measurements. Although we have limited our initial studies to THF solutions at 25 °C, the method can in principle be applied to other solvents and other temperatures. Also, aggregation studies by our technique are generally limited to dilute (10^{-3}-10^{-4} M) solutions; in this respect the method is complementary to colligative measurements, which are generally conducted at higher substrate concentrations. Synthetic chemistry is normally done at higher concentrations but it is clearly important and relevant to understand the dilute solution.

Previous research has established that a tetrameric structure is favored for several lithium enolates at concentrations of ca. 0.1 M,[7,9,12,29] although dimers appear to be favored at low temperature.[10] The present work shows that the cesium enolate of acetophenone is substantially tetrameric even in dilute solutions. In contrast, the cesium enolates of propiophenone and isobutyrophenone are found to exist predominantly as dimers. At present, it is not known what effect the deaggregation of cesium enolates compared to their more common lithium counterparts will have on the reaction chemistry of these important synthetic reagents.

Finally, the true relative pK_a's of the monomeric ion pairs are still not known but are established as greater than those of the aggregates reported. The "effective" pK_a's of the aggregates are readily evaluated by the procedure discussed in this paper, at least over the concentration range for which the n values reported in Table V are constant. These effective pK_a's vary with concentration and such variation may have synthetic significance. However, comparison of these pK's with values in Me_2SO suggests that the association constants of cesium enolates to higher aggregates cannot be very large and that the true ion pair pK values are no more than a few units higher than the apparent values.

Experimental Section

Indicator Acids. The hydrocarbon indicators used in this work either were available from our previous studies, or were synthesized by published procedures. All of the indicators were carefully purified prior to use by repeated recrystallization followed by vacuum sublimation.

Carbonyl Compounds. Acetophenone, propiophenone, isobutyrophenone, and *o*-methoxyacetophenone were obtained from commercial suppliers. All of the ketones were fractionally distilled under vacuum two times and degassed prior to use. The purity of the compounds was determined by vapor-phase chromatography; all compounds gave analyses indicating a purity of at least 99%. All compounds also gave satisfactory elemental analyses.

Acidity Determinations. The procedures used in the acidity determinations have been previously described in detail.[23,26] The cesium ion pair indicator pK_a's used are those of the revised scale.[25]

Acknowledgment. This research was supported in part by NIH Grant No. GM-30369. We are indebted to Scott Gronert for valuable discussions and assistance.

Registry No. ACP, 98-86-2; ACP^-Cs^+, 109839-78-3; PRP, 93-55-0; PRP^-Cs^+, 109839-79-4; IBP, 611-70-1; IBP^-Cs^+, 109839-80-7; MACP, 579-74-8; $MACP^-Li^+$, 109839-81-8; $MACP^-Cs^+$, 109839-82-9.

Iminium Ion and Acyliminium Ion Initiated Cyclization Reactions of Vinylsilanes. Regiocontrolled Synthesis of Tetrahydropyridines and Related Heterocycles[1]

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Abstract: 1,2,5,6-Tetrahydropyridines containing substituents at positions 1, 2, 3, and 4 can be prepared in useful yields, with *complete regioselectivity*, by the cyclization of iminium ions derived from 4-(trimethylsilyl)-3-butenylamines. The general sequence is illustrated in Scheme I. Three methods for generating the iminium ion intermediate are described. Tetrahydropyridines containing a 1-substituent are most easily prepared by the reaction of N-substituted (*Z*)-4-(trimethylsilyl)-3-butenylamines with aldehydes in the presence of <1 equiv of a sulfonic acid (see eq 4 and Table I). Alternatively, tetrahydropyridines of this type can be prepared from the reaction of α-cyanoamines **20** with silver salts (see eq 5 and Table II). This latter more costly procedure is useful when the aldehyde component is precious or, in the case of formaldehyde, when the cyclization reaction is slow. Tetrahydropyridines unsubstituted at position 1 can be prepared in modest yields by the cyclization of nonenolizable imines **23a-c** with excess trifluoroacetic acid (see eq 6 and Table III). The cyclization of the 5-(trimethylsilyl)-4-pentenylamine **26** to give hydroazepine **28** demonstrates that allylically unsaturated heterocycles other than six-membered can also be prepared in this way (eq 7). Acyliminium ion-vinylsilane cyclizations are also successful and can be utilized for the regiocontrolled synthesis of indolizidinones and quinolizidinones **44**. The functionalized indolizidinone **44c** was employed as the key intermediate in a short synthesis of the racemic *elaeocarpus* alkaloids, elaeokanines A and B (see Scheme IV). Several lines of evidence indicate that vinylsilane and allylsilane iminium ions **29** and **32** equilibrate (via a cationic aza-Cope rearrangement) more rapidly than either cation cyclizes to the tetrahydropyridine product.

Electrophilic cyclization reactions of iminium ions and related intermediates (Mannich cyclizations) constitute some of the most important methods for preparing nitrogen heterocycles.[2] In two of the more venerable of these procedures, the Pictet-Spengler and Bishler-Napieralski reactions,[3] an aromatic ring is the nucleophilic reaction component (cyclization terminator). Cyclization reactions of simple alkenes with iminium ions, although well-known, have received much less attention.[4] In part this neglect is due to the fact that the carbonium ion intermediate produced

(1) A mechanistic study of these cyclization reactions is described in the following paper of this series: McCann, S. F.; Overman, L. E. *J. Am. Chem. Soc.*, following paper in this issue.

(2) Katritsky, A.; Rees, C. W., Eds. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984; Vol. 1-6.

(3) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74, 151.

(4) (a) Grewe, V. R.; Hamann, R.; Jacobsen, G.; Nolte, E.; Riecke, K. *Liebigs Ann. Chem.* **1953**, *581*, 85. (b) Cope, A. C.; Burrows, W. D. *J. Org. Chem.* **1965**, *30*, 2163. (c) Cope, A. C.; Burrows, W. D. *Ibid.* **1966**, *31*, 3099. (d) Grob, C. A.; Wohl, R. A. *Helv. Chim. Acta* **1966**, *49*, 217. (e) Bohlmann, F.; Winterfeldt, E. *Chem. Ber.* **1960**, *93*, 1956. (f) Winterfeldt, E.; Wilcock, J. D. *Chem. Ber.* **1974**, *107*, 975. (g) Winterfeldt, E.; Feuerherd, K.-H.; Ahmad, V. U. *Ibid.* **1977**, *110*, 3624. (h) Solladie, G.; Demailly, G. *Tetrahedron Lett.* **1977**, 1885.

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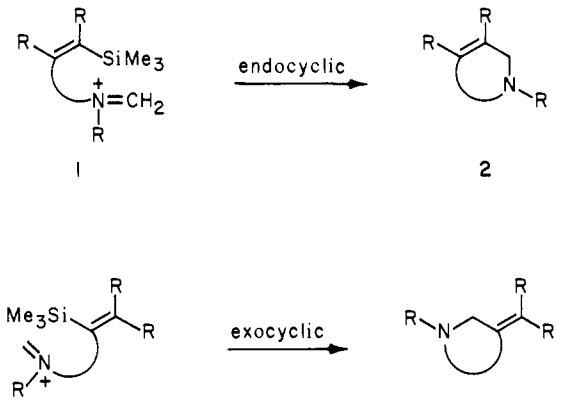


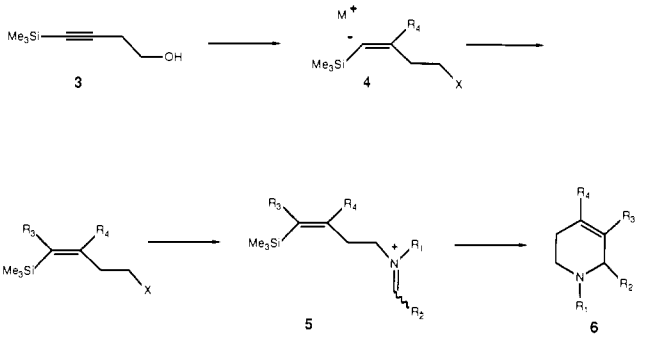
Figure 1.

from the addition of an iminium ion to an alkene often partitions among several reaction manifolds, in contrast to the corresponding cations derived from aromatic terminators which typically deprotonate to give cleanly products of electrophilic aromatic substitution.

One continuing theme in the evolution of cationic cyclization reactions has been the development of selective functionality to initiate and terminate the ring-forming process.[5] For example, recent years have witnessed the important development of the cyclization chemistry of α-*N*-acyliminium ions.[6] This initiating functionality is more reactive than a simple iminium ion and, thus, will react with a wider range of intramolecular nucleophiles. A variety of useful functionalities for terminating cyclization reactions have also been developed. The most powerful of these are ones which both "control" the cyclization process so that a single reaction product is produced and leave the cyclization product with useful functionality for further synthetic manipulation. The ability of a silicon substituent to control the outcome of a cationic cyclization, as first noted by Fleming in his studies of allylsilanes,[7] has led to the emergence of organosilanes (allylsilanes, alkynylsilanes, propargylsilanes, and vinylsilanes) as particularly important functional groups for terminating electrophilic cyclization reactions.[8,9]

Several years ago we initiated a program to explore the intramolecular reaction of vinylsilanes with iminium ions[10] (see Figure 1). As we have discussed in detail elsewhere,[9,10] vinylsilanes are notably attractive components for cyclization-based synthesis strategies since the silicon substituent can be utilized to assist assembly of the cyclization substrate **1** as well as control the outcome of the cyclization reaction. As illustrated in Figure 1, two modes of participation[11] of a vinylsilane are possible.[12] In this paper we describe in detail[14] our recent studies on cyclizations that occur in the endocyclic mode with respect to the vinylsilane terminator (**1** → **2**). As will be demonstrated subsequently, cyclizations of this type represent a powerful new method for regiocontrolled construction of tetrahydropyridines and related

Scheme I

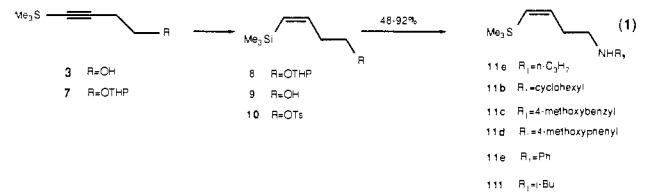


nitrogen heterocycles. The overall preparative sequence is outlined in Scheme I.

Results and Discussion

Preparation of the (*Z*)-4-(Trimethylsilyl)-3-butenylamine Cyclization Substrates. A variety of α-silylvinyl anions **4** are readily prepared from 1-silylalkynes via hydrometalation[15] or carbometalation[16] reactions. All the (*Z*)-4-(trimethylsilyl)-3-butenylamine cyclization substrates utilized in this study were assembled from these key intermediates.

The preparation of the unbranched (*Z*)-4-(trimethylsilyl)-3-butenylamines **11** is summarized in eq 1. A large-scale procedure[17a] for carbon silylation[18a] of 3-butyn-1-ol and subsequent semihydrogenation of 4-(trimethylsilyl)-3-butyn-1-ol (**3**) to give (*Z*)-4-(trimethylsilyl)-3-buten-1-ol (**9**) in 68% overall yield, and 90–95% stereoisomeric purity, has been described. Alternatively, **9** of high isomeric purity (>99%)[19] can be prepared in 81% yield from tetrahydropyranyl (THP) ether **7**[17a,18b] by hydroalumination–protonolysis,[20] followed by cleavage of the THP group, without complications from protodesilylation, by use of the mild acid catalyst pyridinium *p*-toluenesulfonate.[21] Tosylation of **9** (91% yield) and simple aminolysis of **10** with an excess of a primary aliphatic or aromatic amine provided butenylamines **11** in 30–57% overall yield from 3-butyn-1-ol.



Cyclization substrates containing a substituent β to silicon were prepared by treatment of **7** with a Grignard reagent in the presence of trimethylaluminum and a catalytic amount of nickel acetoacetate, see eq 2. This carbometalation procedure[22] provided the substituted vinylsilanes **12b** (95% yield as a 9:1 mixture of *E* and *Z* isomers) and **12a** (40% yield as a 3:1 mixture of *E* and *Z* isomers) in useful yields. These mixtures were used in the subsequent conversion to **15**, which paralleled directly the preparation of **11** from **8**. Thus, **15b** (*E*:*Z* = 9:1) was obtained in 72% overall yield from **12**, while **15a** (*Z*:*E* = 3:1) was obtained in 20% overall yield. Since no attempt was made to optimize the yield of each

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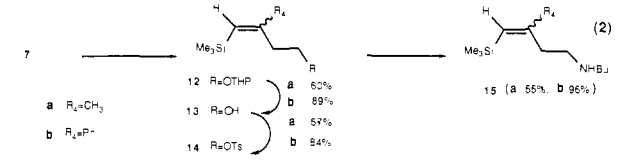
(6) For a recent review, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
(7) Fleming, I.; Pearce, A.; Snowden, R. L. *J. Chem. Soc., Chem. Commun.* **1976**, 182.
(8) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. Colvin, E. *Silicon in Organic Synthesis*; Butterworths: London, 1983.
(9) For a comprehensive review of vinylsilane and alkynylsilane terminated cyclization reactions, see: Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.
(10) For a brief summary of these studies, see: Overman, L. E. *Lec. Heterocycl. Chem.* **1985**, *8*, 59.
(11) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(12) Two additional modes of cyclization are possible. In these the iminium ion participates in an exocyclic sense[11] and a carbocyclic ring is formed. One cyclization of this type has been reported.[13]
(13) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739.
(14) For a preliminary account of a portion of this work, see: Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993.
(15) See, e.g.: (a) Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375. (b) Negishi, E.; Idacavage, M. J. *Ibid.* **1985**, *33*, 1.
(16) See, e.g.: Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.
(17) (a) Brown, M. J.; McCann, S. F.; Overman, L. E. *Org. Synth.*, checked procedure. (b) Flann, C. J.; Malone, T. C.; Overman, L. E. *Org. Synth.*, checked procedure.
(18) (a) Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 392. Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935. (b) Hammound, A.; Descoins, C. *Bull. Soc. Chim. Fr.* **1978**, 299.
(19) A 25 m 5% methylphenylsilicon column was used for this analysis.
(20) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424. Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1979**, *44*, 4623.
(21) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(22) Snider, B. B.; Karras, M.; Conn, R. S. E. *J. Am. Chem. Soc.* **1978**, *100*, 4624.

