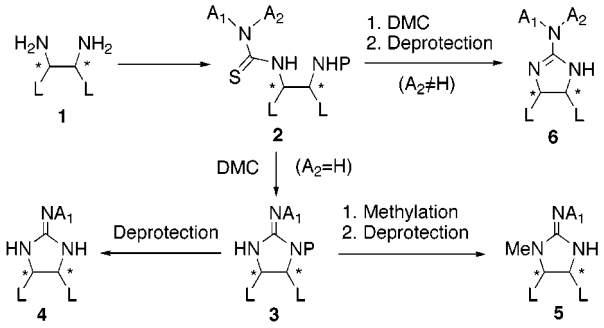
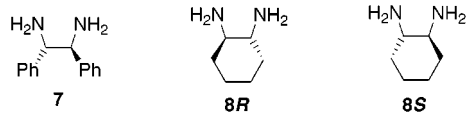
Simple preparation methods for modified guanidines were explored for new chiral superbases. Thus, (4*S*,5*S*)-4,5-diphenyl- and diastereomeric cyclohexane-fused 2-iminoimidazolidines were prepared from (1*S*,2*S*)-1,2-diphenylethylenediamine and (1*R*,2*R*)- or (1*S*,2*S*)-1,2-diaminocyclohexanes through cyclization of protected thiourea intermediates with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) as a key reaction. In the (4*S*,5*S*)-4,5-diphenyl series 1-methyl-2-iminoimidazolidines and 2-diethylaminoimidazoline were also prepared as related guanidines.

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. In the preceding paper[4] we reported the preparation of 1,3-disubstituted 2-iminoimidazolidine derivatives as potential chiral superbases. In this paper we describe the straightforward preparation of thirteen (4*S*,5*S*)-4,5-diphenyl- **67**−**79** and two diastereomeric cyclohexane-fused 2-iminoimidazolidines **80** and **81** as 1,3-unsubstituted 2-iminoimidazolidines from (1*S*,2*S*)-1,2-diphenylethylenediamine (**7**) and (1*R*,2*R*)- or (1*S*,2*S*)-1,2-diaminocyclohexanes (**8*R*** and **8*S***) through cyclization of thiourea derivatives using 2-chloro-1,3-dimethylimidazolinium chloride (DMC).[5] In the 4,5-diphenyl series 2-imino-1-methylimidazolidines **85** and **86** and 2-diethylaminoimidazoline **90** were also prepared as 1-substituted 2-iminoimidazolidines and a related guanidine, respectively.

Scheme 1





Results and Discussion

We planned the preparation of chiral guanidines with an imidazolidine ring system such as **4**, **5**, and **6** from chiral ethylenediamines **1** according to the general synthetic route as shown in Scheme 1, in which a key reaction is the DMC-induced cyclization of a thiourea deivative **2**. In the case of disubstituted thiourea **2** (A_2 = H) cyclization followed by deprotection could afford 1,3-unsubstituted 2-iminoimidazolidine **4**, whereas inclusion of a methylation step on the cyclized product **3** into the above reaction sequence leads to 2-imino-1-methylimidazolidine **5**. On the other hand, the use of trisubstituted thiourea **2** (A_2 = alkyl or aryl) in the DMC-induced cyclization could yield 2-aminoimidazoline **6**. In these

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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.
(4) Isobe, T.; Fukuda, K.; Ishikawa, T. *J. Org. Chem.* 2000, 65, 7770−7773.
(5) (a)Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 5832−5835. (b) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6984−6988. (c) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6989−6992.

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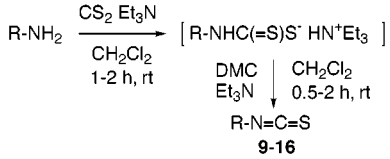
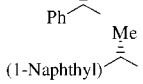
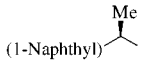
Table 1. Preparation of Isothiocyanates 9−16 from Primary Amines through Thiocarbamates



	Isothiocyanates	
	R	Yield[a] (%)
9[6]		94
10[7]		98
11[7]		94
12		93
13[8]	3,4,5-$(MeO)_3PhCH_2$	93
14[9]	$(Ph)_2CH$	83
15[10]	2-(*t*-Butyl)Ph	14[b]
16	2,5-$(t\text{-Butyl})_2$Ph	19[c]

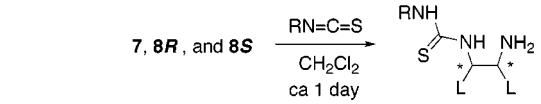
[a]Isolated, not optimized yields through two steps. [b]Reaction was not completed. [c]Reaction was not completed even after 20 h.

