Synthetic Application of Cyanoaminosilanes as Azomethine Ylide Equivalents

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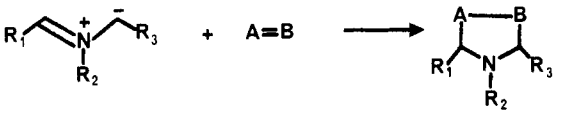
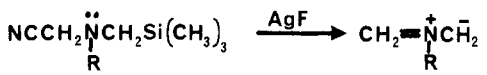
A series of α-cyanoaminosilanes have been found to act as azomethine ylide equivalents. Treatment of these compounds with silver fluoride in the presence of electron-deficient alkynes and olefins gives substituted pyrroles and pyrrolidines in high yield. It was found that *N*-benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine undergoes stereospecific cycloaddition with dimethyl fumarate and maleate. The stereospecificity of the reaction is consistent with a concerted cycloaddition reaction. The cycloaddition behavior of an unsymmetrically substituted α-cyanosilylamine with methyl propiolate was also examined and found to react with high overall regioselectivity. The synthetic utility of cyanoaminosilanes as azomethine ylide equivalents was demonstrated by the preparation of a *Reniera* isoindole alkaloid. The key step in the synthesis involved the reaction of 2-methyl-3-methoxyquinone with *N*-methyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine in the presence of silver fluoride to give 2,5-dimethyl-6-methoxy-2*H*-isoindole-4,7-dione in good yield.

The use of the 1,3-dipolar cycloaddition reaction for the construction of heterocyclic compounds[1] has been extensively utilized in recent years and has proven valuable for the preparation of complex ring systems.[2-12] The ease of the cycloaddition, the rapid accumulation of polyfunctionality in a relatively small molecular framework, the high stereochemical control of the cycloaddition, and the fair predictability of its regiochemistry have contributed to the popularity of the reaction in organic synthesis.[8,9] The vast majority of studies bearing relevance to natural product synthesis have hinged upon the utilization of nitrones[13-20] and nitrile oxides.[21-29] As part of our ongoing interest in synthetic applications of dipolar cycloaddition reactions,[9] we have recently begun to investigate the synthetic potential of cycloadditions using azomethine ylides.[30-33] The pyrrolidine ring is a frequently encountered



structural unit of many synthetically challenging alkaloids.[34] Little attention has been given in alkaloid synthesis to one of the most conceptually simple ways of pyrrolidine formation: a 1,3-dipolar cycloaddition of an azomethine ylide with an olefin.[35-40] This is not surprising since few methods exist for the preparation of nonstabilized azomethine ylides.[41-51] As outlined in this paper, we have found that α-cyanosilylamines **1** are useful and convenient synthons for azomethine ylides.[31] The development of this strategy was based on literature reports that cyanomethylamines can function as convenient iminium ion precursors.[52,53] The propensity of silicon to transfer to a silylophile[54] when bound to an electronegative carbon strongly inferred that the treatment of α-cyanosilylamines with silver fluoride will generate azomethine ylides. This prediction has indeed proven valid. Prior to launching into the synthesis of complex molecular systems using these reagents, we have designed and executed model studies with a series of substituted α-cyanosilylamines in order to probe the stereo and regiospecificity of the cycloaddition. We report here the results of these studies.



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† Alexander von Humboldt Senior Visiting Scientist, 1985, University of Wurzburg.

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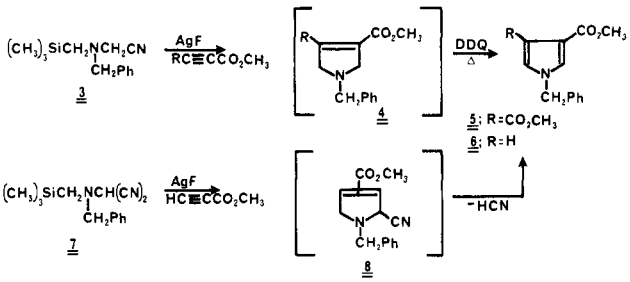
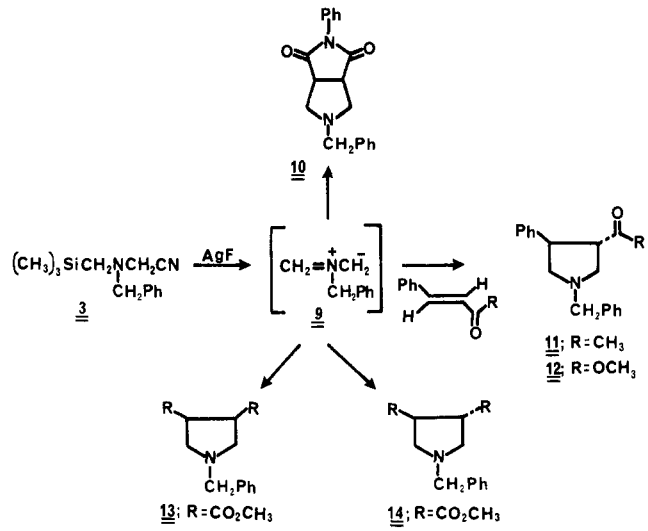
Results and Discussion

In spite of its simplicity and its obvious potential as an azomethine ylide equivalent, *N*-benzyl-α-cyanoaminosilane **3** could not be found in the literature. This reagent was conveniently prepared in multigram quantities by treating benzylamine with (chloromethyl)trimethylsilane followed by reaction of the resulting secondary amine with formaldehyde in the presence of potassium cyanide. A solution of **3** and dimethyl acetylenedicarboxylate in acetonitrile



was allowed to react in the dark with a slight excess of silver fluoride. Stirring was continued at 25 °C over the course of 10 h. The black precipitate that formed was filtered, the solvent was removed under reduced pressure, and the residue was oxidized with DDQ to provide *N*-benzyl-3,4-dicarbomethoxypyrrole (**5**) in 62% yield. Similarly, treatment of **3** with silver fluoride in the presence of methyl propiolate produced pyrrole **6** in 65% yield. No attempts were made to isolate the initially produced dihydropyrroles. Pyrrole **6** was also obtained by treating dicyanosilylamine **7** with silver fluoride in the presence of methyl propiolate.

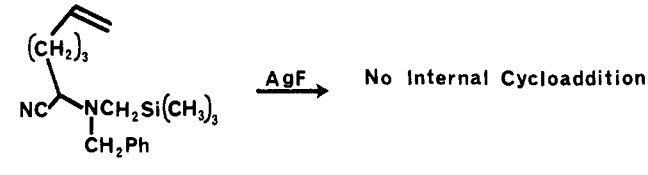
Cycloaddition of the dipole derived from **3** with various alkenes was also studied and was found to produce pyrrolidines **10**–**14** in good to high yields. All octet-stabilized 1,3-dipoles examined so far in the literature have been



shown to undergo stereospecific cis cycloaddition.[55] In order to determine whether azomethine ylide **9** generated from α-cyanosilylamine **3** behaves similarly, we studied the cycloaddition with cis- and trans-disubstituted dipolarophiles. The reaction proceeded with complete stereospecificity with dimethyl fumarate and maleate, giving rise to cycloadducts **13** and **14**. The above cycloadditions show all the characteristics of a concerted reaction, including complete stereospecificity, and therefore are consistent with the intermediacy of an azomethine ylide.

All attempts to obtain a cycloadduct from the reaction of **3** with nonactivated olefins (i.e., cyclohexene, 1-octene, norbornene, etc.) failed. Our inability to isolate a 1,3-cycloadduct with these systems is consistent with the principles of frontier MO theory.[56] Azomethine ylides generally prefer to react with electron-deficient alkenes and alkynes, since such a pair of addends possesses a narrow dipole HOMO–dipolarophile LUMO gap.[57] It should be noted, however, that Beugelmans and co-workers[58] have recently reported that trimethylamine *N*-oxide undergoes reaction with LDA to give an azomethine ylide which cycloadds with simple alkenes. It is not clear to us why the azomethine ylide derived from **3** does not undergo 3 + 2 cycloaddition with alkyl substituted olefins. Perhaps the silver ion used to liberate the dipole coordinates with the π-bond of the alkene, thereby inhibiting the cycloaddition. Further work is needed in order to establish this point.

