28, 109720-75-4; (±)-**35**, 109720-76-5; (±)-**36**, 109720-77-6; (±)-**37**, 109720-78-7; (±)-**40**, 109720-79-8; **42a**, 87682-73-3; **42b**, 87682-72-2; **42c**, 87682-74-4; (±)-**43a**, 109720-80-1; (±)-**43b**, 109720-81-2; (±)-**43c**, 109720-82-3; (±)-**44a**, 87682-75-5; (±)-**44b**, 71779-54-9; (±)-**44c**, 87682-76-6; (±)-**45**, 109720-83-4; (±)-**45**·picrate, 109720-84-5; (±)-**46** (isomer 1), 109720-85-6; (±)-**46** (isomer 2), 109720-90-3; (±)-**47**, 109720-86-7; (±)-**47**·picrate, 109720-87-8; $PrNH_2$, 107-10-8; 4-$MeOC_6H_4CH_2NH_2$, 2393-23-9; $PhNH_2$, 62-53-3; Me_3Al, 75-24-1; $C_6H_{13}CHO$, 111-71-7; $Ph(CH_2)_2NH(CH_2)_2CH{=}C(Me)SiMe_3$, 109720-49-2; 3-$BrC_6H_4CHO$, 3132-99-8; $PhCH_2C(Me_2)CHO$, 1009-62-7; $Me_2S{=}CH_2$, 6814-64-8; (*E*)-$Me_3SiCH{=}CHCHO$, 33755-86-1; PrCHO, 123-72-8; $ClCO_2CH_2CCl_3$, 17341-93-4; *i*-$BuNH_2$, 78-81-9; Me_3SiCN, 7677-24-9; $Ph(CH_2)_2CHO$, 104-53-0; cyclohexylamine, 108-91-8; 2-furfural, 98-01-1; 3-pyridinecarboxaldehyde, 500-22-1; glutarimide, 1121-89-7; diethyl azodicarboxalate, 1972-28-7; succinimide, 123-56-8.

Supplementary Material Available: Experimental details and characterization data for compounds **13a,b**, **14a,b**, **15a,b**, **17b**, **18**, **19**, **20b,c**, **21b-f**, **23b,c**, **24d**, and **43b,c** (11 pages). Ordering information is given on any current masthead page.

Medium Effects and the Nature of the Rate-Determining Step in Mannich-Type Cyclizations

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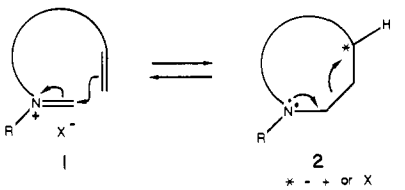
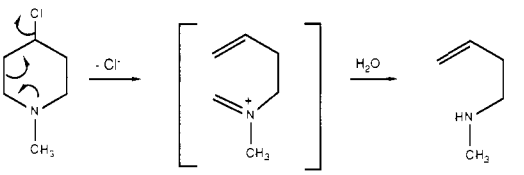
Abstract: The effect of solvent and external nucleophiles on the Mannich cyclization of five secondary amines was examined. Particularly informative were cyclizations of amines **7** and **11** (eq 4 and 5) containing two different tethered π-nucleophiles. In both cases, cyclization with only the vinylsilane terminator was observed in acetonitrile, a solvent of low nucleophilicity, while predominate cyclization with the butenyl terminator was observed in more nucleophilic solvents or in the presence of nucleophilic additives (see Tables II-VI). These results demonstrate that the "reactivity" of a π-cyclization terminator is a function of both the chemical structure of the terminator and the reaction environment. They show clearly that even weakly nucleophilic π-nucleophiles such as a terminal vinyl group can participate effectively in iminium ion cyclizations provided that the reaction medium is sufficiently nucleophilic. In marked contrast, iminium ion-vinylsilane cyclizations are little affected by the reaction environment. These studies also provide, to the best of our knowledge, the first definitive evidence that the cyclization of iminium ions with simple alkenes is not a concerted process, but rather proceeds via a cationic intermediate capable of partitioning between product formation and reversal to the starting iminium cation.

As discussed briefly in the accompanying paper in this series,[1] the recent development of a diverse arsenal of nucleophilic cyclization terminators has greatly broadened the utility of Mannich cyclizations[2,3] for the synthesis of nitrogen heterocycles. The use of this strategy for preparing complex azacyclics typically involves the proper matching of an iminium ion electrophile (cyclization initiator) with an intramolecular nucleophile (cyclization terminator). The cyclization terminator must be stable to the conditions for intramolecular iminium ion generation and react to form a ring of the desired size. For π-nucleophiles, the latter requirement reduces to controlling whether the π bond participates in the cyclization reaction in an endo- or exocyclic sense.[4] Considerable insight is currently available on the effect of ring size and cyclization mode (i.e., endo- or exocyclic) on the rate of ring formation.[5] Conspicuously less information is available on the relative reactivity of nucleophilic terminators[3,6] and the important question of possible reversibility of the key C-C bond-forming step in Mannich cyclization reactions.

The cyclization of a π-nucleophile with an iminium ion (**1** → **2**) results in the development of electron deficiency at the carbon γ to the amine function. That this carbon-carbon bond-forming process might be reversible (**2** → **1**) is strongly indicated by the extensive studies of Grob[7] on fragmentation reactions of amines containing leaving groups at the γ position, e.g., eq 2.



(1)



(2)

During the course of the studies described in the preceding paper,[1] it occurred to us that the cyclization of an iminium ion containing two tethered nucleophiles (see eq 3) would provide an excellent system for studying, by internal competition, the relative reactivity of π-nucleophiles in electrophilic cyclization reactions. Moreover, by studying the effects of cyclization medium on this competition, one might be able to explore the reversibility of Mannich cyclizations, since the transformation of **4** to the neutral products **5** and **6** involves not only C-C bond formation but also the subsequent step(s) that may be involved in the formation of a neutral product (e.g., from **2**, where * = +). If C-C bond formation were reversible, terminator "reactivity" would be a

(1) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) For a review of the early work in this area, see: Hellman, H.; Opitz, G. *α-Aminoalkylierung*; Verlag Chemie: Weinheim, FRG, 1960.

(3) For a review of some of the recent work in this area, see: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 5 and 6. Hart, D. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W.; Ed., Wiley: New York, in press.

(4) See, e.g.: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

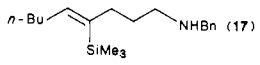
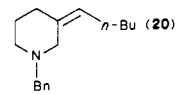
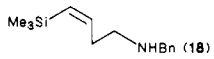
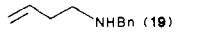
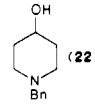
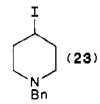
(5) See, inter alia: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983. Illuminati, G; Mandolini, L. *Acc. Chem. Res.* **1981**, 95.

(6) Recent studies of the relative reactivities of selected nucleophilic terminators can be found: (a) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. (b) Nakamura, E.; Fukuzaki, K.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 499.

(7) For reviews, see: Becker, K. B.; Grob, C. A. In *The Chemistry of Double-Bonded Functional Groups*, Part 2; Patai, S., Ed.; John Wiley: New York; 1977; Chapter 8. Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. Grob, C. C.; Shiess, P. W. *Ibid.* **1967**, *6*, 1.

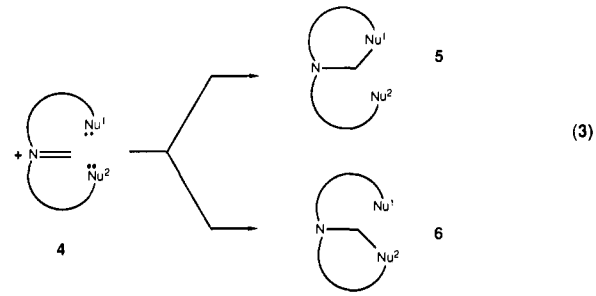
0002-7863/87/1509-6107$01.50/0

Table I. Solvent and Additive Effects on Iminium Ion Cyclizations of Vinylsilanes and a Simple Alkene

entry	substrate	reaction conditions[a] solvent/additive	time, h	temp, °C	product	yield, % isolated (GLC)
1		CH_3CN[b]	0.5	85		85 (100)
2	**17**	HOAc	0.5	100	**20**	85 (100)
3	**17**	H_2O	3	90	**20**	92 (100)
4		CH_3CN[b]	0.5	85	 (21)	90 (100)
5	**18**	HOAc	0.5	85	**21**	82 (100)
6	**18**	H_2O	1	100	**21**	91 (100)
7		CH_3CN[b]	24	100	no reaction	
8	**19**	H_2O	1	100	 (22)	87
9	**19**	H_2O/NaI (5 equiv)	0.2	100	 (23)	92

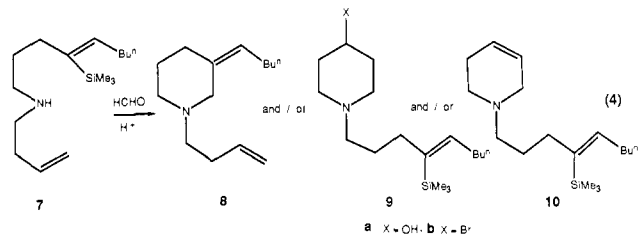
[a] [Substrate] = 0.5 M, 2 equiv of 37% formaldehyde, 1.0 equiv of camphorsulfonic acid. [b] 30 equiv of paraformaldehyde were employed.

function of *both* the chemical structure of the terminator and the reaction environment.