Table I. Preparation of Substituted 1,2,5,6-Tetrahydropyridines **6** from the Reaction of (*Z*)-4-(Trimethylsilyl)-3-butenyl amines with Aldehydes

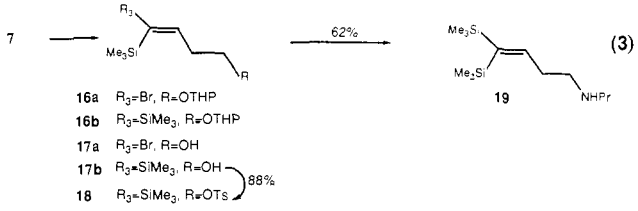
entry	tetrahydro-pyridine	R^1	R^2	R^3	R^4	cyclization step: rxn cond[a]	cyclization step: yield,[b] %
1	**6a**	*n*-C_3H_7	H	H	H	82 °C, 1.5 h	61
2	**6c**	4-methoxybenzyl	H	H	H	82 °C, 1.5 h	95
3	**6e**	Ph	H	H	H	82 °C, 0.7 h	70
4	**6d**	4-methoxyphenyl	H	H	H	82 °C, 1 h	85
5	**6b**	cyclohexyl	H	H	H	82 °C, 2.5 h	(78)[c]
6	**6f**	*i*-C_4H_9	H	H	CH_3	82 °C, 2 h	66
7	**6g**	*i*-C_4H_9	H	H	Ph	82 °C, 2 h	83
8	**6h**	*n*-C_3H_7	H	$SiMe_3$	H	82 °C, 1.2 h	82
9	**6i**	CH_2CH_2Ph	H	CH_3	H	82 °C, 5 h	70
10	**6j**	Ph	*n*-C_6H_{13}	H	H	82 °C, 3 h	68
11	**6k**	*n*-C_3H_7	*n*-C_6H_{13}	H	H	120 °C, 48 h	53
12	**6l**	4-methoxybenzyl	*n*-C_6H_{13}	H	H	120 °C, 72 h	64

[a] In CH_3CN, 3–20 equiv of R^2CHO, 0.95 equiv of camphorsulfonic acid. [b] Yields of isolated product. [c] GC estimate of yield.

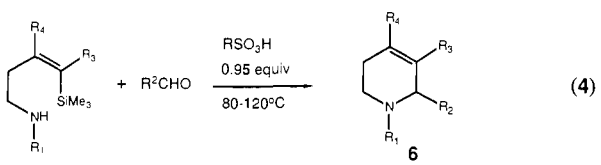
step, the significance, if any, of the differences in yields for these two series is unknown.



Cyclization substrates containing a bromine or trimethylsilyl substituent α to silicon were also prepared from silylalkyne **7**, see eq 3. Thus, hydroalumination followed by treatment with bromine in pyridine[23] gave **16a** in 83% yield, which was deprotected in 93% yield to provide alcohol **17a**. The 1,1-disilylbutenol **17b** was prepared in 61% yield by sequential treatment of **16a** with *sec*-BuLi and Me_3SiBr at −78 °C to provide **16b** followed by alcohol deprotection. Silylation of the vinyl lithium intermediate derived from **16a** with trimethylsilyl chloride or trimethylsilyl triflate provided much lower yields of the desired 1,1-disilyl alkene product. The disilyl amine **19** was then obtained from **17b** in 55% yield by reaction of tosylate intermediate **18** with excess *n*-propylamine.



Iminium Ion–Vinylsilane Cyclizations. A. Scope Studies. Cyclizations of (*Z*)-4-(trimethylsilyl)-3-butenylamines with paraformaldehyde to afford 1,2,5,6-tetrahydropyridines **6** (eq 4, R^2 = H) occurred readily in refluxing acetonitrile in the presence of 0.95 equiv of camphorsulfonic acid. An excess of paraformaldehyde (typically 20 equiv) was employed, since this reactant is lost into the reflux condenser during the course of the reaction. Earlier studies in our laboratories had shown that iminium ion–vinylsilane cyclizations could be successfully accomplished in a variety of solvents: acetonitrile, benzene, toluene, tetrahydrofuran, ethanol, and methanol.[9] Although acetonitrile was employed as the solvent for all the reactions reported here, other solvents could undoubtably be utilized. The accompanying paper describes a detailed study of the effect of solvents and additives on iminium ion initiated cyclization reactions.[1]



(23) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739.

In all cases a *single* tetrahydropyridine product was formed (see Table I), demonstrating that the silicon substituent exercised complete control over the outcome of the cyclization process. Entries 6–9 show that tetrahydropyridines with substituents at carbons 3 and 4 can be prepared selectively in this way. The high-yield synthesis of **6h** (entry 8) is particularly significant, since the silyl substituent is a potential site for further regioselective functionalization of the product tetrahydropyridine.

The stereochemistry of the vinylsilane was not critical for the success of the cyclization reaction. Thus, the *E* stereoisomer of **11a** was converted to **6a** in 73% yield when treated under similar conditions with paraformaldehyde and acid. This result suggests that the mechanism of tetrahydropyridine formation (vide infra) may involve more than simple cyclization to a cyclic β-silyl cation, since earlier investigations in our laboratories had shown that large *Z*/*E* rate ratios would have been expected.[13]

The cyclization of butenylamine **11b** (entry 5), containing an *N*-cyclohexyl substituent, was less clean and furnished 5–20% of *N*-cyclohexyl-*N*-methyl-4-(trimethylsilyl)-3-butenylamine in addition to the desired tetrahydropyridine **6b**. The N-methylated product presumably results from reduction of the formaldehyde iminium ion intermediate (**5** of Scheme I). This reduction most likely arises from traces of formic acid (i.e., classical Eschweiler–Clark reduction) present in the formaldehyde.[4b,c,24] Consistent with this interpretation was the observation that the extent of N-methylation depended on the batch of paraformaldehyde used. Unfortunately, in spite of numerous attempts, we were unable to purify paraformaldehyde or obtain formalin solutions that were devoid of "reducing" activity.[25] As a result, cyclizations that occur slowly in refluxing acetonitrile always produce small amounts of N-methylated butenylamines as side products. This problem can be avoided by use of other formaldehyde iminium ion precursors (vide infra).

Structural assignments for the tetrahydropyridine products were made primarily on the basis of ^1H and ^{13}C NMR data.[26] The 1-alkyl-substituted tetrahydropyridines (**6**: $R^2 = R^3 = R^4$ = H) all showed vinylic hydrogen absorptions at δ 5.68–5.90 and signals between δ 2.9–3.0 and 2.3–2.6 for the hydrogens at C(2) and C(6), respectively. These latter signals of the 1-aryl-substituted tetrahydropyridines were shifted downfield to 3.48–3.74 and 3.17–3.41 ppm, respectively. Tetrahydropyridines **6f** and **6g** showed absorptions for the C(3) vinylic hydrogen at 5.37–5.40 and 6.07–6.10 ppm, respectively, while the C(4) vinylic hydrogens of **6h** and **6i** displayed characteristic multiplets at 5.99–6.04 and 5.6–5.8 ppm, respectively.

Aldehydes other than formaldehyde (see Table I, entries 10–12) can also be employed in cyclizations of (*Z*)-4-(trimethylsilyl)-3-butenylamines to yield cleanly 1,2,3,6-tetrahydropyridines with

(24) Eschweiler, W. *Chem. Ber.* **1905**, *38*, 880. Clark, H. T.; Gillespie, H. D.; Weisshaus, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4751.
(25) Malone, T. C. Ph.D. Thesis, University of California, Irvine, 1986.
(26) Shamma, M. I.; Hindenlang, D. M. *Carbon-13 NMR Shift Assignments of Amines and Alkaloids*; Plenum Press: New York, 1979; pp 36 and 37.

Table II. Preparation of 1,2-Substituted 1,2,5,6-Tetrahydropyridines from Cyanoalkylamines **20**

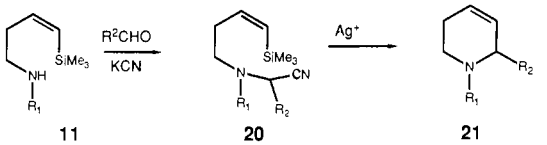
entry	cyanoalkylamine compd	cyanoalkylamine prep[a]	cyanoalkylamine yield, %	tetrahydropyridine	R^1	R^2	conditions	yield, %
1	**20g**	A	99	**6b**	cyclohexyl	H	$AgOCOCF_3$, $CHCl_3$, 100 °C	54
2	**20a**	B	76	**21a**	*n*-Pr	CH_2CH_2Ph	$AgBF_4$, tol., 120 °C, 24 h	73
3	**20b**	B	73	**21b**	4-methoxybenzyl	CH_2CH_2Ph	$AgBF_4$, CH_3CN, 120 °C, 44 h	76
4	**20c**	C	75	**21c**	*n*-Pr	3-bromophenyl	$AgBF_4$, tol., 120 °C, 24 h	40
5	**20d**	B, C	74	**21d**	*n*-Pr	2-furyl	$AgBF_4$, CH_3CN, 120 °C, 20 h	58
6	**20e**	C	76	**21e**	4-methoxybenzyl	3-pyridinyl	$AgBF_4$, CH_3CN, 120 °C, 24 h	82
7	**20f**	B, C	70	**21f**	*n*-Pr	3-pyridinyl	$AgBF_4$, CH_3CN, 120 °C, 24 h	40

[a] See Experimental Section.

substituents at C(2). These reactions were considerably slower than the corresponding reactions with formaldehyde; cyclizations to afford 1,2-dialkyl-1,2,3,6-tetrahydropyridines (entries 11 and 12) required a temperature of 120 °C to achieve a practical cyclization rate. Interestingly, the cyclization of the aniline derivative **11e** (entry 10) was much faster and occurred conveniently in refluxing acetonitrile.

Structural assignments for **6j–l** were again based primarily on NMR data. For example, **6k** showed a characteristic doublet of triplets at δ 2.84 for the C(2) methine hydrogen and ring carbon signals similar to those reported[26] for 1,2-dimethyl-1,2,5,6-tetrahydropyridine.

To avoid the problems of N-methylation in the slower cyclizations of formaldehyde iminium ions (vide supra), we examined the two-step sequence illustrated in eq 5.[27] With use of this procedure the *N*-cyclohexyltetrahydropyridine (**6b**) could be

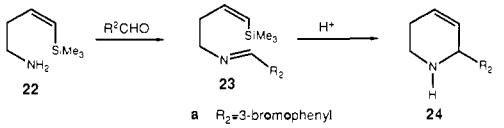


11 20 21 (5)

cleanly prepared from cyanomethylamine **20** (R^1 = *N*-cyclohexyl, R^2 = H) in 51% yield, without contamination from the N-methylated derivative of **11b**. Also summarized in Table II are related studies of the preparation of 1,2-disubstituted 1,2,5,6-tetrahydropyridines from the cyclization of α-cyanoalkylamines **20** ($R^2 \neq$ H). The cyanoalkylamines were prepared either by treatment of the bisulfite adduct of the aldehyde with KCN and the secondary amine **11** at 75 °C[28] or from reaction of the trimethylsilylcyanohydrin derivative of the aldehyde with amine **11**.[29] The latter procedure was preferred with aryl aldehydes.

The optimum condition for the cyclization of cyanoalkylamines **20** is to treat the cyanoalkylamine with 1 equiv of $AgBF_4$ at 120 °C in acetonitrile in a sealed reaction vessel. By using these conditions, tetrahydropyridines with alkyl, aryl, furyl, and pyridinyl substituents at C(2) can be prepared (Table II, entries 2–7). A particular advantage of the two-step cyclization procedure of eq 5 is that only a single equivalent of the aldehyde is utilized, rather than the excess of aldehyde employed in the direct cyclization reaction (see Table I). This fact, of course, would be quite significant if the aldehyde were a valuable reaction component.

The direct preparation of 1-unsubstituted tetrahydropyridines via acid promoted cyclizations of imine precursors (eq 6) is also



22 23 24 (6)

a R_2=3-bromophenyl
b R_2=3-pyridinyl
c R_2=$C(CH_3)_2CH_2Ph$
d R_2=CH_2CH_2Ph

Table III. Preparation of 1-Unsubstituted 1,2,5,6-Tetrahydropyridines **24** from Imines **23**

entry	tetrahydropyridine	cyclization step conditions	yield, %
1	**24a**	CF_3COOH (5 equiv), CH_3CN, 55 °C, 48 h	55
2	**24a**	HCOOH, 60 °C, 40 h	35
3	**24b**	CF_3COOH (5 equiv), CH_3CN, 60 °C, 40 h	33
4	**24b**	CF_3COOH (5 equiv), sulfolane, 60 °C, 40 h	24
5	**24c**	CF_3COOH (5 equiv), CH_3CN, 120 °C, 24 h	66
6	**24c**	CF_3COOH (5 equiv), CH_3CN, 60 °C, 40 h	26

possible. The primary amine **22** is available in excellent yield by aminolysis of **10** and was readily converted in a conventional way[30] to imines **23** (80–90% yield). Our initial expectation was that cyclization could be brought about under essentially neutral conditions by use of 1 equiv, or just less than 1 equiv, of a strong acid.[13] However, treatment of **23a** with 1.0 equiv of CF_3COOH gave **24a** in only very low yield. Surprisingly, the cyclization was better with an excess of CF_3COOH, in spite of the greater opportunity of protodesilylation of vinylsilane moiety[8] under acidic conditions. The optimum conditions were to employ 5 equiv of CF_3COOH and carry out the cyclization in acetonitrile, see Table III. The use of formic acid as the solvent was less successful (see entry 2).