Intramolecular dipolar cycloadditions have much synthetic potential.[8,9] To apply the above methodology in this context we investigated the silver induced reaction of silylcyanoamine **15**. We found, however, that no signs of



an internal cycloadduct could be detected in the crude

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reaction mixture (NMR analysis). When the reaction was carried out in the presence of *N*-phenylmaleimide, however, a good yield of the bimolecular cycloadduct could be obtained. The negative results encountered with **15** are consistent with the large frontier gap which exists between the transient azomethine ylide and the neighboring olefinic double bond. It would seem as though the favorable entropy of reaction is not sufficient to overcome the unfavorable electronic factors.

We also examined the cycloaddition behavior of an unsymmetrically substituted α-cyanosilylamine so as to probe the regioselectivity of the reaction. Treatment of *N*-benzyl-*N*-(α-cyanoethyl)-*N*-[(trimethylsilyl)methyl]amine (**16**) with silver fluoride in the presence of methyl propiolate followed by DDQ oxidation produced a mixture of two pyrroles (17:18 = 8:1). The crude residue was chromatographically separated, and each regioisomer could be obtained in pure form. The structures of **17** and **18** were established by comparison with independently synthesized samples. Thus, 1,3-dipolar cycloaddition of methyl propiolate to Δ^2-oxazolium 5-oxide **19** followed by cycloreversion of carbon dioxide from the initially formed cycloadduct gave an 8:1 mixture of pyrroles **17** and **18**. The reaction of munchnones (i.e., Δ^2-oxazolium 5-oxides) with acetylenic dipolarophiles constitutes a pyrrole synthesis of broad type.[59] Munchnone **19** was readily prepared by the cyclodehydration of *N*-acetyl-*N*-benzylglycine (**20**) with acetic anhydride.[59]

It is important to note that dipolar cycloaddition of the isomeric α-cyanosilylamine **21** with methyl propiolate followed by DDQ oxidation afforded the same ratio of pyrroles **17** and **18** (8:1) as that obtained from **16** and **19**. This result strongly implicates azomethine ylide **22** as a common intermediate in the reaction of silylcyanoamines **16** and **21**. According to FMO theory,[56] regioselectivity is the result of best overlap of the interacting orbitals, i.e., the atoms with the largest orbital coefficients combine preferentially. The dipole HOMO–dipolarophile LUMO interaction with azomethine ylide **22** favors formation of the 2,3-disubstituted isomer (i.e., **17**).

Simple and stable reagents possessing a nucleophilic and an electrophilic site, which can be deployed selectively and sequentially, are of great potential use in synthesis. It occurred to us that the above α-cyanosilylamines might be "decapped" in a sequential fashion, thereby broadening the use of these compounds in organic synthesis. For example, treatment of α-cyanosilylamine **3** with silver nitrate would be expected to afford the electrophilic silyliminium ion **23** whereas reaction with a fluoride source could result in formation of α-aminocarbanion **24**. We were particularly interested in performing the second of the two C–C bond-forming reactions in an intramolecular fashion by using another dipolar reagent of type **25** in order to arrive at heterocyclic systems **26**.

As our first model we chose to investigate the reaction of **16** with silver nitrate in the presence of dimethyl acetylenedicarboxylate. Numerous attempts to isolate a cycloadduct from this reaction failed. The only product (**29**) that we could obtain corresponded to the addition of *N*-benzyl-*N*-trimethylsilylamine **28** to the activated acetylene. This reaction probably proceeds via silyliminium ion **27** which is hydrolyzed under the reaction conditions to the secondary amine. In fact, treatment of **16** with silver nitrate in the absence of the alkyne gave amine **28** in high yield. When cyanosilylamine **16** was allowed to react with cesium fluoride in the presence of dimethyl acetylenedicarboxylate, the only product isolated corresponded to the desilylated cyanoamine **30**. When α-cyanosilylamine **3** was treated with tris(dimethylamino)sulfonium difluorotrimethylsilicate[60] in the presence of benzaldehyde, 3-hydroxy-3-phenylpropionitrile (**32**) was obtained. This reaction can be rationalized in terms of an initial desilylation followed by elimination of acetonitrile carbanion **31** which then undergoes addition to benzaldehyde to give **32**. It is evident from these results that α-cyanosilylamines cannot be used in a sequential fashion to generate "half-capped" dipoles.

Recently, some effort has been directed toward the synthesis of alkaloids using various type of iminium-based 1,3-dipoles.[35-40] We decided to demonstrate the synthetic utility of the α-cyanosilylamine cycloaddition reaction by a total synthesis of the *Reniera* isoindole alkaloid **40**. In

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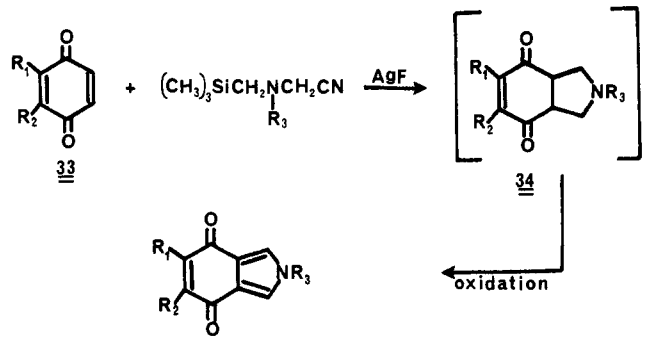
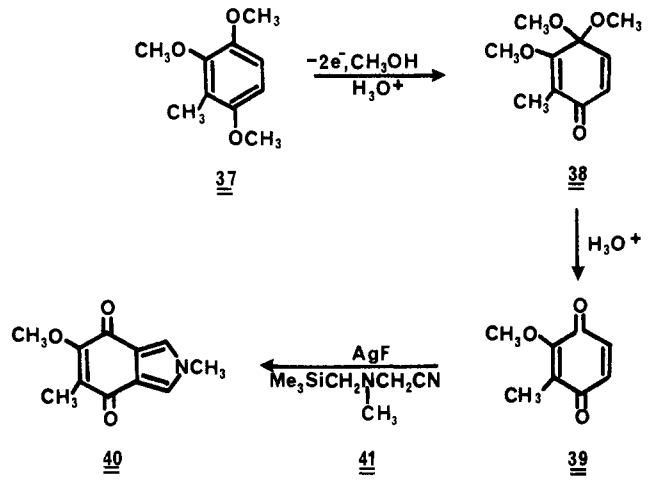
1982, Frincke and Faulkner[61] discovered the first naturally occurring isoindole **40** which was isolated from the bright blue Mexican sponge, *Reniera* sp.[61] Isoindole **40** is active against *Staphylococcus aureus*, *Bacillus subtilis*, *Vibrio anguilarium*, and B-392, a marine pseudomonal. Our investigation of the cycloaddition reaction of an azomethine ylide with a model quinone was initiated by studying the reaction of α-cyanoaminosilane **3** with 5 equiv of silver fluoride in the presence of benzoquinone. A 60% yield of the quinonoid isoindole **35** was obtained directly. The



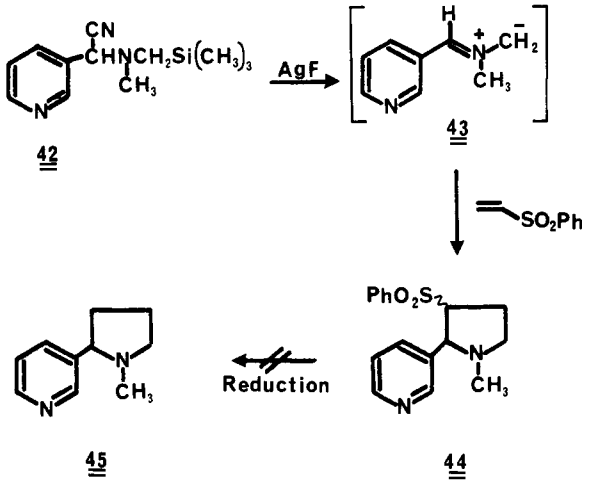
35a; $R_1 = R_2 = H$; $R_3 = CH_2Ph$
35b; $R_1 = R_2 = H$; $R_3 = CH_3$
36a, $R_1 = R_2 = CH_3$; $R_3 = CH_2Ph$
36b; $R_1 = R_2 = CH_3$; $R_3 = CH_3$

reaction presumably proceeds via a 1,3-dipolar cycloaddition followed by oxidation of intermediate **34**. Similar results were obtained using 2,3-dimethylquinone and α-cyanoaminosilane **3** to give **36**. For the synthesis of the *Reniera* alkaloid **40**, we required quinone **39**. This material was prepared by hydrolysis of quinone monoacetal **38**, readily available by application of Swenton's electrochemical oxidation sequence[62] to 1,2,4-trimethoxy-3-methylbenzene (**37**).[63] When cyanosilylamine **41** was



treated with 5 equiv of silver fluoride in the presence of quinone **39**, the *Reniera* isoindole **40** was obtained in 68% yield and was identified by its characteristic spectral properties.[64]