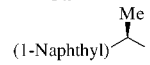
synthetic trials (1*S*,2*S*)-1,2-diphenylethylenediamine (**7**) was chosen as a convenient source of the ring nitrogens in imidazolidine skeletons. Enantiomeric 1,2-diaminocyclohexanes [**8*R*** for (1*R*,2*R*)- and **8*S*** for (1*S*,2*S*)-derivatives] were also examined as additional examples.

Preparation of (4*S*,5*S*)-4,5-Diphenyl-2-Iminoimidazolidines 67−79 and Diastereomeric Cyclohexane-Fused Derivatives 80 and 81 as 1,3-Unsubstituted 2-Iminoimidazolidines. At first the preparation of 1,3-unsubstituted 2-iminoimidazolidines such as compound **4** in Scheme 1 was examined. The intermediate protected thiourea **2** (A_2 = H) in Scheme 1 could be prepared by either formation of the thiourea followed by protection or the reverse sequence. Isothiocyanates serve as a source of thiourea functionality in each case. Thus, six isothiocyanates **9**−**14** were prepared from the corresponding chiral or achiral primary amines in high yields by the DMC-induced elimination[5b] of hydrogen sulfide in triethylammonium dithiocarbamates (Table 1). However, ineffective elimination was observed when aniline derivatives **15** and **16** incorporating sterically bulky *tert*-butyl group at the *ortho* position were used as starting amines. Following the former reaction sequence treatment of ethylenediamines **7**, **8*R***, or **8*S*** with isothiocyanates gave thioureas **17**−**27** (Table 2), conventional protection of which smoothly yielded the corresponding protected thioureas **28**−**41** (Table 3). Amide- or urethane-type protecting groups both proved of utility in the protection reactions.

In the latter sequence, in which protection precedes thiourea formation, diphenylethylenediamine **7** was used as the starting ethylenediamine. Ethoxycarbonylated ethylenediamine **42**, readily derived from **7**, was converted into the corresponding protected thioureas **43**−**47** by treatment with isothiocyanates. Heating was found to be necessary for completion of reaction in the cases of **44**−**47** (Table 4).

Table 2. Preparation of Thioureas 17−27 from Ethylenediamines 7, 8*R*, and 8*S*



Diamines	Isothiocyanates	Thioureas			
			L L	R	Yield[a] (%)
7	**9**	**17**	(*S*,*S*)-Ph Ph		76
7	**10**	**18**	(*S*,*S*)-Ph Ph		79
7	**11**	**19**	(*S*,*S*)-Ph Ph		53[b]
7	**12**	**20**	(*S*,*S*)-Ph Ph	3,4,5-$(MeO)_3PhCH_2$	73[c]
7	**13**	**21**	(*S*,*S*)-Ph Ph	$(Ph)_2CH$	86[d]
7	R=$PhCH_2$[e]	**22**	(*S*,*S*)-Ph Ph	$PhCH_2$	71[f]
7	R=Cyclohexyl[e]	**23**	(*S*,*S*)-Ph Ph	Cyclohexyl	83[g]
7	R=*t*-Butyl[e]	**24**	(*S*,*S*)-Ph Ph	*t*-Butyl	78[c]
7	R=Ethyl[e]	**25**	(*S*,*S*)-Ph Ph	Ethyl	75
8*R*	**10**	**26**	(*R*,*R*)-$(CH_2)_4$		54[h]
8*S*	**10**	**27**	(*S*,*S*)-$(CH_2)_4$		64[i]

[a]Isolated, not optimized yields. [b]Benzene was used as a solvent. [c]After 2 days. [d]MeCN was used as a solvent. After 6 days. [e]Commercially available. [f]After 4 days. [g]MeCN was used as a solvent. [h]After 5 days. [i]After 7 days.

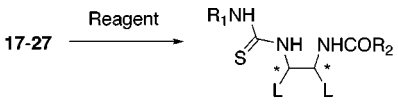
We have shown that DMC is a useful reagent for the construction of heterocycles through intramolecular dehydration.[5c] Thus, we examined the DMC-induced cyclization of thiourea derivatives, leading to protected 2-iminoimdazolidines such as **3** in Scheme 1. Treatment of protected thioureas prepared above with DMC in boiling acetonitrile in the presence of triethylamine (Et_3N) expectedly afforded cyclized products (Table 5). Seventeen 4,5-diphenyl-2-iminoimdazolidine derivatives **48**−**64** and isomeric cyclohexane-fused ones **65** and **66** were thus obtained in moderate to excellent yields, irrespective of the protecting groups used.