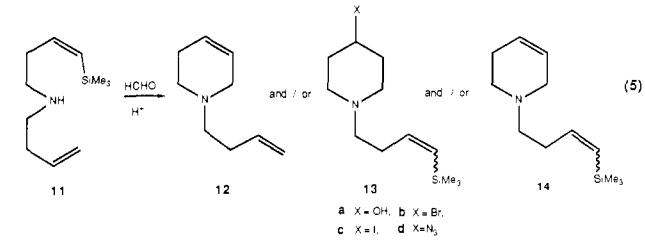


(3)

We targeted for detailed study the competition between simple alkene and vinylsilane[8] terminators, see eq 4 and 5. These two

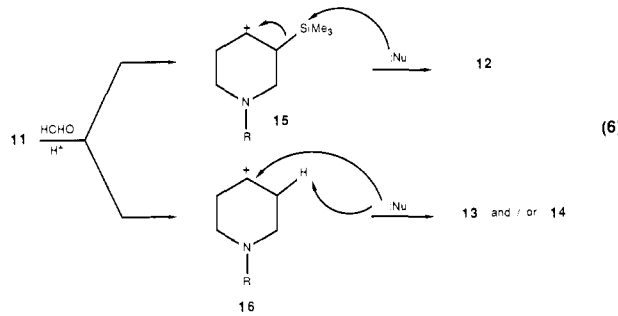


(4)



(5)

types of internal nucleophiles were chosen since we expected that they might represent extremes with regard to the importance of the cyclization medium on reactivity. For example, we had observed in our earlier studies[9] of vinylsilane iminium ion cyclizations that the choice of the reaction solvent or the acid employed in iminium ion generation was not critical. These observations would be consistent with the extensive "internal" stabilization of **15** provided by the β-silyl substituent (see eq 6)[10] and the fact that nucleophilic substitutions at silicon (e.g., the conversion of **15** → **12**) are unusually fast.[10] Thus, the importance of cation solvation is mitigated and the nature of the nucleophile (solvent or nucleophilic anion) to which the Me_3Si group is transferred during decomposition of the presumed β-silylcation intermediate **15** may be relatively unimportant also. On the other hand, we anticipated that the reaction medium would be very important in stabilizing a relatively unstable secondary cation such as **16**.[11]



(6)

In this paper we report that the outcome of the Mannich cyclizations of amines **7** and **11** is *dramatically* affected by the nature of the reaction solvent and the presence of external nucleophiles. We also present clear evidence that the cyclization of iminium ions with simple alkenes proceeds via a cationic intermediate that is capable of partitioning between product formation and reversal to the starting iminium cation.

Results

Before proceeding to the competition experiments, we briefly examined cyclizations of amines **17–19** which contain a single

(8) For a recent comprehensive review, see: Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.

(9) for a brief review, see: Overman, L. E. *Lect. Heterocycl. Chem.* **1985**, *59*.

(10) For general reviews of organosilicon chemistry see: (a) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. (b) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981. (c) Fleming, I. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, p 539. (d) Magnus, P. D.; Sarkar, T.; Djuric, S. In *Comprehensive Organometallic Chemistry*; Wilkinson, G. W., Stone, F. G. A., Abel, F. W., Eds.; Pergamon: Oxford, 1982; Vol. 7, p 515.

(11) Olah, G. A.; Olah, J. A. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley: New York, 1970; Vol. 2, Chapter 7.

Table II. Solvent and Additive Effects on Iminium Ion Cyclizations of Amine **7**

	reaction conditions[a]			products	
				ratio	
entry	solvent/additive	temp, °C	time, h	**8**:**9** (or **27**)[b]	yields[c]
1	CH_3CN	100	1	100:0	**8** (89%)
2	HCOOH (98%)[d]	85	0.5	76:24	**8** (59%), **27** (13%)
3	CH_3COOH[d]	100	1	55:45	**8** (49%), **9a** (38%)
4	H_2O	100	2	6:94	**8** (5%), **9a** (65%)
5	CH_3CN/Bu_4NBr (5 equiv)	100	2	17:83[e]	**8** (16%), **9b** (76%)

[a] [**7**] = 1.0 M; 2.0 equiv of 37% formaldehyde; 1.0 equiv of camphorsulfonic acid. [b] By ^1H NMR analysis of the crude product. [c] Of isolated products. [d] The crude cyclization product was hydrolyzed prior to analysis and product isolation. [e] Ratio determined from yields of isolated products.

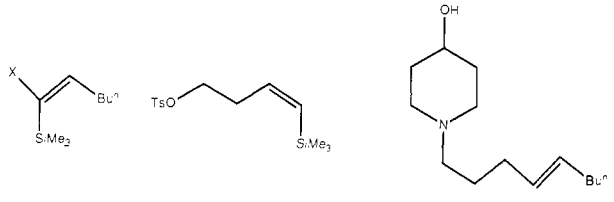
Table III. Solvent and Additive Effects on Iminium Ion Cyclization of Amine **11**

	reaction conditions[a]			products	
entry	solvent/additive	temp, °C	time, h	ratio[b]	yields[c]
1	CH_3CN	100	1	only **12**	**12** (72%)
2	H_2O	80	1	**12**:**13a** = 66:34	**12** (52%), **13a** (33%)[d]
3	CH_3CN/Bu_4NBr (5 equiv)	100	2	*e*	**13b** (43%)
4	H_2O/NaI (10 equiv)[f]	100	0.1	**12**:**13a**:**13c** = 24:13:62	*e*
5	H_2O/NaI (10 equiv)[f]	100	1.0	**12**:**13a**:**13c** = 33:12:55	**12** (25%), **13a** (10%), **13c** (46%)
6	H_2O/NaI (10 equiv)[f]	100	15	**12**:**13a**:**13c** = 59:25:16	*e*

[a] [**11**] = 1.0 M; 2.0 equiv of 37% formaldehyde; 1.0 equiv of camphorsulfonic acid. [b] By ^1H NMR analysis of the crude product. [c] Of isolated products. [d] The crude cyclization product was hydrolyzed prior to analysis and product isolation. [e] Not determined. [f] [**11**] = 0.5 M.

cyclization terminator, see Table I. Cyclizations were carried out with 2–5 equiv of formaldehyde and 1.0 equiv of camphorsulfonic acid. As anticipated,[9] vinylsilanes **17** and **18** cyclized cleanly in all three solvents (CH_3CN, HOAc, and H_2O) to afford only the (*Z*)-pentylidenepiperidine **20** and the known[12] tetrahydropyridine **21**, respectively. In contrast, *N*-benzyl-3-butenylamine (**19**) did not react with formaldehyde and camphorsulfonic acid at 100 °C in acetonitrile, but it was cleanly cyclized at 100 °C in H_2O to give 1-benzyl-4-hydroxypiperidine (**22**).[13] When this latter reaction was conducted in the presence of 5 equiv of NaI as an external nucleophile, 1-benzyl-4-iodopiperidine (**23**) was obtained in >90% yield. The structure of **20** followed directly from the similarity of its spectral properties to related compounds prepared earlier in our laboratories,[1,9] while the presence of the iodo substituent at position 4 of the piperidine ring of **23** followed directly from the ^{13}C NMR spectrum which showed signals for only 8 carbons.

The unsymmetrical secondary amines **7** and **11** required for the competition experiments were prepared in 50–70% yield by simple alkylation of bromide **24** or tosylate **26**[14] with an excess of 3-buten-1-ylamine.[15] Bromide **24** was available in 42% yield from (*E*)-1-bromo-1-(trimethylsilyl)-1-hexene (**25**)[16] by alkylation of the derived lithium reagent[17] with an excess of 1,3-dibromopropane.



24 X = $(CH_2)_3Br$ **26** **27**

25 X = Br

The results obtained from cyclization of **7** with 2 equiv of formaldehyde and 1.0 equiv of acid are summarized in Table II. When this reaction was conducted in dry acetonitrile *only* the pentylidenepiperidine **8**, resulting from participation of the vinylsilane terminator, was observed. Remarkably, the relative order of terminator reactivity could be almost completely reversed by a change of solvent. Thus, identical treatment of **7** in H_2O resulted in cyclization with the butenyl group to provide 4-hydroxypiperidine **9a** as the predominant (>90%) product. Cyclizations of **7** in acetic and formic acid showed intermediate behavior providing substantial amounts of products arising from participation of both nucleophilic terminators (Table II, entries 2 and 3). Since some H_2O was unavoidably present in these reaction mixtures, the 4-substituted piperidine products were mixtures of **9a** and its acetate or formate ester. To simplify this mixture, the crude cyclization product in these cases was hydrolyzed prior to analysis and product isolation. In formic acid, tetrahydropyridine **9** (X = OCHO or OH) suffered protodesilylation under the reaction conditions and, thus, participation of the butenyl terminator was detected by the isolation of hydroxypiperidine **27**. Even in acetonitrile the reaction can be diverted toward predominant participation of the simple butenyl terminator by the addition of tetrabutylammonium bromide (entry 5). In no case was there any indication of the formation of tetrahydropyridine **10** which would have arisen by proton loss from a 4-piperidinyl cation intermediate.