In order to further demonstrate the synthetic usefulness of α-cyanosilylamines, we decided to apply the method toward the total synthesis of nicotine (**45**). For the preparation of **45**, we envisioned a cycloaddition between phenyl vinyl sulfone and azomethine ylide **43**. Earlier reports in the literature demonstrated that phenyl vinyl sulfone can act as an ethylene equivalent in Diels–Alder reactions.[65,66] Our plans were based on the assumption that the resulting cycloadduct **44** would be easily reduced to nicotine. As in our earlier work, the crucial azomethine ylide intermediate **43** can be generated by silver fluoride



desilylcyanation of cyanosilylamine **42**. The initially formed cycloadduct **44** corresponded to a mixture of diastereomers (3:1), but this was of no concern since the asymmetry of the carbon adjacent to nitrogen would be expected to be lost upon reduction. Unfortunately, all attempts to reduce cycloadduct **44** to nicotine failed. On the possibility that the reducing metal (Na(Hg)) might be complexing with the pyrrolidine nitrogen, large excesses of metal were used. This also failed to give a characterizable product and further efforts to reduce **44** to nicotine were abandoned.

In summary, the silver fluoride induced desilylcyanation reaction of α-cyanosilylamines provides ready access to reactive azomethine ylides in synthetically useful yields. This method allows access to nonstabilized azomethine ylides and is currently being used in our laboratory to synthesize a number of alkaloids possessing the pyrrolidine ring.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. ^1H NMR spectra were obtained on a Varian EM-390 and Nicolet FT-360 spectrometers. ^{13}C NMR spectra were recorded on an IBM 200-MHz spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, Ga. Mass spectra were determined with a Finnegan 4000 mass spectrometer at an ionizing voltage of 70 eV.

Preparation of *N*-Benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (3). A solution containing 12.58 g of (chloromethyl)trimethylsilane and 33.10 g of benzylamine was heated with stirring at 200 °C for 2.5 h. At the end of this time a 0.1 N sodium hydroxide solution was added to the mixture in order to hydrolyse the white organic salt which had formed. The mixture was extracted with ether, and the organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was distilled under reduced pressure (5 mm), and the fraction corresponding to *N*-benzyl-*N*-[(trimethylsilyl)-

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methyl]amine which boiled at 89–90 °C was collected: 10.60 g (53%); NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 2.00 (s, 2 H), 3.78 (s, 2 H), and 7.28 (s, 5 H).

To a solution containing 5.00 g of the above compound was added 25.8 mL of a 1.0 N hydrochloric acid solution which caused a white precipitate to form. To the mixture was added 14 mL of tetrahydrofuran, 2.10 g of potassium cyanide, and 2.48 mL of a 37% aqueous formaldehyde solution. The reaction mixture was allowed to stir overnight and was then extracted with ether and washed with water. The ether layer was dried over magnesium sulfate and concentrated under reduced pressure to give 5.63 g (94%) of *N*-benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine as a clear oil: IR (neat) 3004, 2990, 2900, 2800, 1500, 1460, 1430, 1370, 1330, 1250, 1100, 850, 745, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 2.02 (s, 2 H), 3.51 (s, 2 H), and 7.20 (s, 5 H); MS, *m/e* 232 (M^+), 141, 91, and 78; C^{13} NMR ($CDCl_3$, 50 MHz) δ 0.04, 45.0, 46.6, 61.4, 127.7, 128.6, 128.9, and 137. Anal. Calcd for $C_{13}H_{20}N_2Si$: C, 67.19; H, 8.67; N, 12.05. Found: C, 67.24; H, 8.73; N, 12.04.

Cycloaddition of *N*-Benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (3) with Dimethyl Acetylenedicarboxylate. To a stirred solution containing 300 mg of **3** in 5 mL of acetonitrile was added 0.18 mL of dimethyl acetylenedicarboxylate and 190 mg of silver fluoride. The reaction was allowed to stir in the dark for 10 h, and then the reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The crude reaction residue was taken up in 20 mL of benzene, and 340 mg of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was added. The solution was heated with stirring at 70 °C for 10 h. The mixture was filtered, and the remaining solid was washed with ether. The ether layer was extracted with a saturated sodium bicarbonate solution, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified on the Chromatotron unit with a 30% ethyl acetate–hexane mixture as the eluent. The major fraction (62%) contained *N*-benzyl-3,4-dicarbomethoxypyrrole (**5**) as a yellow solid, mp 63–64 °C: IR (KBr) 3170, 3040, 2960, 1680, 1560, 1540, 1450, 1440, 1400, 1270, 1200, 1160, 1070, 970, 770, and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.80 (s, 6 H), 5.02 (s, 2 H), and 7.1–7.4 (m, 7 H); UV (ethanol) 253 nm (7500). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.86; H, 5.51; N, 4.86.

Cycloaddition of *N*-Benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (3) with Methyl Propiolate. To a stirred solution containing 300 mg of **3** in 5 mL of acetonitrile was added 0.13 mL of methyl propiolate and 190 mg of silver fluoride. The reaction was allowed to stir in the dark for 10 h. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The crude reaction residue was taken up in 20 mL of benzene, and 340 mg of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was added. The solution was heated with stirring at 70 °C for 10 h. The mixture was filtered and the remaining solid was washed with ether. The ether layer was washed with a saturated sodium carbonate solution and water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified on the Chromatotron unit with a 20% ethyl acetate–hexane mixture as the eluent. The major fraction (65%) contained *N*-benzyl-3-carbomethoxypyrrole (**6**) as an orange solid, mp 51–52 °C: IR (KBr) 3160, 3040, 2960, 1710, 1650, 1540, 1500, 1450, 1370, 1250, 1200, 1120, 1070, 850, 760, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.60 (s, 3 H), 5.01 (s, 2 H), 6.50 (m, 2 H), and 7.1–7.3 (m, 6 H); UV (ethanol) 232 nm (ε 11 500) and 249 nm (7000). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.49; H, 5.91; N, 6.43.

Preparation of [*N*-Benzyl-*N*-[(trimethylsilyl)methyl]amino]malononitrile (7). A mixture containing 1.93 g of *N*-[(trimethylsilyl)methyl]benzylamine and 3.06 g of butyl formate in 50 mL of benzene was heated at reflux under a nitrogen atmosphere. After 72 h, the reaction mixture was cooled, and the solvent was removed under reduced pressure. The oily residue was taken up in 50 mL of toluene, and 2.03 g of Lawesson's reagent[67] was added. The mixture was heated at reflux for 3 h, and then the solvent was removed under reduced pressure. The resulting residue was subjected to silica gel chromatography using a 7% ethyl acetate–hexane mixture as the eluent. The major fraction contained 1.47 g (62%) of benzyl(trimethylsilylmethyl)thioformamide as a colorless oil: IR (neat) 2950, 1600, 1500, 1275, 1120 and 850 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.11 (s, 9 H), 3.00 and 3.42 (s, 2 H), 4.62 and 5.08 (s, 2 H), 7.07–7.42 (m, 5 H), 9.27 and 9.33 (s, 1 H). This material was used in the next step without further purification.