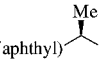
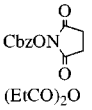
Deprotection of the cyclized products under appropriate conditions, dependent upon the protecting group, smoothly afforded 1,3-unsubstituted 2-iminoimidazolidines (Table 6). Thirteen (4*S*,5*S*)-4,5-diphenyl-2-iminoimdazolidines **67**−**79** and diastereomeric cyclohexane-fused ones **80** and **81** were prepared in high yields. Interestingly in the deprotection of carbobenzyloxy (Cbz) group of compound **60** easier removal under basic conditions (10% MeONa in MeOH, Reagent C in Table 6: 100% after 68 h) was observed compared to standard acidic conditions (30% HBr in AcOH, Reagent D in Table 6: 44% after 216 h).

In the above imidazolidine systems positional isomers[11] [an imino-type isomer **82** with an exo double bond and

(6) Terentev, A. P.; Rukhadze, E. G.; Dunina, V. V. *Dokl. Akad. Nauk. SSSR* **1969**, *187*, 1328−1331 (*Chem. Abstr.* **1969**, *71*, 123767).
(7) Bonfichi, R.; Dallanoce, C.; Lociuro, S.; Spada, A. *J. Chromatogr. A* **1995**, *707*, 355−365.
(8) Bach, E.; Kjaer, A. *Acta Chem. Scand.* **1971**, *25*, 2629−2634.
(9) Jochims, J. C.; Seeliger, A. *Angew. Chem., Int. Ed.* **1967**, *6*, 174−175.
(10) Johnson, A. L. U.S. Patent 3637731, **1972** (*Chem. Abstr.* **1972**, *76*, 113215).

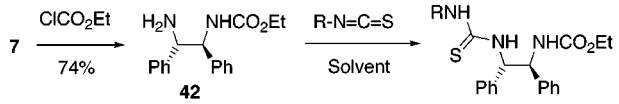
Table 3. Preparation of Protected Thioureas 28−41 by Protection of Thioureas 17−27

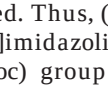


Thioureas	Reagents	Protected Thioureas				
			L L	R_1	R_2	Yield[a] (%)
17	$(Boc)_2O$	**28**	(*S*,*S*)-Ph Ph		^{t}BuO	87
18	$(Boc)_2O$	**29**	(*S*,*S*)-Ph Ph		^{t}BuO	98
18	$(PhCO)_2O$	**30**			Ph	89
19	$(Boc)_2O$	**31**	(*S*,*S*)-Ph Ph		^{t}BuO	85
20	$(PhCO)_2O$	**32**	(*S*,*S*)-Ph Ph	3,4,5-$(MeO)_3PhCH_2$	Ph	100
21	$(PhCO)_2O$	**33**	(*S*,*S*)-Ph Ph	$(Ph)_2CH$	Ph	96
22	$(PhCO)_2O$	**34**	(*S*,*S*)-Ph Ph	$PhCH_2$	Ph	92
23		**35**	(*S*,*S*)-Ph Ph	Cyclohexyl	$PhCH_2O$	85
24	$(PhCO)_2O$	**36**	(*S*,*S*)-Ph Ph	*t*-Butyl	Ph	80
25	$(PhCO)_2O$	**37**	(*S*,*S*)-Ph Ph	Ethyl	Ph	78
25		**38**			$PhCH_2O$	99
25	$(EtCO)_2O$	**39**			Et	94
26	$(PhCO)_2O$	**40**	(*R*,*R*)-$(CH_2)_4$		Ph	94
27	$(PhCO)_2O$	**41**	(*S*,*S*)-$(CH_2)_4$		Ph	87

[a]Isolated, not optimized yields.

Table 4. Preparation of Protected Thioureas 43−47 from Diphenylethylenediamine 7 through the Ethoxycarbonylated Ethylenediamine 42

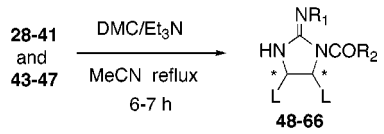


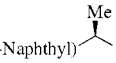
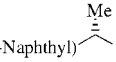
Isothiocyanates	Conditions			Ethoxycarbonylated Thioureas		
	Solvents	Temp (°C)	Time (h)		R	Yield[a] (%)
10	CH_2Cl_2	rt	120	**43**		46
11	CH_2Cl_2	reflux	21	**44**		79
R=Ph[b]	CH_2Cl_2	reflux	15	**45**	Ph	91
15	MeCN	50	15	**46**	2-(*t*-Butyl)Ph	98
16	MeCN	50	8.5	**47**	2,5-(*t*-Butyl)$_2$Ph	92

[a]Isolated, not optimized yields. [b]Commercially available.

an amino-type one **83** with an endo double bond] could be theoretically formed due to the position of a C−N double bond as shown in Figure 1. Although no experimental evidence was available on the protected imidazolidines **82** or **83** (X = COR′, Y = H), X-ray analysis of 2,5-di(*tert*-butyl)phenyl derivative **79** (see Supporting Information) suggested that 1,3-unsubstituted imidazolidines may exist as an imino-type isomers such as **82** (X = Y = H) in the solid state.

