"Advances in Silicon Chemistry"
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THE CHEMISTRY OF CYANOTRIMETHYLSILANE

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Advances in Silicon Chemistry,
Volume 1, pages 65–187.

ISBN: 1-55938-176-0

1. INTRODUCTION

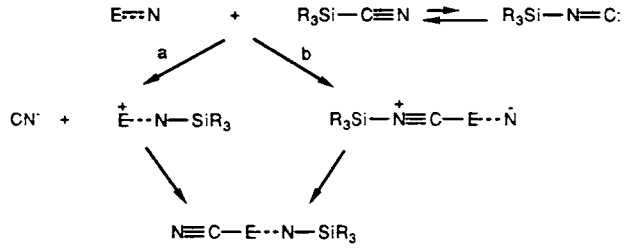
Cyanosilanes have been known in the chemical literature for almost fifty years. For the first thirty of those years, literature reports dealt primarily with the inorganic or organometallic pseudohalide nature of these materials. Aside from the development of synthetic methods, the majority of studies were concerned with spectroscopic characterization and the question of the actual structure, cyanide vs. isocyanide, of these compounds. These topics have been touched upon briefly in the context of early general reviews of organometallic pseudohalides[1] and cyano group containing organosilicon compounds.[2] A more recent review of organometallic pseudohalides contains a much more detailed accounting of this early work.[3] The potential utility of cyanosilanes in synthetic organic chemistry was first demonstrated less than twenty years ago by Evans and co-workers when they conducted the elaboration of some *p*-quinones[4] and converted ketones and aldehydes into β-aminoalcohols.[5] Subsequently, the utilization of this class of organosilanes in a variety of synthetic transformations has grown tremendously, and cyanotrimethylsilane **1**, the most commonly utilized cyanosilane, has been described as one of the most versatile silicon reagents for the purposes of organic synthesis.[6]

$(CH_3)_3SiCN$

1

The preparation and chemistry of cyanosilanes has been described within the context of several broad reviews on the utilization of silicon compounds in organic synthesis,[7–14] and in references therein. In general, these have been only limited accounts, with the most detailed being those of Pike and Mangano[3] and of Weber[6] which cover the literature only through 1980 and 1981, respectively. An English language review of cyanosilanes is not available. Although the relative importance of cyanotrimethylsilane **1** is indicated by the title, the present survey is intended to be a comprehensive review of the chemistry of cyanosilanes which covers both the scientific journal and chemical patent literature through 1988. When possible, *Chemical Abstracts* citations to referenced patents have been included. Cyanosilanes are currently indexed in *Chemical Abstracts* under the headings "Silanecarbonitrile" or "Silanedicarbonitrile". Whenever possible, we have followed the commonly used nomenclature rules for organosilicon compounds, naming these materials as derivatives of silane. Substituents are generally named in alphabetical order when this does not create confusion. In addition, some common abbreviations have been utilized, including TMS for trimethylsilyl, TMSCN (trimethylsilyl cyanide) for cyanotrimethylsilane **1**, and TMCS (trimethylchlorosilane) for chlorotrimethylsilane.

If one considers the interaction of a cyanosilane with a generalized compound EN containing both electrophilic (E) and nucleophilic (N) sites, reaction might be expected to occur via one of two possible pathways (Scheme 1), both of which have



Scheme 1.

been suggested in the literature.[6,11] In pathway *a*, the reaction is initiated by silylation of the nucleophilic site, followed by collapse of the incipient ion pair to give the final product. According to pathway *b*, nucleophilic attack by the isonitrile form of the cyanosilane upon the electrophilic site occurs prior to silicon migration. Catalysis of many of the reactions of cyanosilanes, especially by Lewis acids, has been frequently described in the literature. It is readily apparent that coordination of a Lewis acid with the nucleophilic site would result in catalysis of pathway *b*. Alternatively, interaction of a Lewis acid with the cyano group of the organosilicon reagent would, in effect, make it a better silylating agent, thus catalyzing pathway *a*. Evidence for both of these mechanistic pathways, as well as for nucleophilic catalysis of cyanosilane reactions, have been presented.

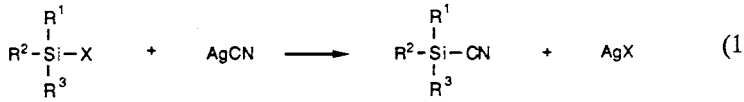
For the purposes of this review, reactions of cyanosilanes have been classified into three main groups. The largest of these, "cyanosilylations", describe reactions in which both the cyano group and the silyl group become incorporated into the final product. Also included are cases in which the above statement is true, except that the silyl group is hydrolyzed (solvolyzed) during workup of the reaction mixture. The second largest group of reactions are "cyanations", in which the sole purpose is the incorporation of a nitrile group into the product. In these cases, the silyl group generally ends up as a volatile silane byproduct, typically a halosilane. The third classification is that of "silylation", in which the cyanosilane serves simply as a silylating agent for active hydrogen containing compounds. Hydrogen cyanide is a product of these reactions. Finally, a short section has been included describing "miscellaneous" reactions which do not fit into the above general classification scheme.

2. PREPARATION AND PROPERTIES OF CYANOSILANES

2.1. Preparation

The first reported preparation of a cyanosilane appeared in 1941 when Emelius described the reaction of gaseous iodosilane, H_3SiI, with solid silver cyanide under

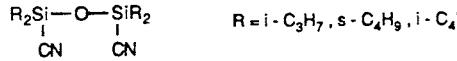
reduced pressure.[15] The product, a colorless solid of mp 34°C, was assigned the structure H_3SiCN. Subsequent syntheses of a variety of silyl cyanides, initially assigned the isonitrile structure, followed this metathetical route (equation 1).



$$R^2R^3R^1Si{-}X + AgCN \longrightarrow R^2R^3R^1Si{-}CN + AgX \qquad (1)$$

Eaborn prepared the first alkyl derivatives, obtaining cyanotriethylsilane (57%), cyanotripropylsilane (50%), and dicyanodiethylsilane (22%) from the corresponding iodides in 1949.[16] A higher yield (90%) was reported for the triethyl derivative in 1950, as was the synthesis of cyanotrimethylsilane (TMSCN, **1**) from the iodide, the sulfide, and the bromide.[17] Using refluxing benzene as a reaction medium, McBride and Beachell[18] obtained TMSCN in yields of 80%, 79.5%, and 14% from the iodide, bromide, and chloride, respectively. Although DuPont workers reported improved yields (38%) from the chloride by carrying out the reaction in an autoclave at elevated temperatures,[19] Evers et al.[20] discovered that the real problem was that TMSCN partially reverts to the chloride when distilled directly from the by product, AgCl. Removal of the latter by filtration prior to distillation resulted in an 86% yield of the desired product. Evans, et al.[5] obtained similar yields in a later modification of this procedure.

In spite of the expense of silver cyanide, its effectiveness made it the reagent of choice for the preparation of cyanosilanes for many years. Muller and Neef[21] used it to prepare ethyldimethyl-, triisopropyl-, tributyl-, and triisobutylcyanosilanes, as well as the bis(dialkylcyano)disiloxanes **2**, from the iodides. Other



$R_2Si(CN)-O-Si(CN)R_2$ $\quad R = i\text{-}C_3H_7, s\text{-}C_4H_9, i\text{-}C_4H_9, C_6H_{11}$

2

cyanosilanes prepared using silver cyanide as reagent include methylcyanosilane,[22–24] cyanodimethylsilane,[25] *t*-butylcyanodimethylsilane,[26] cyanotributylsilane,[27] dicyanodiphenylsilane[28], cyanodiphenylmethylsilane,[26] cyanodimethylphenylsilane,[28] cyanotriphenylsilane,[28] dicyanodimethylsilane,[29] and pentamethyldisilanyl (and higher polysilanyl) cyanides.[30,31] Analogous techniques have been used to prepare the related organogermyl and tin cyanides.[26,32,33]

As a final simplification of the silver cyanide synthetic route, Ryu et al.[34] employed a Soxhlet extractor as the reaction vessel, thus eliminating the need for a filtration step, and obtained dicyanodimethylsilane (85%) and TMSCN (74%) from the corresponding chlorides.

Although cyanotrimethylsilane was reported as a by-product of the interaction of chlorotrimethylsilane, acetonitrile, and sodium,[35] the first systematic search for alternative synthetic methods for organosilyl cyanides was that by the DuPont workers in 1958.[19] Moderate yields were obtained from the reaction of

chlorotrimethylsilane with potassium mercuricyanide in DMF, from the reaction of hexamethyldisilazane with hydrogen cyanide, from the reaction of methoxytriethylsilane with pivaloylcyanide in the presence of aluminum chloride, and from cyanide exchange between chlorotriphenylsilane and cyanotriethylsilane. The first of these procedures was later modified to prepare *t*-butylcyanodimethylsilane.[36] In 1959, TMSCN was prepared in 63% yield on a two-mole scale by reacting a diethyl ether solution of TMCS and HCN with a lithium dispersion in petroleum ether.[20] A modification of this process was later patented.[37] Utilizing preformed lithium cyanide (from LiH and HCN), Evans et al.[5] improved the yield to the 71–84% range. Recognizing the problems associated with the handling of HCN, Livinghouse[38] obtained LiCN from the reaction of acetone cyanohydrin and LiH, and subsequently prepared TMSCN in yields of 59–82%. Thallium(I) cyanide, prepared from the corresponding phenoxide and HCN, reacts with TMCS to produce **1** in 84% yield.[39] Amine bases have also been utilized in the reaction of halosilanes and HCN.[40–42] Reaction of anhydrous HCN with 4-dimethylaminophenyltrimethylsilane at 50°C produced **1** in 88% yield.[43]

Cyanosilanes have been prepared by a variety of other reactions. Moedritzer and Van Wazer[44–46] have studied the exchange equilibria between organosilicon dicyanides and tricyanides **3** (cyanates and thiocyanates were also studied) and other organosilicon compounds (equation 2). Equilibrium was established by

$$\underset{\mathbf{3}\ (n=2,3)}{R_{4-n}Si(CN)_n} + R_{4-n}SiX_n \rightleftharpoons R_{4-n}Si(CN)_{n-m}(X)_m \qquad (2)$$

heating various ratios of the starting materials at 50–150°C in a sealed tube and monitoring the reaction by NMR. These exchange reactions allowed the preparation of a number of mixed cyanosilanes containing additional halo, dimethylamino, alkoxy, mercapto, thiocyano, phenoxy, azido, and cyanato substituents. In another example of an exchange reaction, reaction of bis(trimethylsilyl)sulfide with dicyanodimethylsilane yielded 72% TMSCN along with a quantitative yield of dimethylcyclosilthianes.[47] Cyanotriethylsilane has been obtained from the reaction between mercuric cyanide and bis(triethylsilyl)mercury[48] or chlorotriethylsilane.[49] Interaction of mercuric cyanide with *n*-heptylsilane produced cyano-*n*-heptylsilane in 44% yield.[50] Cyanotrichlorosilane has been prepared by reaction of hexachlorodisilane with mercuric cyanide[51] or by gas phase reaction of trichlorosilane with cyanogen chloride in the presence of triethylamine.[52] Attempted extension of the latter reaction to trimethylsilane or trifluorosilane failed. Reaction of silyl enol ethers with cyanogen bromide produced TMSCN along with high yields of the corresponding α-bromoketones.[53] Upon attempted C-silylation of phenylacetonitrile and allylcyanide with the TMCS/Li/THF system, Calas obtained complex product mixtures including TMSCN (40% and 30%, respectively).[54] TMSCN has been observed as the by-product of photosubstitution of *o*- and *p*-dicyanobenzenes by allylic and benzylic silanes.[55] Reaction of isonitrile **4** with

heterocumulenes **5** produced **1** in 86% and 29%, respectively, along with other products (equation 3).[56]

$$\underset{4}{(TMS)_2N{-}NC} + \underset{5\ (X = O,\ NTMS)}{TMS{-}N{=}S{=}X} \longrightarrow TMSCN + products \qquad (3)$$

As part of a general study on the utility of cyanide salt **6**, Parker observed quantitative conversion of bromotrimethylsilane into **1** by reaction with **6** for 1 h at room temperature in dichloromethane.[57]

$$\underset{6}{Ph_3P{=}\overset{+}{N}{=}PPh_3\ CN}$$

Reaction of trimethylsilylisoselenocyanate with triphenylphosphine yields **1**,[58,59] while TMCS reacts with potassium tellurocyanate to give **1** as the only organometallic product.[59]

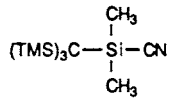
Recent syntheses of cyanosilanes generally involve reaction of a chlorosilane with a more conveniently handled cyanide source, usually an alkali metal cyanide (equation 4). In an early report, KCN and TMCS were heated at 400°C in a

$$R^2{-}\overset{\overset{R^1}{|}}{\underset{\underset{R^3}{|}}{Si}}{-}Cl + \underset{(M = Na,\ K)}{MCN} \longrightarrow R^2{-}\overset{\overset{R^1}{|}}{\underset{\underset{R^3}{|}}{Si}}{-}CN + MCl \qquad (4)$$

LiCl/KCl melt to produce TMSCN in 80% yield.[60] Crown ether-mediated phase transfer catalysis has been utilized in a number of synthetic procedures leading to cyanosilanes. In the first report, Durst and co-workers used methylene chloride as solvent to obtain **1** in moderate but practical yield (45%).[61] This procedure was later modified for the preparation of *t*-butylcyanodimethylsilane in 75% yield.[62] Reaction of chlorotri-*t*- butylsilane with KCN/18-crown-6 in refluxing toluene led to the cyanosilane in 66% yield.[63] Other methods of attempted preparation of this highly hindered cyanosilane failed. Dimethylsila-17-crown-6/KCN in acetonitrile at room temperature produced **1** in 85% yield.[64] Finally, crown ethers have been shown to influence the reaction of KCN with bis(triethylsilyl)mercury, producing cyanotriethylsilane in 38% yield.[65]

Currently preferred routes, however, utilize a high boiling, dipolar, aprotic solvent, typically N-methylpyrrolidinone, from which the product can be distilled directly. In initial reports, Rasmussen and Heilmann obtained a 71% yield of **1** using excess KCN,[66] while Hünig and Wehner obtained 60–70% yield from excess NaCN in the presence of a catalytic amount of a quaternary ammonium salt.[67] A Japanese patent claimed 42% yield using N,N'-dimethylimidazolidinone as solvent.[68] Further improvements on these methods have been reported subsequently. Catalysis of the reaction by a heavy metal cyanide (copper(I) cyanide, copper(II)

cyanide, or zinc cyanide),[69] or by an alkali metal iodide[70-72] reportedly allowed utilization of equimolar amounts of alkali cyanide to TMCS and shorter reaction times, and resulted in yields of >90%. The latter of these procedures undoubtedly involved the intermediacy of iodotrimethylsilane.[70] Reaction of KCN with bromotrimethylsilane in DMF (2.5 h, 25°C) gave **1** at 80% yield.[73] Alternatively, impregnation of the alkali metal cyanide on Amberlite XAD resins afforded rapid reaction rates and high yields of a variety of cyanosilanes.[74,75] Another recent alternative is the use of tetraethylammonium cyanide, which was efficacious in the preparation of tri(*t*-butoxy)silyl cyanide/isocyanide from the corresponding chloride.[76] Rapid reaction rates have also been obtained by the use of bis(trimethylsilyl)sulfate instead of TMCS.[77–80] The very hindered cyanosilane **7** may be prepared by direct nucleophilic displacement of iodide from the corresponding iodosilane using KCN in refluxing methanol or acetonitrile.[81]



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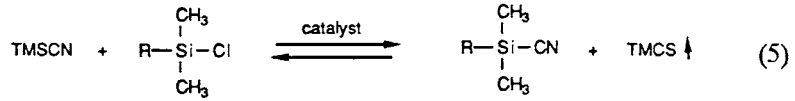
In a few instances, TMSCN (**1**) has been utilized as the starting material to prepare other cyanosilanes. Subsequent to the original report of this procedure,[19] it was utilized to prepare *t*-butylcyanodimethylsilane in 77% yield.[82] In a patented process, dicyanodimethylsilane was produced in 85% yield from the corresponding chloride and **1** in the presence of zinc chloride catalyst.[83] Yields of 90–100% were reported for the synthesis of *n*-butyldimethylsilyl, *t*-butyldimethylsilyl, and phenyldimethylsilyl cyanides using fluoride ion catalysis.[84] These reactions involve equilibria (equation 5), and in many instances were driven to completion by



(5)

distillation of the TMCS by-product as it was formed. Mai and Patil found that LiCN, prepared by reaction of **1** with butyl lithium, reacted with a variety of chlorosilanes to give good yields (58–76%) of the corresponding cyanides.[85]

2.2 Structure and Properties

2.2.1. Spectral Studies

As indicated above, early workers in the area of cyanosilanes referred to these compounds as organo(iso)cyanosilanes.[16–18,22,25,28,86] This interpretation was based largely upon a comparison of physical properties of the silanes and those of

analogous organic nitriles and isonitriles with the same properties of the corresponding iodides. Early chemical evidence also pointed to the existence of the isonitrile isomer, particularly the formation of isonitrile complexes upon reaction with metal carbonyl compounds (see Section 4.1.1.). By 1958, evidence began to accumulate indicating that the "normal" nitrile structure was the predominant form. Bither et al.,[19] using variable-temperature infrared analyses, proposed the existence of a reversible equilibrium between the two forms with the normal form predominating at room temperature. An examination of natural abundance ^{13}C and ^{15}N isotopic shifts in the CN stretching frequency was cited as clear evidence of the normal cyanide structure.[87] This evidence was not convincing to some,[88,89] however, while Raman spectroscopic studies were inconclusive.[90] Whereas general NMR studies of substituent effects on ^{13}C–H coupling constants did not comment on the structure of cyanotrimethylsilane,[91,92] Ebsworth and Frankiss[93] reported a detailed NMR study of the series, $H_nSiMe_{3-n}CN$ (n=0–3). Chemical shifts, ^{13}C–H and ^{29}Si–H coupling constants, and the absence of ^{14}N–H coupling all provided evidence for the normal nitrile structure, a fact which had earlier been confirmed by infrared[94] and by microwave spectroscopy[95,96] for H_3SiCN. IR and Raman studies of cyanopentamethyldisilane and higher cyanopolysilanes were interpreted to be consistent with the normal cyanide as being the major isomer.[97] Infrared spectral shifts due to hydrogen bonding of **1** with phenol provided further support for the nitrile structure.[98] Additional hydrogen-bonding studies have been reported subsequently.[99,100]

It is now generally accepted that Booth and Frankiss[101,102] provided the first unequivocal evidence for the trimethylsilyl cyanide/isocyanide equilibrium (equation 6). A variable-pressure IR study of TMSCN vapor clearly established the

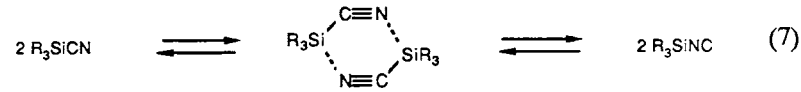
$$(CH_3)_3Si{-}CN \rightleftharpoons (CH_3)_3Si{-}N{=}C: \qquad (6)$$

existence of a minor component, to which was assigned the isonitrile structure. Subsequent synthesis of ^{13}C and ^{15}N enriched **1**, and a detailed study of the isotopic shifts in the IR spectrum provided strong confirmation of this assignment. A variable-temperature IR study allowed estimation of $\Delta H^\circ = 16.75 \pm 0.17$ kJ·mol^{-1} and $\Delta S^\circ = +2.34$ J·K^{-1}mol^{-1} for the equilibrium depicted in equation 6. This allowed the estimation that 0.15 mol % of the isonitrile is present in the mixture at 25°C, an estimate which was later confirmed by Seckar and Thayer.[103] A complete vibrational assignment for TMSCN was also provided, including the assignments for the cyano (2198 cm^{-1} in the vapor, 2190 cm^{-1} in the liquid state) and the isocyano (2095 cm^{-1} in the vapor, 2100 cm^{-1} in the liquid) stretches.[102] Others have reported similar assignments.[104] Detailed IR spectra of other hydrosilanes and cyanosilanes have been published.[105]

Subsequent studies have confirmed the conclusions of Booth and Frankiss. Muller and Neef,[21] on the basis of IR studies of a series of trialkylsilyl cyanides, concluded that chain length and/or branching had little or no effect upon the position of equilibrium. On the other hand, siloxanes **2** contained significantly more

of the isonitrile form at room temperature. Additional studies on H_3SiCN,[106] on cyanotriphenylsilane,[107] and on cyanodimethylsilane[108] showed no evidence of the isonitrile isomer, while Cl_3SiCN displayed a weak IR absorption at 2086 cm^{-1},[109] thus providing additional evidence for substituent effects upon the position of the equilibrium. Durig and co-workers[110] estimated, on the basis of microwave spectroscopy in the gas phase, the presence of 5.3% of the isonitrile form in equilibrium with **1**. A more recent reinvestigation has now indicated that the original estimate was too high and that <0.3% of the isonitrile is actually present.[111] An IR bandshape analysis[112] and reorientational and vibrational correlation functions[113,114] have been determined for liquid TMSCN.