A solution containing 422 mg of the above compound and 0.22 mL of methyl iodide in 10 mL of methylene chloride was heated at reflux under a nitrogen atmosphere for 2 h. The solvent was removed and the residue was taken up in 10 mL of acetonitrile. A sample containing 449 mg of mercuric cyanide was added, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was filtered, and the solvent was removed under reduced pressure. The resulting residue was subjected to silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major fraction contained 340 mg (74%) of [*N*-benzyl-*N*-(trimethylsilyl)methyl]amino]malononitrile (**7**) as a clear oil: IR (neat) 2900, 1600, 1495, 1455, 1425, 1370, 1250, 1180, 850, 755 and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.18 (s, 9 H), 2.28 (s, 2 H), 3.62 (s, 2 H), 4.47 (s, 1 H), and 7.33 (s, 5 H); MS, *m/e* 257 (M^+), 256, 231, 192, 166, 158, 130, 113, 91 (base), 84, 73 (base), and 65. Anal. Calcd for $C_{14}H_{19}N_3Si$: C, 65.23; H, 7.44; N, 16.32. Found: C, 65.35; H, 7.46; N, 16.34.

Reaction of [*N*-Benzyl-*N*-[(trimethylsilyl)methyl]amino]malononitrile (7) with Silver Fluoride in the Presence of Methyl Propiolate. A mixture containing 383 mg of [*N*-benzyl-*N*-[(trimethylsilyl)methyl]amino]malononitrile (**7**), 207 mg of anhydrous silver fluoride, and 260 mg of methyl propiolate in 20 mL of acetonitrile was heated at reflux for 4 h under a nitrogen atmosphere. The reaction mixture was diluted with methylene chloride and was filtered through a pad of Celite. Removal of the solvent under reduced pressure left an oily residue which was subjected to silica gel chromatography using a 15% ethyl acetate–hexane mixture as the eluent. The first fraction isolated from the column contained 148 mg (46%) of *N*-benzyl-3-carbomethoxypyrrole (**6**) whose structure was established by comparison with an authentic sample.[68]

Cycloaddition of *N*-Benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (3) with *N*-Phenylmaleimide. A solution containing 500 mg of **3**, 390 mg of *N*-phenylmaleimide, and 300 mg of silver fluoride in 10 mL of acetonitrile was allowed to stir for 10 h in the dark. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 550 mg (84%) of 2,6-dioxo-1-phenyl-4-benzyl-1,4-diazabicyclo[3.3.0]octane (**10**) as a clear oil: IR (neat) 3145, 3000, 2950, 2900, 2800, 1760, 1700, 1575, 1490, 1445, 1380, 1340, 1310, 1265, 1200, 1155, 1130, 880, 840, 760, 740, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.3–2.7 (m, 2 H), 3.2–3.6 (m, 4 H), 3.60 (s, 2 H), and 7.0–7.7 (m, 10 H); MS, *m/e* 306 (M^+), 149, 91, and 71. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.43; H, 6.05; N, 8.78.

Cycloaddition of *N*-Benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (3) with 4-Phenyl-3-buten-2-one. A solution containing 500 mg of **3**, 330 mg of *trans*-4-phenyl-3-buten-2-one, and 290 mg of silver fluoride in 10 mL of acetonitrile was allowed to stir in the dark for 10 h. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with a 10% acetone–hexane mixture as the eluent. The major fraction (55%) contained 1-benzyl-*trans*-3-acyl-4-phenylpyrrolidine (**11**) as a clear oil: IR (neat) 3040, 2950, 2800, 1710, 1670, 1610, 1495, 1455, 1360, 1260, 1180, 1150, 1080, 1040, 980, 760, and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.03 (s, 3 H), 2.5–3.4 (m, 6 H), 3.67 (s, 2 H), and 7.0–7.6 (m, 10 H). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.53; H, 7.49; N, 4.90.

Cycloaddition of *N*-Benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (3) with Methyl Cinnamate. A

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solution containing 500 mg of **3**, 360 mg of methyl cinnamate, and 290 mg of silver fluoride in 10 mL of acetonitrile was allowed to stir for 10 h in the dark. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained *trans*-3-phenyl-4-carbomethoxy-1-benzylpyrrolidine (**12**) (63%) as a clear oil: IR (neat) 3080, 3040, 2960, 2860, 2800, 1745, 1675, 1605, 1500, 1450, 1440, 1360, 1320, 1250, 1170, 1075, 1030, 8609, 740, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.6–3.3 (m, 6 H), 3.62 (s, 3 H), 3.67 (s, 2 H), and 7.0–7.5 (m, 10 H). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.36; H, 7.05; N, 5.12.

Preparation and Cycloaddition of 1-Cyano-1-[*N*-benzyl-*N*-[(trimethylsilyl)methyl]amino]-5-hexene (15) with *N*-Phenylmaleimide. To a solution containing 355 mg of *N*-benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (**3**) in 1 mL of tetrahydrofuran at 0 °C was added an LDA solution prepared from 1.02 mL of *n*-butyllithium and 2.57 mL of diisopropylamine in 2 mL of tetrahydrofuran. The mixture was allowed to stir at 0 °C for 30 min, and then 228 mg of 1-bromo-4-pentene was added. After stirring for 12 h at 25 °C, the mixture was extracted with ether. The ether extracts were washed with water, dried over magnesium sulfate, and concentrated to give 360 mg of a crude oil. Silica gel chromatography of this material using a 10% ether–hexane mixture afforded 304 mg (65%) of **15** as a clear oil: IR (neat) 3090, 3040, 2980, 2860, 2800, 2215, 1645, 1610, 1500, 1455, 1425, 1370, 1250, 1110, 1080, 1030, 1000, 970, 920, 860, 745, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.2–2.3 (m, 6 H), 3.3 (d, 1 H, J = 13.0 Hz), 3.2–3.6 (m, 2 H), 3.90 (d, 1 H, J = 13.0 Hz), 4.7–5.0 (m, 2 H), 5.2–5.8 (m, 1 H), and 7.2 (s, 5 H). Anal. Calcd for $C_{18}H_{28}N_2Si$: C, 71.94; H, 9.39; N, 9.32. Found: C, 71.83; H, 9.32; N, 9.14.

To a stirred solution containing 261 mg of **15** in 2 mL of acetonitrile was added 150 mg of *N*-phenylmaleimide and 121 mg of silver fluoride. The reaction was allowed to stir in the dark for 12 h and was then worked up in the standard manner. Silica gel chromatography of the residue using a 10% ethyl acetate–hexane mixture gave 269 mg of the expected dipolar cycloadduct (83%): IR ($CHCl_3$) 2940, 2805, 1710, 1600, 1500, 1455, 1380, 1200, 760, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.4–2.3 (m, 6 H), 3.0–3.4 (m, 5 H), 3.65 (d, 1 H, J = 14 Hz), 4.05 (d, 1 H, J = 14 Hz), 5.0 (m, 2 H), 5.5–5.9 (m, 1 H), and 7.2–7.5 (m, 5 H). Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.72; H, 6.91; N, 7.36.

Preparation of *N*-Benzyl-*N*-(α-cyanoethyl)-*N*-[(trimethylsilyl)methyl]amine (16). To a stirred solution containing 1.0 g of *N*-benzyl-*N*-[(trimethylsilyl)methyl]amine in 15 mL of 1.0 N hydrochloric acid solution and 8 mL of tetrahydrofuran was added 1.23 g of potassium cyanide and 1.75 mL of acetaldehyde. The reaction was allowed to stir for 10 h at room temperature, and the solution was poured into water and extracted with ether. The ether extracts were washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 2.2 g (73%) of a yellow oil. This material was subjected to flash chromatography using a 5% ethyl acetate–hexane mixture as the eluent to give *N*-benzyl-*N*-(α-cyanoethyl)-*N*-[(trimethylsilyl)-methyl]amine (**16**) as a clear oil: IR (neat) 3010, 2920, 2850, 1570, 1460, 1420, 1390, 1340, 1220, 1120, 1090, 1040, 840, 720, and 680 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 1.28 (d, 3 H, J = 6.0 Hz), 2.13 (d, 1 H, J = 18.0 Hz), 3.25 (d, 1 H, J = 15.0 Hz), 3.45 (q, 1 H, J = 6.0 Hz), and 3.85 (d, 1 H, J = 15.0 Hz); MS, m/e 246 (M^+), 149, 91, 83, and 73. Anal. Calcd for $C_{14}H_{22}N_2Si$: C, 68.24; H, 9.00; N, 11.37; Found: C, 68.31; H, 9.07; N, 11.34.