Similar conditions were not successful in promoting the cyclization of imines derived from aldehydes containing α-hydrogens, e.g., **23d**. In these cases, the reaction turned rapidly dark, suggesting decomposition via condensation reactions with the enamine tautomer of **23d**. However, tetrahydropyridine **24d** could be prepared in 74% yield by chloroformate dealkylation[31] of the *N*-(4-methoxybenzyl) analogue **21b** with 2,2,2-trichloroethyl chloroformate[32] followed by reductive cleavage[32] of the carbamate substituent.

We also briefly examined the possibility of preparing tetrahydro-1*H*-azepines by related procedures. Utilizing a sequence identical with the one outlined in eq 1, 4-pentyn-1-ol was converted to the (*Z*)-5-(trimethylsilyl)-4-pentenylamine **26** in 41% overall yield (see eq 7).[25] Cyclization of this intermediate with paraformaldehyde and camphorsulfonic acid (0.95 equiv) was slower than cyclizations to form analogous tetrahydropyridines and required 10 h in refluxing acetonitrile. As a result, protodesilylation of **26** occurred competetively, and 1-butyl-2,3,4,7-tetrahydro-1*H*-azepine (**28**) and the pentenylamine **27** were formed in a ratio of 2.6:1 (42% yield). The 250 MHz ^{1}H NMR spectrum of **28** displayed vinylic hydrogen absorptions at 5.93–5.84 and 5.72–5.63 ppm, while the allylic methylene hydrogens adjacent to nitrogen were observed as a doublet (J = 5.5 Hz) at 3.19–3.17 ppm. These chemical shift assignments were confirmed by extensive ^{1}H NMR homonuclear decoupling experiments.[25]

B. Mechanistic Studies. Two mechanisms can be considered for these cyclization reactions (Scheme II). The simplest is direct cyclization of iminium ion **29** to β-silyl cation intermediate **31**,

(27) For recent uses of α-cyanoamines as iminium ion precursors, see inter alia: (a) Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2741. (b) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392.

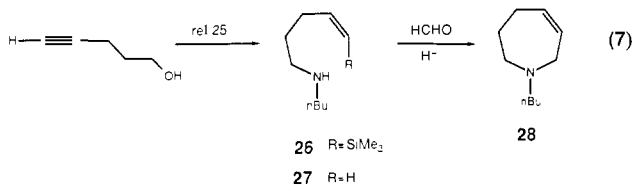
(28) See, e.g.: Ahlbrecht, H.; Raab, W.; Vonderheid, C. *Synthesis* **1979**, 127.

(29) Mai, K.; Patil, G. *Tetrahedron Lett.* **1984**, *25*, 4583. Mai, K.; Patil, G. *Synth. Commun.* **1985**, *15*, 157.

(30) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*; Academic: New York, 1971; Vol. 2, Chapter 12.

(31) For the original report of this general approach to 1-unsubstituted tetrahydropyridines, see: Oediger, H.; Joop, N. *Liebigs Ann. Chem.* **1972**, *764*, 21.

(32) Reincke, M. G.; Daubert, R. G. *J. Org. Chem.* **1973**, *38*, 3281.



(7)

26 R=SiMe$_3$
27 R=H
28

which subsequently loses the trimethylsilyl group to give **30**. Alternatively, **29** could undergo cationic aza-Cope rearrangement[33] to allylsilane iminium ion isomer **32**, which then cyclizes to **30**.[8] Two experiments demonstrate that cationic aza-Cope equilibration occurs more rapidly than cyclization. First, treatment of (*Z*)-vinylsilylamine **11f** in refluxing acetonitrile for 1.2 h with formaldehyde containing a trace of formic acid gave a 6:1:3 mixture of 1-isobutyl-1,2,5,6-tetrahydropyridine and the (*Z*)- and (*E*)-methylated amines **33** and **34**, respectively. Since **11f** does not undergo $Z \rightarrow E$ isomerization in the presence of acid when formaldehyde is absent, the loss of stereochemistry when formaldehyde is present is most consistent with the rapid equilibrium of **29** and **32**. That the *E* and *Z* stereoisomers are equilibrated more rapidly than they cyclize, of course, explains why both stereoisomers of **11a** produce **6a** at nearly identical rates.

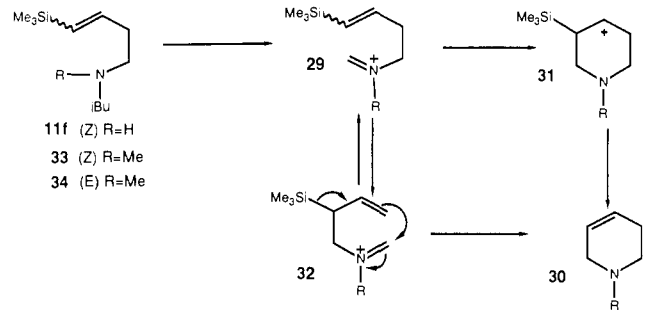
Stronger evidence for the facile formation of rearranged allylsilanes comes from the cyclization of **36**, see Scheme III. This unsaturated amino alcohol was prepared, as an inseparable mixture with regioisomer **37**, by aminolysis of the epoxide **35** formed from the reaction of (*E*)-3-(trimethylsilyl)propenal[34] with dimethylsulfonium methylide.[35] Treatment of this mixture with excess paraformaldehyde and camphorsulfonic acid (0.95 equiv) in refluxing ethanol yielded pyrrolidine **39**, which was isolated as the amino alcohol **40** (86% yield based on **36**) after treatment of the crude product with sodium borohydride. No trace of tetrahydropyridine **41** was seen in the crude reaction product. The formation of pyrrolidine **39** confirms the facile formation of rearranged allylsilane iminium ion which, in this case, is trapped by an intramolecular Mannich cyclization (**38** → **39**).

While neither of these experiments establish which mode of cyclization is actually operative, they do show that the vinylsilane and allylsilane iminium ion isomers equilibrate more rapidly than cyclization to form the tetrahydropyridine product. Since an allylsilane is a stronger nucleophile than a vinylsilane,[8] it is reasonable that the tetrahydropyridine product would result from cyclization of the more reactive allylsilane iminium ion isomer. The important question of whether or not the C–C bond-forming step which establishes the tetrahydropyridine ring is also reversible is treated in detail in the following paper[1] of this series.

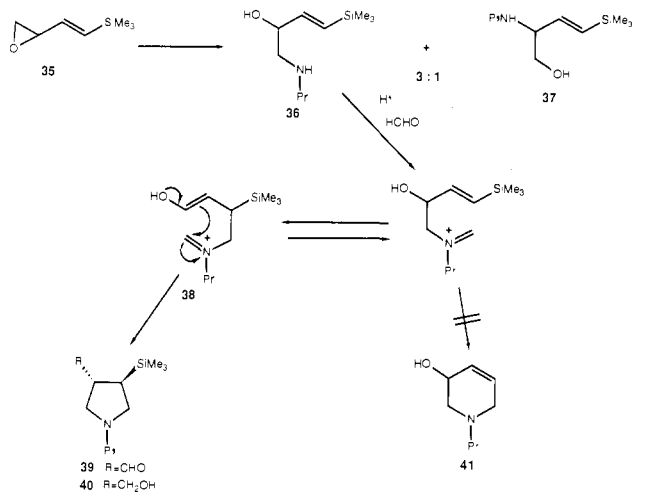
C. Total Synthesis of the Racemic Elaeocarpus Alkaloids, Elaeokaines A and B. Since *N*-acyliminium ions are more reactive cyclization initiators than iminium ions,[6] it was expected that vinylsilane-terminated cyclizations of these initiators would also be successful. The "extra" reactivity of the *N*-acyliminium ion was expected to be significant in cyclizations of vinylsilanes containing electron-withdrawing substituents (e.g., halogens) on the vinylic terminator. For example, iminium ion initiated cyclizations of (*Z*)-4-bromo-4-(trimethylsilyl)-3-butenylamines (prepared from alcohol **17a**) are not successful.[25,36]

In light of the extensive studies of Speckamp and co-workers[6,37] we chose to initially examine cyclization reactions of vinylsilanes with cyclic *N*-acyliminium ions derived from imide precursors.[38] Imides **42** were prepared (59–76%) from the 4-(trimethylsilyl)-3-butenol precursors **9** and **17a** by standard Mitsunobu[39] coupling with succinimide and glutarimide. These intermediates were reduced[37] to the corresponding hydroxylactams by the procedure of Chamberlin[40] (**43a**, 78%; **43b**, 79%; **43c**, 94%).

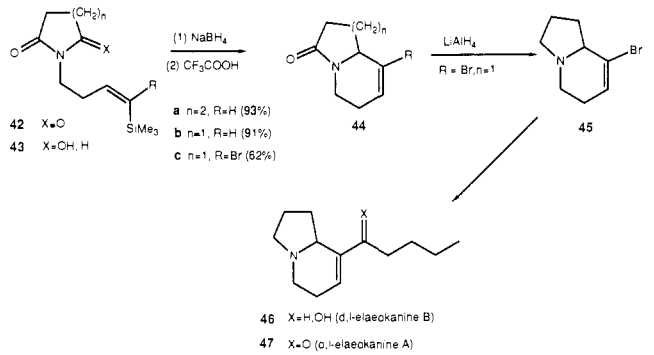
Scheme II



Scheme III



Scheme IV



Dissolution of hydroxylactams **43a** and **43b** in dry trifluoroacetic[6,37] acid occasioned clean cyclization within 15 min at room temperature to afford quinolizidine **44a** (91% yield) and the known indolizidine **44b** (93% yield), respectively. These cyclizations could also be accomplished in refluxing formic acid,[37] although the yields were significantly lower, 74% and 48%, respectively.

Cyclization of hydroxylactam **43c**, which contains the less nucleophilic 1-bromo-1-(trimethylsilyl)alkene terminator, could not be accomplished at room temperature. However, treatment of **43c** in refluxing trifluoroacetic acid for 2.5 h provided the bromoindolizidinone **44a** in 62% yield (90% purity). Protodesilylation of **43c** under these conditions was obviously sufficiently slow that the desired cyclization could be successfully accomplished. Not surprisingly, the bromine substituent must also deactivate the vinylsilane toward protodesilylation, since a simple 1-alkenylsilane undergoes rapid protodesilylation in refluxing trifluoroacetic acid.[6,36]

To provide an illustration of the synthetic opportunities presented by the functionalized alkene group produced in cyclization

(33) See, e.g.: Overman, L. E.; Kakimoto, M.; Okazaki, M.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6629 and references cited therein.
(34) Jung, M. E.; Gaeda, B. *Tetrahedron* **1979**, *35*, 621.
(35) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(36) Unpublished studies of Dr. Chris Flann of these laboratories.
(37) Speckamp, W. N. *Recl. Trav. Chim.* Pays-Bas **1981**, *100*, 345.
(38) Our studies of vinylsilane cyclizations with acylic *N*-acyliminium ion initiators will be reported elsewhere: Flann, C.; Overman, L. E., to be submitted for publication.
(39) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(40) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

products such as **6h** and **44c**, the latter intermediate was employed in a short synthesis of the *Elaeocarpus* alkaloids, elaeokanines B (**46**) and A (**47**). These simple indolizidines are examples of a recently discovered class of alkaloids isolated from the leaves of *Elaeocarpus kaniesis*, a large tree found in the rain forests of New Guinea.[41,42]

These syntheses were culminated as follows. Lithium aluminum hydride reduction of **44c** provided bromoindolizidine **45** in 67% yield. The vinyl lithium derived from this intermediate by treatment with *sec*-BuLi was found to be completely stable to β-elimination at −78 °C. Thus, sequential treatment of **45** with *sec*-BuLi and butanal at −78 °C afforded racemic elaeokanine B (**46**) as a 1:1 mixture of alcohol diastereomers, in 86% yield. Oxidation by the Swern procedure,[43] as described by Weinreb,[44] provided racemic elaeokanine A (**47**) in 56% yield.

Conclusion

The results reported in this paper demonstrate that iminium ion–vinylsilane cyclizations that occur in the endocyclic mode with respect to the vinylsilane (see Figure 1) can be effectively employed to prepare a wide variety of substituted 1,2,5,6-tetrahydropyridines and related unsaturated azacyclics. The 1,2,5,6-tetrahydropyridine ring is found in numerous alkaloids[45] and other pharmacologically active materials and has often been employed as a key intermediate for accessing other azacyclic systems.[46,47] This ring system is most commonly prepared by reduction of a pyridinium[48] salt or from a 4-piperidone precursor.[49,50] The cyclization approach reported here should prove useful for preparing tetrahydropyridines not readily available from these heterocyclic precursors: for example, 1-aryl-substituted tetrahydropyridines, which are not generally available from pyridine precursors.