In terms of the mechanism of the nitrile/isonitrile interconversion, a bimolecular intermediate was originally proposed (equation 7).[19] In support of this

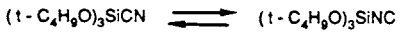


(7)

idea, extensive literature exists which documents bimolecular exchange reactions of cyanosilanes with other silyl halides and pseudohalides (see section 2.1.). ^{14}CN-labeled **1** was shown to undergo complete scrambling with unlabeled cyanotributylsilane within 30 min at room temperature in decalin solution.[27] On the other hand, exchange between **1** and $Et_3Si^{13}CN$ in 1-chloronaphthalene was incomplete after 5 days at room temperature, although exchange was rapid (30 min) at 100°C.[103] In NMR spectral studies, the observation of couplings across the Si–C bond in cyanosilane and TMSCN have shown that if intermolecular exchange occurs, it is not fast on the NMR time scale.[115] The collapse of coupling in CH_2Cl_2 solutions upon standing at room temperature, however, led to the proposal that reaction with polar solvents or with impurities might influence intermolecular exchange. Such an effect might provide an explanation for some of the apparent inconsistencies described above.

A careful kinetic analysis of thermal IR data on the nitrile/isonitrile rearrangement has led Seckar and Thayer[103] to conclude that the reaction was in fact first-order, not second-order as would be expected according to equation 7. Thus, rearrangement may simply involve intramolecular migration of silicon from nitrogen to carbon. The ease of this interconversion as compared to that in analogous carbon compounds, where it is also known to occur, probably explains a number of the transformations and reactions observed in the organosilicon series.[58,103]

Recent work has shed new light on the nitrile/isonitrile equilibrium and on the reactivity of the two species. Hertler et al.[76] have prepared and were able to separate



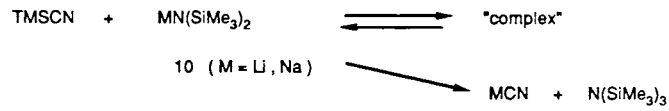
8a **8b**

tri(*t*-butoxy)silyl cyanide **8a** and -isocyanide **8b**. Equilibration in this case occurred with a half-life of about 3 months, which allowed independent study of the reactivity of the two isomers. The isocyanide was found to be much more reactive in the silylation of acetic acid. Isonitrile **8b** also underwent coordination with ethylenebis(triphenylphosphine)platinum, whereas **8a** appeared to be unreactive. Degenerate cyanide exchange was readily observable for TMSCN and for triisopropylsilyl cyanide with tetraethylammonium cyanide, as evidenced by a single time-averaged CN resonance in the respective ^{13}C NMR spectra.[116] Although similar exchange with **8a/8b** was too slow to be observed on the NMR time scale, exchange of $C^{15}N$ was complete over a 3-h period. Exchange appeared to occur via a pentacoordinate cyanosiliconate. Tetrabutylammonium dicyanotrimethylsiliconate **9** was isolated as a relatively unstable crystalline solid.[116]

$$Bu_4N^+\ Me_3Si(CN)_2^-$$

9

In studies of the reaction of **1** with sodium and lithium bis(trimethylsilyl)amide **10**, evidence was obtained for complex formation.[117] Whereas the equilibrium was fast on the NMR time scale for M=Li (leading to a single, averaged signal for the



silyl amide) the spectrum for the sodium salt displayed signals for both free and complexed amide. Increasing the ratio of **10 : 1** led to a longer half-life for the silylation reaction. These observations are analogous to those observed in the group transfer polymerizations catalyzed by $\mathbf{1}/CN^-$ (see Section 3.2.2.), and this "complex" may be another example of a pentacoordinate cyanosiliconate.

The gas phase molecular structure as well as the crystal structure at 140°K of TMSCN has been determined by electron diffraction[118] and by X-ray crystallography,[119] respectively. The crystal structure of dicyanodimethylsilane has also been reported.[29] The molecules are both approximately tetrahedral, and both pack head-to-tail with the nitrogen atom of the nitrile group of one molecule pointing toward the silicon atom of the nearest neighboring molecule, implying a weak interaction.

A number of additional studies have reported NMR parameters of cyanosilanes.[120–122] Typical values relative to tetramethylsilane for **1** are listed in Table I.

2.2.2. Theoretical Calculations

Experimental results on cyanosilanes have been correlated and compared with a variety of theoretical calculations. These studies have centered around bond strengths and stretching frequencies[76,123–126] as well as on molecular

Table I. NMR Parameters for Cyanotrimethylsilane

Solvent	^{1}H	^{13}C *CH3*	^{13}C *CN*	^{29}Si	J_{C-H}(Hz)	*Reference*
CCl_4	0.33s					98
$CDCl_3$	0.27s		126.8	−12.3	122	121
CH_2Cl_2		−1.76		−11.28	121.7	122
C_6H_6	0.069	1.8	126.9	−12.1	122	115
C_6H_{12}	0.27				121.8	93

geometries.[76,127,128] MNDO results for the molecular cations $H_nSi(CN)_{4-n}^{+}$ (n=0–3) have been reported along with those of the parent molecules.[128] Earlier CNDO calculations which predicted cyanosilane, SiH_3CN, to be about 55 kcal/mol more stable than the isocyanide[129] have recently been shown[76] to have significantly underestimated the stability of the latter compound. Ab initio calculations at the SCF level predicted the isonitrile to be slightly more stable than the nitrile; inclusion of electron correlation (MP-2 level), however, predicted the nitrile to be more stable by 7.8 kcal/mol. Likewise, calculations (MP-2) on trihydroxysilyl cyanide, $(HO)_3SiCN$, indicated the nitrile to be more stable by 3.7 kcal/mol. This is in good agreement with the experimentally observed value of 2.6 kcal/mol for the tri(*t*-butoxy)silyl cyanide/isocyanide system.[76] Ab initio calculations have also been reported on pentacoordinate cyanosiliconates,[116] and on monosubstituted silenes including cyanosilene, **11**.[130]

$CH_2{=}SiHCN$

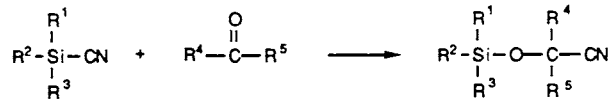
11

3. CYANOSILYLATIONS

3.1. 1,2-Addition to "Simple" Aldehydes and Ketones

3.1.1. Reaction with Preformed Cyanosilanes

General. The 1,2-addition of cyanosilanes to carbonyl compounds, primarily aldehydes and ketones, provides a facile method for the preparation of the corresponding silylated cyanohydrins (equation 8). As correctly pointed out by Evans et al.[5,131] this addition is energetically more favorable than the corresponding reaction with HCN, and has allowed preparation of protected cyanohydrin derivatives from even those substrates which do not react with HCN. Consequently, this transformation has been of tremendous utility in a variety of synthetic schemes,

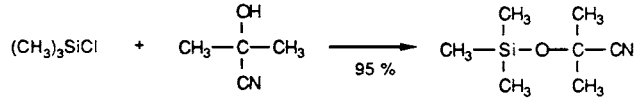


(8)

12

either as a protective strategy for carbonyl groups (which can subsequently be unmasked) or as an efficient route to valuable intermediates for further elaboration.

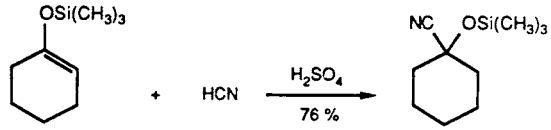
The first reported synthesis of silylated cyanohydrins was that of Frisch and Wolf,[132,133] in which acetone cyanohydrin was reacted with chlorotrimethylsilane, dichlorodimethylsilane, and methyltrichlorosilane in benzene in the presence of pyridine. With the latter two silanes, reaction conditions could be manipulated so



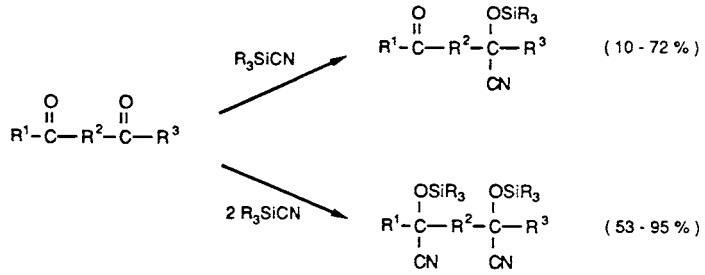
13

as to substitute either one or two of the chlorides. Whereas this procedure can result in high yields of product, it can become cumbersome on a large scale due to the copious amounts of hydrochloride salt which are produced. A convenient alternative appears to be that described by Hall, who obtained a 76% yield of **13** from the reaction of acetone cyanohydrin and hexamethyldisilazane.[134]

A second synthetic route to silylated cyanohydrins involves the sulfuric-acid-catalyzed addition of HCN to O-silylated enolates.[135,136] Moderate to good yields were reported.

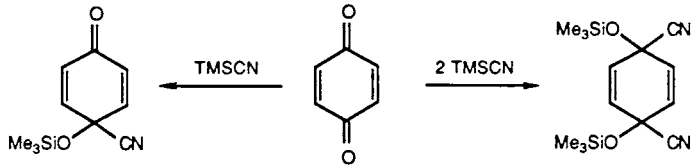


The initial reports of the preparation of silylated cyanohydrins via 1,2-addition of cyanosilanes to aldehydes and ketones (equation 8) appeared in the patent literature.[137–140] Subsequently, reports of the independent investigations by three



groups were published in the open literature in 1973. Neef and Muller[141] detailed the synthesis and characterization of the compounds described in their earlier patents. Good-to-excellent yields were obtained by simply heating the reactants to reflux for 10–18 h. Both 1:1 and 2:1 adducts could be prepared from dicarbonyl compounds by appropriate modification of reaction conditions.

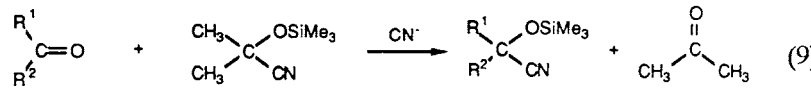
In their studies, Evans et al.[131] reported that silyl enol ether by-products were formed in the uncatalyzed reaction but that these were suppressed in the presence of catalytic amounts of zinc iodide or cyanide ion. The mono- and bis-adducts of *p*-benzoquinone were also prepared. Lidy and Sundermeyer[142] found that



aluminum chloride could be utilized as an effective catalyst, especially for reactions with ketones. Evans et al.[143] subsequently extended their results to a number of additional quinones[143] and ketones.[5] The exclusive formation of 1,2-adducts from α,β-unsaturated carbonyl compounds was also noted.[5,131] In many cases, the silylated cyanohydrin products were formed quantitatively and could be utilized for subsequent reactions without purification. When purification is necessary, the most feasible method is distillation due to the labile nature of the most commonly utilized trimethylsilyl group. This may not be entirely satisfactory, since with higher boiling adducts, partial reversion to starting materials has been noted occasionally.[5,143–145] Use of *t*-butylcyanodimethylsilane was shown to provide chromatographically stable and more hydrolytically resistant products.[36]

Catalysis. Although the early reports showed that silylated cyanohydrins would form in the absence of catalysts, the advantages of catalysis in terms of both reaction rate and yield were quickly realized.[131,142] Catalysis could be accomplished with Lewis acids or with anionic materials, and a variety of either class was shown to be effective. Evans and Truesdale[146] pointed out in 1973 that there appeared to be advantages to the use of the anionic catalysts. Although azide, thiocyanate, and methoxide were also found to be effective, cyanide ion has become the most popular of these anionic materials. Crown-ether complexes of alkali metal cyanides, tetrabutylammonium cyanide, and cyanide bound to tetraalkylammonium ion exchange resins were all reported to be effective.[146] For transcyanosilylations (equation 9), Evans found that cyanide-ion catalysis was much more effective than zinc iodide. For the cyanosilylation of 3-pentanone with **1**, on the other hand, zinc iodide, aluminum chloride, potassium cyanide/18-crown-6, and tetrabutylammonium cyanide were all reported to be of comparable efficiency.

Vyazankin and co-workers have studied the cyanide-catalyzed reactions of pentafluorophenyltrimethylsilane, cyanotrimethylsilane **1**, and cyanomethyl-



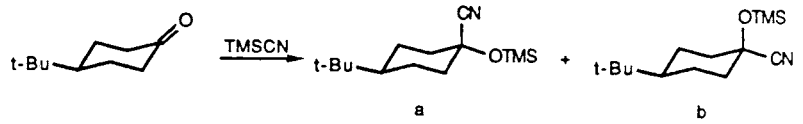
(9)

trimethylsilane with a variety of carbonyl compounds.[147–152] In general, exclusive formation of silylated cyanohydrins was observed in reactions of **1**, even with some highly hindered ketones which would not react with the other two silicon reagents. However, 2,4,6-trimethylacetophenone was transformed into its silyl enol ether in a very slow (6 months) reaction. This was in contrast to α,α,α-trifluoro-2,4,6-trimethylacetophenone, which readily yielded the normal silylated cyanohydrin.[151,152] A review of synthetic uses of organosilicon compounds under nucleophilic catalysis conditions has recently appeared.[153]

Despite the above studies describing the effectiveness of anionic catalysis, zinc iodide has remained the most popular catalyst. For over ten years, only the reactions of *p*-quinones were known to require anionic catalysis.[143] In 1983, Greenlee and Hangauer reported that α-acylaminoketones also failed to react in the presence of zinc iodide but could be readily transformed into the silylated cyanohydrins (81–88% yield, <3 h) in the presence of potassium cyanide/18-crown-6.[154] Interestingly, related BOC-α-aminoaldehydes apparently react with **1**/zinc iodide to produce the silylated cyanohydrins in quantitative yield.[155] Ketones containing other, typically electron withdrawing, substituents were also found to react sluggishly in the presence of zinc iodide.[154] Complexation of the Lewis acid at sites other than the ketone carbonyl was suggested as a contributing factor, although this would not explain the catalyst specificity with quinones. Reaction of 1-benzylimidazole-2-carboxaldehyde with **1**/zinc iodide has more recently been reported to be sluggish, whereas *t*-butylcyanodimethylsilane/potassium cyanide/18-crown-6 works well.[156] In an interesting but related example of cyanide-catalyzed cyanosilylation, 2-acylimidazoles were readily reacted with **1** in the presence of a catalytic amount of *n*-butyllithium.[157] Lithium cyanide is presumably the catalytic species in these reactions. Thus, it now appears that anionic catalysis provides the most general, efficient, and substrate independent method for the 1,2-addition of TMSCN to aldehydes and ketones.

As part of a general investigation of the catalytic utility of protonic acids (e.g., $HClO_4$) generated by electrolysis, Torii et al.[158] reported that cyanosilylation of aldehydes and ketones proceeded in yields of 82–97%. Trimethylsilyl triflate was also described as an excellent cyanosilylation catalyst.[159] Triphenylphosphine has been utilized as a catalyst, although it did not appear to be particularly effective.[160]

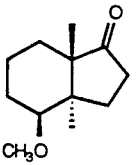
Stereochemistry. As expected, the cyanosilylation of aldehydes and ketones in general produces racemic mixtures of adducts **2** (equation 8). Comments have appeared occasionally, however, regarding the stereochemical course of the addition to certain conformationally rigid substrates. Evans et al.[5] initially reported that 4-*t*-butylcyclohexanone produced a 90 : 10 mixture of isomers **a** and **b**. It was postulated that this ratio was the result of kinetic control since equilibration to



a b

a 78 : 22 ratio could be accomplished in the presence of catalytic potassium cyanide/18-crown-6. Additional support for Evans' proposal has been provided by Agami, who has studied the stereoselectivity of the cyanosilylation of the steroidal ketones 4-cholesten-3-one, 4-methyl-4-cholesten-3-one, 2-cholesten-1-one, 1-cholesten-3-one, and 3-cholestanone as catalyzed by zinc iodide.[161] In all cases, predominant formation (75–100% selectivity) of the axial nitrile via attack from the α-face was observed.

Ketone **14**, which reacted stereoselectively with Grignard reagents, was found to exhibit no selectivity in its reaction with **1**.[162] Similar results were reported for diketone **15**.[163] Whereas reaction with sodium cyanide regiospecifically and



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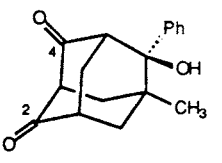

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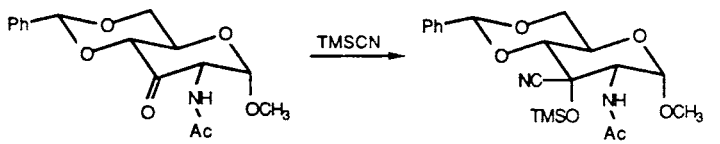
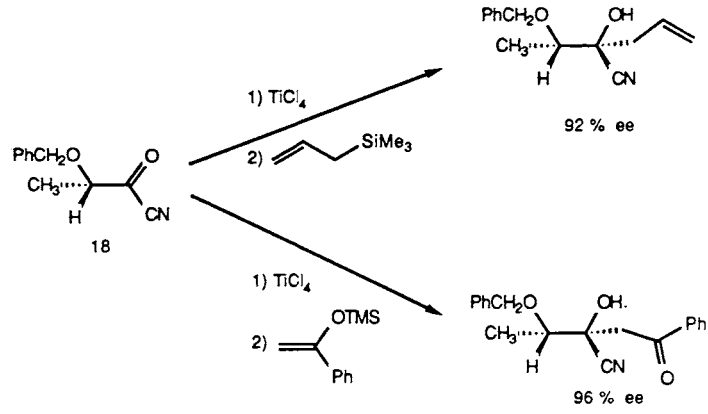
stereospecifically produced the cyanohydrin at position 2 with the nitrile in the axial position, reaction with **1** resulted in loss of stereoselectivity. It is interesting to speculate whether any selectivity would have been observed had anionic catalysts been used rather than zinc iodide, as was the case in both of these examples.