Preparation of *N*-Benzyl-*N*-[α-(trimethylsilyl)ethyl]-*N*-(cyanomethyl)amine (21). A solution containing 10 g of (α-chloroethyl)trimethylsilane and 24 mL of benzylamine was heated with stirring at 180–200 °C for 4 h. This mixture was diluted with ether and washed with a 1 N sodium hydroxide solution. After concentration under reduced pressure, the mixture was distilled at 25 mm to give 8.4 g (70%) of a clear oil whose structure was assigned as *N*-benzyl-*N*-[α-(trimethylsilyl)ethyl]-amine on the basis of its spectral properties: IR (neat) 3500, 3080, 3060, 2960, 2900, 2880, 1500, 1450, 1250, 1100, 1030, 1000, 850, 750, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 0.73 (b, 1 H), 1.05 (d, 3 H, J = 6.0 Hz), 2.00 (q, 1 H, J = 6.0 Hz), 3.59 (d, 1 H, J = 15.0 Hz), and 3.87 (d, 1 H, J = 15.0 Hz).

To a stirred solution containing 1.0 g of the above compound in 5 mL of a 2.0 N hydrochloric acid solution and 4 mL of tetrahydrofuran was added 0.35 g of potassium cyanide and 0.17 g of a 37% formaldehyde solution in water. The mixture was allowed to stir for 10 h and was then poured into water and extracted with ether. The ether extracts were washed with water and a saturated sodium carbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure to give 0.8 g (80%) of a clear oil. This material was subjected to flash chromatography using an 8% ethyl acetate-hexane mixture as the eluent to give *N*-benzyl-*N*-[α-(trimethylsilyl)ethyl]-*N*-(cyanomethyl)amine (**21**) as a clear oil: IR (neat) 3120, 3080, 2960, 2250, 1490, 1460, 1400, 1380, 1345, 1260, 1160, 1140, and 920 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 1.12 (d, 3 H, J = 6.0 Hz), 2.36 (q, 1 H, J = 6.0 Hz), 3.28 (d, 2 H, J = 1.0 Hz), and 3.67 (d, 2 H, J = 1.0 Hz); MS, m/e 246 (M^+), 173, 91, and 73. Anal. Calcd for $C_{14}H_{22}N_2Si$: C, 68.24; H, 9.00; N, 11.37. Found: C, 68.27; H, 9.01; N, 11.35.

Reaction of *N*-Benzyl-*N*-(α-cyanoethyl)-*N*-[(trimethylsilyl)methyl]amine (16) with Silver Fluoride in the Presence of Methyl Propiolate. To a stirred solution containing 0.2 g of **16** in 5 mL of acetonitrile was added 0.1 mL of methyl propiolate and 0.1 g of silver fluoride. The reaction was allowed to stir in the dark for 10 h. The solution was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The crude reaction mixture was taken up in 15 mL of benzene and 0.2 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was added. The solution was heated with stirring at 70 °C for 10 h. The mixture was filtered, the remaining solid was washed with ether, and the solution was concentrated to a small volume under reduced pressure. The crude residue was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent to give 0.21 g (67%) of a yellow oil which contained a 8:1 mixture of two isomeric cycloadducts. The major isomer was obtained as a yellow oil by separation on the Chromatotron unit using a 20% ethyl acetate–hexane mixture as the eluent. The structure of this isomer was assigned as *N*-benzyl-2-methyl-3-carbomethoxypyrrole (**17**) on the basis of its spectral data and by comparison with an independently synthesized sample: IR (neat) 3130, 3050, 2960, 1710, 1560, 1510, 1460, 1450, 1380, 1360, 1280, 1215, 1200, 1160, 1100, 1060, 940, 820, 800, 740, and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.40 (s, 3 H), 3.71 (s, 3 H), 5.00 (s, 2 H), 6.40 (s, 2 H), and 6.8–7.3 (m, 5 H); UV (95% ethanol) 233 nm (10 000); MS, m/e 229 (M^+), 149, 91, 71, and 69. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.24; H, 6.63; N, 6.08.

The minor isomer was assigned the structure of *N*-benzyl-2-methyl-4-carbomethoxypyrrole (**18**) on the basis of its spectral data and by comparison with an independently synthesized sample: IR (neat) 3120, 3040, 3000, 2980, 1710, 1610, 1580, 1530, 1500, 1460, 1440, 1400, 1370, 1220, 1180, 1100, 1010, 930, 760, 750, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.08 (s, 3 H), 3.75 (s, 3 H), 5.00 (s, 2 H), 6.32 (b, 2 H), and 6.8–7.3 (m, 6 H); UV (95% ethanol) 237 nm (4000); MS, m/e 229 (M^+), 198, 91, and 65. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; N, 6.59; N, 6.11. Found: C, 73.08; H, 6.67; N, 6.00.

The same two pyrroles (**17** and **18**) were obtained in 8:1 ratio by treating *N*-benzyl-*N*-[α-(trimethylsilyl)ethyl]-*N*-(cyanomethyl)amine (**21**) with silver fluoride in the presence of methyl propiolate.

Independent Synthesis of *N*-Benzyl-2-methyl-3-carbomethoxypyrrole (17) and *N*-Benzyl-2-methyl-4-carbomethoxypyrrole (18). To a stirred solution containing 5.0 g of *tert*-butyl bromoacetate in 70 mL of anhydrous ether at 0 °C was added 5.6 mL of benzylamine. The reaction was allowed to warm to room temperature and was stirred for 24 h. The crystalline benzylamine hydrochloride was filtered and washed with ether. The filtrate and washings were combined, and the solution was concentrated under reduced pressure to give a clear oil. This material was distilled at 0.8 mm to give 5.2 g (90%) of a clear oil whose structure was assigned as *N*-benzylglycine *tert*-butyl ester on the basis of its spectral data: IR (neat) 3310, 3060, 3000, 2910, 2810, 1720, 1480, 1440, 1360, 1320, 1180, 1120, 1020, 780, and 680 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.42 (s, 9 H), 1.77 (b, 1 H), 3.29 (s, 2 H), 3.77 (s, 2 H), and 7.30 (s, 5 H).

A solution containing 2.0 g of *N*-benzylglycine *tert*-butyl ester and 5 mL of acetic anhydride was allowed to stand at 25 °C for 1 h. The reaction mixture was then heated on a steam bath for 30 min. The acetic acid and acetic anhydride were removed under reduced pressure, and the residue was washed with a 2% sodium bicarbonate solution and water to yield 2.3 g (98%) of a clear oil whose structure was assigned as *N*-acetyl-*N*-benzylglycine *tert*-butyl ester on the basis of its spectral data: IR (neat) 3080, 3100, 3010, 2960, 1760, 1680, 1510, 1450, 1400, 1320, 1290, 1220, 1060, 1020, 780, and 730 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.42 (s, 9 H), 2.08 (rotomer A), 2.17 (rotomer B) (s, 3 H), 3.80 (A), 3.95 (B) (s, 2 H), 4.60 (A), 4.62 (B) (s, 2 H), and 7.1–7.5 (m, 5 H).

To a stirred solution containing 10 mL of nitromethane previously saturated with a hydrochloric acid solution was added 4.0 g of *N*-acetyl-*N*-benzylglycine *tert*-butyl ester. The reaction was cooled with stirring at −4 °C for 12 h in a constant temperature bath unit. The solvent was distilled under reduced pressure leaving behind 2.8 g (90%) of a viscous oil whose structure was assigned as *N*-acetyl-*N*-benzylglycine on the basis of its spectral data: IR (neat) 3600–2400 (b), 1740, 1660, 1600, 1510, 1460, 1420, 1400, 1240, 1200, 1020, 760, and 720 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.27 (s, 3 H), 4.11 (s, 2 H), 4.11 (s, 2 H), 4.68 (s, 2 H) 7.1–7.4 (m, 5 H), and 7.51 (bs, 1 H).