The results of similar competition experiments with secondary amine **11** are summarized in Table III. Terminator reactivity was again found to be a sensitive function of the reaction medium. In acetonitrile, *only* reaction of the vinylsilane terminator was observed to provide butenyltetrahydropyridine **12** as the sole product. In H_2O, both terminators reacted at similar rates to provide a mixture of **12** and 4-hydroxypiperidine **13a**. This latter product is isolated as a mixture of vinylsilane stereoisomers, indicating[1] that cationic aza-Cope equilibration of the formaldeyde iminium ion derivative of **11** is more rapid than cyclization. The occurrence of this equilibrium likely does not greatly bias the terminator competition, since we had previously demonstrated[1] that, at least in acetonitrile, the (*E*)- and (*Z*)-4-(trimethylsilyl)-3-butenyl terminators have comparable reactivities. Iminium ion cyclization of **11** in H_2O in the presence of 10 equiv of NaI provided 4-iodopiperidine **13c** in addition to tetrahydropyridine **12** and small amounts of hydroxypiperidine **13a**. Again tetrahydropyridine **14**, which could have arisen by proton loss from a 4-piperidinyl cation intermediate, was not detected.[18]

Entries 4–6 in Table III demonstrate that although the cyclization of **11** is essentially complete in 5 min at 100 °C, product ratios vary with time. Most apparent is the buildup of tetra-

(12) Oediger, H.; Joop, N. *Liebigs, Ann. Chem.* **1972**, *764*, 21.
(13) Commercially available from Aldrich Chemical Co.
(14) Overman, L. E.; Flann, C. J.; Malone, T. C. *Org. Synth.*, checked procedure.
(15) Renk, E.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 878.
(16) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739.
(17) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1979**, *44*, 4623.

(18) Consistent with this observation is the complete absence of **21** in the crude reaction product (by ^1H NMR or capillary GC analysis) of the cyclization reactions reported in entries 8 and 9 of Table I.

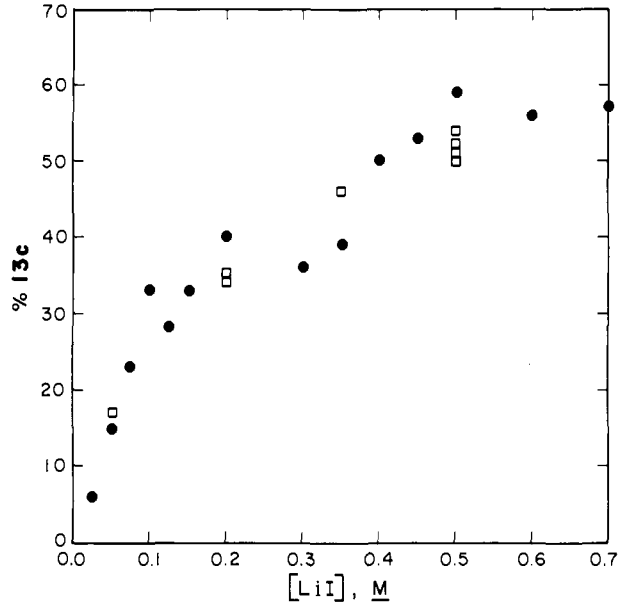
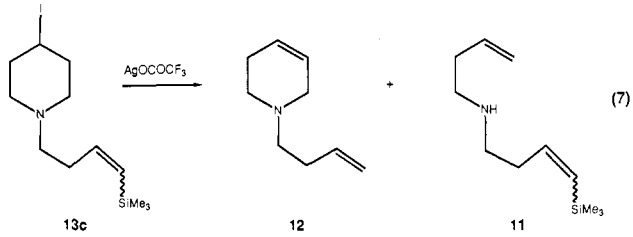


Figure 1. Percentage of 4-iodopiperidine **13c** in the cyclized product as a function of LiI concentration. Temperature = 75 °C, pH 1.25, solvent = H_2O. Reactions conducted at a constant ionic strength of 0.80 are indicated by □.

hydropyridine **12** at the expense of iodide **13c**. Grob fragmentation[7] of **13c** under these conditions would regenerate the formaldehyde iminium ion derivative of **11** and could explain the secondary conversion of **13c** → **12**. This conversion can be demonstrated in acetonitrile at 80 °C by allowing iodide **13c** to react for 30 min with an excess of $AgOCOCF_3$ (see eq 7). This treatment provided, after aqueous workup, a 3:1 mixture of tetrahydropyridine **12** and the secondary amine **11**.



13c 12 11 (7)

To pursue in more quantitative detail the effect of added nucleophiles on the cyclization of amine **11**, we have investigated carefully the cyclization of **11** in H_2O in the presence of added LiI. The results of these experiments are summarized in Table IV and Figure 1. Reactions were conducted at 75 °C and product ratios were determined after 30 min (~50% conversion of **11**) by high-field (500 or 300 MHz) ^1H NMR analysis of the crude reaction product.[19] Cyclizations terminated at 15, 30, or 60 min gave identical (within experimental error) product mixtures (see Table IV, entries 18–24), indicating that the product ratios under these conditions are kinetically controlled. Our early experiments indicated that the ratio of **13c**:**12** increased (at a constant [LiI]) with the amount of camphorsulfonic acid present. As a result all the reactions summarized in Table IV were conducted at pH 1.25 ± 0.10 in the presence of a buffering amount of a 1:1 mixture of camphorsulfonic acid and sodium camphorsulfonate.

The reactions summarized in Table IV correspond to a single determination, with the exception of entries 9–11 and 18–24. The precision of these latter experiments (X ± SD: **13c** = 51 ± 1.5%, **13a** = 10 ± 3.1%, **12** = 39 ± 2.6%) is reasonable for the ^1H NMR analytical technique employed and is sufficiently precise to clearly define the trend between products **12** and **13c**. On the other hand, in cyclizations conducted in the presence of more than 1 equiv of LiI, the amount of alcohol **13a** detected is comparable to the experimental uncertainty. One check of the general accuracy of the ^1H NMR analysis is provided by the experiment reported in Table III, entry 5, where the ratio of **12**:**13a**:**13c** determined by ^1H NMR analysis was essentially identical with that obtained by product isolation.

(19) We found that better reproducibility was obtained with ^1H NMR than with capillary GLC analysis. Compound **13c** required high temperatures for elution on capillary GLC columns and extensive decomposition occurred.

Table IV. Effect of LiI on the Cyclization of Amine **11** in Water at pH 1.25[a]

entry	[LiI], M	[$LiClO_4$], M	μ[b]	pH[c]	product ratio,[d] % 13c	13a	12
1	0.025	0	0.28	1.25	6	17	77
2	0.05	0	0.30		15	14	71
3	0.05	0.50	0.80		17	11	71
4	0.075	0	0.33		23	9	68
5	0.10	0	0.35		33	10	57
6	0.125	0	0.38		28	7	65
7	0.15	0	0.40		33	6	61
8	0.20	0	0.45		40	9	51
9	0.20	0.35	0.80		34	13	53
10	0.20	0.35	0.80		35	13	52
11	0.20	0.35	0.80		35	3	61
12	0.30	0	0.55	1.25	36	7	57
13	0.35	0	0.60		39	4	57
14	0.35	0.20	0.80		46	5	48
15	0.40	0	0.65	1.20	50	6	45
16	0.45	0	0.70	1.30	53	9	38
17	0.50	0	0.75		59	6	35
18	0.50	0.05	0.80		52	4	44
19	0.50	0.05	0.80		50	14	36
20	0.50	0.05	0.80		50	10	40
21[e]	0.50	0.05	0.80		54	8	38
22[e]	0.50	0.05	0.80		51	12	37
23[f]	0.50	0.05	0.80		50	10	40
24[f]	0.50	0.05	0.80		51	10	39
25	0.60	0	0.85	1.25	56	6	38
26	0.70	0	0.95		57	1	42

[a] At 75 °C in a camphorsulfonic acid/sodium camphorsulfonate buffer ($[buffer]_{total}$ = 0.50 M, CSA/NaCSA = 1.0); starting concentration of formalin = 0.10 M; starting concentration of **11** = 0.05 M. [b] Ionic strength ([LiI] + [$LiClO_4$] + [NaCSA]. [c] Measured prior to workup. [d] Determined at 30 min reaction time which corresponds to 50–60% conversion of **11**. [e] Determined at 15 min reaction time. [f] Determined at 60 min reaction time.

Reactions conducted at high concentrations of LiI are heterogeneous at room temperature, but they rapidly become homogeneous upon heating. To establish that the rate of LiI dissolution did not affect the competition, the experiments reported in entries 14, 15, and 20 were conducted in two ways: (1) all reagents were mixed and with stirring were placed in a 75 °C bath (standard procedure, the reaction became homogeneous within 1 min), and (2) the buffered solution of LiI and $LiClO_4$ was preheated to 75 °C before **11** and formalin were added. No significant difference was observed in the product ratios of cyclizations carried out with these two different experimental protocols.

As expected, the data summarized in Figure 1 show that the amount of iodide **13c** produced increases with increasing LiI concentration. The relationship is not, however, a linear one, as the amount of iodide **13c** and tetrahydropyridine **12** produced level off at ~60% and 40%, respectively. Experiments conducted in the presence of added $LiClO_4$ (compare entries 2 and 3, 8–11, 13 and 14, 17 and 18) demonstrate that this saturation phenomenum is not due to the effect of increasing ionic strength. The data points depicted by an open square in Figure 1 correspond to determinations made at a constant ionic strength of 0.8.

To explore whether more tetrahydropyridine **12** would be produced in cyclizations carried out in the presence of a silylphilic nucleophile,[10] the cyclizations reported in entries 12 and 15 were repeated in the presence of added LiCl. As summarized in Table V, the ratio of products produced was identical, within experimental error, with that of cyclizations carried out in the absence of LiCl.