Ketosugar **16** was found to react with **1** in the presence of boron trifluoride etherate to give **17** as the sole isomer in 86% yield.[164]



16 17

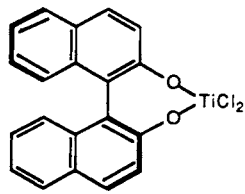
With the recent general advent of effective methodology for chelation-controlled synthesis and chiral catalysis, efforts have been directed toward stereoselective cyanohydrin syntheses as well. Reetz et al.[165] have utilized the chelation of Lewis acids to chiral α-and β-alkoxy acyl cyanides to control asymmetric nucleophilic addition to the carbonyl groups of these substrates. For example, complexation of one equivalent of $TiCl_4$ to acyl cyanide **18**, followed by reaction with allyltrimethylsilane, resulted in isolation, after acidic workup, of the adduct



Scheme 2.

cyanohydrin in 92% ee (98% conversion) (Scheme 2). Similar results were reported for the addition of the silyl enol ether of acetophenone to **18.** These reactions were originally described by Kraus and Shimagaki,[166] who prepared a number of racemic cyanohydrins in 31–92% yield. Presumably, silylated cyanohydrins are the initial products prior to hydrolytic workup. In related studies, a variety of Lewis acids could be utilized for chelation-controlled addition of either TMSCN or *t*-butylcyanodimethylsilane to alkoxyaldehydes, although maximum diastereomeric ratios of 85:15 were obtained.[165]

In the first example of the use of a chiral catalyst for enantioselective trimethylcyanosilylation, chiral boron compounds led to 12–16% enantiomeric excesses of the cyanohydrin derived from 2-methylbutyraldehyde.[167a] In a brief report, the chiral alkoxytitanium and aluminum chlorides **19** and **20** were utilized to prepare



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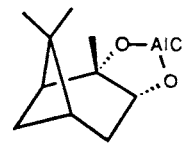
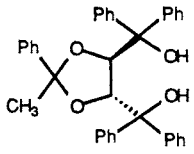


20

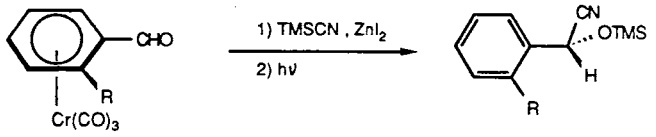
the same cyanohydrin in 82% and 32% ee, respectively.[167b] In a somewhat more detailed study, the chiral titanium reagent derived from diol **21** and dichlorodiisopropoxytitanium was used for the reaction of several aldehydes with **1.**[168] Optical purities of 68–98% were obtained. Similarly, the combination of



21

tetraisopropyltitanate and diisopropyl-L-(+)-tartrate was reported to be useful in converting benzaldehyde to its (R)-(+)-cyanohydrin (94% yield, 93% ee).[169]

Optically pure chiral arenechromium tricarbonyl complexes **22** react with TMSCN **1** in the presence of zinc iodide, followed by decomplexation, to yield the chiral adducts **23** in 94% ee (R=CH_3) and 80% ee (R=CF_3), respectively.[170]

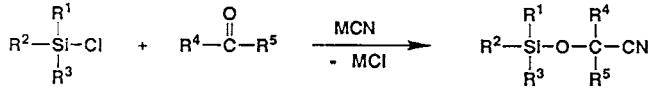


22 R = CH_3, CF_3 23

In a somewhat different approach, Brussee et al.[171] utilized the enzyme oxynitrilase to prepare essentially optically pure cyanohydrins (>98% ee) from benzaldehyde and 4-methoxybenzaldehyde. Silylation with chlorotrimethylsilane or *t*-butylchlorodimethylsilane in the presence of imidazole proceeded in high yield (90–100%) with little or no racemization.

3.1.2. One-Pot Procedures

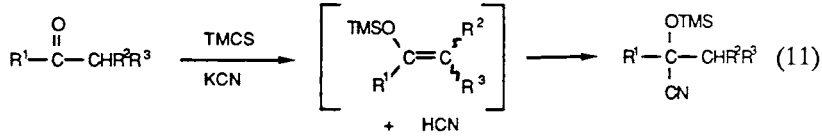
Although the addition of TMSCN (**1**) to carbonyl compounds has provided a general method for the preparation of silylated cyanohydrins, the expense of commercially available **1** (currently $1–2/g) or disadvantages in its modes of synthesis have led to the development of a number of so-called "one-pot" procedures (equation 10). The first such procedure was designed to overcome the fact



(10)

that the reaction of silyl chlorides with silver cyanide is an equilibrium reaction (see Section 2.1). Reaction of an aldehyde or ketone with trimethylsilyl chloride and silver cyanide in the presence of a catalytic amount of aluminum chloride provided the silylated cyanohydrins **12** in 60–85% yield based on silver cyanide[172], as compared with 15–20% yield based on AgCN by the then current two-step methods, i.e., preparation and isolation of the cyanosilane prior to reaction with the

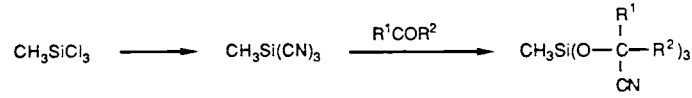
carbonyl component. The results of independent studies showed that inexpensive potassium cyanide (3 equivalents) could be utilized as the cyanide source, providing excellent yields (87–99%) of the adducts **12** in reasonable reaction times.[144,173] The reaction was conveniently conducted at reflux in either acetonitrile in the presence of catalytic zinc salts, or in DMF. With ketone reactants, silyl enol ethers were often observed as by-products when the reaction was conducted in acetonitrile. In DMF solution, silyl enol ether formation was observed only during early stages of the reaction. Further heating resulted in complete conversion to the desired product, possibly due to HCN addition to the carbon–carbon double bond (equation 11). This procedure has been modified by Rawal et al.[174] to provide



(11)

excellent yields of silylated cyanohydrins (86–98% after chromatographic isolation) using hindered silanes. *t*-Butylchlorodimethylsilanes, *t*-butylchlorodiphenylsilanes, and chlorotriisopropylsilanes were effectively utilized for the preparation of silylated cyanohydrins from aldehydes, while ketones again led to silyl enol ether by-products. Crown-ether catalysis of this reaction was not found to be beneficial.[173] A similar result was found employing dichloromethane as solvent in that benzaldehyde was converted to its silylated cyanohydrin in only 60% yield using TMCS/potassium cyanide/18-crown-6.[175]

Duboudin and co-workers[176a] have observed the rapid (about 2 h) and quantitative formation of TMSCN from TMCS and potassium cyanide in acetonitrile in the presence of catalytic amounts of sodium iodide and pyridine (see also Section 2.1.). Addition of a carbonyl compound to this mixture led to rapid formation of the silylated cyanohydrin with no by-products being observed. By this procedure, overall reaction times could be reduced to a few hours at room temperature. In an extension of this method, use of methyltrichlorosilane allowed facile preparation of triscyanohydrins **24**.[176b]



24

Rapid reaction rates and high yields have been reported utilizing two equivalents of TMCS and three equivalents of lithium cyanide in THF.[177] This method was later extended to the synthesis of *t*-butyldimethylsilylated cyanohydrins.[178] Once again, this one-pot procedure was not generally applicable

to ketones, although quantitative conversion of cyclohexanone to its silylated cyanohydrin was noted.

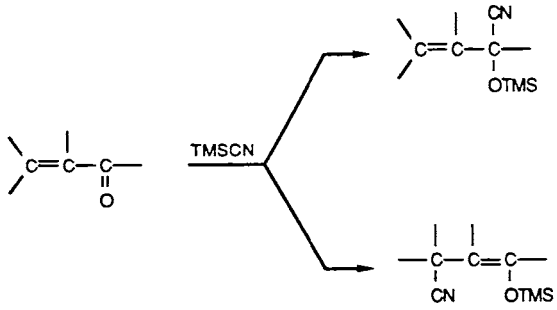
A final one-pot procedure has been reported by Sukata[179] using sodium or potassium cyanide (3 equivalents) impregnated on Amberlite resins. Aldehydes and ketones were readily converted into the corresponding trimethylsilylated cyanohydrins (80–97% yield) by reaction in acetonitrile at 60°C for 4–8 h. Formation of adducts **12** also occurred in other solvents although at much slower rates. Comparison of these rates with the rates of formation of TMSCN from TMCS under similar conditions[74] led the author to postulate that reactions in acetonitrile proceeded via the intermediacy of **1** while those in other solvents involved addition of cyanide to the carbonyl followed by trapping of the cyanoalkoxide with chlorosilane.

3.2. Cyanosilylations of α,β-Unsaturated Carbonyl Compounds

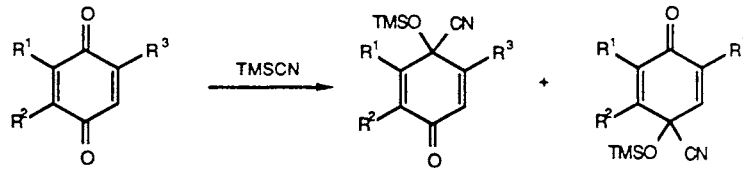
3.2.1. 1,2-Addition

In principle, the reaction of α,β-unsaturated carbonyl compounds with cyanotrimethylsilane **1** might be expected to occur via either 1,2- or 1,4-addition (Scheme 3). 1,4-Addition is the predominate route observed with HCN.[180] As stated previously, however, exclusive 1,2-addition of **1** was observed by Evans et al.[131] This result was confirmed by others for a variety of enones,[5,142,148,158,181,182] acetylenic ketones and aldehydes,[148,149,183] and quinones.[38,143,184] Yields of 1,2-adducts using zinc iodide generally range (with few exceptions) from 80–99%,[131,181,182] whereas the cyanide ion catalyzed reactions with acetylenic substrates were reported to be more variable.

Cyanosilylation of *p*-quinones deserves mention as a special case of 1,2-addition to an α,β-unsaturated ketone (equation 12). Although it was reported that *p*-benzoquinone (**25**, $R^1=R^2=R^3=H$) could be monocyanosilylated at elevated temperatures in the absence of a catalyst,[131] efficient catalysis of this reaction was



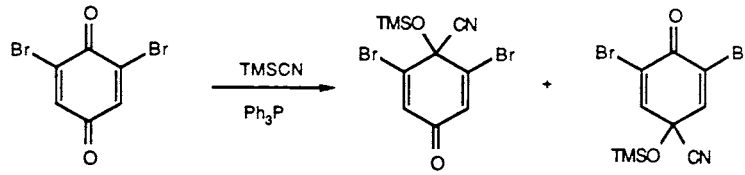
Scheme 3.



(12)

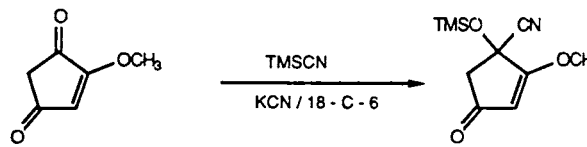
25

found to be restricted to cyanide ion.[143,146] With substituted benzoquinones and naphthoquinones, regioselectivity was quite high, generally leading to 9:1 selectivity for the adduct of the most electrophilic carbonyl group. Steric effects were usually minimal, except with *t*-butyl and isopropyl substituents.[143,185] Subsequent work has verified these early results, and has extended the scope and utility of the reaction[186–189] (see Section 3.4.1.). Similar results have been reported with quinoline and isoquinoline quinones.[184] Reaction of TMSCN **1** with 2,6-dibromo-*p*-benzoquinone **26** is reported to be sensitive to reaction conditions.[190] Adduct **27** was produced in 100% yield in acetonitrile at 0°C in the presence of a catalytic amount of triphenylphosphine. Other solvents or higher temperatures gave a



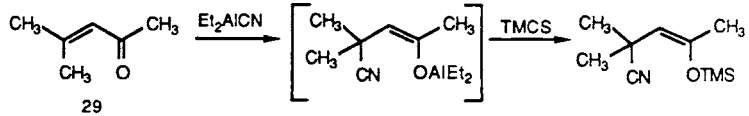
26 27 28

mixture of **27** and **28**, whereas **27** could be isomerized completely into **28** at 40°C in acetonitrile in the presence of the phosphine. In an interesting extension of the quinone reaction, 2-methoxy-1,4-cyclopentenedione has been regiospecifically protected in 91% yield.[191]



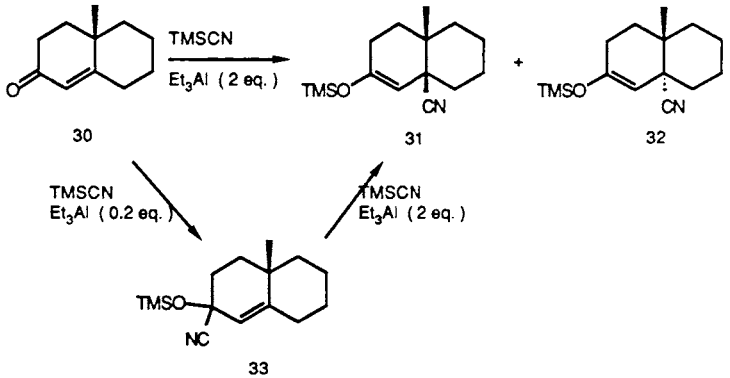
3.2.2. Conjugate Additions

The formal conjugate addition of cyanosilanes to α,β-unsaturated ketones has been accomplished by 1,4-addition of diethylaluminum cyanide (Nagata's procedure[180]) followed by trapping of the aluminum enolate with chlorotrimethylsilane.[192] Formation of β-cyano silyl enol ethers from mesityl oxide **29** and a variety of cyclic unsaturated ketones generally proceeded in good-to-excellent



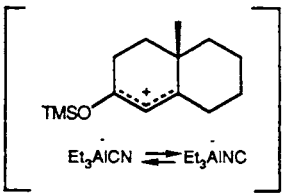
29

yield (80–95%). Utimoto and co-workers[193–195] subsequently reported that similar results could be obtained from the reaction of TMSCN and unsaturated ketones in the presence of a variety of Lewis acid catalysts in THF or toluene solution. These conjugate additions of **1**, however, require somewhat special conditions. For example, formation of 1,4-adducts **31** and **32** from ketone **30** required the use of



30 31 32 33

excess cyanosilane (2.2 equivalents) and "catalyst" (2.0 equivalents of Et_3Al or 3.1 equivalents Et_2AlCl). Reaction in the presence of 0.2 equivalents Et_3Al led exclusively to the 1,2-adduct **33**, which could be converted to the 1,4-adduct by treatment with additional **1** and Et_3Al. Attempted isomerization in the absence of **1** led to a complex mixture. Thus, the 1,2-adduct has been proposed to be the initial product which subsequently rearranges in the presence of excess **1** and Et_3Al via **34**. Reaction time, temperature, and solvent influence the ratio of the 1,4-adducts, with **31** apparently being the thermodynamic product. A variety of other Lewis



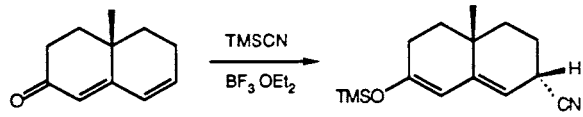
34

acids (aluminum chloride, boron fluoride etherate, tripropylboron, trimethylsilyl triflate, zinc iodide, and stannous chloride) were found to produce a 40 : 60 mixture of **31/32** when employed at a <0.1 equivalent level.[194] Although the reaction appeared to be fairly general with cyclic unsaturated ketones, several acyclic

aldehydes and ketones, with the exception of mesityl oxide, produced only 1,2-adducts. Unfortunately, attempted reaction with similar acyclics was not attempted via the diethylaluminum cyanide/TMCS procedure[192] so that a direct comparison of the two processes cannot be made. In a modification of Utimoto's procedure, hexane solvent was stated to give better results in the 1,4-addition of **1** to cyclopentenone.[196]

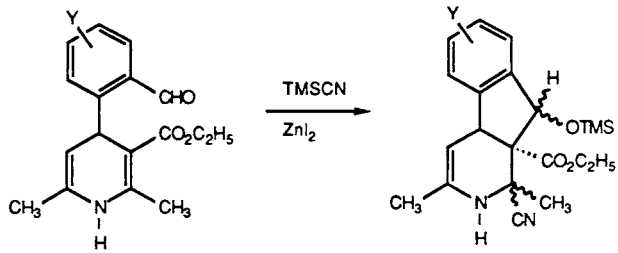
Conjugate addition of TMSCN to a cyclic vinylogous lactone in the presence of boron fluoride etherate proceeded in high yield and stereoselectivity and was a key step in the synthesis of (+)-benzoylpedamide.[197] Exclusive conjugate addition has also been observed in the reaction of 4,4-dimethyl-1-cholesten-3-one with **1** in the presence of zinc iodide.[161]

One example of 1,6-addition of TMSCN has been reported. Dienone **35** was quantitatively transformed into adduct **36** in the presence of boron fluoride etherate whereas other conditions and catalysts led to lower yields or mixtures of **36** and 1,2-adduct.[193,194]



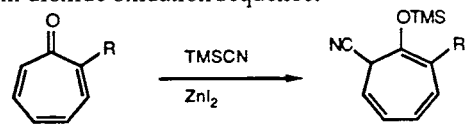
35 36

A fascinating example of 1,7-addition has been observed with the benzaldehydes **37** (Y=H, F, Cl, Br, CF_3, NO_2), producing the ring-closed products as a mixture of two readily separable isomers.[198]



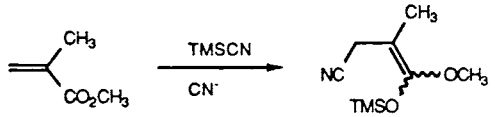
37

Tropone and 2-phenyltropone react with cyanotrimethylsilane to give the products of apparent 1,8-addition **38** in 54% and 59% yield, respectively.[199] These products could be converted to the corresponding 2-cyanotropones via a hydrolysis/selenium dioxide oxidation sequence.



R = H, Ph 38

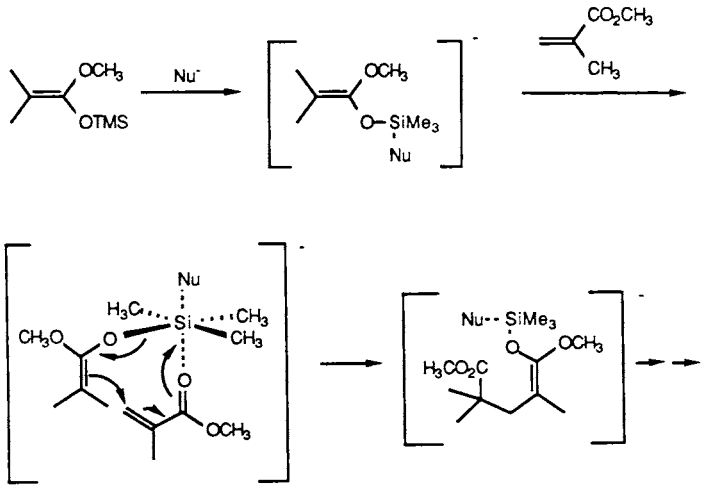
An interesting example of conjugate addition of silyl cyanides, and perhaps the only one involving an ester substrate, is that encountered in group-transfer polymerization, a new polymerization technique introduced by DuPont scientists in 1983. This process involves repeated transfer of a trialkylsilyl group from the growing polymer chain end to the incoming monomer (Scheme 4), and is usually initiated by a trialkylsilylketene acetal in the presence of an anionic or a Lewis acid catalyst. However, the use of other trialkylsilanes as initiators, notably TMSCN, has been exemplified in numerous patents[200–208] and publications. When **1** is used for the initiation of methyl methacrylate polymerization, initial conjugate addition in the presence of cyanide-ion catalyst has been proposed to occur to produce the reactive intermediate **39**.[209–214] NMR kinetic studies have provided some support



39

for this proposal.[210,211] An induction period was observed in these polymerizations, which was proposed to be attributed to strong complexation of the catalyst by **1** (eq 13).

Bandermann and co-workers have reported detailed kinetic studies of these



Scheme 4.