The strength of the iminium ion–vinylsilane approach is the *complete* control of the double bond position exerted by the silicon substituent and the fact that the silicon substituent can be utilized to assist[10] the introduction of substituents at what become the vinylic carbons of the tetrahydropyridine product. This latter feature is well-illustrated by the syntheses of the racemic elaeokanines A and B, in which the vinylic bromine substituent allows attachment of the four-carbon side chain of the alkaloid target.[51] The weakness of the iminium ion–vinylsilane cyclization approach is that typically 3–6 steps are required to assemble the cyclization substrates from commercially available starting materials.

Experimental Section

General experimental procedures have been detailed recently.[52] Experimental details for the preparation of **3**, **7–10**, **11d**, and **6d** are described in ref 17 and can be obtained from the secretary of *Organic Syntheses* or from L.E.O. Tosylate **10** of >98% isomeric purity was used in the procedures that follow.

***N*-Propyl-(*Z*)-4-(trimethylsilyl)-3-buten-1-ylamine (11a).** A solution of **10**[17a] (39.1 g, 0.131 mol) and 330 mL of *n*-propylamine was degassed (vacuum and argon) and heated at reflux for 3 h, and excess *n*-propylamine (approximately 300 mL) was removed by distillation (atmospheric pressure). Aqueous 1 N NaOH (300 mL) was added and the resulting mixture was extracted with hexanes (4 × 200 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by bulb-to-bulb distillation (100 °C, 30 mmHg) to give 22.5 g (92%) of **11a** as a colorless liquid: IR ($CHCl_3$) 2980, 1615, 1250, 1120, 910, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.32 (dt, 1 H, J = 14.1 and 7.3 Hz, $R_3SiCH{=}CHR'$), 5.61 (dt, 1 H, J = 14.1 and 1.3 Hz, $SiCH{=}CHR'$), 2.71 (t, 2 H, J = 7.1 Hz), 2.60 (t, 2 H, J = 7.2 Hz), 2.39–2.31 (app qd, 2H), 1.61–1.46 (m, 2 H), 1.46–0.97 (br s, 1 H, NH), 0.97–0.91 (t, 3 H, J = 7.4 Hz, CH_2CH_3), 0.15 (s, 9 H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.4, 131.1, 52.0, 49.7, 34.2, 23.3, 11.8, 0.3; MS (CI, 2-methylpropane), m/z 186 (MH^+, 19), 72 (100); high-resolution MS (EI, 70 eV) 185.1588 (calcd for $C_{10}H_{23}NSi$, 185.1600).

***N*-Cyclohexyl-(*Z*)-4-(trimethylsilyl)-3-buten-1-ylamine (11b).** By use of a procedure similar to that described in the preparation of **11a**, 4.56 g (15.2 mmol) of **10**[17a] was allowed to react with 60 mL of cyclohexylamine at 60 °C for 18 h to give 2.63 g (77%) of **11b** as a colorless liquid: IR ($CHCl_3$) 2960, 1612, 1455, 1250, 1120, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.31 (dt, 1 H, J = 14.0 and 7.3 Hz, $SiCH{=}CH$), 5.61 (d, 1 H, J = 14.0 Hz, $SiCH{=}CH$), 2.71 (t, 2 H, J = 7.2 Hz, CH_2NH), 2.44–2.31 (m, 3 H), 1.92–1.73 (m, 5 H), 1.32–1.05 (m, 6 H), 0.15 (s, 9 H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.5, 131.2, 57.0, 47.0, 33.9, 26.4, 25.3, 0.42; MS (CI, 2-methylpropane), m/z 226 (MH^+, 32), 112 (100); high-resolution MS (EI, 70 eV) 225.1907 (calcd for $C_{13}H_{27}NSi$, 225.1913).

***N*-(4-Methoxybenzyl)-(*Z*)-4-(trimethylsilyl)-3-buten-1-ylamine (11c).** A solution of **10**[17a] (8.10 g, 27.0 mmol) and 4-methoxybenzylamine (50 mL) was maintained at room temperature for 48 h and the excess amine was then removed by distillation (120 °C, 20 mmHg). Purification of the residue by flash chromatography (9:1 $CHCl_3$–Et_3N) and bulb-to-bulb distillation (100 °C, 0.2 mmHg) gave 3.37 g (49%) of **11c** as a colorless oil: IR (film) 2950, 1615, 1520, 1250, 1175, 1040, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.26–7.22 (m, 2 H), 6.86 (dd, 2 H, J = 9.7 and 2.0 Hz), 6.28 (dt, 1 H, J = 14.1 and 7.3 Hz, $SiCH{=}CH$), 5.58 (d, 1 H, J = 14.1 Hz, $SiCH{-}CH$), 3.80 (s, 3 H, $ArOCH_3$), 3.74 (s, 2 H, $NHCH_2Ar$), 2.69 (t, 2 H, J = 7.1 Hz, CH_2NH), 2.38–2.32 (m, 2 H, CH_2CH_2NH), 1.49 (br s, 1 H, NH), 0.12 (s, 9 H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.5, 146.2, 132.4, 130.8, 129.0, 113.6, 54.9, 53.2, 48.8, 0.17; MS (CI, 2-methylpropane), m/z 264 (MH^+, 16), 150 (20), 121 (100); high-resolution MS (EI, 70 eV) 263.1696 (calcd for $C_{15}H_{25}NOSi$, 263.1705).

***N*-Phenyl-(*Z*)-4-(trimethylsilyl)-3-buten-1-ylamine (11e).** A solution of **10**[17a] (7.16 g, 24.0 mmol) and 125 mL of aniline was degassed and heated at 60 °C for 15 h. The excess aniline was removed by vacuum distillation (80 °C, 20 mmHg), and the residue was diluted with CH_2Cl_2 (50 mL) and extracted with 1 N NaOH (30 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by flash chromatography (silica gel, 90:10 $CHCl_3$–Et_3N) and bulb-to-bulb distillation (100 °C, 18 mmHg) to give 2.54 g (48%) of **11e** as a yellow oil: IR ($CHCl_3$) 3415, 2950, 1610, 1508, 1325, 1255, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.22–7.16 (m, 2 H, ArH) 6.72 (t, 1 H, J = 7.3 Hz, ArH), 6.62 (d, 2 H, J = 8.5 Hz, ArH), 6.33 (dt, 1 H, J = 14.1 and 7.3 Hz, $SiCH{=}CH$), 5.69 (dt, 1 H, J = 14.1 and 1.2 Hz, $SiCH{=}CH$), 3.66 (br s, 1 H, NH), 3.20 (t, 2 H, J = 6.8 Hz, CH_2NH), 2.52–2.44 (m, 2 H), 0.15 s, 9 H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 148.3, 145.5, 132.2, 129.3, 117.4, 112.9, 43.4, 33.4, 0.4; MS (CI, 2-methylpropane), m/z 220 (MH^+, 15), 106 (100); high-resolution MS (EI, 70 eV) 219.1438 (calcd for $C_{13}H_{21}NSi$, 219.1443.

(*Z* and *E*)-4-(Trimethylsilyl)-3-methyl-3-buten-1-yl Tetrahydropyran-2-yl Ether (12a). According to the general method of Snider,[22] trimethylaluminum (3.3 mL of a 2 M solution in toluene) was added dropwise to a stirring solution of nickel acetoacetate (1.69 g, 6.6 mmol) and 130 mL of THF. The resulting dark brown solution was stirred for 5 min and **7**[17a,18b] (15.0 g, 66.2 mmol) was added. The reaction mixture was cooled to −78 °C and methyl magnesium bromide (83 mL of a 2.9 M solution in Et_2O) was added dropwise. After being stirred for 12 h at room temperature the reaction mixture was cooled to 0 °C and quenched by the cautious addition of H_2O. An additional 50 mL of aqueous 1 N HCl was added and the reaction mixture was stirred until the remaining magnesium salts had dissolved. The resulting solution was extracted with hexanes (4 × 60 mL), and the combined organic phases were washed with H_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, 5:1 hexanes–CH_2Cl_2) to give 6.39 g (40%) of **12a** as a colorless liquid which was a 72:28 mixture of *Z* and *E* isomers (GC analysis),[19] respectively: IR (film) 2980, 1620, 1440, 1250, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.30 (d, 1 H, J = 1.3 Hz, $C{=}CH$, major isomer), 5.27 (s, 1 H, $C{=}CH$, minor isomer), 4.62–4.59 (app t, 1 H), 3.89–3.79 (m,

(41) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Can. J. Chem.* **1971**, *25*, 817.

(42) For a recent review of the synthesis of *elaeocarpus* alkaloids, see: Herbert, R. B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley & Sons: New York, 1985; Chapter 6.

(43) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(44) Weinreb, S. M.; Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J. *J. Am. Chem. Soc.* **1981**, *103*, 6387.

(45) Glasby, J. S. *Encyclopedia of the Alkaloids*; Plenum: New York; Vol. 1–4.

(46) (a) Coutts, R. T.; Scott, J. R. *Can. J. Pharm. Sci.* **1971**, *6*, 78. *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic: New York, 1986; Vol. 21, and earlier volumes in this series. (b) A notable recent example is 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) which induces symptoms indistinguishable from Parkinson's disease. For a recent brief discussion of MPTP, see: *Chemical and Engineering News* **1986**, *May 5*, 28.

(47) For examples, see: Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1. Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.*, submitted. Reference 27b.

(48) Lyle, R. E.; Anderson, P. S. *Adv. Heterocycl. Chem.* **1966**, *6*, 45.

(49) For a recent example, see: Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285.

(50) Another useful approach is hetero-Diels-Alder cycloadditions: Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

(51) Another example is provided by the tandem cyclization reported in: Flann, C.; Overman, L. E. *J. Am. Chem. Soc.*, the third paper in this issue.

(52) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745.

2 H, OCH_2), 3.55–3.45 (m, 2 H, OCH_2), 2.44 (t, 2 H, J = 7.3 Hz, major isomer), 2.37 (t, 2 H, J = 7.4 Hz, minor isomer), 1.86 (d, 3 H, J = 1.3 Hz, CH_3, major isomer), 1.81 (d, 3 H, J = 0.5 Hz, CH_3, minor isomer), 1.75–1.49 (m, 6 H), 0.10 (s, 9 H, $SiCH_3$); MS (CI, 2-methylpropane), m/z (relative percent, 20% cutoff) 243 (MH^+, 22), 275 (25), 141 (20), 85 (100).

(*Z* and *E*)-4-(Trimethylsilyl)-3-phenyl-3-buten-1-yl Tetrahydropyran-2-yl Ether (12b). By use of a procedure identical with that described for the preparation of **12a**, trimethylaluminum (1.1 mL of a 2 M solution in toluene) was added to a stirring solution of nickel acetoacetate (560 mg, 2.2 mmol) in 44 mL of THF. The resulting brown solution was stirred for 5 min and **7**[17a,18b] (5.00 g, 22.1 mmol) was added. The reaction mixture was cooled to −78 °C and phenyl magnesium bromide (36.7 mL of a 3 M solution in ether) was added dropwise. The reaction mixture was then stirred at room temperature for 12 h. Workup followed by flash chromatography (silica gel, 1:1 hexane–CH_2Cl_2) gave 6.4 g (95%) of **12b** as a viscous yellow green oil: a 87:13 mixture of isomers by GLC analysis;[19] IR (film) 2970, 1600, 1250, 850, 760, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.42–7.14 (m, 5 H), 5.86 (s, 1 H, C=C*H*, major isomer), 5.66 (s, 1 H, C=C*H*, minor isomer), 4.54–4.49 (app t, 1 H, C*H*), 4.01–3.66 (m, 2 H, CH_2O), 3.48–3.32 (m, 2 H, CH_2O), 2.96 (t, 2 H, J = 7.6 Hz, C=CCH_2, major isomer), 2.72 (t, 2 H, J = 7.2 Hz, C=CCH_2R, minor isomer), 1.84–1.43 (m, 6 H), 0.21 (s, 9 H, $SiCH_3$, major isomer), −0.19 (s, 9 H, $SiCH_3$, minor isomer); MS (CI, 2-methylpropane), m/z (relative percent, 30% cutoff) 305 (MH^+, 100), 215 (38), 203 (49), 85 (99).

(*E*)-4-(Trimethylsilyl)-4-bromo-3-buten-1-yl Tetrahydropyran-2-yl Ether (16a). According to the general method of Zweifel,[23] diisobutylaluminum hydride (7.4 mL, 41.4 mmol) was added at 23 °C slowly to a stirring solution of **7**[17a,18b] (7.39 g, 32.6 mmol) and 70 mL of hexane. The reaction mixture was heated at 40 °C for 2 h and cooled to 0 °C, and then pyridine (5.30 mL, 69.2 mmol) was added. The resulting yellow solution was cooled to −78 °C and bromine (2.80 mL, 56 mmol) in 10 mL of CH_2Cl_2 was added dropwise over a 1-h period. After being stirred for an additional 15 min at −78 °C, the reaction mixture was poured into a mixture of 1 N NaOH (100 mL), hexane (100 mL), and ice (100 g), and the resulting mixture was stirred for 45 min. The organic phases were separated, washed with aqueous 1 N HCl (2 × 50 mL) and H_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated to give 8.34 g (83%) of **16a** as a colorless liquid: IR (film) 2980–2880, 1255, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.81 (t, 1 H, J = 8.0 Hz, C=C*H*), 4.62 (app t, 1 H, C*H*$(OR)_2$), 2.43 (dt, 2 H, J = 7.9 and 6.7 Hz, C=CHCH_2), 1.73–1.54 (m, 6 H), 0.30 (s, 9 H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 144.5, 129.5, 99.0, 66.3, 62.3, 33.0, 30.8, 25.7, 19.6, 0.4; high-resolution MS (EI, 70 eV), m/z 306.0653 (calcd for $C_{12}H_{23}{}^{79}BrO_2Si$, 306.0651).