We also briefly examined whether this saturation phenomenum would be observed with another nucleophile, NaN_3. The results

Table V. Effect of Added LiCl on the Cyclization of Amine **11** in Water at pH 1.25 in the Presence of LiI[a]

[LiI], M	[LiCl], M	μ[b]	product ratio,[c] % 13c	13a	12
0.30	0.25	0.80	37	6	57
0.30	0.25	0.80	43	8	49
0.40	0.15	0.80	52	6	42
0.40	0.15	0.80	48	5	47

[a] At 75 °C in a camphorsulfonic acid/sodium camphorsulfonate buffer ($[buffer]_{total}$ = 0.50 M, CSA/NaCSA = 1.0); starting concentration of formalin = 0.10 M; starting concentration of **11** = 0.05 M. [b] Ionic strength ([LiI] + [$LiClO_4$] + [NaCSA]). [c] Determined at 30 min reaction time which corresponds to 50–60% conversion of **11**.

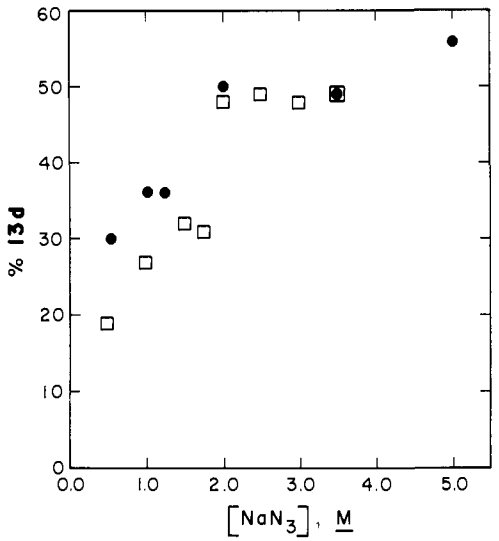


Figure 2. Percentage of 4-azidopiperidine **13d** in the cyclized product as a function of NaN_3 concentration. Temperature = 75 °C, pH 5.9 ± 0.3, solvent = H_2O. Reactions conducted at a constant ionic strength of 4.3 are indicated by □.

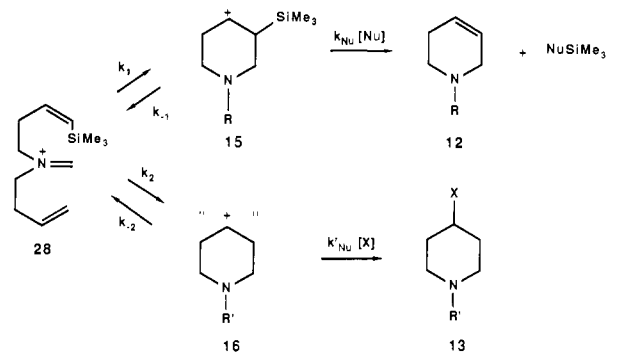
of this study are summarized in Figure 2. The amount of 4-azidopiperidine **13d** (see eq 5) formed did increase with increasing NaN_3 concentration, but again in a nonlinear fashion. At azide concentrations of 2.0 M or greater, the only products produced were tetrahydropyridine **12** and azidopiperidine **13d**, and these were formed in nearly equal amounts.[20] A comparison of the concentrations of trapping nucleophiles employed in the experiments summarized in Figures 1 and 2 shows that azide is a much less effective trapping agent than iodide.

Discussion

Implications for Synthesis. The results obtained from the cyclizations of the unsymmetrical amines **7** and **11** demonstrate the profound affect that solvent and counterions can have on the outcome of Mannich cyclizations. Thus, while amine **7** cyclizes in H_2O with predominate (94%) participation of the butenyl group, cyclization of **7** in acetonitrile under identical conditions occurs *only* with the tethered vinylsilane nucleophile. Similar trends, although less dramatic, were observed in Mannich cyclizations of amine **11**. These studies highlight the fact that the reactivity of cyclization terminators is intimately tied to the nature of the reaction environment (solvent, counterions, etc.). Widely differing orders of relative π-terminator reactivity will be observed under different cyclization conditions.

In complex synthesis applications where cyclization with more than one intramolecular nucleophile is possible, our results suggest that the reaction environment might be rationally modified to control the cyclization outcome. The reaction of π-nucleophiles whose participation forms relatively unstable carbocationic intermediates will be favored by increases in solvent polarity and reaction medium nucleophilicity. On the other hand, less polar and less nucleophilic reaction conditions will favor participation of π-nucleophiles that afford more stabilized carbocationic intermediates or intermediates that can dissipate charge in an intramolecular fashion. In this latter group would be cyclization terminators that undergo facile loss of a β-substituent (allyl- and vinylsilanes and stannanes, silyl enol ethers, etc.) and terminators capable of internal charge stabilization (e.g., by a neighboring heteroatom nucleophile).

Scheme I



Our studies, together with the recent studies by Grieco and others,[21] demonstrate that even weak π-nucleophiles such as terminal vinyl groups can participate effectively in iminium ion cyclizations provided that the reaction medium is sufficiently nucleophilic. In this way, substituted piperidines, containing a wide variety of 4-substituents, can be prepared simply from 3-butenylamine precursors.

Mechanism of Iminium Ion Cyclizations. The experiments reported here for the Mannich cyclization of amines **7** and **11** are inconsistent with mechanisms in which C–C bond formation is the sole rate-determining step. These experiments are best interpreted in terms of mechanistic sequences such as the one shown in Scheme I for the cyclization of the iminium ion derived from amine **11**. The observation that the yield of 4-iodopiperidine **13c** and 4-azidopiperidine **13d** does *not* increase linearly with increasing concentrations of I^- and N_3^- rigorously establishes that **13** is *not* produced by a concerted reaction of a nucleophile X with the iminium cation **28**. Since our studies shed no light on the structure of the intermediate that intervenes between **28** and **13**, we will depict it simply as a 4-piperidinyl cation. We would stress, however, that a bridged cation[22] or a π-complex[23] is likely a better description of this intermediate.[24] We also note that the experiments reported in the accompanying paper of this series[1] strongly suggest that **28** is undergoing cationic aza-Cope equilibration with its allylsilane iminium ion isomer more rapidly than cyclization.[25] Since both silyl terminators will form the same β-silyl cation **15** upon cyclization, the intervention of the allylsilane sigmatropic isomer in the conversion of **28** → **15** will be omitted from this discussion for simplicity. It should be stressed that the effects of reaction medium on the cyclization of amine **7** are not complicated by sigmatropic rearrangement of the silyl terminator and are well interpreted by a mechanistic sequence similar to the one depicted in Scheme I.

The formation of only tetrahydropyridine **12** from cyclization of **28** in acetonitrile is rationalized by the inability of the weak

(20) Less than 10% of alcohol **13a** was formed even at low NaN_3 concentrations. These results are summarized in Table VI which is included as Supplementary Material.

(21) (a) Larsen, S. D.; Grieco, P. A.; Fobare, W. F. *J. Am. Chem. Soc.* **1986**, *108*, 3512. (b) Hartman, G. D.; Hakzenko, W.; Phillips, B. T.; Pitzenberger, S. M.; Springer, J. P.; Hirshfield, J. *J. Org. Chem.* **1986**, *51*, 2202.

(22) See, inter alia: Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. Harding, K. E. *Bioorg. Chem.* **1973**, *2*, 248. Reference 3, Chapter 5.

(23) For a recent discussion, see: Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744. For a recent experimental study, see: Pock, R.; Mayr, H.; Rubow, M.; Wilheim, E. *J. Am. Chem. Soc.* **1986**, *108*, 7767.

(24) (a) The stereoselectivity[3,21] of iminium ion cyclizations of more complex substrates would suggest that "totally" free cations are not intermediates.[3] (b) We recognize that a simple secondary 4-piperidinyl cation is an unlikely intermediate for energetic reasons.

(25) The butenyl group is undoubtedly undergoing degenerate cationic aza-Cope rearrangement as well.

nucleophile acetonitrile[26] to trap the cationic intermediate **16**.[24] As long as **28** can be formed reversibly from **16**, the cyclization product produced in acetonitrile would be derived solely from the β-silyl cation **15**. The formation of **12** from silver-assisted fragmentation of 4-iodopiperidine **13c** (eq 7) provides support for this proposal. The high-yield formation of **12** in acetonitrile demonstrates that the β-silyl cation **15** can effectively transfer its trimethylsilyl group to even a weakly nulceophilic reaction medium such as acetonitrile.

The ratio of products produced in cyclizations conducted in the presence of added nucleophiles depends critically on the partitioning of intermediate **16**. The fact that ~40% of **12** is formed even in the presence of a large excess of LiI suggests that loss of the Me_3Si group from **15** is more rapid than fragmentation of this intermediate to **28**. Thus, under saturating conditions of high LiI concentration,[27] the 0.8 ratio of products **12**:**13c** represents simply the rate constant ratio k_1/k_2. Consistent with the irreversible formation of **15** from **28** was the observation that the addition of the silylphilic[10] nucleophile Cl^- had no effect on the yield of tetrahydropyridine **12**. If the ratio of tetrahydropyridine to 4-iodopiperidine products at high concentrations of LiI reflects only the rate of cyclization of **28** with the two different intramolecular π-nucleophiles, then this ratio should be independent of the added nucleophile, as long as the nucleophile concentration is sufficient to trap **16** more rapidly than it reverts to **28**. The experiments conducted in the presence of added NaN_3 (Figure 2) are in full accord with this prediction.