To a stirred solution containing *N*-acetyl-*N*-benzylglycine and 0.1 mL of methyl propiolate was added 5 mL of acetic anhydride. The reaction mixture was heated with stirring at 115 °C for 3 h. Upon cooling, the reaction mixture was poured into water in order to hydrolyse the excess acetic anhydride. After being stirred for 30 min, the aqueous reaction mixture was extracted with ether. The combined ethereal extracts were washed with water, a saturated sodium carbonate solution, and water. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to give a yellow oil which contained a 8:1 mixture of two isomeric cycloadducts. The cycloadducts were separated on the Chromatotron unit with a 10% ethyl acetate–hexane solution as the eluent. The first component eluted was identified a *N*-benzyl-2-methyl-3-carbomethoxypyrrole (**17**) (140 mg, 60%). The second component eluted was identified as *N*-benzyl-2-methyl-4-carbomethoxypyrrole (**18**) (15 mg, 8%). Both cycloadducts were identical with the products obtained by treating either **16** or **21** with silver fluoride in the presence of methyl propiolate.

Reaction of *N*-Benzyl-*N*-(α-cyanoethyl)-*N*-[(trimethylsilyl)methyl]amine (16) with Dimethyl Acetylenedicarboxylate in the Presence of Silver Nitrate. To a solution containing 500 mg of *N*-benzyl-*N*-(α-cyanoethyl)-*N*-[(trimethylsilyl)methyl]amine (**16**) in 6 mL of acetonitrile was added 0.30 mL of dimethyl acetylenedicarboxylate and 0.35 g of silver nitrate. The reaction was allowed to stir 24 h in the dark. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with a 10% ethyl acetate mixture as the eluent to give 0.48 g (72%) of a clear oil whose structure was assigned as *N*-benzyl-*N*-[(trimethylsilyl)-methyl]-*N*-1,2-(*Z*)-dicarbomethoxyethene]amine (**29**) on the basis of its spectral properties: IR (neat) 2900, 2850, 2250, 2000, 1730, 1670, 1560, 1430, 1360, 1250, 1200, 1150, 1040, 1000, 910, 850, and 730 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 2.61 (s, 2 H), 3.60 (s, 3 H), 3.88 (s, 3 H), 4.27 (s, 2 H), 4.58 (s, 1 H), and 7.30 (m, 5 H).

The structure of **29** was further verified by an independent synthesis. A mixture containing 200 mg of *N*-benzyl-*N*-[(trimethylsilyl)methyl]amine (**28**) and 0.13 mL of dimethyl acetylenedicarboxylate in 4 mL of acetonitrile was stirred at room temperature for 24 h. The reaction mixture was diluted with chloroform and concentrated under reduced pressure. The residue was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent to give 0.3 g (95%) of a clear oil whose structure was identical with that obtained from the reaction of **16** with dimethyl acetylenedicarboxylate in the presence of silver nitrate.

Reaction of *N*-Benzyl-*N*-(α-cyanoethyl)-*N*-[(trimethylsilyl)methyl]amine (16) with Silver Nitrate. A mixture containing 200 mg of **16** and 0.15 g of silver nitrate in 4 mL of acetonitrile was allowed to stir in the dark for 24 h. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent. The major fraction contained 0.16 g (90%) of *N*-benzyl-*N*-[(trimethylsilyl)methyl]amine (**28**) as a clear oil; IR (neat) 3090, 3040, 2960, 2900, 2800, 1600, 1500, 1450, 1360, 1250, 1190, 1100, 1030, 860, 730, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 2.05 (s, 2 H), 3.78 (s, 2 H), and 7.28 (s, 2 H).

Reaction of *N*-Benzyl-*N*-(α-cyanoethyl)-*N*-[(trimethylsilyl)methyl]amine (16) with Cesium Fluoride. A mixture containing 200 mg of **16**, 0.1 mL of methyl propiolate, and 150 mg of cesium fluoride in 4 mL of anhydrous methanol was allowed to stir for 24 h. The reaction mixture was diluted with water and extracted with ether. The ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to flash chromatography using a 10% ethyl acetate–hexane mixture as the eluent. The major fraction (75%) contained *N*-benzyl-*N*-(α-cyanoethyl)-*N*-methylamine (**30**) as a clear oil; IR (neat) 3080, 3040, 3000, 2960, 2860, 2800, 2240, 1600, 1500, 1450, 1360, 1320, 1240, 1160, 1130, 1100, 1070, 1030, 960, 920, 820, 740, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.46 (d, 3 H, J = 7.0 Hz), 2.30 (s, 3 H), 3.26 (d, 1 H, J = 13.0 Hz), 3.68 (q, 1 H, J = 7.0 Hz), 3.79 (d, 1 H, J = 13.0 Hz), and 7.32 (s, 5 H).

The structure of **30** was further verified by an independent synthesis. To a solution containing 1.0 g of *N*-methylbenzylamine was added 16 mL of a 1N hydrochloric acid solution which caused a white precipitate to form. To the mixture was added 8 mL of tetrahydrofuran, 1.0 g of potassium cyanide, and 0.7 g of acetaldehyde. The reaction mixture was allowed to stir overnight and was then poured into water and extracted with ether. The ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 1.37 g (95%) of *N*-benzyl-*N*-(α-cyanoethyl)-*N*-methylamine (**30**) as a clear oil. This structure was identical with that obtained from the reaction of **16** with methyl propiolate in the presence of cesium fluoride.

Reaction of *N*-Benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (3) with Tris(dimethylamino)sulfonium Difluorotrimethylsilicate in the Presence of Benzaldehyde. To a solution containing 200 mg of *N*-benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (**3**) in 4 mL of acetonitrile was added 0.09 mL of benzaldehyde and 300 mg of tris(dimethylamino)sulfonium difluorotrimethylsilicate.[60] The mixture was allowed to stir overnight and was cooled to 0 °C. To the reaction mixture was added 1.1 mL of chlorotrimethylsilane, and the reaction was stirred for another 2 h at 0 °C. The reaction was diluted with water and extracted with ether. The ethereal layer was washed with water, dried over sodium sulfate, and concentrated under reduced pressure to give 80 mg (60%) of a yellow oil. This material was subjected to flash chromatography using a 10% ethyl acetate mixture as the eluent to give 3-hydroxy-3-phenylpropionitrile (**32**) as a clear oil; IR (neat) 3600–3200 (b), 2270, 1700, 1500, 1460, 1420, 1100, 1060, 960, 880, 775, and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.71 (d, 2 H, J = 7.0 Hz), 2.91 (bs, 1 H), 5.02 (t, 1 H, J = 7.0 Hz) and 7.28 (s, 5 H).

The structure of this material was confirmed by an independent synthesis. To a solution containing 5.0 g of diisopropylamine in 150 mL of tetrahydrofuran at −78 °C was added 34 mL of a 1.5 M solution of *n*-butyllithium in hexane. The mixture was stirred at −78 °C for 0.5 h and then added to a solution containing 1.6 mL of acetonitrile in 100 mL of tetrahydrofuran at −78 °C. The reaction was allowed to stir at this temperature for 2.5 h, and then 3.3 mL of benzaldehyde was added, and the mixture was allowed to stir for 2 additional h. To this solution was added 25 mL of a 3 N hydrochloric acid solution, and the mixture was diluted with water and extracted with ether. The ethereal layer was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure to give 3.2 g (70%) of a yellow oil. This materal was subjected to silica gel chromatography using a 20% ethyl acetate–hexane mixture as the eluent to give 3-hydroxy-3-phenylpropionitrile as a clear oil whose structure was identical with that obtained from the reaction of *N*-benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine with tris(dimethylamino)sulfonium difluorotrimethylsilicate in the presence of benzaldehyde.