Table 5. Preparation of Protected 2-Iminoimidazolidines 48−66 by the DMC-Induced Cyclization of Thiourea Derivatives 28−41 and 43−47



Protected Thioureas	Protected 2-iminoimidazolidines				
		L L	R_1	R_2	Yield[a] (%)
28	**48**	(*S*,*S*)-Ph Ph		^{t}BuO	81
29	**49**	(*S*,*S*)-Ph Ph		^{t}BuO	71
30	**50**			Ph	95
43	**51**			EtO	94
31	**52**	(*S*,*S*)-Ph Ph		^{t}BuO	91[b]
44	**53**	(*S*,*S*)-Ph Ph		EtO	91[c]
32	**54**	(*S*,*S*)-Ph Ph	3,4,5-$(MeO)_3PhCH_2$	Ph	50
33	**55**	(*S*,*S*)-Ph Ph	$(Ph)_2CH$	Ph	82
34	**56**	(*S*,*S*)-Ph Ph	$PhCH_2$	Ph	83
35	**57**	(*S*,*S*)-Ph Ph	Cyclohexyl	$PhCH_2O$	61
36	**58**	(*S*,*S*)-Ph Ph	*t*-Butyl	Ph	86
37	**59**	(*S*,*S*)-Ph Ph	Ethyl	Ph	56
38	**60**			$PhCH_2O$	51
39	**61**			Et	65
45	**62**	(*S*,*S*)-Ph Ph	Ph	EtO	96
46	**63**	(*S*,*S*)-Ph Ph	2-(*t*-Butyl)Ph	EtO	70
47	**64**	(*S*,*S*)-Ph Ph	2,5-(*t*-Butyl)$_2$Ph	EtO	91
40	**65**	(*R*,*R*)-$(CH_2)_4$		Ph	45
41	**66**	(*S*,*S*)-$(CH_2)_4$		Ph	52

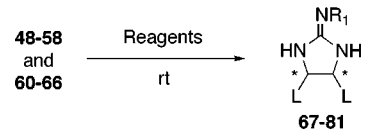
[a]Isolated, not optimized yields. [b]After 10 h. [c]After 19 h.

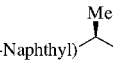
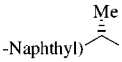
Preparation of (4*S*,5*S*)-4,5-Diphenyl-2-imino-1-methylimidazolidines 85 and 86 as 1-Substituted 2-Iminoimidazolidines and 2-Diethylaminoimidazoline 90 as a Related Guanidine. Second, the preparation of 2-imino-1-methylimidazolidines such as **5** in Scheme 1 as the 1-substituted imidazolidines was examined. Thus, (4*S*,5*S*)-4,5-diphenyl-2-[(*R*)-1-phenylethylimino]imidazolidine (**48**) protected with *tert*-butoxycarbonyl (Boc) group was converted into the corresponding 3-methyl derivatives **84** in 93% yield by treatment with *n*-BuLi followed by methylation with methyl iodide. Removal of the Boc group with 30% trifluoroacetic acid (TFA) in dichloromethane (CH_2Cl_2) afforded (4*S*,5*S*)-4,5-diphenyl-1-methyl-2-[(*R*)-1-phenylethylimino]imidazolidine (**85**) in 97% yield as a desired 1-substituted 2-iminoimidazolidine (Scheme 2). The corresponding diastereomeric guanidine **86** was also given in 88% yield from (4*S*,5*S*)-1-Boc-4,5-diphenyl-2-[(*S*)-1-phenylethylimino]imidazolidine (**49**) through two steps by the same treatment mentioned above.

In the methylated imidazolidines, positional isomers [See Figure 1; **82** or **83** (X = COR′, Y = Me)] are also possible. Examination of the NMR spectra of the methylated product **84** including $^1H-^{15}N$ HMBC experiments[12]

(11) Tanatani, A.; Yamaguchi, K.; Azumaya, I.; Fukutomi, R.; Shudo, K.; Kagechika, H. *J. Am. Chem. Soc.* **1998**, *120*, 6433−6442.