4,4-Bis(trimethylsilyl)-3-buten-1-yl Tetrahydropyran-2-yl Ether (16b). A solution of **16a** (15.5 g, 50.5 mmol) in 200 mL of THF was cooled to −78 °C and treated with *sec*-butyllithium (42.1 mL of a 1.3 M solution in cyclohexane). The resulting solution was stirred for 30 min and then treated with bromotrimethylsilane (7.0 mL, 53.0 mmol) at −78 °C for 30 min. Workup afforded 15.0 g of crude material which was not purified but used directly for the synthesis of **17b**. An analytical sample of **16b** was obtained by preparative gas chromatography: IR (film) 2950, 1520, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.63 (t, 1 H, J = 6.9 Hz, C=C*H*), 4.63 (t, 1 H, J = 2.9 Hz, OCHO), 3.87 (m, 2 H, OCH_2), 3.55–3.42 (m, 2 H, OCH_2), 2.59–2.51 (app q, 2 H, C=CCH_2), 1.85–1.49 (m, 6 H), 0.18 (s, 9 H, $SICH_3$), 0.08 (s, 9 H, $SICH_3$); mass spectrum (CI, 2-methylpropane), m/z (relative percent, 10% cutoff) 301 (MH^+, 10), 201 (18), 200 (24), 199 (100), 176 (12), 175 (84), 173 (42), 143 (13), 129 (41), 127 (14), 111 (36), 103 (17).

(*Z*)-4-(Trimethylsilyl)-4-bromo-3-buten-1-ol (17a). By use of a procedure identical with that described for the preparation of **9**,[17] a solution of **16a** (3.00 g, 9.76 mmol) and pyridinium *p*-toluenesulfonate (150 mg, 0.65 mmol) in 200 mL of MeOH was heated at 40 °C for 8 h. Workup gave 2.08 g (93%) of **17a** as a colorless oil: IR (film) 3380, 2950, 1605, 1255, 1050, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.77 (t, 1 H, J = 8.0 Hz, C=C*H*), 3.68 (t, 2 H, J = 6.3 Hz, CH_2OH), 2.37 (dt, 2 H, J = 14.4 and 6.4 Hz, C=CHC*H*), 1.74 (br s, 1 H, OH), 0.29 (s, 9 H, $SiCH_3$); MS (CI, 2-methylpropane), m/z (relative percent, 5% cutoff) 225 (MH^+, 5), 144 (12), 143 (100), 135 (38), 133 (37), 127(8), 123 (6), 103 (39), 91 (10), 75 (5), 73 (26).

Preparation of 13ab, 14ab, 15ab, 17b, 18, and 19. Tetrahydropyranyl ethers **12a,b** and **16b** were converted to the title compounds by using procedures similar to those described for the preparation of **9**–**11**. Complete experimental details may be found in the Supplementary Material.

1-Propyl-1,2,3,6-tetrahydropyridine (6a). A mixture of **11a** (1.51 g, 8.14 mmol), paraformaldehyde (7.28 g, 2.42 mmol), camphorsulfonic acid (1.92 g, 7.68 mmol), and 160 mL of dry CH_3CN was degassed and heated under an argon atmosphere at reflux for 1.5 h. The reaction mixture was allowed to cool to room temperature, was vacuum filtered to remove excess paraformaldehyde, and was concentrated. The residue was partitioned between CH_2Cl_2 (50 mL) and aqueous 1 N NaOH (30 mL), and the aqueous phase was re-extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated to give 0.62 g (61%) of **6a** as a colorless liquid which contained no detectable impurities in its 250-MHz ^1H NMR spectrum: IR ($CHCl_3$) 3000, 2700, 1470, 1380, 1140, 1087, 650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.78–5.66 (m, 2 H, R′C*H*=C*H*R), 2.99–2.96 (m, 2 H), 2.56 (t, 2 H, J = 5.7 Hz, NCH_2CH_2), 2.41–2.35 (t, 2 H, J = 7.9 Hz, NCH_2CH_2CH), 2.23–2.17 (m, 2 H), 1.62–1.50 (m, 2 H), 0.94 (t, 3 H, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 125.5, 125.2, 60.9, 52.9, 50.2, 26.3, 20.3, 12.1; MS (CI, 2-methylpropane), m/z 126 (MH^+, 100), 113 (27), 97 (24), 73 (50), 71 (31).

An analytical sample of the oxalate salt (mp 177–179 °C) was obtained by recrystallization from hot 2-propanol. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96, N, 6.51. Found: C, 55.75; H, 7.98; N, 6.50.

1-(4-Methoxybenzyl)-1,2,3,6-tetrahydropyridine (6c). Amine **11c** (1.60 g, 6.07 mmol) was cyclized in a similar manner as **11a** to give 1.17 g (95%) of **6c** as a colorless liquid which was greater than 90% pure by capillary GC analysis:[19] IR ($CHCl_3$) 3020–2700, 1615, 1510, 1040, 820, 800, 750, 650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2 H), 6.86 (d, 2 H, J = 7.7 Hz), 5.63–5.47 (m, 2 H, C*H*=C*H*), 3.80 (s, 3 H, OCH_3), 3.52 (s, 2 H, CH_2Ar), 2.97–2.93 (m, 2 H), 2.54 (t, 2 H, J = 5.7 Hz), 2.18–2.13 (m, H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.9, 130.6, 130.5, 125.6, 125.4, 113.7, 62.5, 55.4, 52.9, 49.2, 23.9; MS (CI, 2-methylpropane), m/z 204 (MH^+, 100), 5 (24), 81 (24), 79 (21).

An analytical sample of the oxalate salt (mp 162 °C) was obtained by recrystallization from hot 2-propanol. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.42; H, 6.54; N, 4.78.

1-Phenyl-1,2,5,6-tetrahydropyridine (6e). Amine **11e** (713 mg, 3.25 mmol) was cyclized in a similar manner to **11a** to give a crude product (572 mg) which was bulb-to-bulb distilled at 75 °C (4 mmHg) to give 360 mg (70%) of **6c** as a pale yellow solid which was greater than 98% pure by capillary GC analysis:[19] IR ($CHCl_3$) 3020–2800, 1600, 1500, 1380, 1240, 920, 650 cm^{-1}; ^1H NMR (25 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2 H), 6.94 (d, 2 H, J = 7.9 Hz), 6.83 (t, 1 H, J = 7.2 Hz), 5.94–5.80 (m, 2 H, C*H*=C*H*), 3.74–3.70 (m, 2 H), 3.39 (t, 2 H, J = 5.6 Hz), 2.36–2.30 (m, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 151.3, 129.3, 125.6, 125.2, 118.9, 115.3, 48.6, 45.9, 26.6; MS (CI, 2-methylpropane), m/z 160 (MH^+, 100), 159 (21).

An analytical sample of the oxalate salt (mp 143 °C) was obtained by recrystallization from hot 2-propanol. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.94, H, 6.07; N, 5.62. Found: C, 62.61; H, 6.09; N, 5.61.

1-(2-Methylpropyl)-4-methyl-1,2,3,6-tetrahydropyridine (6f). Amine **15a** was cyclized in a similar manner to **11a** to give a crude product which was purified by bulb-to-bulb distillation (60 °C, 2 mmHg) to afford 170 mg (66%) of **6f** as a colorless liquid which showed no detectable impurities in its 250-MHz ^1H NMR spectra: IR (film) 2850, 1460, 1380 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.40–5.37 (m, 1 H, C=C*H*), 3.03–2.99 (m, 2 H, $CHCH_2N$), 2.57 (t, 2 H, J = 5.7 Hz), 2.55–2.45 (m, 2 H), 2.10–2.00 (br s, 2 H), 1.66 (s, 3 H, vinyl CH_3), 1.65–1.58 (m, 1 H), 1.36–1.28 (m, 1 H), 1.00 (d, 3 H, J = 6.5 Hz, CH_3CH), 0.90 (t, 3 H, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 132.6, 120.1, 60.4, 48.2, 45.4, 31.7, 26.1, 23.0, 14.0, 11.5; MS (CI, 2-methylpropane), m/z 154 (MH^+, 100), 152 (25), 124 (46). Anal. Calcd for $C_{17}H_{27}NSO_3$.

An analytical sample of the *p*-toluenesulfonate salt was obtained from ethyl acetate. Anal. Calcd for $C_{17}H_{27}NSO_3$: C, 62.74; H, 8.36; N, 4.30. Found: C, 62.65; H, 8.38; N, 4.26.

1-(2-Methylpropyl)-4-phenyl-1,2,3,6-tetrahydropyridine (6g). Amine **15b** was cyclized in a manner similar to **11a** to give 366 mg (83%) of **6g** as a viscous yellow oil which was pure by TLC analysis: IR (film) 2950, 1380, 830 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.41–7.48 (m, 5 H, ArH), 6.10–6.07 (m, 1 H, C=C*H*), 2.76–2.71 (m, 2 H), 2.61–2.63 (m, 3 H), 1.73–1.63 (m, 1 H), 1.42–1.33 (m, 1 H), 1.06 (d, 3 H, J = 6.5 Hz, $CHCH_3$), 0.93 (t, 3 H, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.3, 135.2, 128.3, 126.9, 125.0, 122.9, 60.4, 48.7, 45.6, 29.0, 26.3, 14.1, 11.5; MS (CI, 2-methylpropane), m/z 216 (MH^+, 100); high-resolution MS (EI, 70 eV) 215.1668 (calcd for $C_{15}H_{21}N$, 215.1674).

1-(4-Methylbenzyl)-2-(*n*-hexyl)-1,2,5,6-tetrahydropyridine (6l). Amine **11c** (214 mg, 0.81 mmol) was cyclized in a manner similar to **11a** to give 154 mg (64%) of **6l** as a colorless oil which was greater than 85% pure by capillary GC analysis:[19] IR (film) 3020–2800, 1615, 1515, 1039, 830 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.28–7.24 (m, 2 H), 6.85 (d, 2 H, J = 8.7 Hz), 5.80–5.73 (m, 1 H, C*H*=CH), 5.64–5.57 (m, 1 H, CH=C*H*), 3.80 (s, 3 H, OCH_3), 3.60 (ABq, 2 H, CH_2Ar), 2.92–2.82 (m, 2 H), 2.40–2.31 (m, 1 H), 2.02–1.99 (m, 2 H), 1.62–1.26 (m, 12 H), 0.90–0.85 (app t, 3 H, CH_2CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.8,

132.0, 130.5, 130.1, 125.2, 113.7, 59.0, 57.7, 55.3, 46.2, 33.6, 32.1, 29.8, 25.5, 24.2, 22.8, 14.3; MS (CI, 2-methylpropane), m/z 288 (MH^+, 100), 202 (18).

An analytical sample of the oxalate salt (mp 117 °C) was obtained by recrystallization from hot 2-propanol. Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.71; H, 8.30; N, 3.65.

1-Propyl-3-(trimethylsilyl)-1,2,3,6-tetrahydropyridine (6h). Amine **19** was cyclized in a manner similar to **11a** to give 88.2 mg (82%) of **6h** as a colorless liquid which was pure by TLC analysis: IR ($CHCl_3$) 3000, 2800, 1250, 830 cm^{-1}; ^1H NMR (25 MHz, $CDCl_3$) δ 6.04–5.99 (m, 1 H, C=C*H*), 3.07–3.04 (m, 2 H, CH_2CH), 2.58 (t, 2 H, J = 5.9 Hz), 2.45–2.38 (m, 2 H), 2.29–2.22 (m, 2 H), 1.65–1.53 (m, 2 H), 0.92 (t, 3 H, J = 7.3 Hz, CH_2CH_3), 0.06 (s, 9 H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 137.5, 133.7, 61.1, 54.8, 49.9, 28.0, 20.4, 12.2, −1.9; MS (CI, 2-methylpropane), m/z 198 (MH^+, 100); high-resolution MS (EI, 70 eV) 197.1584 (calcd for $C_{11}H_{23}NiSi$, 197.1600).

4-Methyl-*N*-(2-phenylethyl)-(*Z*)-4-(trimethylsilyl)-3-buten-1-ylamine (6i). A stirring solution of *N*-(2-phenylethyl)-(*Z*)-4-methyl-4-(trimethylsilyl)-3-buten-1-ylamine (6.9 mg, 0.026 mmol), paraformaldehyde (16 mg, 0.53 mmol), and CH_3CN (1 mL) was degassed under argon and stirred at reflux for 45 min. The resulting solution was cooled to room temperature and partitioned between CH_2Cl_2 (10 mL) and 1 N KOH (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic phases were dried (K_2CO_3) and concentrated to yield 5.0 mg (94%) of crude **6i** as a yellow oil that was purified by flash chromatography (silica gel, 2 g; 10:1:0.2 hexanes–ethyl acetate–triethylamine) to give 3.7 mg (70%) of pure **6i** as a clear oil: IR (CCl_4) 3000–2700, 1684, 1497, 1454, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.36–7.19 (m, PhH), 5.48 (dd, J = 3.4, 1.7 Hz, C=CH), 2.94 (br s, 2 H), 2.90–2.85 (m, 2 H), 2.71–2.65 (m, 2 H), 2.60 (t, J = 7 Hz, 2 H), 2.22–2.16 (m, 2 H), 1.69 (br s, CH_3); MS (CI), m/e 202 (MH^+, 100); high-resolution MS (EI, 70 eV) 201.1520 (201.1517 calcd for $C_{14}H_{19}N$).