Conclusion

These studies provide dramatic evidence of the pronounced affect that cyclization medium can have on the outcome of Mannich-type cyclizations. In particular, our results clearly demonstrate that the "reactivity" of a π-cyclization terminator is a function of both the chemical structure of the terminator and the reaction environment. These studies also provide, to our knowledge, the first definitive evidence that the cyclization of iminium ions with simple alkenes is not a concerted process, but rather proceeds via a cationic intermediate capable of partitioning between product formation and reversal to the "starting" iminium cation.[30] In marked contrast, iminium ion–vinylsilane cyclizations are little affected by reaction environment as a result of the facility of silicon loss from the (incipient) β-silyl cation intermediate.

Experimental Section[31]

***N*-Benzyl-3-buten-1-ylamine (19).** A solution of benzylamine (1.89 g, 17.6 mmol), 4-bromo-1-butene (0.480 g, 3.53 mmol), and ethanol (5 mL) was deoxygenated with argon and treated with NaI (ca. 20 mg) at room temperature. The resulting solution was heated at 75 °C for 4 h, cooled to room temperature, and partitioned between CH_2Cl_2 (50 mL) and 1 N KOH (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic phases were dried (K_2CO_3) and concentrated, and the resulting residue was purified by flash chromatography (10:1:0.2 hexane–EtOAc–Et_3N) to give 530 mg (93%) of **19** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.25 (m, PhH), 5.85–5.75 (m, C=CH), 5.13–5.03 (m, C=CH_2), 3.80 (s, $PhCH_2$), 2.78–2.70 (m, NCH_2), 2.35–2.30 (m, 2 H), 1.45 (br s, NH); IR (film) 1640, 1450, 1110, 913, 734, 698 cm^{-1}; MS (CI), *m/e* 162 (MH, 100); high-resolution MS (EI), *m/e* 161.1210 (161.1204 calcd for $C_{11}H_{15}N$).

Cyclization of 19 in H_2O with NaI. Formation of 1-Benzyl-4-iodopiperidine (23). A solution of **19** (14 mg, 0.09 mmol), camphorsulfonic acid (21 mg, 0.09 mmol), NaI (66 mg, 0.44 mmol), 37% aqueous formaldehyde solution (0.014 mL, 0.17 mmol), and H_2O (0.2 mL) was heated at 100 °C for 10 min in a sealed vial. The resulting mixture was cooled to room temperature and partitioned between CH_2Cl_2 (15 mL) and 0.1 N KOH (20 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated and purified by flash chromatography (10:1:0.2 hexane–EtOAc–Et_3N) to give 24 mg (92%) of **23** (>98% pure by capillary GLC analysis)[28] as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.22 (m, PhH), 4.37–4.25 (br s, ICH), 3.49 (s, $PhCH_2$), 2.70–2.60 (m, 2 H), 2.30–2.10 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 137.9, 129.1, 128.3, 127.2, 83.1, 54.2, 38.4, 28.3; IR (film) 1456, 1170, 1140, 992, 738, 699, 686 cm^{-1}; MS (EI, 22 eV), *m/e* 301 (M, 5.7), 174 (M – I, 100); high-resolution MS (EI), *m/e* 301.0323 (301.0326 calcd for $C_{12}H_{16}NI$).

***N*-Benzyl-(*Z*)-4-(trimethylsilyl)-3-buten-1-ylamine (18).** A solution of (*Z*)-4-(trimethylsilyl)-3-butenyl *p*-toluenesulfonate[14] (377 mg, 1.26 mmol), benzylamine (672 mg, 6.32 mmol), and ethanol (1 mL) was heated at 75 °C for 5 h, cooled to room temperature, and partitioned between CH_2Cl_2 (25 mL) and 1 N KOH (25 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried (K_2CO_3) and concentrated, and the residue was purified by flash chromatography (10:1:0.2 hexane–EtOAc–Et_3N) to give 251 mg (85%) of **18** (contaminated with 4% of the *E* isomer by capillary GLC analysis[28]) as a clear oil: ^1H NMR (300 Mz, $CDCl_3$) δ 7.40–7.25 (m, PhH), 6.30 (dt, 14, 7 Hz, SiC=CH), 5.60 (d, *J* = 7 Hz, SiCH=C), 3.82 (s, $PhCH_2$), 2.71 (app t, *J* = 7 Hz, NCH_2), 2.37 (app q, *J* = 7 Hz, C=CCH_2), 1.40 (br s, NH), 0.15 (s, $SiCH_3$); IR (film) 1607, 1249, 856, 838, 763, 734, 697 cm^{-1}; MS (CI), *m/e* 234 (MH, 41), 120 (100); high-resolution MS (EI), *m/e* 233.1571 (233.1600 calcd for $C_{14}H_{23}NSi$).

Cyclization of 18 in Acetic Acid. Formation of 1-Benzyl-1,2,5,6-tetrahydropyridine (21). A solution of amine **18** (43 mg, 0.18 mmol), camphorsulfonic acid (43 mg, 0.18 mmol), acetic acid (0.2 mL), and 37% aqueous formaldehyde solution (0.029 mL, 0.39 mmol) was heated at 85 °C for 30 min in a sealed vial. The resulting solution was cooled to room temperature and partitioned between ethyl acetate (15 mL) and saturated $NaHCO_3$ solution (10 mL). The organic layer was washed with saturated $NaHCO_3$ solution (10 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by flash chromatography (10:1:0.1 hexane–EtOAc–Et_3N) to give 28 mg (82%) of the known[12] tetrahydropyridine **21**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.25 (m, PhH), 5.80–5.60 (m, C=CH), 3.58 (s, $PhCH_2$), 3.00–2.95 (m, C=CCH_2N), 2.57 (t, *J* = 7 Hz, 2H), 2.20–2.12 (m, 2 H); IR (film) 1454, 1134, 1118, 1036, 1029, 763, 730, 698, 653 cm^{-1}, MS (CI), *m/e* 174 (MH, 100); high-resolution MS (EI), *m/e* 173.1198 (173.1201 calcd for $C_{12}H_{15}N$).

***N*-Benzyl-(*Z*)-4-(trimethylsilyl)-4-nonen-1-ylamine (17).** A solution of bromide **24** (204 mg, 0.74 mmol) and benzylamine (394 mg, 3.67 mmol) was heated at 80 °C for 5 h and then cooled to room temperature. The resulting residue was purified by flash chromatography (10:1:0.2 hexane–EtOAc–Et_3N) to give 192 mg (86%) of **17** as a clear, light yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.25 (m, PhH), 5.93 (t, *J* = 7.5 Hz, SiC=CH), 3.79 (s, $PhCH_2$), 2.62 (t, *J* = 7 Hz, NCH_2), 2.12–2.04 (m, 4 H), 1.55 (app q, *J* = 7 Hz, 2 H), 1.45–1.28 (m, 5 H), 0.90 (distorted t, CH_3), 0.14 (s, $SiCH_3$); IR (film) 1611, 1455, 1256, 835, 756, 697 cm^{-1}; MS (CI), *m/e* 304 (MH, 100); high-resolution MS (EI), *m/e* 303.2369 (303.2374 calcd for $C_{19}H_{33}NSi$). Anal. Calcd for $C_{21}H_{35}NO_4Si$ (oxalate salt, mp 222 °C dec): C, 64.08; H, 8.96; N, 3.56. Found: C, 63.95; H, 8.97; N, 3.56.

Cyclization of 17 in Acetonitrile. Formation of 1-Benzyl-(*Z*)-3-(1-pentylidene)piperidine (20). A solution of amine **17** (20 mg, 0.067 mmol) camphorsulfonic acid (16 mg, 0.067 mmol), acetonitrile (0.1 mL), and paraformaldehyde (10 mg, 0.3 mmol) was heated at 85 °C for 30 min in a sealed vial. After the mixture was cooled to room temperature, the reaction was partitioned between CH_2Cl_2 (15 mL) and 1 N KOH (15 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL) and the combined organic layers were dried (K_2CO_3) and concentrated and the residue was purified by flash chromatography (10:1:0.2 hexane–EtOAc–Et_3N) to afford 14 mg (85%) of **20** (>95% pure by capillary GLC analysis[28]) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.25 (m, PhH), 5.18 (t, *J* = 7 Hz, C=CH), 3.58 (s, $PhCH_2$), 2.98 (s, C=CCH_2N), 2.52 (distorted t, 2 H), 2.15–2.08 (m, 2 H), 1.95–1.87 (m, 2 H), 1.70–1.60 (m, 2 H), 1.32–1.28 (m, 4 H), 0.89 (distorted t, CH_3); IR (film) 1454, 1250, 1138, 948, 940, 836, 736, 698 cm^{-1}; MS (CI), *m/e* 244 (MH, 100); high-resolution MS (EI), *m/e* 243.2005 (243.1961 calcd for $C_{17}H_{25}N$).

***N*-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]-3-buten-1-ylamine (11).** A solution of (*Z*)-4-(trimethylsilyl)-3-butenyl toluenesulfonate[14] (960 mg, 3.24 mmol), 3-buten-1-ylamine[15] (460 mg, 6.46 mmol), and ethanol (5

(26) See, e.g.: Kevill, D. N.; Lin, G. M. L. *J. Am Chem. Soc.* **1979**, *101*, 3916.