Preparation of *N*-Methyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (41). To a solution containing 5.0

g of *N*-methyl-*N*-[(trimethylsilyl)methyl]amine[69] in 50 mL of a 1 N hydrochloric acid solution was added 2.9 g of potassium cyanide and 3.5 g of a 37% aqueous formaldehyde solution. The reaction mixture was allowed to stir overnight and was then poured into water and extracted with ether. The ether layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 6.1 g (92%) of *N*-methyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (**41**) as a clear oil: IR (neat) 2960, 2900, 2800, 2240, 1460, 1450, 1420, 1320, 1250, 1120, 1110, 1030, 850, 770, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 2 H), 2.36 (s, 3 H), and 3.50 (s, 2 H). Anal. Calcd for $C_7H_{16}N_2$: C, 53.79; H, 10.32; N, 17.92. Found: C, 53.85; H, 10.33; N, 17.83.

Reaction of *N*-Benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (3) with Benzoquinone. A solution containing 200 mg of **3**, 94 mg of benzoquinone, and 550 mg of silver fluoride in 5 mL of acetonitrile was allowed to stir for 10 h in the dark. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was purified on the Chromatotron unit with a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained 130 mg (60%) of 2-benzyl-2*H*-isoindole-4,7-dione (**35a**) as a yellow solid, mp 170–171 °C: IR (KBr) 3160, 2960, 1650, 1500, 1450, 1340, 1160, 1100, 850, and 750 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 5.0 (s, 2 H), 6.60 (s, 2 H), and 7.1–7.4 (m, 7 H); MS, *m/e* 237 (M^+), 149, 91, and 71; UV (methanol) 373 nm (4000), 242 nm (15 000), and 226 nm (20 000). All attempts to obtain a satisfactory analysis for this compound failed due to its hydroscopic lability.

Reaction of *N*-Methyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (41) with Benzoquinone. A solution containing 200 mg of **41**, 138 mg of benzoquinone, and 800 mg of silver fluoride in 6 mL of acetonitrile was allowed to stir for 10 h in the dark. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was purified on the Chromatotron unit with a 30% ethyl acetate–hexane mixture as the eluent. The major fraction contained 140 mg (64%) of 2-methyl-2*H*-isoindole-4,7-dione (**35b**) as a yellow solid, mp 161–162 °C: IR (KBr) 3120, 2940, 1650, 1550, 1450, 1340, 1230, 1150, 1030, 870, and 750 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.77 (s, 3 H), 6.60 (s, 2 H), and 7.18 (s, 2 H); MS, *m/e* 161 (M^+, 147, 120, 107, 91, 90, and 71; UV (methanol) 366 nm (2000), 262 nm (10 000), and 225 nm (12 000). All attempts to obtain a satisfactory analysis for this compound failed due to its hydroscopic lability.

Reaction of *N*-Benzyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (3) with 2,3-Dimethylbenzoquinone. A solution containing 220 mg of **3**, 130 mg of 2,3-dimethylbenzoquinone, and 600 mg of silver fluoride in 6 mL of acetonitrile was allowed to stir for 10 h in the dark. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was purified on the Chromatotron unit with a 20% ethyl acetate–hexane mixture as the eluent. The major fraction contained 180 mg (75%) of 2-benzyl-5,6-dimethyl-2*H*-isoindole-4,7-dione (**36a**) as a yellow solid, mp 159–160 °C: IR (KBr) 3120, 3080, 2940, 1650, 1540, 1460, 1410, 1370, 1220, 1200, 1140, 870, 820, 730, 700, and 630 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.07 (s, 6 H), 5.10 (s, 2 H) and 7.1–7.5 (m, 7 H); MS, *m/e* 265 (M^+), 167, 149, 105, and 91; UV (methanol) 366 nm (2900), 264 nm (11 000), 226 nm (19 000). All attempts to obtain a satisfactory analysis for this compound failed due to its hydroscopic lability.

Reaction of *N*-Methyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (41) with 2,3-Dimethylbenzoquinone. A solution containing 200 mg of **41**, 175 mg of 2,3-dimethylbenzoquinone, and 800 mg of silver fluoride in 6 mL of acetonitrile was allowed to stir for 10 h in the dark. The reaction was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was purified on the Chromatotron unit with a 30% ethyl acetate–hexane mixture as the eluent. The major fraction contained 150 mg (75%) of 2,5,6-trimethyl-2*H*-isoindole-4,7-dione (**36b**) as a yellow solid, mp 161–162 °C; IR (KBr) 3120, 3080, 2940, 1650, 1550, 1450, 1370, 1320, 1230, 1150, 1030, 870, and 730 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.07 (s, 6 H), 3.77 (s, 3 H), and 7.19 (s, 2 H); MS, *m/e* 189 (M^+), 120, 119, 107, 91, and 90; UV (methanol) 366 nm (2000), 265 nm (10 500), 233 nm (10 000). All attempts to obtain a satisfactory analysis for this compound failed due to its hydroscopic lability.

Reaction of *N*-Methyl-*N*-(cyanomethyl)-*N*-[(trimethylsilyl)methyl]amine (41) with 2-Methyl-3-methoxybenzoquinone. A solution containing 40 mg of **41**, 38 mg of 2-methyl-3-methoxybenzoquinone,[63] and 160 mg of silver fluoride in 4 mL of acetonitrile was allowed to stir for 10 h in the dark. The reaction mixture was diluted with chloroform, filtered through Celite, and concentrated under reduced pressure. The residue was purified on the chromatotron unit using a 40% ethyl acetate–hexane mixture as the eluent. The major fraction contained 23 mg (45%) of 2,5-dimethyl-6-methoxy-2*H*-isoindole-4,7-dione (**40**) as a yellow solid, mp 160–161 °C: IR (KBr) 3140, 2960, 1650, 1340, 1160, 1100, 1000, 910, 850, 750, and 730 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.99 (s, 3 H), 3.73 (s, 3 H), 4.03 (s, 3 H), 7.14 (d, 1 H, J = 2.0 Hz), and 7.16 (d, 1 H, J = 2.0 Hz); UV (methanol) 361 nm (3000), 273 nm (11 000), 232 nm (12 000), and 223 nm (14 000).

Preparation and Cycloaddition of *N*-(Cyano-3-pyridylmethyl)-*N*-methyl-*N*-[(trimethylsilyl)methyl]amine (42). To a stirred solution containing 3.05 g of *N*-methyl-*N*-[(trimethylsilyl)methyl]amine in 26 mL of a 1.0 N hydrochloric acid solution and 13 mL of tetrahydrofuran was added 2.03 g of potassium cyanide and 2.79 g of nicotinaldehyde. The solution was allowed to stir for 10 h and was then poured into water and extracted with ether. The ether extracts were washed with water and a saturated sodium chloride solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was chromatographed on a silica gel column with a 20% ethyl acetate–hexane solution as the eluent to give 5.9 g (90%) of a pale yellow oil whose structure was assigned as *N*-(cyano-3-pyridylmethyl)-*N*-methyl-*N*-[(trimethylsilyl)methyl]amine (**42**) on the basis of its spectral properties: IR (neat) 3060, 2960, 2900, 2800, 2240, 1600, 1580, 1480, 1450, 1420, 1250, 1130, 1020, 920, 850, 790, 740, and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.10 (s, 9 H), 1.97 (s, 2 H), 2.28 (s, 3 H), 4.88 (s, 1 H), 7.36 (dd, 1 H, J = 9.0 and 6.0 Hz), 7.87 (dd, 1 H, J = 9.0 and 2.0 Hz), 8.63 (dd, 1 H, J = 6.0 and 2.0 Hz), and 8.79 (d, 1 H, J = 2.0 Hz); UV (95% ethanol) 270 nm (ϵ 2300), 259 nm (ϵ 3000), 254 nm (ϵ 2800); MS, *m/e* 233 (M^+), 160, 133, 107, 106 and 73. Anal. Calcd for $C_{12}H_{19}N_3Si$: C, 61.76; H, 8.21; N, 18.00. Found: C, 61.85; H, 8.23; N, 17.99.