Table 6. Deprotection of Protected Imidazolidines 48−58 and 60−66 to Chiral 1,3-Unsubstituted 2-Iminoimidazolidines 67−81



Protected Imidazolidines	Reagents[a]	Time (h)	1,3-Unsubstituted 2-Iminoimidazolidines			
				L L	R_1	Yield[b] (%)
48	A	17	**67**	(*S,S*)-Ph Ph		100
49	A	5				85
50	B	0.3	**68**	(*S,S*)-Ph Ph		89
51	B	6				100
52	A	68	**69**	(*S,S*)-Ph Ph		95
53	C	24	**70**	(*S,S*)-Ph Ph		87
54	C	1	**71**	(*S,S*)-Ph Ph	3,4,5-$(MeO)_3PhCH_2$	74
55	C	2	**72**	(*S,S*)-Ph Ph	$(Ph)_2CH$	92
56	C	1	**73**	(*S,S*)-Ph Ph	$PhCH_2$	93
57	C	42	**74**	(*S,S*)-Ph Ph	Cyclohexyl	99
58	C	1.5	**75**	(*S,S*)-Ph Ph	*t*-Butyl	98
60	C	68				100
60	D	216	**76**	(*S,S*)-Ph Ph	Ethyl	44
61	E	0.2				100
62	C	18	**77**	(*S,S*)-Ph Ph	Ph	98
63	C	1	**78**	(*S,S*)-Ph Ph	2-(*t*-Butyl)Ph	96
64	B	4	**79**	(*S,S*)-Ph Ph	2,5-$(t\text{-Butyl})_2$Ph	93
65	C	1	**80**	(*R,R*)-$(CH_2)_4$		100
66	C	1	**81**	(*S,S*)-$(CH_2)_4$		87

[a]A: 30% Trifluoroacetic acid-CH_2Cl_2; B: 5% MeONa-MeOH; C: 10% MeONa-MeOH; D: 30% HBr-AcOH; E: 28% MeONa-MeOH. [b]Isolated, not optimized yields.

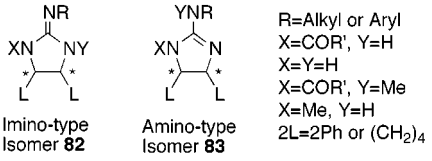


Figure 1. Possible positional isomers of the imidazolidine systems.

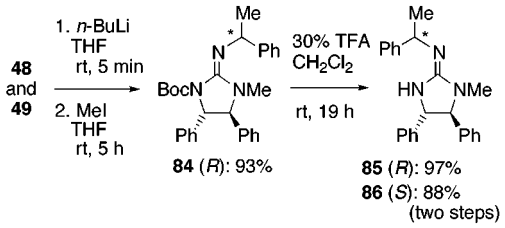
allowed us to deduce that methylation occurred at the internal nitrogen to give **84** with an exo double bond.[13]

Finally the preparation of 2-aminoimidazoline derivative was examined. The use of diethylthiocarbamoyl chloride (**87**) instead of an isothiocyanate in the reaction with an ethoxycarbonylated diamine **42** gave a trisubstituted thiourea **88**. The DMC-induced cyclization of **88** without purification afforded a cyclized product **89** in 63% yield through two steps. Treatment of **89** with 14% MeONa in MeOH yielded (4*S*,5*S*)-2-diethylamino-4,5-diphenylimidazoline (**90**) quantitatively as an alternative 1,3-unsubstituted guanidine (Scheme 3).

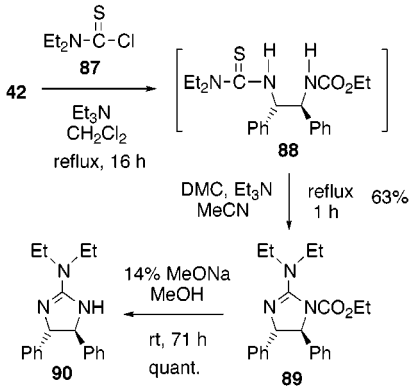
(12) For example, a strong cross-peak between an imino nitrogen (δ_N −176.8) and benzyl methyl protons (δ_H 1.37) was observed.

(13) No examination was carried out on identifying possible geometrical isomers around the exo C=N double bond.

Scheme 2



Scheme 3



Conclusions

It has been shown that 1,3-unsubstituted and 1-substituted 2-iminoimidazolidines could be simply prepared from optically active ethylenediamines. The related 2-diethylaminoimidazoline was also prepared as an alternative 1,3-unsubstituted guanidine. Thus, 15 novel 1,3-unsubstituted and two 1-substituted 2-iminoimidazolidines and one 2-aminoimidazoline have been described in this present paper. This method should be widely applicable to preparation of the same class of guanidines by use of appropriate chiral ethylenediamines.