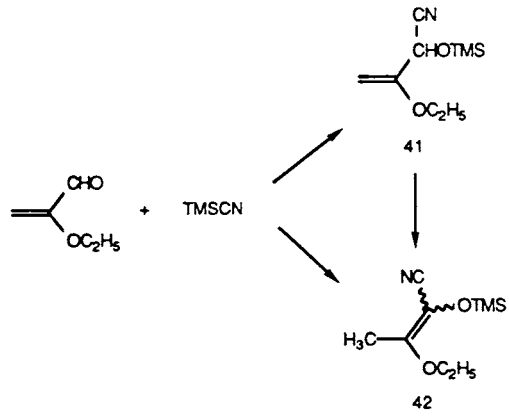
$$(CH_3)_3SiCN + CN^- \rightleftharpoons (CH_3)_3Si(CN)_2^- \quad (13)$$

40

polymerizations catalyzed by cyanide and bifluoride ion.[212,213,215,216] Although the tetrabutylammonium salt of complex **40** has been isolated[116] (see Section 2.2.1.), direct supporting evidence for the intermediacy of **39** has not been published. It has been reported that the cyanosilane initiator can be formed *in situ* by reaction of TMCS and tetraalkylammonium cyanide.[217] A Japanese patent described the *in situ* preparation of an initiator for group-transfer polymerization by reacting a β-diketone or β-ketoester with a base and a silylating agent such as TMSCN.[218] Finally, initial reaction of two equivalents of **1** with α,ω-poly(caprolactone)diacrylate, followed by the addition of methyl methacrylate, allowed preparation of the ABA block polymer, copoly(MMA-b-caprolactone-b-MMA).[214,219]

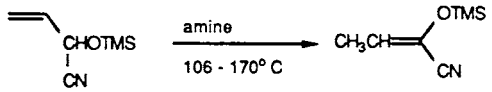
3.2.3. Rearrangement of 1,2-Adducts

Whereas clean formation of 1,2-adducts from α,β-unsaturated ketones and TMSCN is generally seen under normal conditions, anomalous results have occasionally been noted with aldehydes. In a study of the cyanosilylation of 2-ethoxyacrolein, Voronkov and co-workers[220] observed formation of the normal 1,2-adduct **41** in the presence of zinc iodide or freshly prepared $H_2PtCl_2 \cdot 6H_2O$ (Speier's catalyst). An "old" Speier's catalyst (aged for more than 3 months), however, led to formation of rearranged 1,2-adduct **42** (81%). Rearrangement of **41** to **42** could be accomplished by heating (105°C) in the presence of the "old"



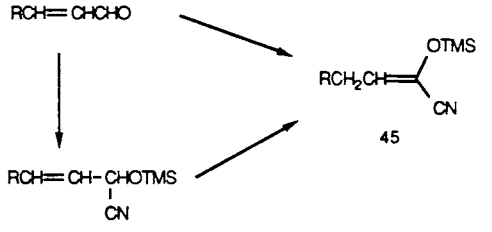
catalyst or by heating alone at 160°C. In a subsequent study, the 1,2-adduct of acrolein was found to isomerize to adduct **43** in the presence of a secondary or

tertiary amine.[221] The formation of a 1 : 1 mixture of conjugated and nonconjugated silylated cyanohydrins from 3-diethylphosphonoacrolein has been noted as well.[222]



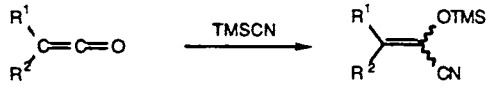
43

Reaction of cinnamaldehyde with **1** catalyzed by potassium cyanide/18-crown-6 was found to produce acrylonitrile **45** (R = Ph),[148] whereas **44** (R = H) rearranged to **45** (R = H) in the presence of potassium *t*-butoxide in HMPT.[72] Hünig and

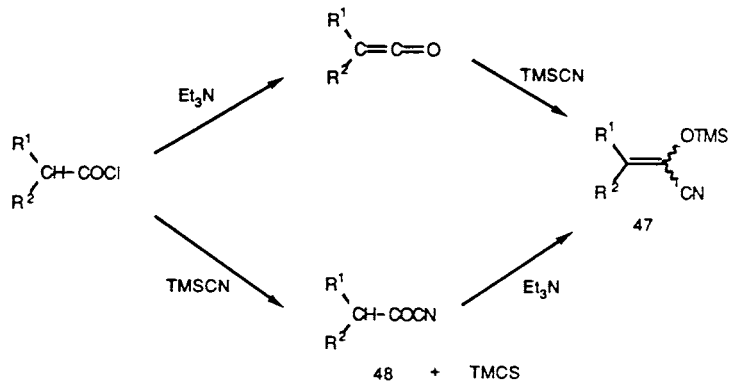


Reichelt[223] later observed rearrangements in the cinnamaldehyde series catalyzed by triethylamine or tetrabutylammonium iodide. Rearrangement of adducts **44** to trimethylsilyloxyacrylonitriles **45** was subsequently shown to be a general reaction.[224] When R is an aromatic group, cyanide ion is sufficient to catalyze isomerization. When R is not aromatic, however, a much stronger base is needed. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was found to be a particularly efficient catalyst for this isomerization, allowing isolation of the products **45** in good-to-excellent yields (68–95%).[224] Thus, proper choice of reaction conditions allows isolation of high yields of either isomer of the carbonyl adduct.

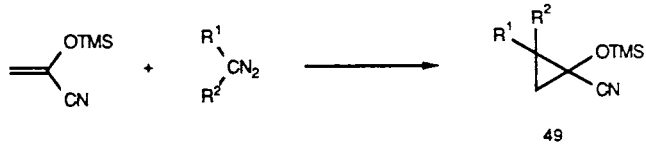
Although α-silyloxyacrylonitriles may be prepared by the rearrangement reaction described above, the first approach to the synthesis of this class of compounds was the 1,2-addition of cyanosilanes to ketenes.[225–227] Adducts **47** were obtained in yields of 60–97% from free ketenes **46** or from ketenes generated *in situ* by dehydrochlorination of aliphatic acid chlorides. This latter route appears, at least in some cases, to involve not only ketenes but also acyl cyanides **48** as intermediates[72] (see Section 3.3.2.). The effect of the substituents on the acidity of the α-proton was found to dictate conditions necessary for the conversion of **48** into **47**. A general approach to **47** (R^1, R^2 = alkyl) was developed which involved



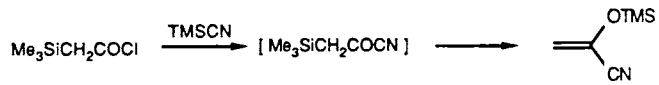
46 47



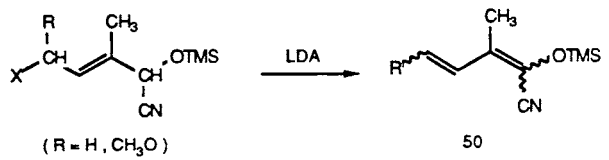
dropwise addition of the mixture of **48** and TMCS to excess triethylamine. A modification of this procedure, utilizing pyridine as the base, has been described as a convenient preparative method for 2-(trimethylsilyloxy)acrylonitrile itself.[228] Reaction of this compound with diazoalkanes provided a convenient route to the silylated cyanohydrins of substituted cyclopropanones **49**,[228] compounds which could not be prepared by other routes.[229]



Trialkylsilyl- and trialkylgermylketenes (**46**, R^1 = R_3Si or R_3Ge; R^2 = H or CH_3) have similarly been transformed into the corresponding adducts **47**.[148,230] Reaction of trimethylsilylacetyl chloride with **1**, however, results in rapid isomerization of the initially formed acyl cyanide.[230]



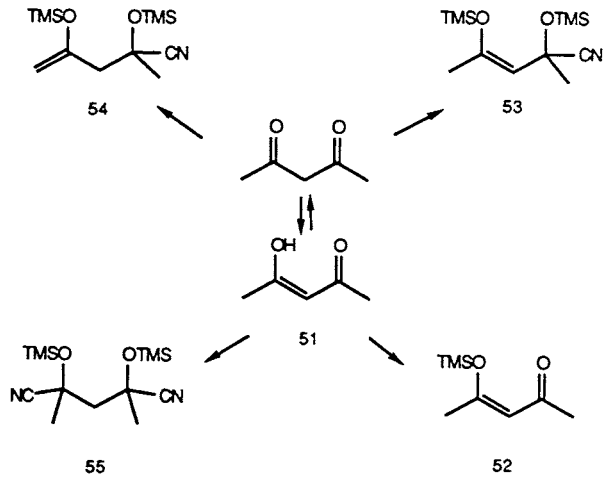
Vinyl substituted 2-(trimethylsilyloxy)acrylonitriles **50** may be prepared via 1,4-elimination reactions.[182]



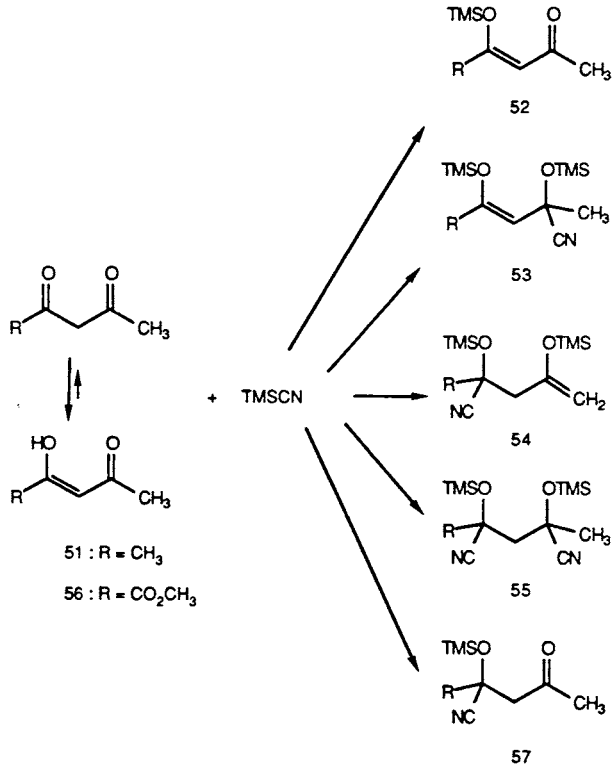
3.3. Cyanosilylation of Other Carbonyl Compounds

3.3.1. Reaction with β-Diketones

The reaction of β-diketones with TMSCN **1** has been known in the literature since the earliest reports on cyanosilylation, yet the mechanistic details of these reactions remained unclear until recently. Neef and Muller[140,141] initially reported that acetylacetone **51** produced silyl enol ether **52** or adduct **53** upon thermal (90°C) reaction with one equivalent or excess **1**, respectively (Scheme 5). Ryu et al.[231] commented that it was not possible to prepare **53** without formation of substantial amounts of isomer **54**. Gostevskii et al.,[149,150] on the other hand, were unable to verify the formation of **54**. In agreement with Neef and Muller, they obtained **52** at room temperature or **53** at elevated temperature in the absence of catalyst. However, **55** was formed in the presence of either zinc iodide or potassium cyanide/18-crown-6 catalysts. Reactions with other β-diketones, 1-phenyl-1,3-butanedione, 1,3-cyclohexanedione, and 5,5-dimethyl-1,3-cyclohexanedione, led to similar results with the exception that the cyclic ketones did not yield products analogous to **53** or **54**.[232] Detailed studies on the course of these reactions and of the reactions of the related substrate, methyl 2,4-dioxopentanoate **56**, have led to a clarification of the reaction mechanism.[233,234] Using ^{1}H NMR, Foley has discovered that in room temperature reactions, the initially formed products, in the presence or absence of catalysts, are the silyl enol ethers **52** and HCN. These products were shown to be in equilibrium with the starting materials. The product actually isolated, however, was dependent upon a number of factors, notably the stoichiometric amount of TMSCN added and the catalyst used. For example, with one equivalent of **1**, zinc-iodide catalysis produced adducts **53** while potassium cyanide/18-crown-6 catalysis led to adducts **57**. With an excess of **1**, additional products such as **55** were formed. The mechanistic sequences have been worked

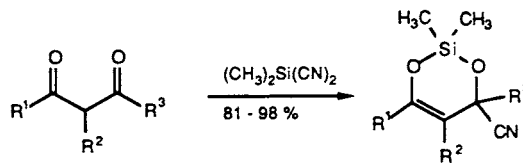


Scheme 5.



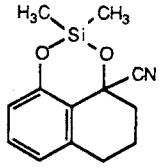
out in detail.[234] These results again emphasize the fact that the two types of catalysis are not equivalent (see also Sections 3.1.1. and 3.2.3.).

Whereas room temperature reactions of **1** and β-diketones do not lead, as discussed above, to adducts of the type **53** in the absence of catalysts, related adducts **58** are readily obtained even at –40°C utilizing dicyanodimethylsilane.[231] When $R^1 \neq R^3$, mixtures of double bond isomers were generally obtained. Adducts **59** and **60** were also obtained from the corresponding phenols in 85% and 62%, respectively.



58

Silyl enol ether **61** was postulated as an intermediate.



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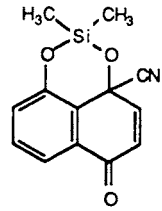
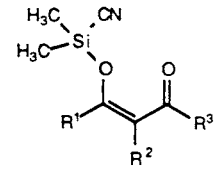
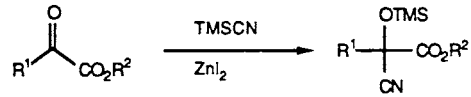


60



61

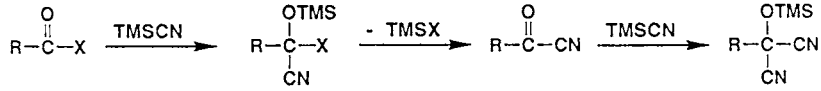
Normal 1,2-addition of TMSCN to a variety of substituted glyoxylic esters has been reported.[235,236]



(R^1 = H, CH_3, Ph)

3.3.2. Addition to Acid Halides

The reaction of carboxylic acid halides with TMSCN has been exploited as a mild, general procedure for the preparation of the corresponding acyl cyanides, a class of highly reactive compounds which are particularly prone to hydrolysis and dimerization reactions.[237,238] Depending upon the nature of the substrate and the reaction conditions, silyloxydinitriles may also be produced. The first reports concerning the reaction of **1** with acid halides were from Sundermeyer and co-workers.[142,239–241] Carbonyl fluoride was converted to fluorocarbonyl cyanide (**64**, R = F) in 26% yield.[239] Phosgene, oxalyl chloride, and trifluoroacetyl chloride,



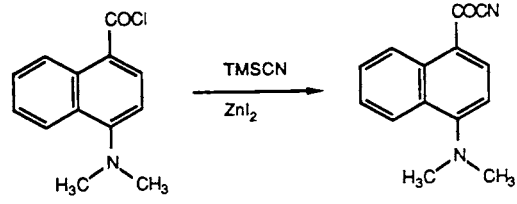
62 63 64 65

on the other hand, produced only bisadducts **65** (R = CN, $C(CN)_2(OTMS)$, and CF_3, respectively), presumably due to the high reactivity of their carbonyl groups.[142] Independently prepared **64**, R = CF_3, was shown to react quantitatively with **1** to produce **65**, R = CF_3.[241] Reaction of acetyl and benzoyl chloride with **1** at reflux in the presence of a catalytic amount of pyridine led to the corresponding malononitriles **65** (65% and 85%, respectively).[240]

More detailed studies of these reactions subsequently led to the development of general syntheses for aliphatic acyl cyanides. Herrmann and Simchen[237] found that the reaction exhibited an induction period, but that this could be eliminated by utilizing a catalytic amount of a halotrimethylsilane in the reaction mixture. The silylated cyanohydrin **63** was postulated as an intermediate. Hünig and co-workers[72,238] found that Lewis acids also catalyzed the reaction. Yields via these

two procedures are generally high, although the reported range is from 33–100%. A 46% yield of **64**, R = pentachloro-1,3-butadienyl, has been reported.[242]

Several aroyl cyanides have been prepared as useful derivatization reagents for chromatographic separation of hydroxyl compounds. Zinc iodide was used as the catalyst in methylene chloride solution at room temperature, allowing preparation of naphthoyl cyanide **66**,[243] 1- and 9-anthroyl cyanides (approximately 80%



66

yields),[244,245] and the racemic and optically pure isomers of 2-methyl-1,1′-binaphthalene-2′-carbonyl cyanide.[246] Ferrocenoyl chloride, on the other hand, yielded only about 20% of the cyanide under these conditions.[247]

Olah and co-workers,[248] citing problems with the zinc-iodide catalyzed procedure and other earlier procedures for the preparation of aroyl cyanides, developed a new, general procedure employing stannic chloride as the catalyst. Reaction in dichloromethane at room temperature for 2 h provided the aroyl cyanides in 80–95% yield.

3-Chloro-2,6-dimethylpropionyl chloride,[249] chloroformates,[240] and carbamoyl chlorides[250] have also been converted to the corresponding cyanides.

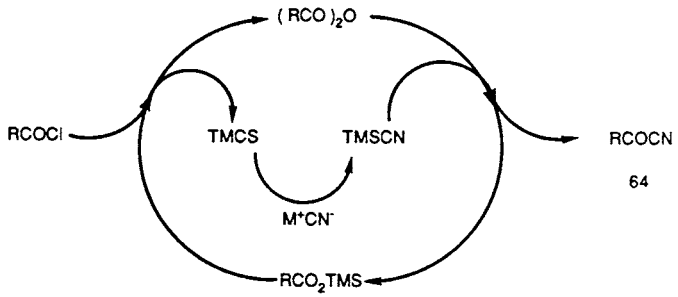
Although a second equivalent of **1** will react with acyl cyanide **64** to produce the dinitrile **65**, this second step is normally much slower than that which produces **64**. In the presence of tetrabutylammonium iodide catalyst, however, rapid formation of **65** was observed, even when only one equivalent of **1** was used.[72,238] Formation of tetrabutylammonium cyanide (equation 14), addition of cyanide to

$$n\text{-}Bu_4N^+I^- + TMSCN \rightleftharpoons n\text{-}Bu_4N^+CN^- + Me_3SiI \qquad (14)$$

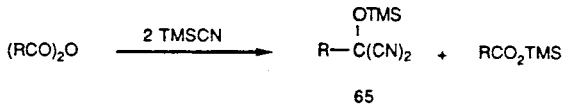
the carbonyl of **64**, and trapping by iodotrimethylsilane were proposed to account for this result.[72] Alternatively, it is conceivable that **64** could be first silylated by the iodosilane followed by trapping by cyanide.

Yamaguchi and co-workers[251,252] have utilized the reaction of aromatic acid chlorides with TMSCN in the presence of pyridine at 120°C to prepare the corresponding silyloxymalononitriles in yields generally exceeding 70% (see also Section 3.4.4.).

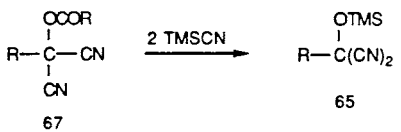
Findeisen and coworkers[253–255] have patented a number of processes for the preparation of acyl cyanides **64** and silyloxymalononitriles **65**, both of which are useful intermediates for herbicide and insecticide syntheses (see Section 3.4.3.). Reaction of carboxylic acid anhydrides with one equivalent of TMSCN provided a general and industrially feasible process for **64** production.[253] The by-product trimethylsilyl ester could be recycled by reaction with the corresponding acid



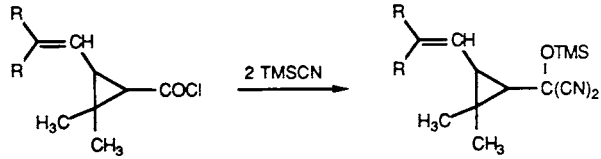
chloride; likewise, recycling of TMCS was possible, thus suggesting the feasibility of continuous processing. This reaction may be catalyzed by Lewis acids or by bases, particularly tertiary amines such as triethylamine or DABCO, leading to product yields in the range of 81–99%. Similarly, reaction of anhydrides with two equivalents of **1** was found to produce dinitriles **65** in excellent yield (78–98%).[254]



Similar advantages of this process to that described above were cited. Lewis acids again were found to be useful catalysts. Finally, improved processes for the preparation of malononitriles have been described.[255] In process *a*, an acid halide was treated with at least two equivalents of TMSCN under such conditions that the TMCS produced was constantly removed from the reaction mixture. Catalysts may be used although this process was preferrably carried out in their absence. Process *b*, a variant of *a*, was conducted by reacting the acid halide with at least an equimolar amount of **1**, removing the TMCS by-product, then treating the acyl cyanide thus formed with additional **1** at a temperature of 10–40°C. Process *c* was identical to process *b* except that the starting material was an acyl cyanide. In a previously unreported reaction, process *d* reacted dimeric acyl cyanides **67** with two equivalents of **1** to give the desired products. Although Lewis acids or bases were optional in all of the processes, DABCO was cited as being particularly advantageous, especially for sensitive substrates, since it considerably lowered the required reaction temperatures.



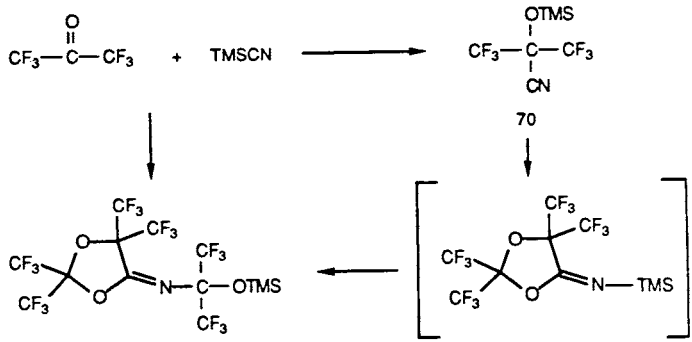
The reaction of cyclopropyl acid chlorides **68**, R = Cl or Br,with TMSCN has been used to prepare malononitriles **69**, which are useful intermediates for the production of insecticides.[256]



68 69

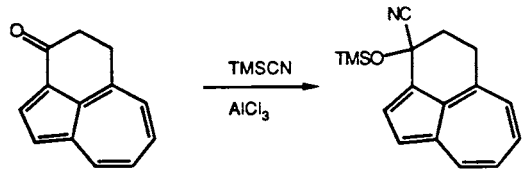
3.3.3. *Miscellaneous*

Reaction of hexafluoroacetone with TMSCN has been found to take an unusual course.[257] In the presence of excess **1**, the unstable 1 : 1 adduct **70** was produced. Excess ketone, on the other hand, led to 3 : 1 adduct **71**. The 2 : 1 adduct **72** was postulated to be an intermediate.