(27) Under these conditions $k'_1[I^-] \gg k_{-2}$.

(28) A 25 m SE-30 fused-silica capillary column was used in these analyses.

(29) Establishment of (*E*) stereochemistry was made by spectroscopic comparison with similar (*E*) and (*Z*) alkenes whose preparation and characterization are described in ref 1 (see also ref 52 therein).

(30) For recent experimental evidence for the stepwise nature of polyene cyclizations in nitromethane containing 0.5 M H_2O, see: Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806. Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522.

(31) General experimental details are described in the following: Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. In addition, ^1H NMR and ^{13}C NMR spectra were determined with either a Bruker WM 250, a GE QE-300, or a GE GN-500 spectrometer. High-resolution mass spectra were determined on a VG 7070 E-HF mass spectrometer. IR spectra were determined on a Nicolet 50XB FT-IR spectrometer. Flash chromatography was performed on silica gel (230–400 mesh, E.M. Science) with adsorbent–sample ratios of ca. 100:1.

mL) was deoxygenated with argon and then treated with a catalytic amount of NaI (ca. 30 mg). The resulting mixture was heated at reflux under argon for 15 h, and the crude product was isolated as described for **19**. Purification by flash chromatography (25:1:0.1 $CHCl_3$–EtOH–48% NH_4OH) gave 332 mg (52%) of **11** (as a 95:5 mixture of *Z*:*E* isomers by capillary GLC[28]) as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 6.28 (dt, J = 14.1, 7.3 Hz, SiC=CH), 5.84–5.73 (m, 1 H), 5.58 (dt, J = 14.1, 1.2 Hz, SiCH=C), 5.13–5.02 (m, 2 H), 2.72–2.65 (m, 4 H), 2.37–2.22 (m, 4 H), 1.2 (br s, NH), 0.13 (s, $SiCH_3$); IR (film) 1641, 1608, 1249, 857, 763 cm^{-1}; MS (CI), *m/e* 198 (MH); high-resolution MS (EI), *m/e* 197.1563 (197.1594 calcd for $C_{11}H_{23}NSi$).

(*Z*)-1-Bromo-4-(trimethylsilyl)-4-nonene (24). According to the general procedure of Miller,[17] *sec*-BuLi (79.9 mL of a 1.31 M solution in cyclohexane, 105 mmol) was added over 15 min to a stirring solution of (*E*)-1-bromo-1-(trimethylsilyl)-1-hexene[16] (22.4 g, 95 mmol) and THF (500 mL) at −70 °C. The resulting solution was stirred at −70 °C for 1 h and then a chilled solution (ca. −70 °C) of 1,3-dibromopropane (90 g, 0.40 mol) and THF (50 mL) was added rapidly via cannula. The resulting solution was stirred at −70 °C for 4 h and then allowed to warm to room temperature. The resulting heterogeneous mixture was poured into saturated NH_4Cl solution (700 mL), and the organic layer was separated. The aqueous layer was extracted with pentanes (3 × 150 mL) and the combined organic extracts were washed with brine (2 × 150 mL), dried ($MgSO_4$), and concentrated. Excess 1,3-dibromopropane was removed from the crude product by distillation (bp 58–59 °C, 10 mmHg), and the residue was distilled to give 10.9 g (42%) of **24** (contaminated by 4% of the *E* isomer by capillary GLC analysis[28]) as a clear oil: bp 96–102 °C (1 mmHg); ^1H NMR (250 MHz, $CDCl_3$) δ 5.98 (t, J = 7 Hz, C=CH), 3.37 (t, J = 8 Hz, $BrCH_2$), 2.20–2.00 (m, C=CCH_2), 1.85 (app q, J = 7 Hz, 2 H), 1.35–1.25 (m, 4 H), 0.89 (distorted t, CH_3), 0.13 (s, $SiCH_3$); IR (film) 1609, 1450, 1246, 829, 750, 680, 639 cm^{-1}; MS (CI), *m/e* 277, 279, 261. Anal. Calcd for $C_{12}H_{25}BrSi$: C, 51.97; H, 9.09; Br, 28.82. Found: C, 52.09; H, 9.06; Br, 28.76.

***N*-(3-Butenyl)-(*Z*)-4-(trimethylsilyl)-4-nonen-1-ylamine (7).** A solution of bromide **24** (1.07 g, 3.9 mmol), 3-buten-1-ylamine[15] (0.82 g, 12 mmol), and EtOH (1 mL) was heated in a sealed vial at 85 °C for 5 h. The resulting red solution was partitioned between CH_2Cl_2 (25 mL) and 1 N KOH (25 mL), and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic extracts were dried (K_2CO_3) and concentrated, and the residue was purified by flash chromatography (7:1:0.2 hexane–EtOAc–Et_3N) to give 722 mg (70%) of **7** (>94% pure by capillary GLC analysis[28]) as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 5.94 (t, J = 7 Hz, SiC=CH), 5.90–5.70 (m, 1 H), 5.13–5.02 (m, C=CH_2), 2.68 (t, J = 7 Hz, 2 H), 2.59 (t, J = 7 Hz, 2 H), 2.26 (app q, J = 7 Hz, 2 H), 2.15–2.00 (m, 7 H), 1.55 (app q, J = 7 Hz, 2 H), 1.40–1.30 (m, 4 H), 0.89 (distorted t, CH_3), 0.13 (s, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 143.5, 138.4, 136.4, 116.4, 49.5, 48.8, 36.1, 34.2, 32.4, 31.9, 31.0, 22.5, 14.1, 0.4; IR (film) 1640, 1615, 1455, 1250, 995, 915, 835 cm^{-1}; MS (CI), *m/e* 268 (MH, 100); high-resolution MS (EI), *m/e* 267.2385 (267.2384 calcd for $C_{16}H_{33}NSi$). Anal. Calcd for $C_{18}H_{35}NO_4Si$ (oxalate salt, mp 210–211 °C): C, 60.46; H, 9.87; N, 3.92. Found: C, 60.36; H, 9.91; N, 3.90.

Cyclization of 7 in Acetic Acid. Formation of 1-(3-Butenyl)-(*Z*)-3-(1-pentylidene)piperidine (8) and 4-Hydroxy-1-[(*Z*)-4-(trimethylsilyl)-4-nonenyl]piperidine (9a). A solution of amine **7** (112 mg, 0.40 mmol), camphorsulfonic acid (94 mg, 0.40 mmol), acetic acid (0.4 mL) and 37% aqueous formaldehyde solution (0.061 mL, 0.81 mmol) was heated at 100 °C for 1 h in a sealed vial. The resulting solution was cooled to room temperature and partitioned between CH_2Cl_2 (10 mL) and 1 N KOH (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic layers were dried (K_2CO_3) and concentrated to give 125 mg of a yellow oil. This sample was hydrolyzed with K_2CO_3 (0.5 g) in MeOH (2 mL) and H_2O (0.3 mL) at 25 °C for 3 h and then was partitioned between CH_2Cl_2 (25 mL) and 1 N KOH (25 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL) and the combined organic extracts were dried (K_2CO_3) and concentrated to give 110 mg of a crude product. Purification by flash chromatography (20:1:0.1 $CHCl_3$–EtOH–48% NH_4OH) provided 42 mg (49%) of **8** (>97% pure by capillary GLC analysis[28]) as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 5.88–5.75 (m, C*H*=CH_2), 5.19 (t, J = 7.2 Hz, C=CH), 5.12–4.96 (m, C=CH_2), 2.98 (s, C=CCH_2N), 2.58–2.42 (m, 4 H), 2.38–2.25 (m, 2 H), 2.15–2.00 (m, 4 H), 1.70–1.60 (m, 2 H), 1.37–1.28 (m, 4 H), 0.90 (distorted t, CH_3); IR (film) 1677, 1640, 1465, 1250, 910, 836 cm^{-1}; MS (CI), *m/e* 208 (MH, 100); high-resolution MS (EI), *m/e* 207.2001 (207.1981 calcd for $C_{14}H_{25}N$).

Further elution with 3:1:0.1 $CHCl_3$–EtOH–48% NH_4OH gave 47 mg (38%) of **9a** as a viscous yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 5.92 (t, J = 7.5 Hz, SiC=CH), 3.67 (app s, J = 4.5 Hz, OCH), 2.81–2.73 (m, 2 H), 2.36–2.25 (m, 2 H), 2.20–1.96 (m, 7 H), 1.96–1.85 (m, 2 H), 1.65–1.45 (m, 4 H), 1.37–1.25 (m, 4 H), 0.90 (distorted t, CH_3), 0.12 (s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.5, 67.9, 58.6, 51.4, 36.4, 34.5, 32.5, 31.9, 28.2, 22.6, 14.3, 0.6; IR (film) 3300 (v br), 1612, 1248, 1075, 836, 757, 734 cm^{-1}; MS (CI), *m/e* 298 (MH, 61), 280 (32), 114 (100); high-resolution MS (EI), *m/e* 297.2471 (297.2488 calcd for $C_{17}H_{35}NOSi$).

The relative amounts of the cyclization products in the crude mixture were determined by the integrals of the signals at δ 2.98 (C=CH_2N, s of **8**, 2 H) and at δ 3.67 (OCH, app septet of **9a**, 1 H).