1-Phenyl-2-(*n*-hexyl)-1,2,5,6-tetrahydropyridine (6j). A solution of amine **11e** (370 mg, 1.68 mmol), *n*-heptanal (572 mg, 5.06 mmol), camphorsulfonic acid (400 mg, 1.6 mmol), and dry CH_3CN (35 mL) was degassed and heated at reflux for 3 h. Workup as described for the preparation of **6a** gave 277 mg (68%) of **6j** as a yellow oil which was greater than 94% pure by capillary GC analysis:[19] IR (film) 3020, 3000–2980, 1601, 1510, 1390, 740, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25–7.18 (m, 2 H), 6.85 (d, 2 H, J = 7.9 Hz), 6.72 (t, 1 H, J = 7.4 Hz), 5.84–5.82 (m, 2 H, C*H*=C*H*), 4.05–4.00 (m, 1 H), 3.67–3.59 (m, 1 H), 3.27–3.15 (m, 1 H), 2.40–2.28 (m, 1 H), 2.03–1.94 (m, 1 H), 1.63–1.26 (m, 11 H), 0.89–0.84 (app t, 3 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.4, 130.1, 129.3, 125.5, 117.7, 115.3, 56.3, 40.8, 33.1, 32.0, 29.7, 26.5, 24.4, 22.8, 14.2.

An analytical sample of the hydrochloride salt was obtained by recrystallization from hot ethyl acetate. Anal. Calcd for $C_{17}H_{26}NCl$: C, 72.96; H, 9.37; N, 5.01. Found: C, 72.96; H, 9.38; N, 5.01.

1-Propyl-2-(*n*-hexyl)-1,2,5,6-tetrahydropyridine (6k). A solution of **11a** (302 mg, 1.63 mmol), *n*-heptanal (555 mg, 4.89 mmol), camphorsulfonic acid (381 mg, 1.52 mmol), and 30 mL of CH_3CN was degassed and heated in a Fisher–Porter pressure bottle at 120 °C for 48 h. Workup as described for the preparation of **6a** gave, after bulb-to-bulb distillation (80 °C, 1 mmHg), 182 mg (53%) of **6k** as a colorless oil, which was >90% pure by GLC analysis:[19] IR (film) 3000–2980, 1470, 1380, 900, 810, 730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.73–5.52 (m, 2 H, C*H*=C*H*), 2.93–2.84 (m, 1 H), 2.84–2.74 (m, 1 H), 2.60–2.20 (m, 3 H), 2.03–1.96 (m, 2 H), 1.50–1.23 (m, 12 H), 0.88–0.80 (m, 6 H, CH_3CH_2); ^{13}C NMR (63 MHz, $CDCl_3$) δ 130.5, 125.0, 59.3, 56.2, 46.7, 33.3, 32.1, 29.8, 25.8, 24.4, 20.7, 14.2, 12.1; MS (CI, 2-methylpropane), m/z 210 (MH^+, 87), 158 (100).

Preparation of α-Cyanomethylamines. Method A. *N*-Cyclohexyl-*N*-(cyanomethyl)-(*Z*)-4-(trimethylsilyl)-3-buten-1-ylamine (20g). A solution of **11b** (500 mg, 2.22 mmol), potassium cyanide (180 mg, 2.76 mmol), paraformaldehyde (120 mg, 4.00 mmol), H_2O (25 mL), and THF (25 mL) was neutralized (pH 7) by dropwise addition of concentrated HCl. The reaction mixture was stirred for 32 h at room temperature and diluted with ether (25 mL), and the organic layer was separated. The aqueous phase was extracted with additional ether (4 × 15 mL) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. the residue was distilled (80 °C, 0.5 mmHg) bulb-to-bulb to give 600 mg (99%) of **20g** as a colorless liquid: IR (film) 2940, 2860, 1610, 1250, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.28 (dt, 1 H, J = 14.1, 7.1 Hz, SiCH=C*H*), 5.58 (d, 1 H, J = 14.1 Hz, SiC*H*=CH), 4.33 (s, 2 H, CH_2CN), 2.71 (t, 2 H, J = 7.1 Hz, CH_2N), 2.49–2.48 (m, 1 H), 2.34–2.24 (app q, 2 H), 1.90–1.60 (m, 5 H), 1.29–1.18 (m, 5 H), 0.13 (s, 9 H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 145.6, 131.2, 117.3, 61.6, 50.3, 38.7, 32.2, 30.2, 26.1, 25.7, 0.34; high-resolution MS (CI, 100 eV) 265.2113 (calcd for $C_{15}H_{29}N_2Si$, 265.2100).

Method B. 2-(*N*-(*n*-Propyl)-[(*Z*)-4-(trimethylsilyl)-3-butenylamino])-4-phenylbutanenitrile (20a). 3-Phenylpropanal (530 μL, 4.0 mmol) was added to a saturated solution of sodium bisulfite (10 mL) at 0 °C.[28] After the mixture was stirred for 15 min at 0 °C, a white suspension was formed and the ice bath was removed. Amine **11a** (750 mg, 4.0 mmol) was then added in one portion. Potassium cyanide (4.0 mL of a 1.0 M solution) was then added and the reaction mixture was heated at 75 °C for 2 h at which time the reaction mixture had separated into two layers. This mixture was cooled to 0 °C and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (9:1 hexane–ether) gave 998 mg (76%) of chromatographically pure **20a** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5 H, ArH), 6.26 (dt, 1 H, J = 14.1, 7.1 Hz, C*H*=CHTMS). 6.21 (d, 1 H, J = 14.1 Hz, CH=C*H*TMS), 3.55 (t, 1 H, J = 7.8 Hz, NR_2CHCN), 2.8 (t, 2 H, J = 7.4 Hz, CH_2Ph), 2.68–2.24 (m, 6 H), 2.07 (q, 2 H, J = 7.6 Hz, CH_2CH_2Ph), 1.35–1.65 (m, 2 H, $CH_2CH_2CH_3$), 0.91 (t, 3 H, J = 7.4 Hz, $CH_2CH_2CH_3$), 0.13 (s, 9 H, $SiCH_3$); IR (neat) 2959, 2906, 2874, 1606, 1093, 858, 838 cm^{-1}.

Method C. α-(*N*-(*n*-Propyl)-[(*Z*)-4-(trimethylsilyl)-3-butenylamino])furancarbonitrile (20d). Zinc iodide (10 mg, 0.03 mmol) was added to a mixture of 2-furfural (250 μL, 3.0 mmol) and trimethylsilyl cyanide (470 μL, 3.6 mmol) at 0 °C, and the resulting mixture was stirred for 30 min.[29] The ice bath was removed and a solution of amine **11a** and methanol (4 mL) was added, and the resulting solution was heated at 65 °C for 3 h. The reaction mixture was concentrated and the residue purified by flash chromatography (9:1 hexane–ether) to give 735 mg (74%) of chromatographically pure **20d** as a pale yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.44 (br s, 1 H), 6.6–6.5 (m, 1 H), 6.4–6.3 (m, 1 H), 6.19 (dt, 1 H, J = 14.1, 7.1 Hz, C*H*=CHTMS), 5.55 (d, 1 H, J = 14.1 Hz, CH=C*H*TMS), 4.98 (s, 1 H, C*H*CN), 2.7–2.1 (m, 6 H), 1.6–1.4 (m, 2 H), $CH_2CH_2CH_3$, 0.87 (t, 3 H, J = 7.1 Hz, $CH_2CH_2CH_3$), 0.10 (s, 9 H, $SiCCH_3$); IR (neat) 2960, 2902, 2876, 1607, 1462, 1249, 859, 838 cm^{-1}.

1-Cyclohexyl-1,2,3,6-tetrahydropyridine (6b). A stirring solution of **20g** (528 mg, 2.00 mmol), silver trifluoroacetate (463 mg, 2.09 mmol) and 8 mL of $CHCl_3$ was degassed and heated for 110 °C for 10 h in a Fisher-Porter pressure bottle. The reaction was allowed to cool to room temperature and 30 mL of CH_3Cl was added. The reaction mixture was filtered and concentrated, and the residue was purified by flash chromatography (silica gel, 20:1.0:0.1 $CHCl_3$–MeOH–NH_4OH) followed by bulb-to-bulb distillation (100 °C, 1 mmHg) to give 179 mg (54%) of **6b** as a colorless liquid: IR (film) 2920, 1450, 1135, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.77–5.65 (m, 2 H, *H*C=C*H*), 3.13–3.09 (m, 2 H, NCH_2C=C), 2.66–2.62 (t, 2 H, J = 5.7 Hz, NCH_2CH_2), 2.37–2.28 (m, 1 H, NC*H*), 2.20–2.13 (m, 2 H), 1.92–1.78 (m, 4 H), 1.65–1.61 (br d, 1 H, J = 11.8 Hz), 1.33–1.11 (m, 5 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 126.3, 125.5, 63.5, 48.7, 46.1, 29.0, 27.2, 26.7, 26.3.

An analytical sample of the *p*-toluenesulfonate salt was obtained by recrystallization from hot ethyl acetate. Anal. Calcd for $C_{18}H_{27}NSO_3$: C, 64.07; H, 8.06; N, 4.15. Found: C, 64.16; H, 8.08; N, 4.11.

1-Propyl-2-(phenylethyl)-1,2,5,6-tetrahydropyridine (21a). Silver tetrafluoroborate (124 mg, 0.640 mmol) was added to a degassed solution of cyanoamine **20a** (202 mg, 0.63 mmol) and toluene (10 mL) in a Fisher-Porter pressure bottle. A white precipitate, presumed to be silver cyanide, formed immediately. This suspension was heated at 120 °C for 24 h. The reaction mixture was then cooled to room temperature and vacuum filtered and that solution was concentrated. The residue was redissolved in CH_2Cl_2, washed with 1 M NaOH, dried (K_2CO_3), and concentrated. Purification of the residue by flash chromatography (20:1 $CHCl_3$–EtOH) gave 107 mg (73%) of chromatographically pure **2** as an amber oil. An analytical sample was prepared by bulb-to-bulb distillation (140 °C, 0.3 mmHg): ^1H NMR (250 MHz, $CDCl_3$) δ 7.36–7.20 (m, 5 H, ArH), 5.85 (m, C*H*=CH), 5.70 (m, 1 H, CH=C*H*), 2.95–3.10 (m, 2 H), 2.9–2.3 (m, 5 H), 2.1–2.2 (m, 2 H), 1.85–1.95 (m, 2 H), 1.65–1.50 (m, $CH_2CH_2CH_3$, 0.95 (t, 3 H, J = 7.4 Hz, $CH_2CH_2CH_3$); IR (neat) 3062, 3026, 2956, 2933, 1496, 1454, 1076 cm^{-1}; MS (CI 2-methylpropane), m/z 272 (MH^+, 11%), 230 (86), 124 (100); high-resolution MS (EI, 70 eV) 229.1830 (calcd for $C_{10}H_{23}N$, 229.1830).

Preparation of 1,2-Disubstituted 1,2,5,6-Tetrahydropyridines 21b–f. These tetrahydropyridines were prepared and purified in a fashion similar to **21a**. Cyclizations were conducted on a 1.0-mmol scale, and the yields of purified products are reported in Table II. Complete characterization can be found in the Supplementary Material.

2-(3-Bromophenyl)-1,2,5,6-tetrahydropyridine (24a). Magnesium sulfate (1.0 g) was added to a solution of (*Z*)-4-(trimethylsilyl)-3-buten-1-ylamine[1] (**22**) (184 mg, 1.28 mmol), dry Et_2O (5 mL), and 3-bromobenzaldehyde (150 μL, 1.28 mmol) at room temperature, and the resulting suspension was stirred for 30 min. The mixture was then vacuum filtered, and the filtrate was concentrated. Bulb-to-bulb distil-

lation (140 °C, 0.4 mmHg) then gave 333 mg (84%) of imine **23a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.21 (s, 1 H, N=C*H*Ar), 7.91 (t, 1 H, *J* = 1.5 Hz, ArH), 7.62 (d, 1 H, *J* = 7.6 Hz, ArH), 7.55 (d, 1 H, *J* = 7.8 Hz, ArH), 7.25 (m, 1 H, ArH), 6.32 (dt, 1 H, *J* = 14.4, 7.4 Hz, C*H*=CHSi), 5.61 (d, 1 H, *J* = 14.4 Hz, CH=C*H*Si), 3.68 (t, 2 H, *J* = 7.1 Hz, CH_2NH$_2$), 2.54 (q, 2 H, *J* = 7.1 Hz, CH_2CH=CHSi), 0.13 (s, 9 H, SiCH_3); IR (neat) 2955, 2897, 2840, 1648, 1567, 1248, 1067, 859 cm^{-1}; MS (CI, 2-methylpropane), *m/z* 312 (MH$^+$, 100), 310 (MH$^+$, 68), 89 (8); high-resolution MS (EI, 70 eV) 309.0528 (calcd for $C_{14}H_{20}BrSi$, 309.0548).