70 71 72

The dark green ketone 4,5-dihydro-3H-benzo[cd]azulen-3-one **73** has been reported to yield silylated cyanohydrin **74** (50%) as a violet colored oil.[258]



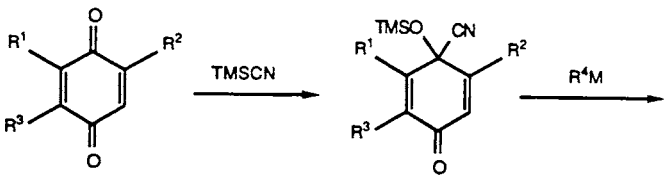
73 74

3.4. Utility of Silylated Cyanohydrins

3.4.1. *Carbonyl Protection*

The use of cyanotrimethylsilane to temporarily block or protect a carbonyl group, thereby allowing functionalization of another site in a molecule, was first described by Evans et al.[143] in connection with the elaboration of some *p*-quinones.

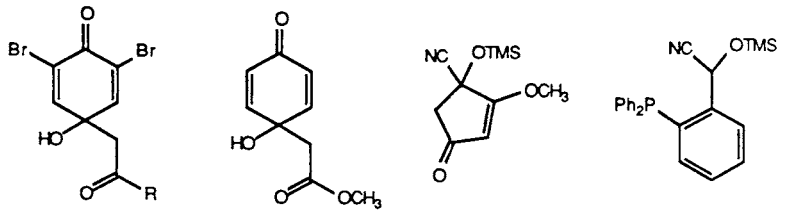
A number of substituted *p*-benzoquinones and *p*-naphthoquinones **75** were found to react cleanly with TMSCN to give good yields (65–100%) of the mono-protected adducts **76** (see also Section 3.2.1). Organolithium and magnesium reagents (R^4M, R^4 = Me, *n*-Bu, Ph) were shown to react selectively with the carbonyl groups of **76** without interferring with the nitrile or silyl ether groups. Desilylation to produce the quinol **77** could be effected in high yield under mild conditions by treatment with silver fluoride in aqueous THF. This methodology has been extended to the



75 76

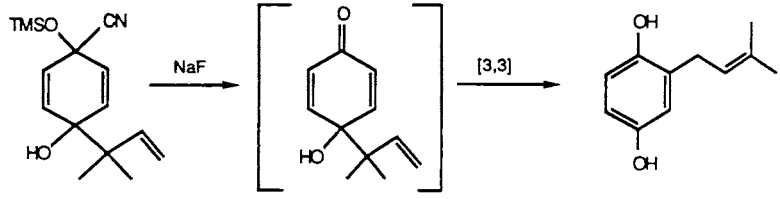
77

reactions of mono-protected quinones with ester and amide enolates for the synthesis of some antibacterial *p*-quinols **78** (R = OEt or NH_2) of marine origin[190] and for the preparation of some *p*-quinol benzoates.[259] The approach has also been utilized in studies directed toward the synthesis of naphthoquinols[189] and in the synthesis of the antitumor agent jacaranone **79**[188] and of (iso)quinoline quinols related to **79**.[184] 2-Lithio-1,3-dithiane, (phenylthio)methyllithium, and (benzyloxy)methyllithium were shown to add efficiently to the carbonyl of **75** (R^1, R^2, R^3 = H).[188] Alkylation of the protected cyclopentanone **80** has been reported,[191] as has the attempted metallation of **81** with $(CO)_5ReH$.[260]



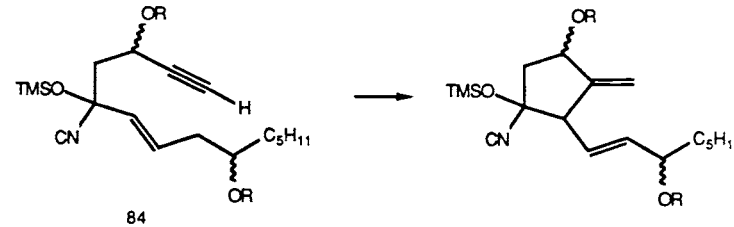
78 79 80 81

In an extension of the above strategy, Evans and Hoffman[186] developed a new procedure for quinone isoprenylation via [3,3] sigmatropic rearrangements of intermediate quinols (e.g., **82** - **83**). In some cases, quinols **82** have been isolated.[187]



82 83

Protection of carbonyl groups as the silylated cyanohydrins prior to other rearrangements have also been reported. Stork and Kraus[261] prepared a prostaglandin precursor via a thermal ene reaction of enyne **84**, and Ziegler developed a new synthesis of δ,ε-unsaturated esters based on the Cope rearrangement of 1,5-dienes such as **85**.[262] Adam et al.[263] found that silylated cyanohydrins of α,β-unsaturated aldehydes exhibited different reactivities and diastereoselectivities in ene reactions with singlet oxygen than did the unprotected aldehydes. For example, although the precursor aldehyde was completely unreactive, **86** reacted readily with singlet oxygen to give a mixture of ene-type products.



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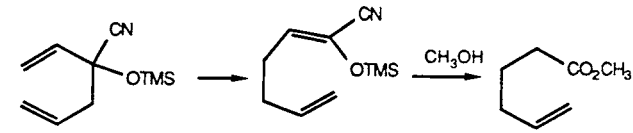

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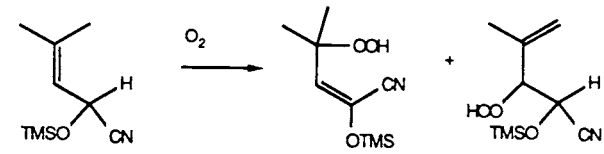
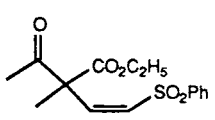


86

In other studies, protection of the ketone carbonyl of β-ketoesters such as **87** prior to desulfurization with aluminum amalgam was necessary for clean reduction,[264] and protected compounds **88** were found to be more reactive toward nucleophiles than the corresponding 2-acylimidazolium salts.[157]



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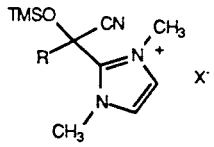
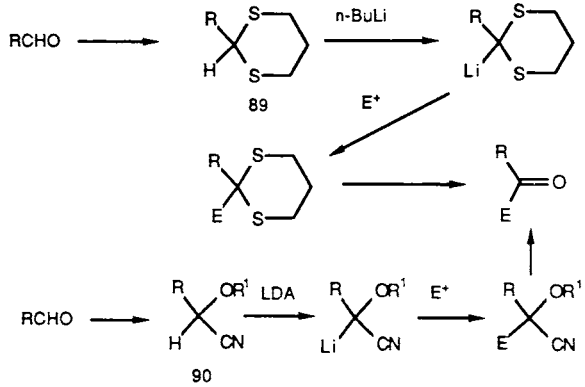


88

3.4.2. Umpolung

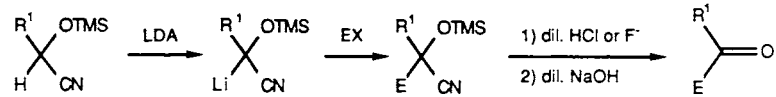
The term "umpolung" was suggested by Seebach[265,266] to describe "reactivity reversal", i.e., transforming a normally electrophilic carbonyl group into a protected or masked form which can subsequently function as a nucleophile. A variety of acyl anion equivalents[267] have been developed, the most common of which are metallated derivatives of 1,3-dithiane **89** and of protected cyanohydrins **90**.[268] Although a number of R^1 groups, including ethoxyethyl and 2-tetrahydropyranyl, have been used for the latter reagents, the trimethylsilylated derivatives (**90**, R^1 = TMS)[269] are certainly among the most useful acyl anion equivalents.



E⁺ = electrophile
LDA = lithium diisopropylamide

Described initially by Hünig in 1973,[270] the utilization of silylated cyanohydrins as umpolung reagents has seen continuous expansion and development. As noted previously, an advantage of the use of cyanotrimethylsilane for the protection of aldehydes and ketones is the facility and high yield of the addition reaction. When the silylated cyanohydrin product is derived from an aromatic, heteroaromatic, or α,β-unsaturated aldehyde, the methine proton is relatively

acidic and can be removed by strong base. Although 1,3-dithiane derivatives **89** may be metallated by treatment with *n*-BuLi, a non-nucleophilic base usually must be used to deprotonate silylated cyanohydrins in order to avoid reaction with the nitrile group. Lithium diisopropylamide (LDA) is the base most commonly used for this purpose. Thus, treatment of the silylated cyanohydrin **91** with 1.0–1.1 equivalents of LDA (usually in tetrahydrofuran (THF) or dimethoxyethane (DME) solution at –78°C) affords the lithiated acyl anion equivalent **92**. This reactive intermediate may be trapped by a variety of electrophiles (EX) to yield the new silylated cyanohydrin **93**.



91 92 93 94

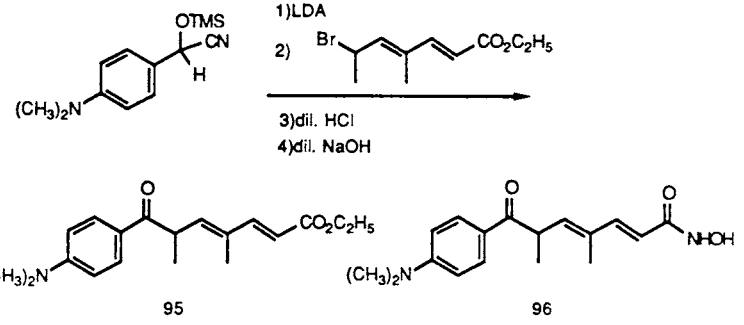
Another real advantage of the use of silylated cyanohydrins as umpolung reagents is revealed in the next step. Removal of the protecting group to give the new, elaborated ketone may be accomplished chemoselectively in high yield and under very mild conditions, by treatment with dilute acid followed by dilute base or with a source of fluoride ion. As noted by the representative examples in Table II, alkylation of **92** to yield ketones worked well when EX (RX in Table II) was a primary or secondary alkyl iodide, bromide, chloride, tosylate, or sulfonate.[270-272] The reaction was also successful when E = *t*-butyl but failed when E = neopentyl or adamantyl. The possibility that these coupling reactions proceed via one electron transfer from **92** to the electrophile followed by radical coupling has been raised.[273]

The above carbon–carbon bond forming reaction has been applied to the

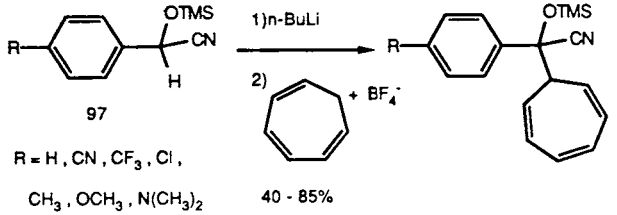
Table II. Alkylation of Anios from Silylated Cyanohydrins of Aromatic Aldehydes[270–272]

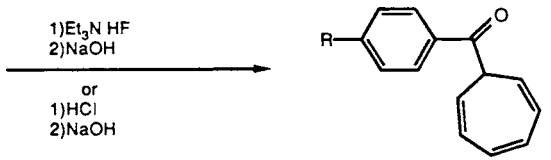
R^1	*RX*	*Yield of* **94** *(E = R), %*
C_6H_5	CH_3I	98
C_6H_5	*n*-C_4H_9Br	72
C_6H_5	C_2H_5OTs	85
C_6H_5	$(CH_3O)_2SO_2$	92
C_6H_5	*i*-C_3H_7I	95
C_6H_5	*c*-$C_6H_{11}Br$	48
C_6H_5	*t*-C_4H_9I	75
m-C_6H_4	$C_6H_5CH_2Br$ (2 equiv.)	52
3-pyridyl	$C_6H_5CH_2Br$	84
2-furyl	CH_3I	92

preparation of elaborated ketone **95**, a precursor to the antifungal natural product trichostatin A (**96**).[274]



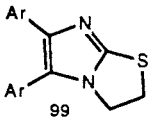
Trapping the anions derived from **97** with tropylium tetrafluoroborate, followed by hydrolysis, generated the 2,4,6-cycloheptatrien-1-yl ketones **98**.[275] Note that in this case, *n*-BuLi was used to metallate the silylated cyanohydrin.





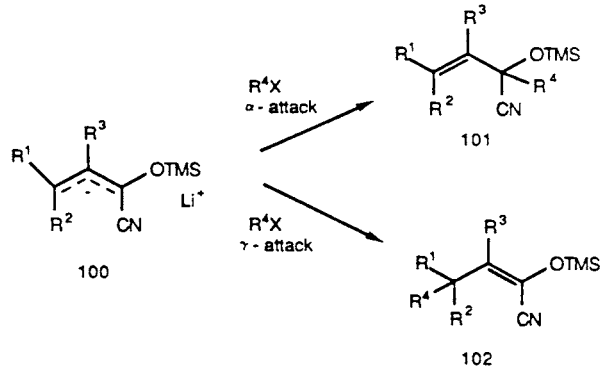
98

Application of the umpolung reactions of **91** (R^1 = Ph, 3- or 4-pyridyl) enroute to substituted 2,3-dihydroimidazo[2,1-b]thiazoles **99** has been described,[276] as have alkylations of **91** (R^1 = 3-thienyl or 2-benzofuranyl) leading to intermediates for the preparation of compounds with antihypertensive activity[277,278] and of **91** (R^1 = 2-pyrazinyl) for the preparation of antifungal agents.[279]



99

As is the case with silylated cyanohydrins derived from (hetero)aromatic aldehydes, those derived from α,β-unsaturated aldehydes (see Section 3.2.1.) may also be smoothly deprotonated by treatment with a strong, non-nucleophilic base and utilized as umpolung reagents. Hertenstein et al.[181,182] have shown that the allylic anions **100** may be effectively trapped with the same types of alkylating



agents that react with anions derived from the aromatic species. In this case, the product that results after deprotection is an α,β-unsaturated ketone. A complication present with the allylic anions **100**, however, is the possibility of alkylation at both the α-site, forming silylated intermediate **101**, and the γ-site, forming product **102**. As indicated in Table III, studies by Hünig and co-workers[223,280,281] have shown that, in most cases, reaction at the α-site greatly predominated over reaction at the

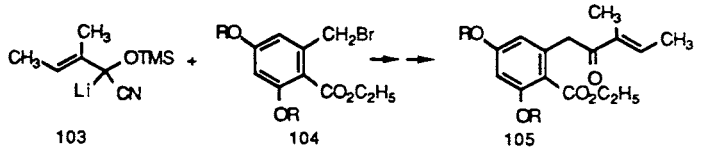
Table III. Alkylation of Allylic Anions **100**

R^1	R^2	R^3	R^4X	**101**, % *Yield*	**102**, % *Yield*[a]
H	H	H	CH_3I	77	—
CH_3	H	H	C_2H_5I	85	—
CH_3	H	H	*i*-C_3H_7Br	78	—
CH_3	H	H	$C_6H_5CH_2Br$	76	—
CH_3	CH_3	H	CH_3I	88	—
C_6H_5	CH_3	H	CH_3I	73	—
C_6H_5	H	CH_3	CH_3I	66	—
C_6H_5	H	H	*i*-C_3H_7Br	80	—
C_6H_5	H	H	CH_3I	45	32
p-$CH_3OC_6H_4$	H	H	CH_3I	77	10
p-ClC_6H_4	H	H	CH_3I	22	29
p-CNC_6H_4	H	H	CH_3I	—	42

[a]The product of γ-alkylation was usually isolated as the amide after treatment of the reaction mixture with aqueous ammonium chloride.

γ-site. Although temperature and leaving group in the electrophile had little effect on the ratio of α/γ alkylation, increasing amounts of γ-alkylation were observed in more polar solvents (DME vs. THF) or upon addition of HMPT, with larger alkali metal ions, and with smaller alkyl groups in the electrophile.

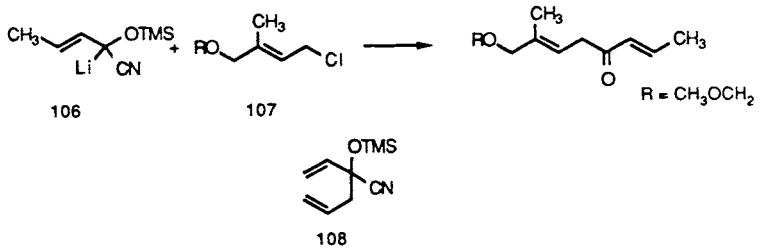
Alkylation of anion **103** with the substituted benzyl bromide **104** has been reported to be a useful approach to dihydroisocoumarin precursors **105**.[282] Addi-



103 104 105

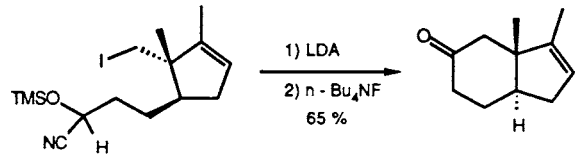
R = MEM (β-methoxymethyl)

tion of anion **106** to allylic chloride **107** was reported as an early step in an approach to the macrocyclic antibiotic kijanolide,[283] and umpolung reactions of **100** (R^1 = R^2 = R^3 = H) with other allylic halides provided 1,5-dienes **108**.[262]



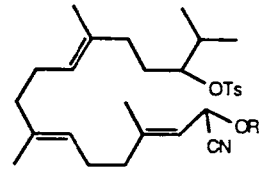
106 107 108

Silylated cyanohydrin carbanions which are not stabilized by an adjacent (hetero)aromatic group or double bond are generally difficult or impossible to prepare and react with electrophiles,[284] although one example of an intramolecular alkylation has been reported as a route to transhydrindenones.[285] The most efficient



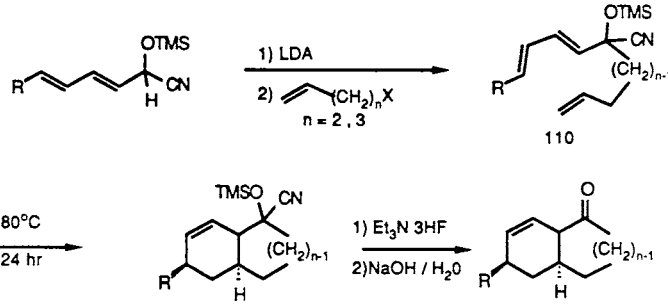
route to other cyanohydrin ethers is often via the silylated cyanohydrin, however, since it may be prepared in high yield and be easily cleaved to the cyanohydrin (see Section 3.4.4.). Reaction of the cyanohydrin with ethyl vinyl ether or dihydropyran then provides the new protected cyanohydrin. This strategy was used in the preparation of an "unstabilized" 2-tetrahydropyranyl cyanohydrin for umpolung alkylation in the synthesis of antihypercholesterolemic agents.[286] It has also been

used for preparation of some macrocycles by intramolecular umpolung reactions in which the anions of the trimethylsilylated cyanohydrins (e.g., **109**, R = TMS) were apparently too labile to survive the reaction conditions (refluxing THF or benzene). Conversion to the ethoxyethyl cyanohydrins (R = $CH(CH_3)OCH_2CH_3$) allowed successful cyclization.[287–289]



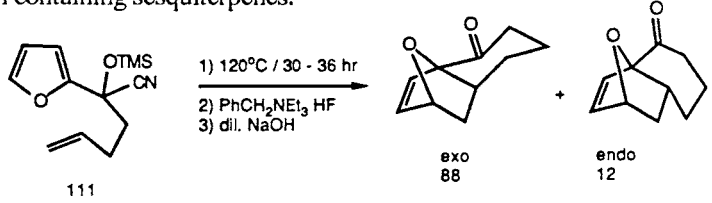
109

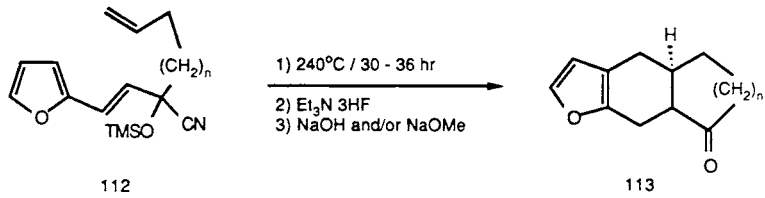
Fischer and Hünig[290] have shown that reactions of lithiated silylated cyanohydrins of dienals with alkylating agents containing a terminal double bond provided products **110**. These adducts contained both diene and dienophilic moieties, and underwent nearly quantitative intramolecular Diels–Alder cycload-



ditions. The carbonyl group was regenerated under very mild conditions, avoiding isomerization of the double bond. Reactions of analogues of **110** ($n = 3$) having an unprotected carbonyl group gave products in which the double bond had migrated into conjugation with the carbonyl group.