A mixture containing 234 mg of **42**, 168 mg of phenyl vinyl sulfone, and 127 mg of silver fluoride in 20 mL of acetonitrile was stirred at 25 °C for 24 h. The mixture was filtered and the solvent was removed under reduced pressure. The resulting residue was chromatographed on a silica gel column with a 9:1 ethyl acetate–hexane mixture as the eluent. The first component isolated from the column contained 72 mg (24%) of a colorless solid, mp 108–109°C, whose structure was assigned as *cis*-2-(3-pyridyl)-3-(phenylsulfonyl)-*N*-methylpyrrolidine (**44**) on the basis of its spectral properties: IR (KBr) 1600, 1590, 1450, 1440, 1340, 1310, 1300, 1250, 1095, 1030, 750, and 730 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.67 (s, 3 H), 1.75 (m, 1 H), 2.03 (m, 2 H), 2.49 (dd, 1 H, J = 9.9 and 6.5 Hz), 3.16 (m, 1 H), 3.62 (dd, 1 H, J = 11.2 and 2.5 Hz), and 6.75–8.50 (m, 9 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.5, 39.3, 56.2, 61.4, 68.3, 123.7, 128.8, 129.1, 133.7, 134.9, 136.1, 137.9, and 149.3. Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.54; H, 6.01; N, 9.25. Found: C, 63.57; H, 6.04; N, 9.25.

The second fraction isolated from the column contained 152 mg (69%) of a crystalline solid, mp 104–105 °C, whose structure was assigned as *trans*-2-(3-pyridyl)-3-(phenylsulfonyl)-*N*-methylpyrrolidine (**44**): IR (KBr) 1585, 1460, 1450, 1435, 1315, 1305, 1290, 1260, 1200, 1150, 1090, 810, 740, 720, 700, and 600 cm^{-1}; NMR (benzene-d_6; 360 MHz) δ 1.87 (s, 3 H), 1.75 (m, 1 H), 2.16 (m, 1 H), 2.47 (m, 1 H), 2.71 (dd, 1 H, J = 8.3 and 8.1 Hz), 3.40 (ddd, 1 H, J = 10.3, 6.8 and 3.3 Hz), 3.70 (d, 1 H, J = 6.70 Hz), 6.65–8.65 (m, 9 H). Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.54; H, 6.01; N, 9.25. Found: C, 63.48; H, 6.04; N, 9.24. All attempts to reduce either diastereomer to nicotine using sodium amalgam failed, and further work with these systems was abandoned.

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Registry No. **3**, 87813-07-8; **5**, 78394-12-4; **6**, 18159-18-7; **7**, 97998-39-5; **9**, 97998-53-3; **10**, 93102-03-5; **11**, 87813-01-2; **12**, 87813-03-4; **15**, 97998-43-1; **16**, 97998-44-2; **17**, 87281-49-0; **18**, 87281-50-3; **20**, 7662-79-5; **21**, 97998-45-3; **29**, 97998-47-5; **30**, 97998-48-6; **32**, 17190-29-3; **35a**, 96611-44-8; **35b**, 95832-83-0; **36a**, 95832-84-1; **36b**, 95832-85-2; **40**, 79664-59-8; **41**, 95832-82-9; **42**, 97998-49-7; *cis*-**44**, 97998-50-0; *trans*-**44**, 97998-51-1; $TMSCH_2N^+(CH_2Ph)$=CHSMe·I^-, 97998-42-0; pyrrolidine, 123-75-1; (chloromethyl)trimethylsilane, 2344-80-1; benzylamine, 100-46-9; *N*-benzyl-*N*-[(trimethylsilyl)methyl]amine, 53215-95-5; formaldehyde, 50-00-0; dimethyl acetylenedicarboxylate, 762-42-5; methyl propiolate, 922-67-8; butyl formate, 592-84-7; benzyl(trimethylsilylmethyl)formamide, 97998-40-8; benzyl(trimethylsilylmethyl)thioformamide, 97998-41-9; *N*-phenylmaleimide, 941-69-5; 4-phenyl-3-buten-2-one, 1896-62-4; methyl cinnamate, 103-26-4; 1-bromo-4-pentene, 1119-51-3; 5-benzyl-1,3-dioxo-4-(1-penten-5-yl)-2-phenylpyrrolo[3,4-*c*]pyrrole, 97998-52-2; acetaldehyde, 75-07-0; (α-chloroethyl)trimethylsilane, 7787-87-3; *N*-benzyl-*N*-[α(trimethylsilyl)ethyl]amine, 97998-46-4; *tert*-butyl bromoacetate, 5292-43-3; *N*-benzylglycine *tert*-butyl ester, 7662-76-2; *N*-acetyl-*N*-benzylglycine *tert*-butyl ester, 7662-78-4; *N*-methylbenzylamine, 103-67-3; tris(dimethylamino)sulfonium difluorotrimethylsilicate, 59218-87-0; benzaldehyde, 100-52-7; acetonitrile, 75-05-8; *N*-methyl-*N*-[(trimethylsilyl)methyl]amine, 18135-05-2; benzoquinone, 106-51-4; 2,3-dimethylbenzoquinone, 526-86-3; 2-methyl-3-methoxybenzoquinone, 2207-57-0; nicotinaldehyde, 500-22-1; phenyl vinyl sulfone, 5535-48-8; nicotine, 54-11-5.

Silicon Directed *N*-Acyliminium Ion Cyclizations. Highly Selective Syntheses of (±)-Isoretronecanol and (±)-Epilupinine

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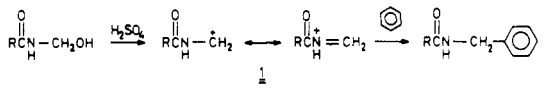
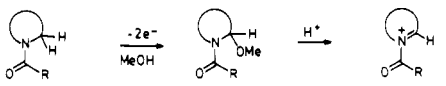
Intramolecular reactions of *N*-acyliminium ions with allyl- and propargylsilanes are described. The cyclization precursors are hydroxy lactams **4b–10b**, derived from succinimide and glutarimide, with the π-nucleophile connected to the nitrogen via an ethylene or propylene chain. Cyclizations are induced by treatment with trifluoroacetic or formic acid and lead to products containing the pyrrolizidine (**4c**, **7c**), indolizidine (**5c**, **8c**), or quinolizidine (**6c**, **9c**) ring system with a vinylidene substituent (propargylsilane cyclization) or a vinyl substituent (allylsilane cyclization). Reactions proceed in high yield with complete regiocontrol (governed by the β-effect of silicon) and with complete stereocontrol (chair-like transition-state conformations). Two allylsilane cyclization products **7c** and **9c** are further transformed into racemic isoretronecanol (**7e**) and epilupinine (**9e**), respectively.

N-Acyliminium ions (**1–3**) are highly useful intermediates in organic synthesis.[1] The ease of generation and the high reactivity of simple representatives (**1**) have been known since the beginning of this century, when the Tscherniac–Einhorn reaction (eq 1) was discovered.[2] The



(1)

acid-catalyzed heterolysis of *N*-(α-oxyalkyl)amides, as shown in eq 1, is still the most direct and successful route for the formation of *N*-acyliminium ions. Obviously, the shortest synthesis of such functionalized amides is the reaction of primary or secondary amides with aldehydes or ketones, but this reaction is not always useful. The development of two novel and versatile methods for the preparation of *N*-(α-alkoxyalkyl)amides, some 10 years ago, spurred an upsurge of the interest in the synthetic potential of *N*-acyliminium ions, in particular cyclic ones (**2** or **3**). These new methods are the electrochemical oxidation of amides[1c,3] (eq 2) and the pH controlled $NaBH_4$ reduction of imides[1d,4] (eq 3). Such new entries into the



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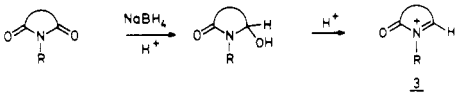

(3)

chemistry of *N*-acyliminium ions enabled a more systematic study of their reactivity and a more subtle use in synthesis. Intramolecular reactions with acetylenes and olefins need special attention in this respect. These reactions have shown in several cases to be attended with high regio- and stereocontrol, permitting highly selective total syntheses of alkaloids such as perhydrohistrionicotoxin,[5] vertaline,[6] and gephyrotoxin.[7] Equation 4 illustrates regioselectivity in the intramolecular reaction of *N*-acyliminium ions with electronically unbiased acetylenes.[8] The results are explained on the basis of stability of vinyl cations and ring strain. Linear vinyl cations are

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