Trifluoroacetic acid (380 μL, 5.0 mmol) was added to a degassed solution of freshly prepared imine **23a** (310 mg, 1.06 mm) in dry acetonitrile (5 mL). The resulting solution was heated at 55 °C for 48 h. The solution was cooled to room temperature and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with 1 M NaOH (3 × 5 mL). These washes were combined and re-extracted with CH_2Cl_2 (1 × 5 mL). The combined organic phases were then dried (K_2CO_3) and concentrated. Purification of the residue by flash chromatography 20:1 $CHCl_3$–EtOH gave 141 mg (55%) of chromatographically pure **18** as a nearly colorless liquid. An analytical sample was prepared by bulb-to-bulb distillation (130 °C, 0.3 mmHg): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.51 (t, 1 H, *J* = 1.6 Hz, ArH), 7.38 (dt, 1 H, *J* = 1.2, 7.4 Hz, ArH), 7.29 (t, 1 H, *J* = 1.2 Hz, ArH), 7.20 (t, 1 H, *J* = 7.4 Hz, ArH), 5.95 (m, 1 H, C*H*=CH), 5.68 (dq, 1 H, *J* = 10.2, 2.1 Hz, CH=C*H*), 4.42 (app, quintet, 1 H, *J* = 2.7 Hz, NHC*H*Ar), 3.1–2.9 (m, 2 H, CH_2N), 2.3–2.0 (m, 2 H, CH_2CH=CH), 1.8 (s, N*H*); IR (neat) 3250, 3028, 2948, 2831, 2798, 1592, 1567, 1473, 1070, 878, 860, 818 cm^{-1}; MS (CI, 2-methylpropane), *m/z* 240 (MH$^+$, 98), 238 (MH$^+$, 100), 160 (12); high-resolution MS (EI, 70 eV) 237.0163 (calcd for $C_{11}H_{12}BrN$, 237.0153).

2-(3-Pyridyl)-1,2,5,6-tetrahydropyridine (24b). Imine **23b** (prepared in 85% from **22** and 3-pyridinecarboxaldehyde) was cyclized on a 1.3-mmol scale, as described in the preparation of **24a**, to yield **24b** (33%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.55 (d, 1 H, *J* = 2.2 Hz), 8.47 (dd, 1 H, *J* = 4.8, 1.6 Hz, ArH), 7.67 (dt, *J* = 8.0, 2.0 Hz, ArH), 7.23 (ddd, 1 H, *J* = 7.8, 3.8, 0.5 Hz, ArH), 5.95 (m, 1 H, C*H*=CH), 5.66 (dq, *J* = 10.1, 2.2 Hz, CH=C*H*), 4.47 (app quintet, 1 H, *J* = 2.6 Hz, NHC*H*Ar), 3.1–2.9 (m, 2 H, NHCH_2), 2.3–1.95 (m, 3 H, CH_2CH=CH + N*H*); IR (neat) 3250, 3172, 3050, 2954, 1649, 1592, 1457, 1100, 1029, 862, 836, 807 cm^{-1}; MS (CI, 2-methylpropane), *m/z* 161 (MH$^+$, 100); high resolution MS (EI, 70 eV) 160.0987 (calcd for $C_{10}H_{12}N_2$, 160.1000).

2-[(1,1-Dimethyl-2-phenyl)ethyl]-1,2,5,6-tetrahydropyridine (24c). Imine **23c** (prepared in 80% yield from **22** and 2,2-dimethyl-3-phenylpropanal) was cyclized on a 1.5-mmol scale as described for the preparation of **24a** to give **24c** (66%) as a colorless liquid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30–7.15 (m, 5 H, ArH), 5.95–5.85 (m, 1 H, C*H*=CH), 5.82 (br d, 1 H, *J* = 11.5 Hz, CH=C*H*), 3.25–3.15 (m, 2 H), 2.86 (dt, 1 H, *J* = 11.5, 4.5 Hz, NCH), 2.7 (d, 1 H, *J* = 13.0 Hz, C(CH$_3$)$_2$CH_2Ph), 2.57 (d, 1 H, *J* = 13.0 Hz, C(CH$_3$)$_2$CH_2Ph), 2.4–2.1 (m, 1 H, CH_2CH=CH), 2.0–1.8 (m, 1 H, CH_2CH=CH), 1.8 (br s, 1 H, NH), 0.88 (s, 3 H, CH$_3$), 0.87 (s, 3 H, CH$_3$); IR (neat) 3200, 3209, 2950, 1610, 1465, 1387, 1116, 863 cm^{-1}; MS (CI, 2-methylpropane), 216 (100%, MH$^+$), 82 (59); high-resolution MS (EI, 70 eV) 215.1663 (calcd for $C_{15}H_{21}N$, 215.1674).

1-Butyl-2,3,4,7-tetrahydro-1*H*-azepine (28). By use of a procedure identical with that described for the preparation of **6a**, a solution of *N*-butyl-(*Z*)-5-(trimethylsilyl)-4-penten-1-ylamine[25] (**26**) (639 mg, 2.99 mmol), paraformaldehyde (4.90 g, 1.63 mmol), camphorsulfonic acid (707 mg, 2.83 mmol), and 60 mL of CH_3CN was degassed and heated at reflux for 10 h. Workup followed by bulb-to-bulb distillation (100 °C, 1.0 mmHg) of the crude reaction product gave 317 mg of material that was a 2.6:1 mixture of **28** and **27**.[25] Capillary GC analysis[19] showed that these two compounds composed 85% of the distillate. An analytical sample of **28** was obtained by preparative gC: IR (film) 2940, 1450, 1220 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.93–5.84 (app p, 1 H, C=C*H*), 5.72–5.63 (app p, 1 H, C=C*H*), 3.19–3.17 (d, 2 H, *J* = 5.5 Hz, C = CCH_2N), 2.87–2.83 (t, 2 H, *J* = 5.7 Hz), 2.50–2.43 (app t, 2 H), 2.25–2.18 (m, 2 H), 1.71–1.61 (m, 2 H), 1.51–1.25 (m, 4 H), 0.91 (t, 3 H, *J* = 7.1 Hz, CH$_2$CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 133.6, 129.4, 58.3, 56.3, 53.8, 29.8, 28.4, 25.8, 21.0, 14.3; MS (CI, 2-methylpropane), *m/z* 154 (MH$^+$, 100), 152 (16).

(*E*)-4-(Trimethylsilyl)-3-butene 1,2-Oxide (35). A solution of trimethylsulfonium methylide was prepared from 5.14 g (25.2 mmol) of trimethylsulfonium methiodide in a mixture of dry Me_2SO (28 mL) and THF (8 mL) as described by Corey.[35] To this solution at 10 °C was added 3.09 g (24.9 mmol) of (*E*)-3-(trimethylsilyl)propenal.[34] The reaction mixture turned bright red and was maintained at 0 °C for h and then quenched with H_2O (100 mL) and extracted with ether (7 × 25 mL). The combined organic phases were washed with H_2O (2 × 25 mL), and the organic phase was then dried ($CaSO_4$), filtered, and concentrated. The oily red residue was bulb-to-bulb distilled (70 °C, 17 mmHg) to give 1.51 g (65%) of **35** as a colorless liquid: IR (film) 2950, 1620, 1250; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.22 (d, 1 H, *J* = 18.7 Hz, SiC*H*=CH), 5.66 (ddd, 1 H, *J* = 18.7, 7.2, and 1.0 Hz, SiCH=C*H*), 3.36–3.31 (m, 1 H), 3.00–2.95 (m, 1 H), 2.69 (dd, 1 H, *J* = 5.2 and 2.6 Hz), 0.08 (s, 9 H, SiCH_3); MS (CI, 2-methylpropane), *m/z* 143 (MH$^+$, 7), 131 (5), 118 (11), 117 (100), 99 (10).

***N*-Propyl-(*E*)-4-(trimethylsilyl)-2-hydroxy-3-buten-1-ylamine (36) and *N*-Propyl-1-(hydroxymethyl)-3-(trimethylsilyl)-2-propenamine (37).** A degassed solution of epoxide **35** (2.03 g, 14.5 mmol) and *n*-propylamine (50 mL) was heated at 125 °C for 32 h in a Fisher-Porter pressure bottle. The reaction mixture was cooled to room temperature and concentrated. The residue was diluted with ether (50 mL) and extracted with aqueous 1 N HCl (5 × 40 mL). The combined aqueous phases were washed with ether (2 × 30 mL), made basic with solid NaOH, and extracted with ether (7 × 25 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated to yield 1.04 g (36%) of a 72.28 mixture of **36** and **37**: IR (film) 3300, 1620, 1460, 1250, 990, 850 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.98 (d, *J* = 3.3 Hz, 2 H, SiC*H*=C*H*), major isomer), 5.83 (d, *J* = 2.8 Hz, 2 H, SiC*H*=C*H*, minor isomer), 4.17–4.08 (m, 1 H, C*H*OH, major isomer), 3.60 (dd, 1 H, *J* = 10.2 and 4.5 Hz, minor isomer), 3.63–3.15 (m, 2 H, minor isomer), 3.18–3.15 (m, 1 H, minor isomer), 2.76 (dd, 1 H, *J* = 12.1 and 3.6 Hz, major isomer), 2.66–2.39 (m, 3 H), 2.24–2.14 (br s, 2 H, NH, OH), 1.57–1.43 (m, 2 H), 0.96–0.89 (m, 3 H, CH_3), 0.07 (s, 9 H, SiCH_3); MS (CI, 2-methylpropane), *m/z* 202 (MH$^+$, 100), 72 (21).

[1-Propyl-4-(trimethylsilyl)propolidin-3-yl]methanol (40). A solution of **36** and **37** (220 mg, 1.09 mmol, a 72:28 mixture of isomers), paraformaldehyde (940 mg, 31.3 mmol), camphorsulfonic acid (240 mg, 0.96 mmol), and 20 mL of ethanol was degassed and heated at reflux for 2.5 h. The reaction mixture was allowed to cool at room temperature and was concentrated, and the residue was diluted with CH_2Cl_2 (30 mL) and washed with aqueous 1 N NaOH (15 mL). The aqueous phase was separated and extracted with additional CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was diluted with MeOH (30 mL) and cooled to 0 °C and sodium borohydride ($NaBH_4$) (202 mg, 5.45 mmol) was added. After being stirred for 1 h, the reaction mixture was quenched into saturated aqueous $NaHCO_3$. This solution was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by flash chromatography (silica gel, 4.5:4.5:1.0 hexanes–ether–triethylamine) to give 117 mg of **40** (86% based on **36**) as a colorless oil: IR (film) 3600–3000, 1255; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.26 (1 H, OH), 3.60 (dd, 1 H, *J* = 9.8, 3.1 Hz), 3.39–3.33 (app dd, 1 H), 3.05 (t, 1 H, *J* = 8.8), 2.92 (d, 1 H, *J* = 7.9 Hz), 2.32–2.26 (app t, 2 H), 2.12–2.02 (m, 2 H), 1.87–1.79 (app t, 1 H), 1.54–1.39 (m, 2 H), 1.18–1.08 (m, 1 H), 0.89–0.83 (app t, 3 H), –0.04 (s, 9 H, SiCH_3); ^{13}C NMR (63 MHz, CCl_3) δ 68.2, 59.2, 57.9, 41.4, 26.8, 22.0, 12.1, –2.9; MS (CI, 2-methylpropane) 216 (MH$^+$, 100); high-resolution MS (EI, 70 eV) 215.1685 (calcd for $C_{11}H_{25}NOSi$, 215.1705).

***N*-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]glutarimide (42a).** According to the general method of Mitsunobu,[39] a solution of alcohol **9** (2.11 g, 14.6 mmol), glutarimide (1.64 g, 14.6 mmol), triphenylphosphine (3.80 g, 14.6 mmol), and 30 mL of THF was cooled to 0 °C and diethyl azodicarboxalate (2.29 mL, 14.6 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and maintained there for 12 h. The reaction mixture was concentrated, the residue was dissolved in $CHCl_3$ (50 mL) and washed with 5% aqueous KOH (2 × 20 mL), 1 N HCl (2 × 20 mL), and brine (2 × 20 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, $CHCl_3$) to give 2.05 g (59%) of **42a** as a light pink oil: IR (film) 2950, 1735, 1685, 1610, 1350, 1250, 850 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.23 (dt, 1 H, *J* = 14.0 and 7.1 Hz, SiCH=C*H*), 5.56 (d, 1 H, *J* = 14.0 Hz, SiC*H*=CH), 3.84–3.78 (app t, 2 H), 2.63 (t, 4 H, *J* = 6.5 Hz, CH_2C=O), 2.39–2.30 (app q, 2 H), 1.96–1.88 (m, 2 H), 0.09 (s, 9 H, SiCH$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.5, 144.6, 132.0, 39.0, 33.0, 32.3, 17.3, 0.26; MS (CI, 2-methylpropane), *m/z* 240 (MH$^+$, 100); high-resolution MS (EI, 70 eV) 239.1340 (calcd for $C_{12}H_{21}NO_2Si$, 239.1342).

***N*-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]succinimide (42b).** By use of a procedure identical with that described for the preparation of **42a**, alcohol **9** (3.07 g, 21.3 mmol) was condensed with succinimide (2.29 g, 22.9 mmol) to give 3.45 g (72%) of **42b** as a white solid (mp 54–57 °C): IR ($CHCl_3$) 2950, 1780, 1710, 1610, 1400, 1250, 1155, 900, 845 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.17 (dt, 1 H, *J* = 14.0, 7.4 Hz, SiCH=C*H*), 5.57 (d, 1 H, *J* = 14.0 Hz, SiC*H*=CH), 3.53 (t, 2 H, *J* = 7.1 Hz, NCH_2), 2.66 (s, 4 H, CH_2C=O), 2.42–2.32 (app q, 2 H), 0.06 (s, 9 H, SiCH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.1, 143.8, 132.8, 38.4, 31.9,

28.3, 0.2; MS (CI, 2-methylpropane), m/z 226 (MH^+, 100), 71 (30); high-resolution MS (EI, 70 eV) 225.1172 (calcd for $C_{11}H_{19}NO_2Si$, 225.1185).