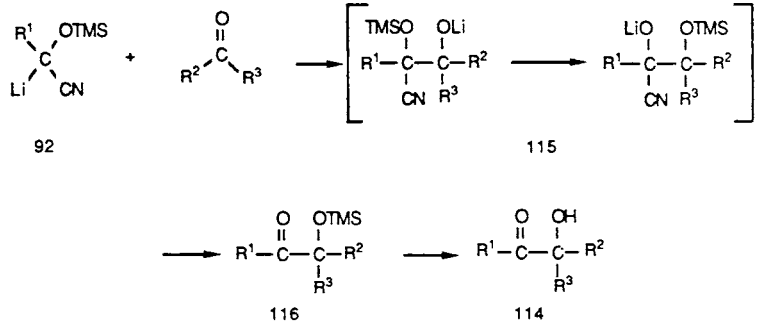
Intramolecular Diels–Alder reactions of the furan containing umpolung products **111** and **112** have also been reported.[291,292] Similar reactions of analogues of **111** containing a free carbonyl group did not proceed. The authors noted that the previously unknown tricyclic ketones **113** could prove very useful in the synthesis of furan containing sesquiterpenes.





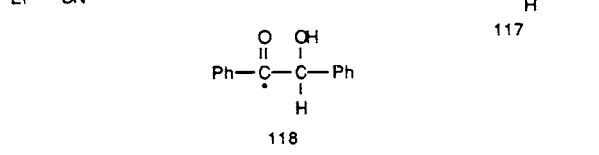
112 113

In addition to reactions with alkylating agents to generate new ketones, additions of the lithiated cyanohydrins **92** to carbonyl compounds have proven to be very useful in organic synthesis for the generation of new α-hydroxy ketones **114.** Extensive studies by Hünig have shown that suitably stabilized anions **92** added readily to ketones and aldehydes to form intermediates **115.** These intermediates underwent a 1,4-shift of the TMS group with subsequent loss of LiCN, providing



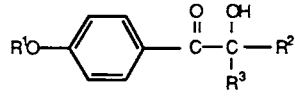
92 115 116 114

protected acyloins **116.**[293–298] Desilylation (dilute acid or base, or fluoride ion) provided the free acyloins **114** in excellent overall yield. For example, addition of the lithiated TMS cyanohydrin of benzaldehyde to various aldehydes and ketones produced the corresponding acyloins in 78–96% yield.[294] This sequence has been used by Bertz[299] for the regiospecific preparation of ^{13}C-labeled benzoin **117.** Although the labeled benzoin was very sensitive to base and heat, the mildness of the deprotection step (aqueous acetic acid) avoided isomerization to **118.** The author noted that isomerization could have been a serious problem if a different acyl anion equivalent (e.g., a dithiane), which would have required more vigorous conditions for deprotection, had been used.



117 118

Since many acyloin ethers are useful photoinitiators for free radical polymerization of vinyl monomers, the umpolung reactions of some substituted benzaldehyde silylated cyanohydrins have been used to prepare the substituted acyloin silyl ethers **119**.[300] These photoinitiators may be incorporated into polymers through copolymerization or hydrosilylation reactions.[300,301]

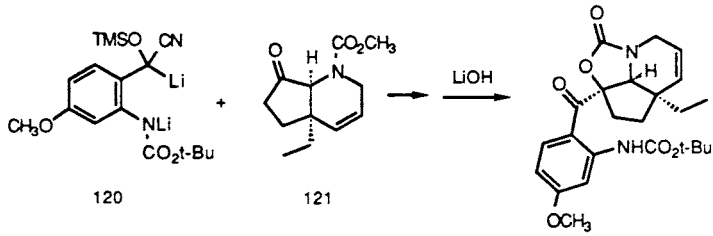


R^1 = CH_2CHCH_2O or $HSi(CH_3)_2OSi(CH_3)_2(CH_2)_3$

R^2, R^3 = $(CH_2)_5$ or Ph, CH_3

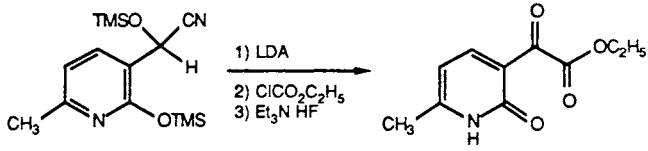
119

In studies related to the total synthesis of some pentacyclic alkaloids, Overman and co-workers[302,303] have reported the addition of **120** to **121** in 80% yield. The authors noted that attempts to add basic nucleophiles to cyclopentanone substrates were often frustrated by the facile enolization of the cyclopentanone. This problem was not experienced with dianion **120**.

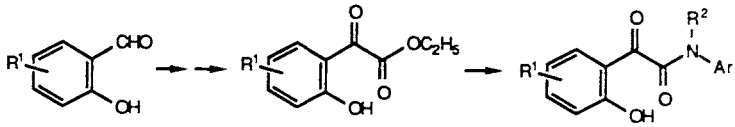


120 121

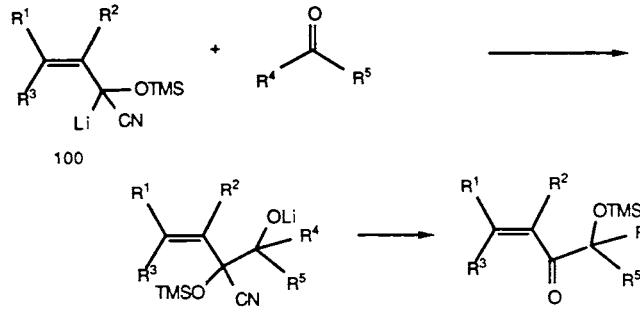
The addition of lithiated TMS cyanohydrins of substituted benzaldehydes to the ketone carbonyl of N-acetyl-4-piperidone has been reported in the synthesis of some analgesic benzazepines.[304,305] Acylation reactions of anions **92** with ethyl chloroformate also proceeded as expected.[306] Similar acylations have been ap-



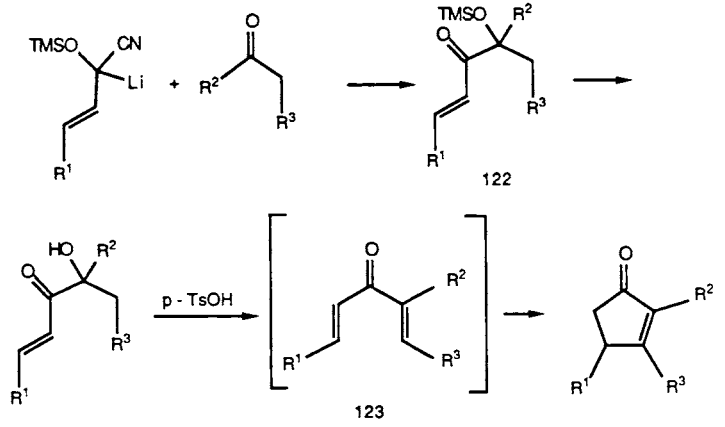
plied to substituted salicylaldehydes to prepare intermediates in the synthesis of lipoxygenase inhibiting (2-hydroxyphenyl)glyoxylamides.[307]



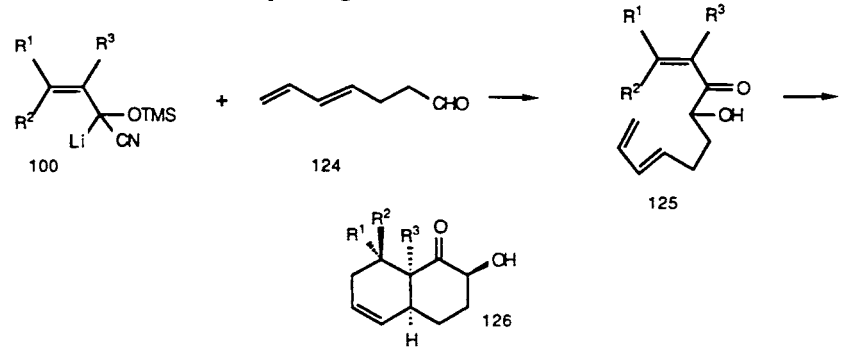
Addition of allylic anions **100** to carbonyl compounds has been reported to occur by predominant, if not exclusive, reaction at the α-position of **100**.[297,308,309] In the isolated products, 1,4-migration of the silyl group was again observed.



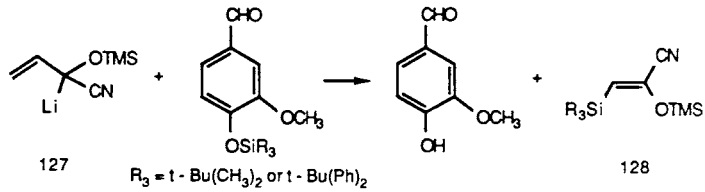
Jacobson and coworkers[308,309] have developed a high-yield process for cyclopentanone annelation based on this reaction. Thus, for example, deprotection of initial adducts **122**, followed by dehydration with *p*-toluene sulfonic acid, afforded 3-keto-1,4-diene intermediates **123** which underwent electrocyclic ring closure (Nazarov cyclization).



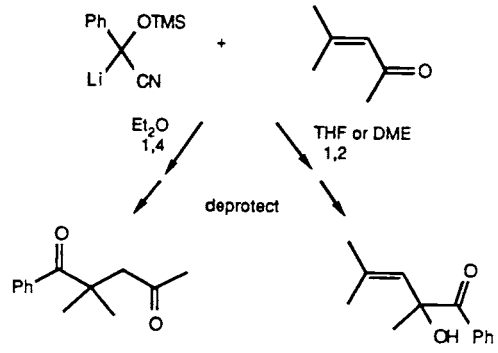
Another entry into substrates for intramolecular cycloaddition reactions was reported by Fischer and Hünig.[298] Addition of **100** to dienal **124**, for example, afforded adducts **125** after hydrolysis. Cyclization to **126** occurred at temperatures from ambient to 100°C, depending on the substituents.



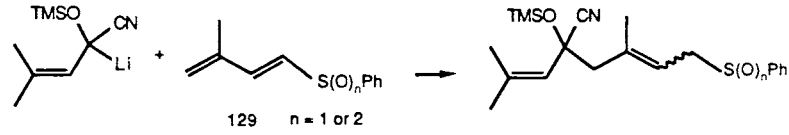
Attempted addition of anion **127** to the aldehyde group of silylated vanillin derivatives reportedly failed, resulting in attack at silicon and formation of **128**.[310]



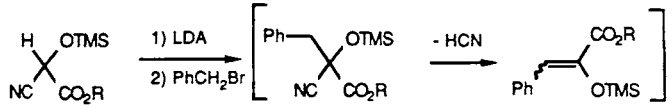
Umpolung reagents derived from silylated cyanohydrins have been reported to react with α,β-unsaturated enones.[295–297] The course of the reaction (1,2- vs. 1,4-addition) was greatly affected by solvent. The reagent derived from benzaldehyde, for example, added to enones by exclusive 1,4-addition in ether. In the more polar solvents THF or DME, the 1,2-addition product predominated, becoming the exclusive product if HMPT or 12-crown-4 was added to the reaction mixture.



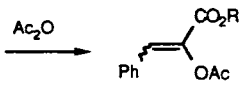
Conjugate additions to α,β-unsaturated esters have also been reported.[295,297,311] Similarly, conjugate additions to the electrophilic butadienes **129** occurred readily.[312]



Umpolung reactions of silylated cyanohydrins derived from glyoxylic esters **130** have been reported as a route to enol acetates **131**.[236]

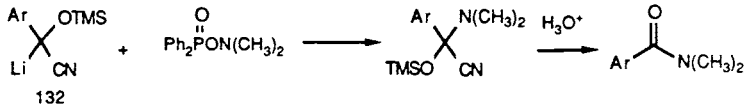


130 R = CH_3 or C_2H_5



131

Finally, amination of anions **132** with N,N-dimethyl-O-(diphenylphosphinyl)hydroxylamine provided a mild method for the oxidation of an aldehyde to an amide.[313]

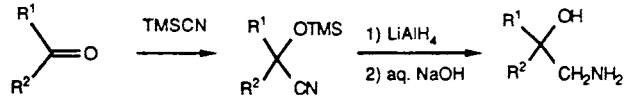


132

3.4.3. Elaborations of the Nitrile Functional Group

The synthetic potential of silylated cyanohydrins as intermediates in organic synthesis is due in part to the presence of the nitrile functional group. In this section, we consider manipulations of this group and have classified these reactions as reductions, additions of organometallic reagents, and hydrolyses.

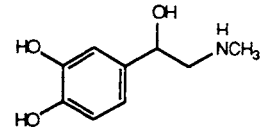
Reduction. Reduction of the nitrile group of a silylated cyanohydrin followed by hydrolysis of the silyl ether represents overall conversion of an aldehyde or ketone to a β-aminoalcohol. This transformation was first reported by Evans et al.,[5] who utilized excess lithium aluminum hydride in ether for the reduction followed by hydrolysis with aqueous sodium hydroxide to effect conversion of a variety of ketones to β-aminoalcohols **133** in high overall yields. Like many of the other transformations discussed in this section, it was often not necssary to isolate or purify the silylated cyanohydrin prior to reduction. This reaction sequence sub-



133

sequently has become well-established in organic synthesis as a route to a variety of useful aminoalcohols. It has been used to prepare intermediates for conversion into indoles and tryptamines,[314,315] pyrroles,[316] pyrrolizidines,[317] prostaglandin analogs,[318] oxazolidinone derivatives with central nervous system (CNS) activity,[319] oxazolidines with activity as herbicidal antidotes,[160] and cardiovascular agents.[320] The preparations of elaborated catechol estrogens for evaluation of CNS activity[321] and of a derivative of epiandrosterone as an affinity ligand for the separation of human serum proteins[322] have been reported.

Since the β-aminoalcohol moiety is a common structural feature of the phenethanolamine adrenergic agents related to epinephrine **134**, $LiAlH_4$ reductions of silylated cyanohydrins of various substituted aldehydes and ketones have been used to prepare a large number of analogs of **134** for evaluation of biological activity.[323–341]



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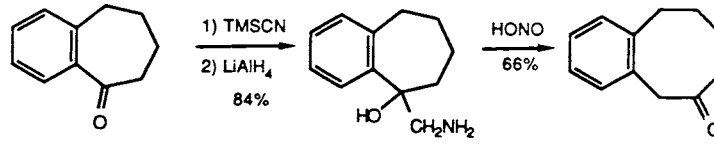
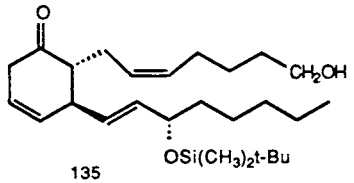
A typical utilization of β-aminoalcohols in organic synthesis is as substrates for the Tiffeneau–Demjanov ring expansion via treatment with nitrous acid. The ring expansion of benzosuberone is typical.[342]



This general sequence of converting a cyclic ketone to the silylated cyanohydrin followed by $LiAlH_4$ reduction and nitrous acid initiated ring expansion has been utilized in the syntheses of cyclohexadecanone,[343] carbathromboxane precursor **135**,[344] and various bicyclic and tricyclic ketones such as bicyclo[3.3.0]oct-2-en-6-one **136**,[345] bicyclo[3.1.1]heptan-2-one **137**,[346] 9-oxabicyclo[4.2.1]non-7-en-3-one **138**,[347] 4-homoadamantanone-5-^{13}C **139** (using $Me_3Si^{13}CN$),[348] 1,3-bishomoadamantane precursor **140**,[349] 2,4-bishomobrendan-2-one **141**[350,351] and an isomer **142**,[352,353] the 3-oxawurtzitane precursor **143**,[354,355] homobrexanone **144**,[356] and tricyclo[5.3.1.$0^{1,5}$]undecan-10-one **145**.[357]

Although reduction of the nitrile group of silylated cyanohydrins has been accomplished most often with $LiAlH_4$, other reagents have been used as well for this purpose. Reduction of the TMS cyanohydrin of *p*-anisaldehyde with BH_3·THF was reported to afford a higher yield of the β-aminoalcohol than was obtained with $LiAlH_4$.[358] A general method for the catalytic hydrogenation of the nitrile group of silylated cyanohydrins using Raney nickel or Ru/Al_2O_3 catalysts in dioxane or THF at elevated pressures (ca. 100 atm) has been patented.[359] Under these conditions the silyl ether survived the reduction, allowing isolation of the β-silyloxyamine **146**. Catalytic hydrogenation of the nitrile group of **147** (X = CH, N) using a cobalt boride catalyst gave the primary amine which underwent cyclization to **148** in the synthesis of some nucleoside antibiotic analogs.[360,361] In studies directed toward similar goals, however, attempted reduction of **149** (R^1 = CH_3 or CH_2Ph, R^2 = NO_2 or NHAc) using $LiAlH_4$, BH_3·Me_2S, or catalytic hydrogenation was not successful.[82]



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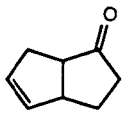

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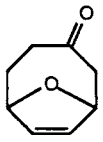

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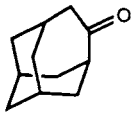

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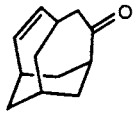

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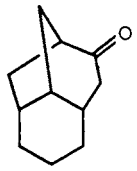

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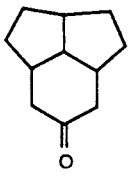

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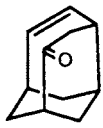

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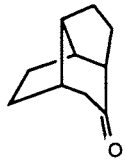

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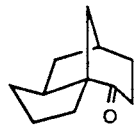

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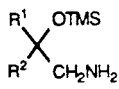

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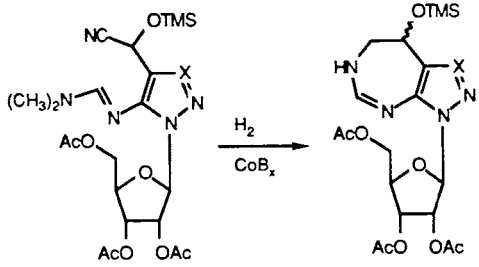
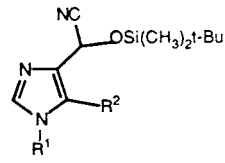
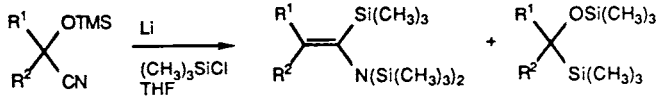


147 148



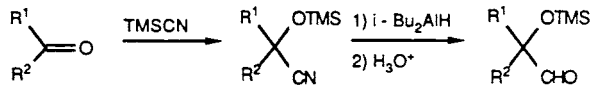
149

Reductive silylation of silylated cyanohydrins with lithium metal in the presence of chlorotrimethylsilane led to a mixture of enamines of acylsilanes **150** and the α-silyloxy silanes **151**.[362]



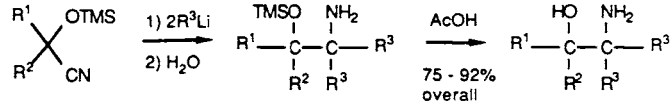
150 151

The reaction of diisobutylaluminum hydride (DIBAL-H) with silylated cyanohydrins was reported to result in reduction of the nitrile to the imine, which usually was converted to the aldehyde *in situ* by hydrolysis with cold, dilute H_2SO_4.[363,364] Since the silyl ether survived this treatment, the sequence represents a general method for the one-carbon homologation of ketones to protected α-hydroxyaldehydes **152**. The authors noted that use of THF as solvent in the reduction was essential, since reaction in hydrocarbons or other solvents of poor complexing ability resulted in overreduction of the nitrile to the amine.