Experimental Section

General. Starting chiral ethylenediamines were purchased from Wako Co. Ltd. (Japan). Melting points are uncorrected. ^1H (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 extracts were 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) or NH-type silica gel (NH−SiO_2) (Chromatorex NH-DM1020; Fuji Silysia Chemical Ltd.).

General Procedure for Preparation of Isothiocyanates (Table 1). A solution of an amine (31 mmol), CS_2 (31 mmol), and Et_3N (7.48 g, 74 mmol) in CH_2Cl_2 (80 mL) was stirred at room temperature for 1 h. To the mixture was dropped a solution of DMC (37 mmol) in CH_2Cl_2 (30 mL), and then the whole was stirred at room temperature for 1 h. After evaporation, the residue was purified by column chromatography (SiO_2, hexane or hexane−$CHCl_3$) to afford an isothiocyanate.

General Procedure for Preparation of Thioureas (Table 2). An isothiocyanate (26 mmol) was dropped to a solution of an ethylenediamine (26 mmol) in CH_2Cl_2 (50 mL), and then the whole was stirred at room temperature for ca. 1 day. After evaporation, the residue was purified by column chromatography (SiO_2: $CHCl_3$ or $CHCl_3$−MeOH) to afford a thiourea.

General Procedure for Protection of Thioureas (Table 3). A mixture of a thiourea (16.6 mmol), a protecting agent (16.6 mmol), and Et_3N (1.68 g, 16.6 mmol) in CH_2Cl_2 (100 mL)

was stirred at room temperature. After completion of reaction, the mixture was successively washed with water and saturated $NaHCO_3$ aqueous solution. The residue obtained from organic extract was purified by column chromatography (SiO_2, $CHCl_3$ or $CHCl_3$−MeOH), in some cases followed by recrystallization, to afford a protected thiourea.

General Procedure for Preparation of Protected Thioureas from 42 (Table 4). 42 (4.04 g, 14.2 mmol) was treated with an isothiocyanate (14.2 mmol) in an appropriate solvent (100 mL) under the conditions noted in Table 4 and cooled. The residue was purified by column chromatography (SiO_2, $CHCl_3$ or $CHCl_3$−MeOH), in some cases followed by recrystallization, to afford a protected thiourea.

General Procedure for Preparation of Protected 2-Iminoimidazolidines (Table 5). To a solution of a protected thiourea (15.1 mmol) and DMC (3.07 g, 18.2 mmol) in MeCN (100 mL) was added Et_3N (4.58 g, 45.4 mmol), and the whole was refluxed. After cooling, the whole was poured into water and extracted with CH_2Cl_2. The residue was purified by column chromatography (SiO_2, $CHCl_3$ or $CHCl_3$−MeOH), in some cases followed by recrystallization, to afford a protected 2-iminoimidazolidine.

Preparation of 1,3-Unsubstituted 2-Iminoimidazolidines (Table 6). (i) A Typical Procedure for Deprotection with 30% TFA in AcOH (Method A): (4*S*,5*S*)-4,5-Diphenyl-2-[(*S*)-1-phenylethylimino]imidazolidine (68) from 49. TFA (2.58 g, 22.7 mmol) was added to a solution of **49** (1.00 g, 2.27 mmol) in CH_2Cl_2 (6.5 mL) at room temperature. The whole was stirred at room temperature for 5 h, poured into 5% NaOH aqueous solution, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (NH−SiO_2, $CHCl_3$) to afford an amorphous mass (0.56 g, 85%); IR (KBr) ν_{max} 1600, 1575 cm^{-1}; $[\alpha]^{23}_D$ −33.3 (*c* 1.00, $CHCl_3$); UV λ_{max} 207.2 (ϵ 34600) nm; ^1H NMR δ 1.46 (d, J = 6.8 Hz, 3H), 4.12 (br s, 2H), 4.52 (s, 2H), 4.73 (q, J = 6.8 Hz, 1H),7.05−7.39 (m, 15H); ^{13}C NMR δ 23.9, 53.0, 72.8, 126.0, 126.2, 127.1, 127.2, 128.5, 128.7, 143.9, 145.2, 159.8; HRFABMS *m*/*z* 342.1945 (M + H^+, $C_{23}H_{24}N_3$ requires *m*/*z* 342.1970).