***N*-[(*E*)-4-(Trimethylsilyl)-4-bromo-3-butenyl]succinimide (42c).** By use of a procedure identical with that described for the preparation of **42a**, alcohol **17a** (7.74 g, 34.6 mmol) was condensed with succinimide (4.10 g, 41.0 mmol) to give, after flash chromatography (silica gel, $CHCl_3$), 7.93 g (76%) of **42c** as a white crystalline solid (mp 41–42 °C): IR ($CHCl_3$) 2950, 1710, 1400, 1250, 1160, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.68 (t, 1 H, J = 8.0 Hz, C=C*H*), 3.59–3.53 (app t, 2 H, NCH_2), 2.71 (s, 4 H, CH_2C=O), 2.43–2.34 (m, 2 H), 0.26 (s, 9 H, SiCH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.0, 143.0, 130.9, 37.7, 30.7, 28.3, 0.3; MS (CI, 2-methylpropane), m/z 306 (MH^+, 100), 304 (MH^+, 99); high-resolution MS (EI, 70 eV) 305.0255 (calcd for $C_{11}H_{18}BrNO_2Si$, 305.0270), 303.0286 (calcd for $C_{11}H_{18}BrNO_2Si$, 303.0290).

Preparation of 1,2,3,6,7,9a-Hexahydro-4(4*H*)-quinolizinone (44a). According to the general method of Chamberlin,[40] a solution of **42a** (1.00 g, 4.18 mmol) and 83 mL of MeOH was cooled to −5 °C and excess $NaBH_4$ (635 g, 16.72 mmol) was added. The reaction was stirred for 3 h at 0 °C and then quenched into a mixture of CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (200 mL). The mixture was stirred until bubbling had ceased, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, ether) to give 782 mg (78%) of **43a** as a crystalline solid (mp 52–54 °C): IR ($CHCl_3$) 3300, 2950, 1680, 1250, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.25 (dt, 1 H, J = 14.0, 7.4 Hz, SiCH=C*H*), 5.58 (d, 1 H, J = 14.0 Hz, SiC*H*=CH), 4.94 (app t, 1 H, J = 3.3 Hz, NC*H*OH), 4.30–3.90 (br s, 1 H, OH), 3.71–3.60 (m, 1 H), 3.32–3.21 (m, 1 H), 2.45–1.64 (m, 9 H), 0.10 (s, 9 H, SiCH_3); ^{13}C NMR ($CDCl_3$) δ 170.7, 145.5, 132.1, 80.3, 45.2, 32.5, 31.2, 14.0, 0.3; MS (CI, 2-methylpropane), m/z 242 (MH^+, 100), 224 (23).

A 296-mg sample of this intermediate was dissolved in 25 mL of anhydrous trifluoroacetic acid. After 15 min, the solution was concentrated and the residue purified by flash chromatography (silica gel, ether) and bulb-to-bulb distilled (120 °C, 1 mmHg) to give 168 mg (91%) of **43a** as a colorless liquid which was greater than 90% pure by capillary GC analysis:[19] IR (film) 2950, 1640, 1450 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.91–5.85 (m, 1 H, HC=C*H*), 5.59–5.53 (m, 1 H, C*H*=CH), 4.86 (dd, 1 H, J = 12.8, 5.6 Hz, equatorial CONCH_2), 4.06–4.00 (m, 1 H), 2.70–2.21 (m, 4 H), 2.12–1.38 (m, 5 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.9, 129.0, 125.9, 55.2, 38.3, 32.4, 30.2, 25.11, 19.7; MS (CI, 2-methylpropane), m/z 152 (MH^+, 100); high-resolution MS (EI, 70 eV) 151.0992 (calcd for $C_9H_{13}NO$, 151.0997).

1,5,6,8a-Tetrahydro-3-(2*H*)-indolizinone (44b). Imide **42b** (2.60 g, 11.6 mmol) was reduced in a fashion identical with that for **42a** to give 2.08 g (79%) of *N*-[(*Z*)-4-(trimethylsilyl)-3-butenyl]-5-hydroxypyrrolid-2-one (**43b**). A 574-mg (2.53 mmol) samaple of this intermediate was dissolved in 57 mL of anhydrous trifluoroacetic acid. After 15 min, the solution was concentrated and the residue purified by flash chromatography (silica gel, ether), and bulb-to-bulb distillation (110 °C, 1 mmHg) gave 321 mg (92%) of **44b** as a colorless liquid which was greater than 95% pure by capillary GC analysis:[19] IR (film) 2950, 1680, 1440, 1310, 1200 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.83–5.66 (m, 2 H, C*H*=C*H*), 4.24–4.12 (m, 2 H), 2.92–2.79 (m, 1 H), 2.50–2.03 (m, 5 H), 1.68–1.52 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.9, 128.2, 124.8, 54.8, 36.1, 31.5, 26.1, 24.4; MS (CI, 2-methylpropane), m/z 138 (MH^+, 100); high-resolution MS (EI, 70 eV) 137.0826 (calcd for $C_8H_{11}NO$, 137.0840).

8-Bromo-1,5,6,8a-tetrahydro-3-(2*H*)-indolizinone (44c). Imide **42c** (1.30 g, 4.27 mmol) was reduced in a fashion identical with that of **42a** to give *N*-[(*E*)-4-(trimethylsilyl)-3-bromo-3-butenyl]-5-hydroxypyrrolid-2-one (**43c**) in 94% yield. A 413-mg (1.37 mmol) sample of this intermediate was dissolved in 15 mL of anhydrous trifluoroacetic acid and heated at reflux for 2.5 h. The reaction mixture was allowed to cool to room temperature and concentrated, and the residue was purified by flash chromatography (silica gel, ether) and bulb-to-bulb distillation (120 °C, 5 mmHg) to give 200 mg (70%) of **44c** as a viscous oil that was 90% pure by capillary GC analysis:[19] IR ($CHCl_3$) 2950, 1680, 1428, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.12 (d, 1 H, J = 6.1 Hz, C=C*H*), 4.28–4.20 (m, 2 H), 2.93–2.81 (m, 1 H), 2.50–2.10 (m, 5 H), 1.87–1.69 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.0, 127.0, 122.1, 59.3, 35.6, 31.0, 27.2, 26.2; MS (CI, 2-methylpropane), m/z 218 (MH^+, 97), 216 (MH^+, 100).

Preparation of 8-Bromo-1,2,5,6,8a-hexahydroindolizine (45). A solution of **44c** (632 mg, 2.92 mmol, 85% pure) and 2 mL of anhydrous ether was added dropwise to a slurry of lithium aluminum hydride (444 mg, 11.7 mmol) in 100 mL of ether. This mixture was heated at reflux for 2.3 h, cooled to 0 °C, and quenched with small amounts of solid $Na_2SO_4 \cdot 10H_2O$. Stirring was continued until the frothing had stopped and then for an additional 30 min. The reaction mixture was suction filtered through a bed of Celite, and the Celite was rinsed with several portions of ether. The combined washings were dried (Na_2SO_4), filtered, and concentrated. The residue was bulb-to-bulb distilled (50 °C, 100 μmHg) to give 390 mg (67%) of **45** as a colorless liquid which was greater than 90% pure by capillary GC analysis:[19] IR (film) 2950, 1640, 1430, 1330, 1210, 970, 830 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.07–6.04 (m, 1 H, C=C*H*), 3.64–3.60 (m, 1 H), 3.04–2.76 (m, 4 H), 2.49–2.34 (m, 1 H), 2.14–1.73 (m, 5 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 126.9, 63.7, 50.7, 44.7, 30.3, 24.9, 22.7; MS (CI, 2-methylpropane), m/z 204 (MH^+, 76), 203 (19), 202 (MH^+, 88), 122 (100), 118 (17).

An analytical sample of the picrate salt was obtained by recrystallization from hot ethanol. Anal. Calcd for $C_{14}H_{15}BrN_4O_7$: C, 38.99; H, 3.51; N, 12.99. Found: C, 39.00; H, 3.55; N, 12.99.

α-Propyl-1,2,3,5,6,8a-hexahydro-8-indolizinemethanol (Elaeokanine B) (46b). A stirring solution of **45** (43.3 mg, 0.22 mmol) and 1.1 mL of THF was cooled to −78 °C and *sec*-butyllithium (0.50 mL of a 0.87 M solution in cyclohexane) was added dropwise. After 30 min, cold butanal (90 μL, 1.02 mmol) was added dropwise and the reaction mixture was stirred for 15 min at −78 °C and then allowed to warm to room temperature. The organic phase was extracted with aqueous 1 N HCl (3 × 10 mL) and the combined aqueous phases were extracted with ether (10 mL), made basic with solid K_2CO_3, and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give 38.0 mg (86%) of **46** as a 1:1 mixture of diastereomeric alcohols: IR (film) 3250, 2950 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.69–5.62 (m, 1 H, C=C*H*), 4.05 (app t, 0.5 H, C*H*OH), 3.96 (app t, 0.5 H, C*H*OH), 3.03–1.25 (m, 16 H), 0.95–0.87 (m, 3 H); MS (CI, 2-methylpropane), m/z 196 (MH^+, 76), 178 (100), 122 (25).

Preparation of (+)-1-(1,2,3,5,6,8a-hexahydro-8-indolizinyl)-1-butanone (Elaeokanine A) (47). A 88-mg (0.45 mmol) sample of **46** was oxidized by the Swern procedure[43] as described by Weinreb[44] to give, after purification by flash chromatography (silica gel, 10:1.0:0.1 $CHCl_3$–MeOH–NH_4OH), 47.9 mg (56%) of **47** as a colorless oil which showed no detectable impurities in its 250-MHz ^1H NMR spectrum. This sample showed spectral properties identical with authentic spectra of elaeokanne A provided by Professor Weinreb[44] and was identical by TLC analysis with a sample of racemic elaeokanine A provided by Professor Chamberlin.[40]

An analytical sample of the picrate salt was obtained by recrystallization from hot ethanol: mp 136–137 °C (lit.[44] mp 139.5–140.5 °C). Anal. Calcd for $C_{18}H_{22}N_4O_8$: C, 51.21; H, 5.25; N, 13.26. Found: C, 51.21; H, 5.27; N, 13.25.

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Registry No. 6a, 53385-78-7; **9a**·oxalate, 109720-41-4; **6b**, 87682-64-2; **6b**·*p*-toluenesulfonate, 109720-66-3; **6c**, 87682-65-3; **6c**·oxalate, 109720-42-5; **6e**, 87682-63-1; **6e**·oxalate, 109720-43-6; **6f**, 109720-44-7; **6f**·*p*-toluenesulfonate, 109720-45-8; **6g**, 109720-46-9; **6h**, 109720-48-1; **6i**, 109720-50-5; (±)-**6j**, 87682-68-6; (±)-**6j**·HCl, 109720-51-6; (±)-**6k**, 109720-52-7; (±)-**6l**, 87682-67-5; (±)-**6l**·oxalate, 109720-47-0; (±)-**7**, 109720-21-0; **9**, 87682-77-7; **10**, 87682-62-0; **11a**, 109720-20-9; **11b**, 87682-60-8; **11c**, 87682-61-9; **11e**, 87682-59-5; (±)-(*Z*)-**12a**, 109720-22-1; (±)-(*E*)-**12a**, 109720-23-2; (±)-(*Z*)-**12b**, 109720-24-3; (±)-(*E*)-**12b**, 109720-25-4; (*Z*)-**13a**, 94012-61-0; (*E*)-**13a**, 94012-62-1; (*Z*)-**13b**, 109744-46-9; (*E*)-**13b**, 109720-29-8; (*Z*)-**14a**, 109720-30-1; (*E*)-**14a**, 109720-31-2; (*Z*)-**14b**, 109720-32-3; (*E*)-**14b**, 109720-33-4; (*Z*)-**15a**, 109720-34-5; (*E*)-**15a**, 109720-35-6; (*Z*)-**15b**, 109720-36-7; (*E*)-**15b**, 109720-37-8; (±)-**16a**, 109720-26-5; (±)-**16b**, 109720-27-6; **17a**, 109720-28-7; **17b**, 109720-38-9; **18**, 109720-39-0; **19**, 109720-40-3; (±)-**20a**, 109720-54-9; (±)-**20b**, 109720-57-2; (±)-**20c**, 109720-58-3; (±)-**20d**, 109720-55-0; (±)-**20e**, 109720-59-4; (±)-**20f**, 109720-60-7; **20g**, 109720-53-8; (±)-**21a**, 109720-56-1; (±)-**21b**, 109720-61-8; (±)-**21b**-(1-[(2,2,2-trichloroethoxy)carbonyl]derivative), 109720-88-9; (±)-**21c**, 109720-62-9; (±)-**21d**, 109720-63-0; (±)-**21e**, 109720-64-1; (±)-**21f**, 109720-65-2; **22**, 109720-67-4; **23a**, 109720-68-5; **23b**, 109720-69-6; **23c**, 109720-70-9; (±)-**24a**, 109720-71-0; (±)-**24b**, 109720-72-1; (±)-**24c**, 109720-73-2; (±)-**24d**, 109720-89-0; **26**, 109720-74-3; **27**, 28031-49-4;

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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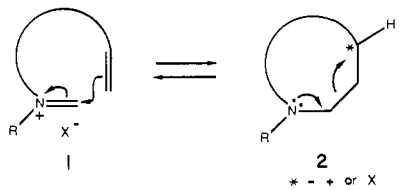
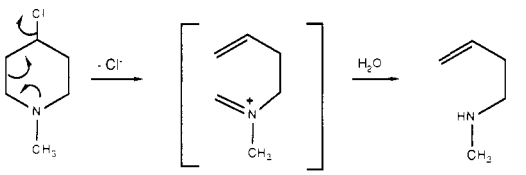
Abstract: The effect of solvent and external nucleophiles on the Mannich cyclization of five secondary amines was examined. Particularly informative were cyclizations of amines **7** and **11** (eq 4 and 5) containing two different tethered π-nucleophiles. In both cases, cyclization with only the vinylsilane 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

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

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(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.

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