Cyclization of 7 in Formic Acid. Formation of 8 and 4-Hydroxy-1-[(*E*)-4-nonenyl]piperidine (27). The preceding experiment was repeated with 98% formic acid as the solvent. In this manner, 126 mg (0.47 mmo6) of **7** gave 57 mg (59%) of **8** and then, after further elution with 7:1:0.1 $CHCl_3$–EtOH–48% NH_4OH, 14 mg (13%) of **27**:[29] ^1H NMR (250 MHz, $CDCl_3$) δ 5.42–5.37 (m, HC=CH), 3.69 (app s, J = 4.5 Hz, OCH), 2.81–2.73 (m, 2 H), 2.34–2.27 (m, 2 H), 2.11 (app t, J = 10 Hz, 2 H), 2.02–1.87 (m, 7 H), 1.65–1.50 (m, 4 H), 1.35–1.25 (m, 4 H), 0.89 (distorted t, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.1, 129.8, 68.3, 58.3, 51.4, 34.7, 32.5, 32.0, 30.8, 27.3, 22.4, 14.2; IR (film) 3300 (v br), 1670, 1467, 1457, 1076, 967 cm^{-1}; MS (CI), *m/e* 226 (MH, 100); high-resolution MS (EI), *m/e* 225.2089 (225.2086 calcd for $C_{14}H_{27}NO$).

The relative amounts of the cyclization products in the crude mixture were determined from the integrals of the signals at δ 2.98 (C=CCH_2N, s of **8**, 2 H) and at δ 3.69 (OCH, app septet of **27**, 1 H).

Cyclization of 7 in CH_3CN Containing $(n\text{-Bu})_4NBr$. Formation of 8 and 4-Bromo-1-[(*Z*)-4-(trimethylsilyl)-4-nonenyl]piperidine (9b). A solution of amine **7** (89 mg, 0.33 mmol), camphorsulfonic acid (78 mg, 0.33 mmol), $n\text{-}Bu_4NBr$ (539 mg, 1.7 mmol), paraformaldehyde (50 mg, 1.7 mmol), and acetonitrile (1.5 mL) was heated in a sealed ampule at 100 °C for 2 h. This solution was cooled to 25 °C and partitioned between CH_2Cl_2 (20 mL) and 1 N KOH (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried (K_2CO_3) and concentrated to give a crude product that contained excess $(n\text{-Bu})_4NBr$. The crude product was purified by flash chromatography (2:1 hexane–EtOAc) to give 92 mg (76%) of **9b** as a clear yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 5.94 (t, J = 7.4 Hz, C=CH), 4.22–4.15 (m, BrCH), 2.78–2.68 (m, 2 H), 2.35–1.98 (m, 12 H), 1.55–1.42 (m, 2 H), 1.38–1.28 (m, 4 H), 0.90 (distorted t, CH_3), 0.13 (s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 138.4, 58.3, 52.3, 50.2, 36.4, 36.1, 32.3, 31.8, 28.1, 22.4, 14.1, 0.38; IR (film) 1605, 1467, 1450, 1249, 837, 756, 714 cm^{-1}; MS (CI), *m/e* 360 (MH); high-resolution MS (EI), *m/e* 361.1633 (361.1613 calcd for $C_{17}H_{34}{}^{81}BrNSi$), 359.1640 (359.1636 calcd for $C_{17}H_{34}{}^{79}BrNSi$).

Cyclization of 11 in H_2O. Formation of 1-(3-Butenyl)-1,2,5,6-tetrahydropyridine (12) and 4-Hydroxy-1-[(*Z*)- and (*E*)-4-(trimethylsilyl)]-3-butenylpiperidine (13a). A solution of amine **11** (106 mg, 0.54 mmol), camphorsulfonic acid (124 mg, 0.54 mmol), 37% aqueous formaldehyde solution (0.08 mL, 1.1 mmol), and H_2O (0.6 mL) was heated at 80 °C for 1 h in a sealed vial. The resulting solution was partitioned between CH_2Cl_2 and 1 N KOH (25 mL), the aqueous layer was extracted with CH_2Cl_2 (25 mL), and the combined organic layers were dried (K_2CO_3) and concentrated to give 106 mg of a crude product that was purified by preparative layer TLC (15:1:0.1 $CHCl_3$–EtOH–48% NH_4OH) to give 38 mg (52%) of **12** as a yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 5.90–5.63 (m, 3 H, vinylic), 5.11–4.98 (m, 2 H, vinylic), 3.00–2.96 (m, C=CCH_2N), 2.57 (t, J = 5.7 Hz, NCH_2), 2.52–2.46 (m, NCH_2), 2.35–2.28 (m, 2 H), 2.22–2.16 (m, 2 H); IR (film) 1743, 1245, 860 cm^{-1}; MS (CI), *m/e* 138 (MH, 100); high-resolution MS (EI), *m/e* 137.1243 (137.1201 calcd for $C_9H_{15}N$).

The slower eluting fraction consisted of 40 mg (33%) of **13a** as a 1:1 mixture of *E* and *Z* vinylsilane stereoisomers by ^1H NMR analysis: (250 MHz, $CDCl_3$) δ 6.26 (dt, J = 14, 7 Hz, SiC=CH, *Z* isomer), 5.98 (dt, J = 18.5, 6 Hz, SiC=CH, *E* isomer), 5.69 (br d, J = 18.5 Hz, C=CHSi, *E* isomer), 5.55 (br d, J = 14 Hz, C=CHSi, *Z* isomer), 3.70 (app septet, J = 4 Hz, OCH), 2.85–2.75 (m, 2 H), 2.47–1.89 (m, 9 H), 1.68–1.55 (m, 2 H), 0.12 (s, $SiCH_3$, *Z* isomer) 0.04 (s, $SiCH_3$, *E* isomer); IR (film) 3300 (v br), 1610, 1248, 1073, 858, 838, 762 cm^{-1}; MS (CI), *m/e* 228 (MH, 65), 210 (41), 114 (100); high-resolution MS (EI), *m/e* 227.1670 (227.1699 calcd for $C_{12}H_{25}NOSi$).

^1H NMR analysis of the crude product showed that the products **12** and **13a** were present in a ratio of 66:34 as determined by the integrals of the signals at δ 3.00–2.96 (C=CH_2N, m of **12**, 2 H) and at δ 3.70 (OCH, app septet of **13a**, 1 H).

Cyclization of 11 in CH_3CN Containing $(n\text{-Bu})_4NBr$. Formation of 4-Bromo-1-[(*Z*)- and (*E*)-4-(trimethylsilyl)-3-butenyl]piperidine (13b). A solution of **11** (67 mg, 0.34 mmol), camphorsulfonic acid (79 mg, 0.34 mmol), $(n\text{-Bu})_4NBr$ (545 mg, 1.69 mmol), paraformaldehyde (51 mg, 1.69 mmol), and CH_3CN (1.5 mL) was heated at 100 °C for 2 h in a sealed vial. The resulting mixture was cooled to 25 °C and partitioned between CH_2Cl_2 (25 mL) and 1 N KOH (25 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL), and the combined organic layers

were dried (K_2CO_3) and concentrated to give a crude product that contained excess (n-Bu_4)NBr. Flash chromatography of the crude product (3:1 hexanes–EtOAc) gave 42 mg (43%) of **13b** as a 2:1 mixture of *Z* and *E* isomers. HPLC purification (silica column; 25:1 CH_2Cl_2–MeOH) of **13b** provided analytical samples of the two isomers. The faster eluting (*Z*)-**13b** was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) 6.27 (dt, J = 14, 7 Hz, SiC=CH), 5.56 (br d, J = 14 Hz, C=CHSi), 4.20 (br s, CHBr), 2.78–2.73 (m, 2 H), 2.45–2.00 (m, 10 H), 0.13 (s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 130.8, 58.5, 52.3, 50.3, 36.5, 31.3, 0.4; IR (CCl_4) 1607, 1249, 1196, 1124, 859, 840 cm^{-1}; MS (CI), *m/e* 292 (MH, ^{81}Br), 290 (MH, ^{79}Br); high-resolution MS (EI), 276.0602 (276.0601 calcd for $C_{11}H_{21}{}^{81}BrNSi$, M – CH_3).

The slower eluting (*E*)-**13b** was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (dt, J = 18.6, 6.2 Hz, SiC=CH), 5.69 (br d, J = 18.6 Hz, C=CHSi), 4.20 (br s, CHBr), 2.79–2.69 (m, 2 H), 2.51–2.00 (m, 10 H), 0.05 (s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 131.8, 57.9, 52.3, 50.3, 36.4, 34.5, –1.0; IR (CCl_4) 1617, 1249, 1196, 1124, 991, 866, 840 cm^{-1}; MS (CI), *m/e* 292 (MH, ^{81}Br), 290 (MH, ^{79}Br); high-resolution MS (EI), *m/e* 276.0611 (276.0601 calcd for $C_{11}H_{21}{}^{81}BrNSi$, M – CH_3).

Cyclization of 11 in H_2O Containing NaI. Formation of 12, 13a, and 4-Iodo-1-[(*Z*)- and (*E*)-4-(trimethylsilyl)-3-butenyl]piperidine (13c). A solution of amine **11** (152 mg, 0.77 mmol), camphorsulfonic acid (179 mg, 0.77 mmol), NaI (1.15 g, 7.70 mmol), 37% aqueous formaldehyde (0.12 mL, 1.54 mmol), and H_2O (1.5 mL) was heated at 100 °C for 1 h in a sealed vial. After being cooled to 25 °C, the reaction mixture was partitioned between CH_2Cl_2 (50 mL) and 1 N KOH (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 197 mg of a crude product that was purified by flash chromatography (30:1 CH_2Cl_2–MeOH) to first give 120 mg (46%) of **13c** as a 3:2 mixture of *Z* and *E* isomers (by ^{1}H NMR analysis) and then 26 mg (25%) of **12**. Further elution with 5:1 CH_2Cl_2–MeOH gave 17 mg (10%) of **13a** as a 1:1 mixture of *Z* and *E* isomers by ^{1}H NMR analysis.