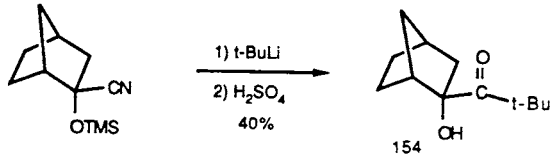
152

Addition of Organometallic Reagents. Further elaboration of silylated cyanohydrins has been accomplished by reaction with organolithium reagents.[365] This represents another method for the synthesis of β-aminoalcohols, in this case β-aminoalcohols **153** in which the amine group is attached to a tertiary carbon. Because of the high reactivity of organolithium reagents, the two additions of R^3Li (R^3 = Me or Bu) generally proceeded with similar rates, and it was not possible to limit the addition to one equivalent of R^3Li, or to successively introduce two different organic groups.[365] This procedure was utilized to prepare aminoalcohols as intermediates for the preparation of N-acyloxazolidinones.[366]



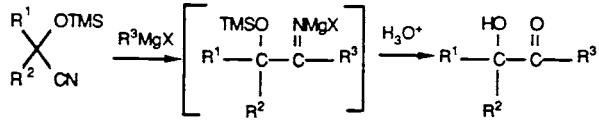
153

When the hindered reagent *t*-BuLi was reacted with the hindered TMS cyanohydrin of norcamphor, however, the product, after hydrolysis, was the α-hydroxyketone (acyloin) **154**.[367]



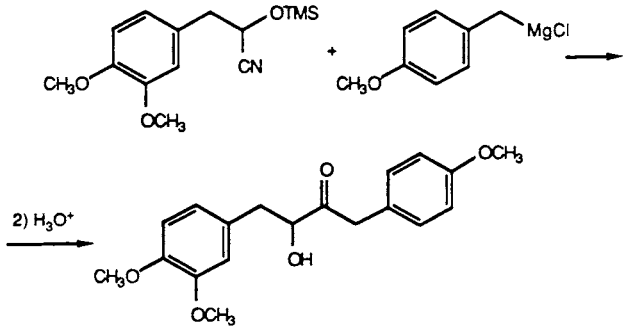
154

In an isolated example, an unspecified yield of the corresponding acyloin was obtained upon reaction of methyl magnesium iodide with the silylated cyanohydrin of acetone.[132] This reaction was subsequently improved upon and developed into a general method for the efficient preparation of α-hydroxyketones, including benzoins.[368–370] The decreased reactivity of Grignard reagents compared to organolithiums resulted in addition of only one equivalent of Grignard reagent to the nitrile group. An interesting feature of this process was a simple purification step — extraction of the etheral reaction mixture from the Grignard reaction with dilute aqueous acid resulted in extraction of the desired imine intermediate into the aqueous phase. Subsequent slow hydrolysis of the imine to the ketone caused the α-hydroxyketone **155** to separate from the aqueous phase in very pure form.



155

A number of acyloins **155** where R^3 is an aromatic group are efficient photoinitiators for radical polymerization, and have been prepared by the Grignard/silylated cyanohydrin route.[371] This method has also been successfully applied to the preparation of the unsymmetrical benzyl acyloin **156** in the syntheses of some fungal pigments,[372–374] in the syntheses of optically active acyloins from optically active silylated cyanohydrins,[171] and in the preparation of an acyloin derived from acetol.[375] Attempted reaction of **157** with either MeLi or MeMgI,



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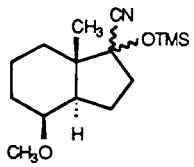

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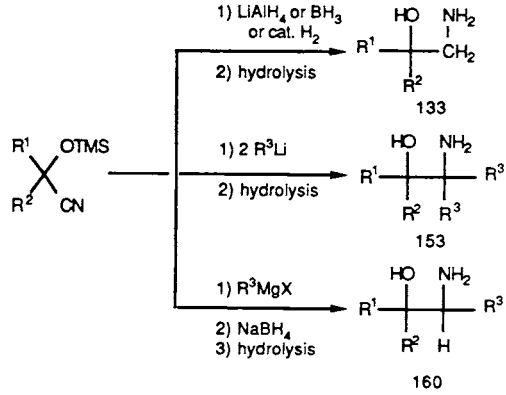
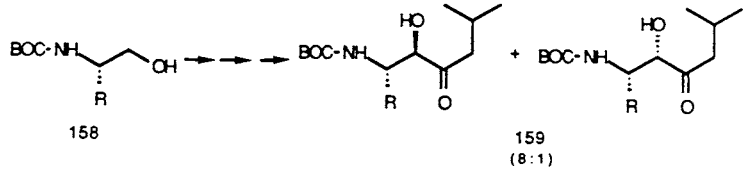


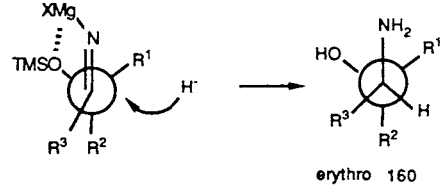
Scheme 4.

however, was reported to effect desilylation rather than nitrile functionalization.[162] The Grignard route to hydroxyketones **159**, intermediates to 1,2,3-aminodiols, was reported to proceed in >99% overall yield from BOC-alaninols **158**.[155]



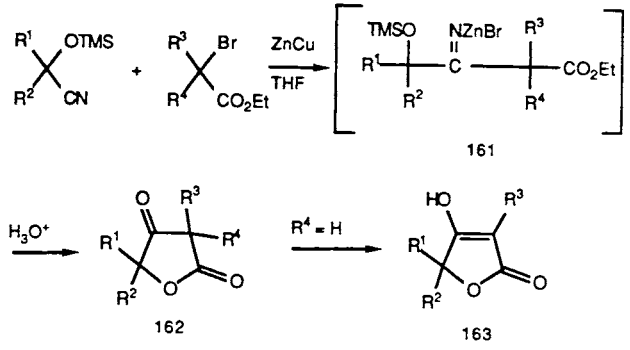
The synthetic potential of the Grignard reagent/silylated cyanohydrin reaction has been extended recently. Treatment of the imine intermediate with a reducing agent such as sodium borohydride/methanol prior to hydrolysis allowed isolation of β-aminoalcohols **160** in high yield.[376,377] Thus, depending on the reagent, β-aminoalcohols of varying substitution pattern can be prepared from silylated cyanohydrins (Scheme 4).

With β-aminoalcohols **160**, diastereomers are possible when $R^1 \neq R^2$. Choice of reducing agent ($NaBH_4$, $LiAlH_4$, or $Zn(BH_4)_2$) was shown to effect the diastereomeric ratio.[376,377] Highest selectivity (erythro : threo = 24) was obtained with $NaBH_4$ at reduced temperatures. This selectivity was attributed to reduction of the chelated intermediate from the least hindered side (R^1 substituent smaller than R^2) as indicated below. This method was used to prepare optically active

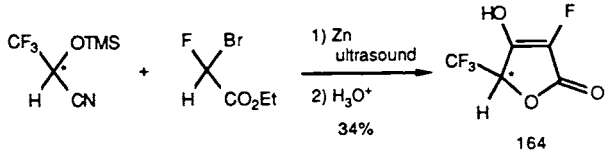


aminoalcohols with high diastereoselectivities from optically active silylated cyanohydrins.[170]

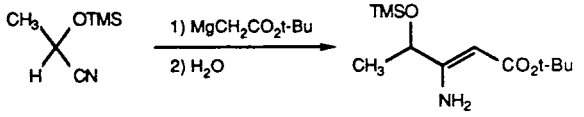
Reformatsky reagents have also been shown to be reactive with the nitrile group of silylated cyanohydrins.[378] Hydrolysis of the intermediate adduct **161** with aqueous acid produced a γ-hydroxy-β-keto-ester which readily cyclized to form a β-keto-γ-butyrolactone **162**. When R^4 = H, **162** isomerized to the tetronic acid **163**, a common structural feature of a large number of sponge, fungal, and lichen



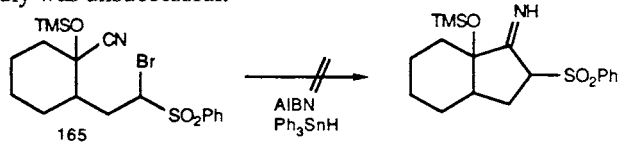
metabolites. Although yields from this process were moderate (21–72%), the method constituted a simple, one-pot procedure for the preparation of otherwise difficultly accessible compounds. This method has been applied to the synthesis of fluorinated, optically active analogues, e.g., **164**.[379,380] The lower reactivity/stability of the fluorinated organozinc reagents necessitated the use of ultrasound to promote these reactions.



One example of a magnesium ester enolate addition to a silylated cyanohydrin has been reported.[381,382]

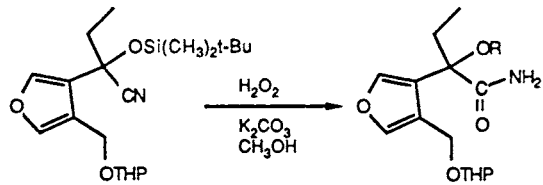


Finally, attempted radical cyclization onto the nitrile of silylated cyanohydrin **165** reportedly was unsuccessful.[383]

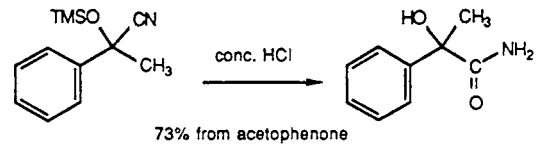


Hydrolysis. In addition to the various reductive treatments of the nitrile group of silylated cyanohydrins described above, a number of hydrolytic procedures for the elaboration of the nitrile group have been reported.

Hydrolysis of the nitrile group of the *t*-butyldimethylsilylated cyanohydrin **166** to the amide with basic H_2O_2 was used to prepare an intermediate in the total synthesis of the antitumor agent camptothecin.[36] Conversion of silylated cyanohydrins of aromatic ketones to α-hydroxyamides, e.g., **167**, by reaction with concentrated HCl or HNO_3/HCO_2H have also been described.[384] This method was used to prepare α-hydroxyamides for evaluation as antiatherosclerotic agents,[385] and hydrolysis of silyloxydinitriles such as **168** with sulfuric acid was used to prepare α-hydroxydiamides **169** which exhibited insecticidal activity.[254,386–388]

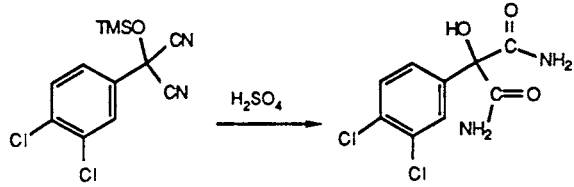


166 R = H, SiR_3



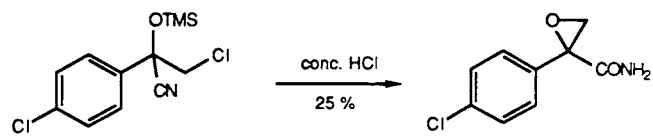
73% from acetophenone

167



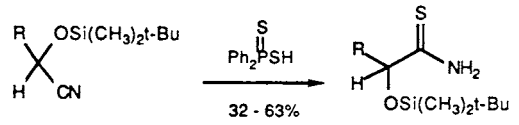
168 169

Hydrolysis of silylated cyanohydrin **170** to the corresponding amide was accompanied by ring closure to the epoxide, albeit in low yield.[389]



170

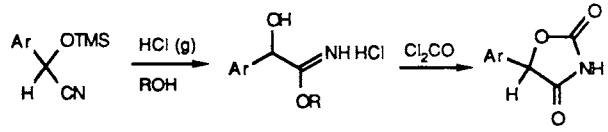
Conversion of silylated cyanohydrins **171** to protected α-hydroxythioamides **172** by treatment with diphenylphosphinodithioic acid has been reported.[156]



171 172

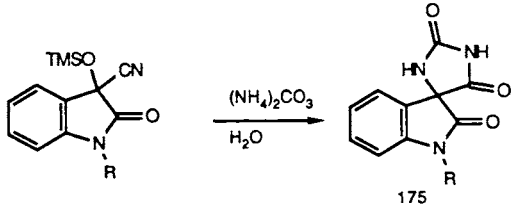
Hydrolysis of silylated cyanohydrins to α-hydroxyacids with concentrated HCl, generally under reaction conditions more rigorous than those for hydrolysis to the α-hydroxyamide, has also been investigated.[390,391] In some studies, the hydrolysis was carried out in two stages, i.e., hydrolysis of the silylated cyanohydrin to the cyanohydrin (see also Section 3.4.4.) in the first step, followed by isolation and further hydrolysis in the second step.[392,393] Usually, however, this two-step procedure was not necessary.[394]

Conducting the nitrile solvolysis reaction in acidic alcoholic media allowed isolation of α-hydroxyesters after aqueous workup.[395] This transformation of silylated cyanohydrins was used to prepare α-hydroxyester intermediates in the syntheses of compounds with antibiotic,[306] cholinergic,[396] and antiasthmatic[397] activities. On the other hand, treatment of silylated cyanohydrins of aromatic aldehydes with gaseous HCl in alcohol solvents under strictly anhydrous conditions has been reported as a route to imidate esters **173**. Cyclization of **173** with phosgene gave the oxazolidin-2,4-diones **174**, a number of which displayed hypoglycemic activities.[398–412] The spirohydantoins **175**, prepared by Bucherer–Bergs reactions



173 174

of the silylated cyanohydrins of indoline-2,3-diones[413] and the related spirooxazolidinediones **176**,[414] were also reported to be useful for the treatment of certain complications of diabetes.



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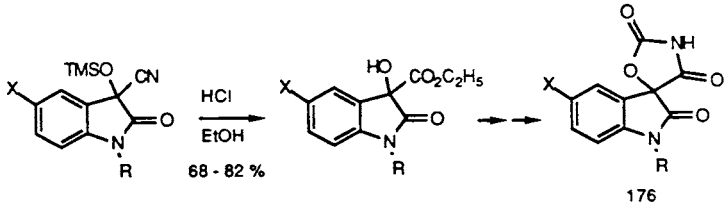
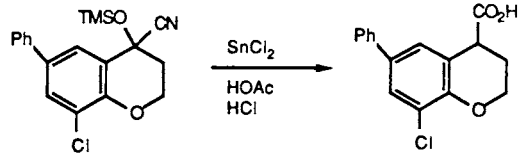


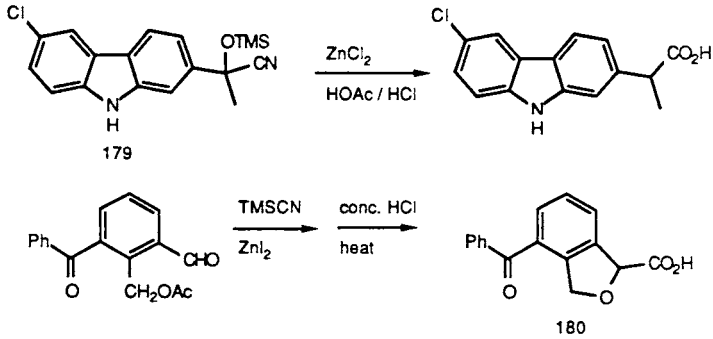
176

Finally, reductive hydrolysis of silylated cyanohydrins of unhindered aromatic ketones, e.g., **177**, to the acids **178** with stannous chloride, acetic acid, and concentrated HCl has been reported.[415] Some analogs of **178** were reported to be biologically active agents for the treatment of complications of diabetes.[416] The method was also used to prepare phenylacetic acid intermediates in the syntheses of diethylstilbestrol[417] and antithrombotic agents.[418] Similarly, carbazole **179** was



177 178

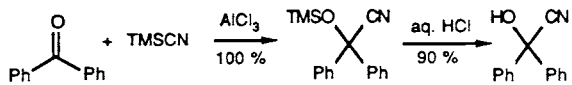
converted to the corresponding acid in high yield,[145] and dihydroisobenzofuran **180** was produced in 39% yield from 2-acetoxymethyl-3-benzoylbenzaldehyde via a cyanosilylation/hydrolysis sequence.[419]



179 180

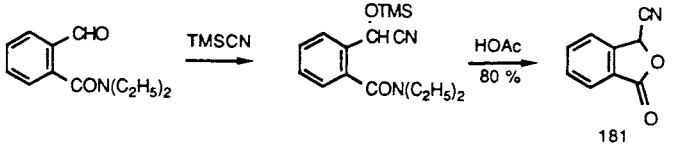
3.4.4. *Elaborations of the Silyloxy Functional Group*

Hydrolysis. An effective utilization of cyanotrimethylsilane (**1**) is to prepare cyanohydrins of carbonyl compounds which are otherwise difficult or unable to be prepared by conventional methods. Boutte and Auroux[420] first reported this method in the patent literature. Benzophenone cyanohydrin was synthesized in 90% yield by aqueous hydrochloric acid treatment of the corresponding silylated cyanohydrin, obtained quantitatively by aluminum chloride catalyzed addition of **1** to benzophenone.



Gassman and Talley[421,422] extended this reaction to other ketones using zinc iodide as the catalyst for formation of the silylated cyanohydrins and aqueous hydrochloric acid (3*N*; 25–45°C; 0.5–3.0 h) to effect desilylation. Selected dialkyl,

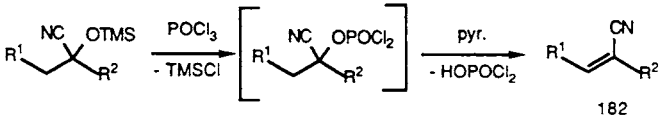
diaryl, and alkyl-aryl ketones provided 90+% overall yields of cyanohydrins in the two-step process. The unmodified procedure of Gassman and Talley has been applied more or less routinely in synthesis; syntheses of trimethylcyclopentanecarboxylic acids,[423] bicyclic dicarboxylic acids,[424] and the cyanodiphenylmethyl cation[425] are illustrative. Variations of the hydrolysis reaction have been elaborated, however, primarily to protect other sensitive groups which may be present. These variations include use of 0.1*N* HCl in THF at 0°C,[426a] 0.5*N* HCl in dioxane at room temperature,[426b] benzyltrimethylammonium fluoride in THF and water at 0°C,[288] and 5% hydrogen fluoride in acetonitrile.[427] Glacial acetic acid at room temperature has also been utilized to effect hydrolysis of the silylated cyanohydrin intermediates in the transformation of *o*-formyl-N,N-diethylbenzamides to 3-cyano-1(3H)-isobenzofuranones **181**.[428]



181

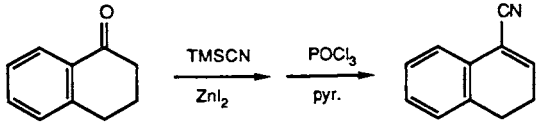
In related studies, Reetz and co-workers[165] developed stereoselective syntheses of secondary cyanohydrins which involved either 1,2- or 1,3-asymmetric induction. The syntheses typically involved titanium tetrachloride-catalyzed addition of TMSCN (and *t*-butylcyanodimethylsilane) to chiral alkoxy aldehydes, followed by acidic hydrolytic workup (see Section 3.1.1).

Elimination of Trimethylsilanol. Although silylated cyanohydrins can be hydrolyzed to cyanohydrins and subsequently dehydrated,[429–433] Oda et al.[434] first reported that α,β-unsaturated nitriles could be formed in good-to-excellent yields directly from silylated cyanohydrins by refluxing with phosphorous oxytrichloride and pyridine. The reaction was thought to involve initial formation of a dichlorophosphinate intermediate with concomitant loss of chlorotrimethysilane; base-catalyzed elimination of dichlorophosphinic acid provided the α,β-unsaturated nitrile **182**. An indication of the synthetic control achievable with this

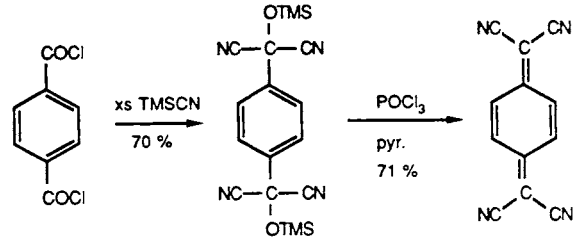


182

procedure was the conversion of α-tetralone into 1-cyano-3,4-dihydronaphthalene (89% yield), a compound inaccessible via traditional cyanohydrin chemistry. Later reports have also indicated that excellent results, i.e., 73–100% isolated yields, could be achieved with a variety of methoxy substituted tetralones.[435]

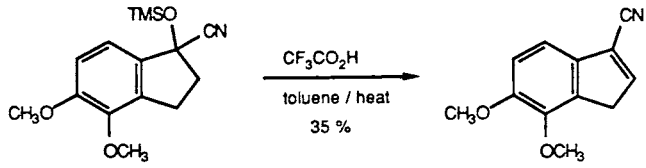


A clever application of the elimination reaction to the synthesis of 7,7,8,8-tetracyanoquinodimethane (TCNQ, **183**) was developed by Yamaguchi and Hanafusa[252,436] and recently extended to hydroxy-functional derivatives by Miura et al.[437] The method is illustrated by cyanosilylation of terephthaloyl chloride (see Section 3.3.2), followed by loss of two molecules of trimethylsilanol from the silylated cyanohydrin intermediate to form TCNQ.