(ii) A Typical Procedure for Deprotection with 10% MeONa in MeOH (Method C): (4*S*,5*S*)-2-*tert*-Butylimino-4,5-diphenylimidazolidine (75) from 58. A solution of **58** (5.00 g, 12.6 mmol) in 10% MeONa in MeOH (78 g) was stirred at room temperature for 1.5 h, poured into water, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (SiO_2, $CHCl_3$) followed by recrystallization from CH_2Cl_2−hexane to afford colorless fine prisms (3.50 g, 98%), mp 177−178 °C; IR (KBr) ν_{max} 1625, 1595, 1565 cm^{-1}; $[\alpha]^{26}_D$ −20.7 (*c* 1.00, $CHCl_3$); UV λ_{max} 206.4 (ϵ 28600) nm; ^1H NMR δ 1.41 (s, 9H), 4.23 (br s, 2H), 4.56 (br s, 2H), 7.22−7.32 (m, 10H); ^{13}C NMR δ 29.5, 50.9, 126.4, 127.0, 128.4, 144.4, 159.2; Anal. Calcd for $C_{19}H_{23}N_3$: C, 77.77; H, 7.90; N, 14.32. Found: C, 77.92; H, 8.01; N, 14.41.

(iii) A Typical Procedure for Deprotection with 30% HBr in AcOH (Method D): (4*S*,5*S*)-4,5-Diphenyl-2-ethyliminoimidazolidine (76) from 60. A solution of **60** (0.900 g, 2.23 mmol) in 30% HBr in AcOH (13.3 g) was stirred at room temperature for 216 h, poured into water, and washed with hexane. The aqueous solution was made alkaline with 5% NaOH and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (NH−SiO_2, $CHCl_3$−MeOH = 25:1) followed by recrystallization from MeCN to afford colorless fine prisms (0.262 g, 44%), mp 171−172 °C; IR (KBr) ν_{max} 1625, 1595, 1560 cm^{-1}; $[\alpha]^{22}_D$ −40.0 (*c* 1.00, $CHCl_3$); UV λ_{max} 206.4 (ϵ 26300) nm; ^1H NMR δ 1.11 (t, J = 7.1 Hz, 3H), 3.15−3.27 (m, 2H), 4.55 (s, 2H), 7.18−7.31 (m, 10H); ^{13}C NMR δ 15.4, 37.7, 73.4, 126.6, 128.5, 143.9, 160.7. Anal. Calcd for $C_{17}H_{19}N_3$: C, 76.94; H,7.22; N, 15.84. Found: C,76.70; H, 7.17; N, 15.89.

(4*S*,5*S*)-1-*tert*-Butoxycarbonyl-4,5-diphenyl-3-methyl-2-[(*R*)-1-phenylethylimino]imidazolidine (84). A 1.54 M solution of *n*-BuLi in hexane (5.9 mL, 9.07 mmol) was dropped to an ice-cooled solution of **48** (4.00 g, 9.07 mmol) in THF (31 mL) with stirring. After stirred at room temperature for 5 min, methyl iodide (1.80 g, 12.7 mmol) was added. The whole was stirred at room temperature for 5 h, poured into water, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (SiO_2, hexanes−EtOAc = 1:1) to afford **84** as a colorless viscous oil (3.86 g, 93%); IR (neat) ν_{max} 1725, 1660 cm^{-1}; $[\alpha]^{24}_D$ −19.6 (c 1.00, $CHCl_3$); UV λ_{max} 207.2 (ϵ 46300) nm; ^1H NMR δ 1.19 (s, 9H), 1.37 (d, J = 6.4 Hz, 3H), 2.85 (s, 3H), 4.12 (d, J = 2.9 Hz, 1H), 4.85 (d, J = 2.9 Hz, 1H), 4.99 (q, J = 6.4 Hz, 1H), 7.16−7.42 (m, 13H), 7.56 (d, J = 7.3 Hz, 2H); ^{13}C NMR δ 27.6, 27.7, 32.1, 57.0, 68.0, 69.7, 82.1, 125.8, 125.9, 126.2, 126.6, 127.87, 127.91, 128.1, 128.8, 129.0, 140.7, 142.1, 145.4, 148.1, 153.1; HRFABMS *m*/*z* 456.2645 (M + H^+, $C_{29}H_{34}N_3O_2$ requires *m*/*z* 456.2651).