Analytical samples of (*Z*)-**13c** and (*E*)-**13c** were obtained by HPLC separation (silica column; 25:1 CH_2Cl_2–MeOH). The more rapidly eluting (*Z*)-**13c** was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (dt, J = 14, 7 Hz, SiC=CH), 5.55 (br d, J = 14 Hz, C=CHSi), 4.35–4.20 (br s, CHI), 2.70–2.55 (m, 2 H), 2.45–2.05 (m, 10 H), 0.12 (s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 130.7, 58.6, 53.4, 38.3, 31.2, 28.4, 0.4; IR (CCl_4) 1607, 1249, 1192, 1122, 858, 840 cm^{-1}; MS (CI); *m/e* 338 (MH); high-resolution MS (EI), *m/e* 337.0686 (337.0716 calcd for $C_{12}H_{24}INSi$).

The slower eluting (*E*)-**13c** was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) 5.98 (dt, J = 18.5, 6.2 Hz, SiC=CH), 5.68 (br d, J = 18.6 Hz, C=CHSi), 4.35–4.20 (m, 2 H), 2.50–2.10 (m, 10 H), 0.04 (s, $SiCH_3$); IR (CCl_4) 1617, 1248, 1172, 1122, 991, 866, 840 cm^{-1}; MS (CI), *m/e* 338 (MH); high-resolution MS (EI), *m/e* 337.0727 (337.0716 calcd for $C_{12}H_{24}INSi$).

^{1}H NMR analysis of the crude reaction mixture showed the products **12**, **13a**, and **13c** to be present in a ratio of 33:12:55 as determined by the integrals of the signals at δ 3.00–2.96 (C=CCH_2N, m of **12**, 2 H), 3.70 (OCH, app septet of **13a**, 1 H), and at 4.35–4.20 (ICH, m of **13c**, 1 H).

Cyclization of 11 in H_2O Containing NaN_3. Formation of 12, 13a, and 4-Azido-1-[(*Z*)- and (*E*)-4-(trimethylsilyl)-3-butenyl]piperidine (13d). A solution of amine **11** (65 mg, 0.33 mmol), camphorsulfonic acid–sodium camphorsulfonate buffer solution (1.64 mL of a 1.0 M aqueous solution, buffer ratio = 1.0), NaN_3 (1.07 g, 16.4 mmol), 37% aqueous formaldehyde (53 μL, 0.66 mmol), and H_2O (4.9 mL) was heated behind a safety shield at 75 °C for 1 h in a sealed vial. After being cooled thoroughly in a dry ice–acetone bath, the vial was carefully opened and the contents were allowed to warm to 25 °C. The resulting solution was partitioned between CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ solution (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried ($NaSO_4$) and concentrated, giving 76 mg of a crude product that was purified by flash chromatography (12:1 hexanes–EtOAc) to give 30 mg (36%) of **13d** as a 3:1 mixture of *Z* and *E* isomers as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (dt, J = 14, 7 Hz, SiC=CH, *Z* isomer), 5.97 (dt, J = 18, 6 Hz, SiC=CH, *E* isomer), 5.68 (br d, J = 18 Hz, C=CHSi, *E* isomer), 5.54 (br d, J = 14 Hz, C=CHSi, *Z* isomer), 3.46–3.33 (m, N_3CH), 2.85–2.75 (m, 2 H), 2.42–2.28 (m, 4 H), 2.18 (app t, J = 10 Hz, 2 H), 1.98–1.88 (m, 2 H), 1.75–1.60 (m, 2 H), 0.12 (s, $SiCH_3$, *Z* isomer), 0.03 (s, $SiCH_3$, *E* isomer); IR (film) 2094, 1608, 1248, 1136, 858, 838, 753 cm^{-1}; MS (CI), *m/e* 253 (MH, 100).

Further elution with 2:1 hexanes–EtOAc provided 22 mg (49%) of **12**. Further elution with 1:1:0.5 hexanes–EtOAc–TEA gave 5 mg (6%) of **13a**.

^{1}H NMR analysis of the crude reaction mixture showed the products **13d**, **12**, and **13a** to be present in a ratio of 37:59:4 as determined by the integrals of the signals at δ 3.46–3.33 (N_3CH, m of **13d**, 1 H), 3.00–2.96 (C=CH_2N, m of **12**, 2 H), and 3.70 (OCH, app septet of **13a**, 1 H).

Typical Experiment for the Cyclization Reactions Summarized in Table IV. A 1-dram screw-cap vial equipped with a magnetic stir bar was charged with amine **11** (5.5 mg of 0.028 mmol), aqueous LiI solution (98 μL of a 2.0 M solution, 0.20 mmol), aqueous camphorsulfonic acid–sodium camphorsulfonate buffer solution (140 μL of a 1.0 M solution, buffer ratio = 1.0), H_2O (316 μL), and a 37% formalin solution (5 μL, 0.06 mmol). This sealed heterogeneous mixture was placed in a 75 °C oil bath (the stirred reaction vial became homogeneous within 1 min) and was kept at that temperature for 30 min. The resulting solution was cooled to room temperature and partitioned between CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL), and the combined organic layers were dried (K_2CO_3) and concentrated (at ca. 50 mm, care was taken to avoid loss of the more volatile **12**) to give 7 mg of a crude mixture that contained **12**, **13a**, **13c**, and unreacted **11**.

The product ratio of the crude reaction mixture was determined by the integrals of the diagnostic ^{1}H NMR signals measured at either 300 MHz (GE QE-300) or 500 MHz (GE GN-500). Quantitation of the ^{1}H NMR signals in the trimethylsilyl region (δ 0.20–0.00) required that the reactions be worked-up in absence of silicone stopcock grease. In addition, spectra were measured in $CDCl_3$, with the omisssion of Me_4Si (the $CHCl_3$ peak was used as a reference, δ 7.27). It was determined that the workup procedure (partitioning between the aqueous base and an organic solvent) removed all traces of the Me_3Si residue (e.g., Me_3SiOH and $Me_3SiOSiMe_3$) that was formed in a vinylsilane-terminated cyclization.

To probe the possible effect that the mixture's initial heterogeneity might have on product ratios, the procedure detailed above was repeated except that **11** and formalin were combined and treated with a preheated (75 °C) solution of LiI and camphorsulfonic acid–sodium camphorsulfonate. The resulting homogeneous solution was then heated at 75 °C and worked-up exactly as described above.

Fragmentation of 13c in CH_3CN in the Presence of $AgOCOCF_3$. A solution of $AgOCOCF_3$ (12.1 mg, 0.055 mmol), (*Z*)-**13c** (3.7 mg, 0.011 mmol), and CH_3CN (1 mL) was heated at reflux for 30 min, cooled to room temperature, and partitioned between CH_2Cl_2 (15 mL) and saturated $NaHCO_3$ solution (15 mL). The organic layer was dried (K_2CO_3) and concentrated to give 2 mg of a crude product that contained **12** and **11** in a ratio of 3:1 by ^{1}H NMR analysis [using integrals of the signals at δ 6.28 (C=CHSi, dt of **11**, 1 H) and at 3.00–2.96 (C=CCH_2N, m of **12**, 2 H)]. No **13c** was present in the crude product (by ^{1}H NMR or capillary GLC[28] analysis).

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Registry No. 7, 109838-98-4; **7** oxalate, 109862-71-7; **8**, 109838-99-5; **9a**, 109839-00-1; **9b**, 109839-02-3; (*Z*)-**11**, 109838-95-1; (*E*)-**11**, 109838-96-2; **12**, 109839-03-4; (*E*)-**13a**, 109839-04-5; (*Z*)-**13a**, 109839-05-6; (*Z*)-**13b**, 109839-06-7; (*E*)-**13b**, 109839-07-8; (*Z*)-**13c**, 109839-08-9; (*E*)-**13c**, 109839-09-0; (*Z*)-**13d**, 109839-10-3; (*E*)-**13d**, 109839-11-4; **17**, 109838-92-8; **17** oxylate, 109838-93-9; (*Z*)-**18**, 109838-89-3; (*E*)-**18**, 109838-90-6; **19**, 17150-62-8; **20**, 109838-94-0; **21**, 40240-12-8; **23**, 109838-88-2; (*Z*)-**24**, 109838-91-7; (*E*)-**24**, 109838-97-3; **27**, 109839-01-2; $PhCH_2NH_2$, 100-46-9; $Br(CH_2)_2CH{=}CH_2$, 5162-44-7; HCHO, 50-00-0; (*Z*)-$Me_3SiCH{=}CH(CH_2)_2OTs$, 87682-62-0; $CH_2{=}CH(CH_2)_2NH_2$, 2524-49-4; (*E*)-$CH_3(CH_2)_3CH{=}CBrSiMe_3$, 66270-62-0; $Br(CH_2)_3Br$, 109-64-8; NaN_3, 26628-22-8.

Supplementary Material Available: Table VI giving the effect of NaN_3 on the cyclization of amine **11** in water at 75 °C (1 page). Ordering information is given on any current masthead page.