(4*S*,5*S*)-4,5-Diphenyl-1-methyl-2-[(*R*)-1-phenylethylimino]imidazolidine (85). A solution of **84** (3.39 g, 7.45 mmol) and TFA (12.0 g, 105.2 mmol) in CH_2Cl_2 (28 mL) was stirred at room temperature for 19 h, poured into 5% NaOH aqueous solution, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (NH−SiO_2, hexane-$CHCl_3$ = 1:1) to afford **85** as colorless prisms (2.56 g, 97%), mp 43−45 °C; IR (neat) ν_{max} 1645, 1595, 1575 cm^{-1}; $[\alpha]^{27}_D$ +84.2 (*c* 1.00, $CHCl_3$); UV λ_{max} 207.2 (ϵ 36900) nm; ^1H NMR (on the HCl salt) δ 1.93 (d, J = 6.8 Hz, 3H), 3.21 (s, 3H), 4.39 (d, J = 8.6 Hz, 1H), 4.60 (d, J = 8.6 Hz, 1H), 4.83 (m, 1H), 7.10−7.13 (m, 4H), 7.34−7.45 (m, 9H), 7.59−7.62 (m, 2H); ^{13}C NMR (on the HCl salt in CD_3OD) δ 23.8, 31.7, 55.4, 68.5, 76.3, 127.7, 128.5, 129.1, 129.7, 130.6, 130.8, 131.2, 131.3, 137.9, 139.9, 143.4, 159.2; HRFABMS *m*/*z* 356.2135 (M + H^+, $C_{24}H_{26}N_3$ requires *m*/*z* 356.2127).

(4*S*,5*S*)-2-Diethylamino-4,5-diphenyl-1-ethoxycarbonylimidazoline (89). A mixture of **42** (4.19 g, 14.8 mmol), Et_3N (1.53 g, 15.2 mmol), and diethylthiocarbamoyl chloride (**87**) (2.30 g, 15.2 mmol) in CH_2Cl_2 (50 mL) was refluxed for 16 h with stirring, acidified with 10% HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was successively washed with water and saturated $NaHCO_3$ aqueous solution. The residue (6.03 g) obtained from the organic extract was dissolved in MeCN (10 mL) containing DMC (3.91 g, 23.1 mmol). To the solution was dropped Et_3N (4.67 g, 46.3 mmol), and the whole was refluxed for 1 h. After addition of water, the mixture was extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (SiO_2, hexanes−EtOAc = 3:1) to afford **89** as a colorless viscous oil (3.41 g, 63%); IR (neat) ν_{max} 1725, 1620 cm^{-1}; $[\alpha]^{23}_D$ +6.4 (*c* 1.00, $CHCl_3$); UV λ_{max} 205.6 (ϵ 32800) nm; ^1H NMR δ 1.14 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.1 Hz, 6H), 3.26−3.38 (m, 2H), 3.53−3.64 (m, 2H), 4.03−4.15 (m, 2H), 4.84 (d, J = 2.0 Hz, 1H), 5.09 (d, J = 2.0 Hz, 1H), 7.21−7.39 (m, 10H); ^{13}C NMR δ 12.8, 14.2, 43.7, 62.2, 70.9, 73.6, 125.8, 125.9, 127.3, 127.7, 128.7, 128.8, 142.3, 143.7, 152.9, 157.0; HRFABMS *m*/*z* 366.2179 (M + H^+, $C_{22}H_{28}N_3O_2$ requires *m*/*z* 366.2182).

(4*S*,5*S*)-2-Diethylamino-4,5-diphenylimidazoline (90). A solution of **89** (1.82 g, 4.99 mmol) in 14% MeONa in MeOH (15.6 g) was stirred at room temperature for 71 h, poured into water, and extracted with CH_2Cl_2. The residue obtained from the organic extract was purified by column chromatography (NH−SiO_2, $CHCl_3$) to afford **90** (1.46 g, 100%) as colorless prisms, mp 99−100 °C; IR (KBr) ν_{max} 1600, 1580, 1495 cm^{-1}; $[\alpha]^{22}_D$ −11.9 (*c* 1.00, $CHCl_3$); UV λ_{max} 206.4 (ϵ 35400) nm; ^1H NMR δ 1.24 (t, J = 7.1 Hz, 6H), 3.28−3.51 (m, 4H), 4.03 (br s, 1H), 4.64 (s, 2H), 7.22−7.34 (m, 10H); ^{13}C NMR δ 13.9, 42.8, 74.0, 126.5, 127.1, 128.5, 144.6, 160.9. Anal. Calcd for $C_{19}H_{23}N_3$: C, 77.77; H, 7.90; N, 14.32. Found: C, 77.64; H, 7.92; N, 14.34.

Supporting Information Available: Characterization data of **12** and **16**−**81**, ^1H and ^{13}C NMR charts of **68**, **84**, **85**, and **89**, 2D NMR charts of **84.** This material is available free of charge via the Internet at http://pubs.acs.org.

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