183

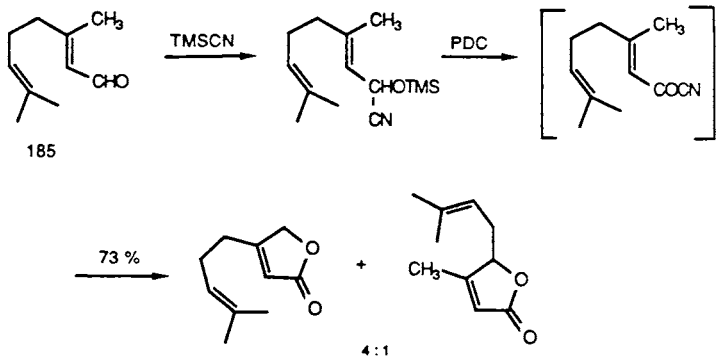
The general transformation of silylated cyanohydrins to α,β-unsaturated nitriles has been effectively applied in the syntheses of highly strained, multicyclic ring systems.[438–440] Utilization of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a co-catalyst has also been reported to result in markedly increased yields in certain instances.[438b,440] Thionyl chloride or phosphorous trichloride may be used in lieu of phosphorous oxytrichloride; pyridine may be replaced with collidines, lutidines, or quinoline.[441] Alternatively, strong acid catalyzed eliminations have been used in the preparation of cyanoindenes such as **184**,[433] cyanoindoles,[442a,b] and derivatives of naphthacene carbonitriles.[442c,d]



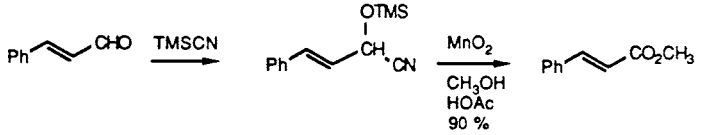
184

Oxidation. The oxidation of silylated cyanohydrins was first reported by Corey and Schmidt.[443] Δ^2-Butenolides were the major products resulting from oxidation using pyridinium dichromate, provided that the silylated cyanohydrin was disubstituted on the β-carbon and the γ-carbon possessed at least one hydrogen. This represented a somewhat general transformation of α,β-unsaturated aldehydes to Δ^2-butenolides, although several exceptions were indicated. The oxidation of geranial **185** is illustrative. Acyl cyanides, proposed as key reaction intermediates, were actually isolated in certain instances.

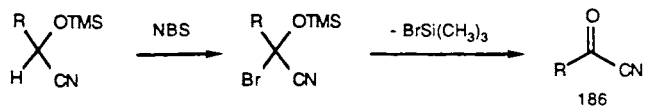
Bal et al.[444] reported oxidation of silylated cyanohydrins using manganese dioxide in methanol containing acetic acid. Transformation of α,β-unsaturated aldehydes to α,β-unsaturated methyl esters was observed to be very efficient, providing 83–92% isolated yields. Although the mechanism of this oxidation was



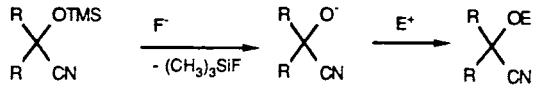
not specified, desilylation and subsequent oxidation of a manganese ester of the cyanohydrin to an intermediate acyl cyanide probably occurs in analogous fashion to that with pyridinium dichromate.



Harle and Jochims[445] reported the oxidation of silylated cyanohydrins under Wohl-Ziegler conditions (with N-bromosuccinimide). Either thermal or photochemical activation of the NBS resulted in variable yields (42–93%) of acyl cyanides **186**. The oxidation procedure could not be applied to silylated cyanohydrins which contained other oxidizable functional groups or to α,β-unsaturated derivatives, the latter of which were recovered unchanged. Bromine and N-bromophthalimide were effective oxidizing agents as well, while N-chlorosuccinimide, trichloroisocyanuric acid, sulfuryl chloride, and chloramine-T were ineffective. The proposed mechanism involved free-radical formation of an α-bromo intermediate followed by ionic elimination of bromotrimethysilane.

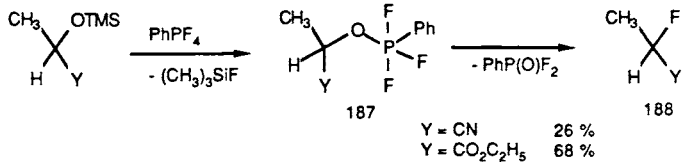


Substitution. A common synthetic manipulation involving the silyloxy group of silylated cyanohydrins focusses on the very high strength of the Si-F bond (160 kcal/mole)[446] leading to highly chemoselective attack at the silicon atom. Treatment of silylated cyanohydrins with fluoride ion causes desilylation by formation of fluorotrimethylsilane. The resulting alkoxide can then react with an electrophilic reagent (E^+ in equation 15 below) to effect overall transformation into a different cyanohydrin derivative.



(15)

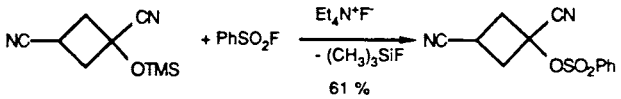
Riess and co-workers, in a series of papers, first exploited this idea using phenyltetrafluorophosphorane as the source of fluoride.[447–449] The monoalkoxyfluorophosphoranes **187** which resulted were thermally unstable and provided carbon-fluorinated products **188.** Yields were considerably better from the α-carboalkoxy stabilized compounds than from the nitriles.



187 188

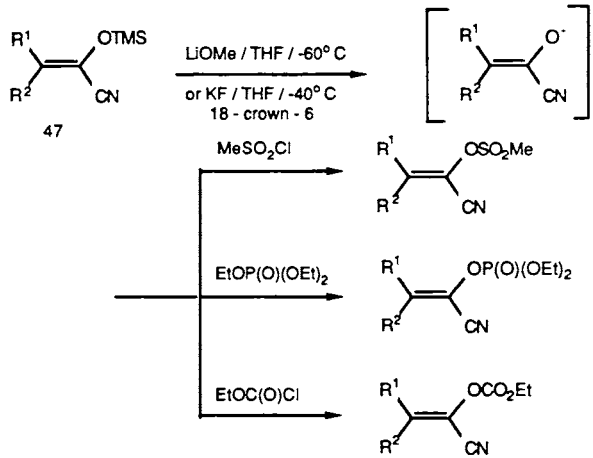
Y = CN 26 %
Y = $CO_2C_2H_5$ 68 %

Ykman and Hall[134] extended the fluoride desilylation to more conventional electrophilic reagents by examining the reaction of silylated cyanohydrins and benzenesulfonyl fluoride in the presence of a catalytic amount of fluoride ion. Thus, 1,3-dicyano-1-(trimethylsilyloxy)cyclobutane **189** was converted to the corresponding sulfonate in 61% isolated yield.

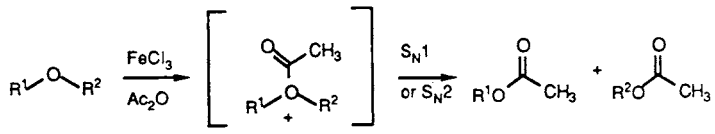


189

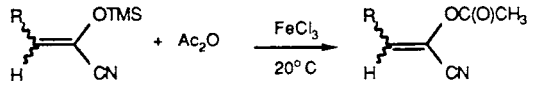
Hertenstein and co-workers applied the procedure to 2-trimethylsilyloxy-2-propenitriles **47**, obtaining a variety of other protected cyanohydrin derivatives including mesylates, phosphates, and carbonates.[72,450] The overall procedure involved desilylation either with fluoride or by attack at silicon by alkoxide.



Alternative procedures have also been developed for the preparation of acylated cyanohydrin derivatives. Ganem and Small[451] originally formulated acetic anhydride containing ferric chloride as a mild reagent for cleaving ethers. The purpose of the ferric chloride was to complex and activate the anhydride (or ether) so that an oxonium ion intermediate might form. Hertenstein et al.[72] first examined the



effect of this reagent on 2-trimethylsilyloxy-2-propenitriles. The trimethylsilyl group was cleanly removed, and high yields, i.e., 91–96%, of the corresponding α-acetoxynitriles **190** were obtained. The reaction also worked well using trifluoroacetic anhydride.[72,450] More recently, the reaction has been applied in the syntheses of precursors to substituted trimethylenemethanes,[452] of 4-amino-2(5H)-furanones,[453] and of 2-arylpropanoic acids.[454]



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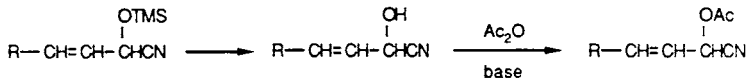
α-Acetoxynitriles may also be prepared in a two-step sequence involving initial hydrolysis to the cyanohydrin followed by acylation. This procedure has been utilized primarily for the preparation of the allylic derivatives **191**,[455–457] although



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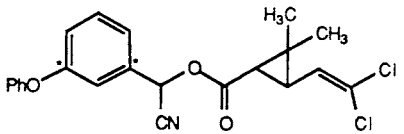
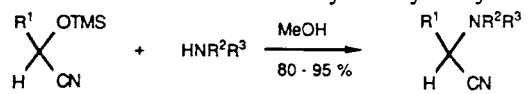
modifications of the procedure were utilized in the preparation of ^{14}C-labeled insecticide **192**[458a] and of some insecticidal phosphate esters.[458b] Also, the sily-



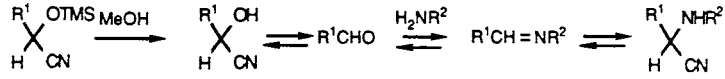
192

lated cyanohydrin of (R)-2,3-isopropylideneglyceraldehyde has been converted to the corresponding benzyloxycarbonyl-protected cyanohydrin by hydrolysis and subsequent treatment with benzylchloroformate.[459]

The reaction of silylated cyanohydrins with amines was first reported by Mai and Patil.[460,461] The reaction worked best with silylated cyanohydrins derived from

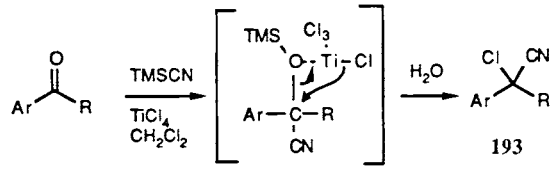


aldehydes and required an alcohol solvent. At first glance the reaction would appear to involve a nucleophilic substitution of the amine for the silyloxy group. This was later shown to be unlikely.[462] The authors proposed the following sequence of reactions:

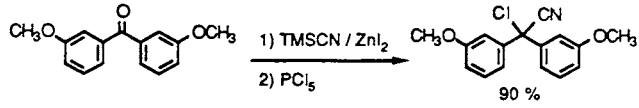


If this proposal were correct, one should be able to treat an aldehyde directly with the amine and **1** in methanol. This was found to be possible, and an improved procedure was developed which involved combining a neat mixture of the aldehyde, the amine, and **1**.[463] With the improved procedure, it was even possible to extend the reaction to ketones in high yield. The reaction was subsequently applied to asymmetric synthesis of aminontriles using optically active amine reagents.[464,465] With (R)-α-methylbenzylamine and *o*-chlorobenzaldehyde, for example, the reaction proceeded to give a ratio of R,R:R,S diastereomers of 5.7 : 1. Similar selectivity has been observed in the syntheses of modified polyoxin derivatives and was interpreted by applying Cram's rule to the addition of HCN to the imine intermediate.[466] This one-step reaction has also been effectively applied in a regio-controlled synthesis of tetrahydropyridines[467] and in the synthesis of quinocarcin[468].

Aromatic aldehydes and ketones have been converted in one pot to the corresponding α-chloronitriles **193** by treatment with TMSCN and titanium tetrachloride at 0°C.[469] Only cyanohydrins were isolated from nonaromatic carbonyl compounds, however. A proposed reaction intermediate was the titanium-complexed silylated cyanohydrin, which internally collapsed to form the α-chloronitrile.

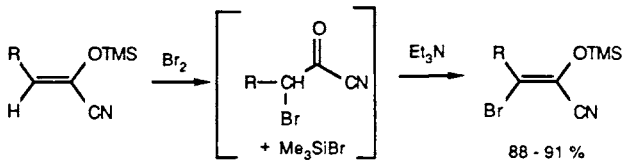


With other silylated cyanohydrins, especially those in which elimination of trimethylsilanol is disfavored, phosphorous oxytrichloride,[251] phosphorous pentachloride,[470] thionyl chloride,[445] and diethylaminosulfur trifluoride[471] have been shown to be effective reagents as well for α-halonitrile formation.

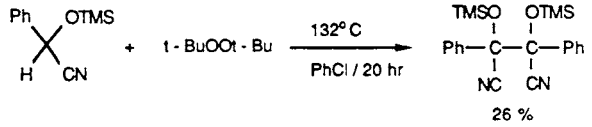


3.4.5. *Other Reactions of Silylated Cyanohydrins*

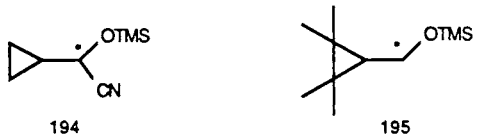
2-Trimethylsilyloxy-2-propenitriles[72] and related compounds[445] have demonstrated silyl enol etherlike reactivity in their reactions with bromine/triethylamine.



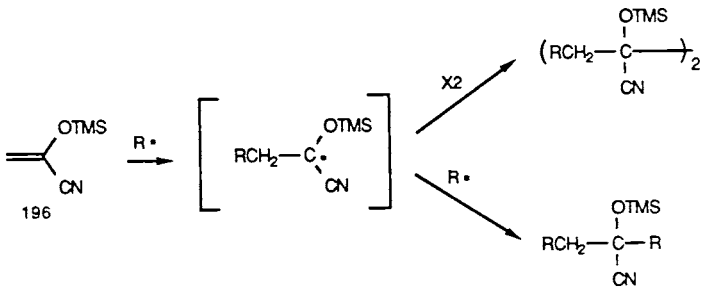
The free-radical dimerization of the trimethylsilylated cyanohydrin of benzaldehyde by di-*t*-butyl peroxide has been reported by Harle and Jochims.[445] In a



related study examining the stability of free radicals of silylated cyanohydrins derived from aldehydes, it was determined that free radicals with both silyloxy and cyano groups enjoy significant stabilization because of the so-called capto-dative effect.[472] Thus, free radical **194** showed no rearrangement by ring opening of the cyclopropyl ring up to 305K, whereas radical **195** provided ring-opened products



at 90K. Reactions of **196** with various free radicals have provided additional evidence for capto-dative stabilization.[450,473]

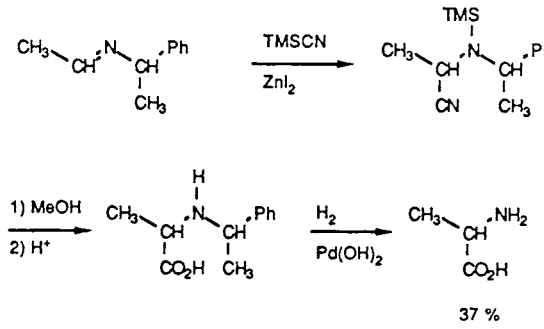


3.5. Cyanosilylation of Carbon–Nitrogen Multiple Bonds

3.5.1. Carbon–Nitrogen Double Bonds

Imines. The cyanosilylation of imines by TMSCN, which proceeds analogously to that of simple carbonyl compounds, was reported simultaneously by two groups in 1975.[474,475] Nakajima et al.[474] converted the initial cyanosilylated products into

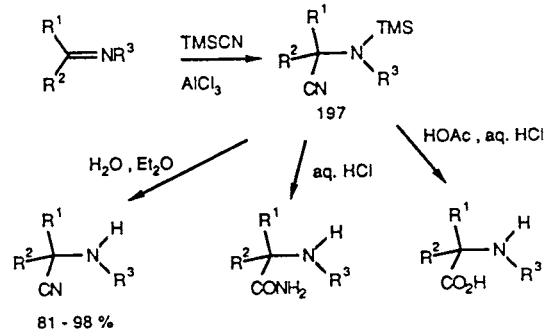
α-aminoacids via hydrolysis and subsequent reduction. Ojima et al.[475,476] examined the reaction at room temperature in the presence of several Lewis acids including aluminum chloride, zinc iodide, titanium tetrachloride, and aluminum isopropoxide. The cyanosilylated adducts **197** could be isolated but were generally



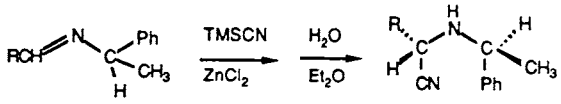
hydrolyzed under mild conditions to α-aminonitriles or under more severe conditions to α-aminoamides and α-aminoacids (Scheme 6).

The reaction has been extended to optically active imines,[477,478] where significantly greater enantiomeric excesses were observed with **1** than with HCN. Choice of Lewis acid was also important, with zinc chloride providing the highest optical yields of the catalysts evaluated. A series of N-alkylidene-(1-methylbenzyl)amines gave excellent chemical yields (>97%) of predominantly S,S diastereomeric products **198.**

The reactivity of α,β-unsaturated imines has been examined as well. Reaction of **1** and a series of cinnamaldehyde anils in the presence of aluminum chloride provided 80–90% isolated yields of the corresponding 1,2-addition products; no evidence of conjugate addition was indicated.[479]



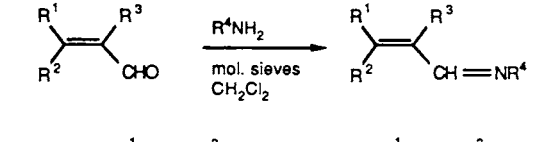
Scheme 6.



198 (S, S)

R	% ee
Et	63.4
n - Bu	68.4
i - Pr	75.0
i - Bu	61.4

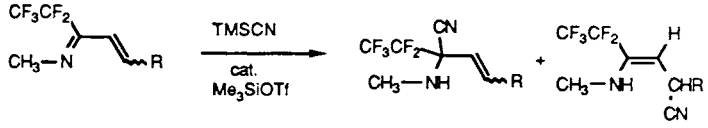
Although the essential procedure had been conducted earlier[474] and apparently gone unnoticed, a one-pot synthesis of α,β-unsaturated aminonitriles was described utilizing an α,β-unsaturated aldehyde, an amine, and **1** in the absence of any catalyst.[480] The α,β-unsaturated amines **199** were somewhat unstable and were generally hydrolyzed to aminoacids **200** prior to isolation.



199 200

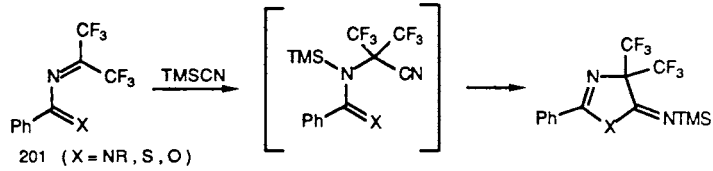
40 - 70 %

With perfluoroalkyl substitution on the α,β-unsaturated imine, significant 1,4-addition has been observed although the ratio of 1,2- to 1,4-addition was



R	total % yield	
c-C_6H_{11}	91	18 : 82
Ph	89	100 : 0

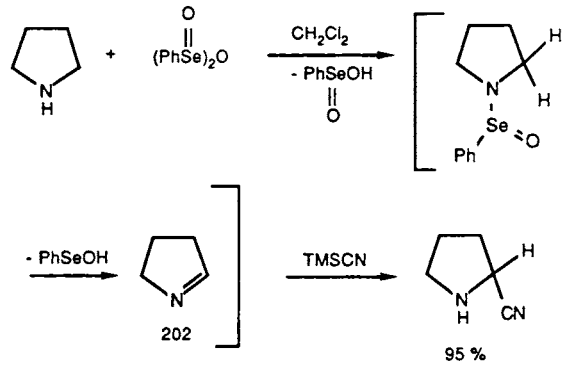
dependent on other substituents as well.[481] Products resulting from reaction of TMSCN and 1-hetero-3-aza-1,3-dienes **201** have been postulated as being derived from initial cyanosilylation of the imine functionality.[482]



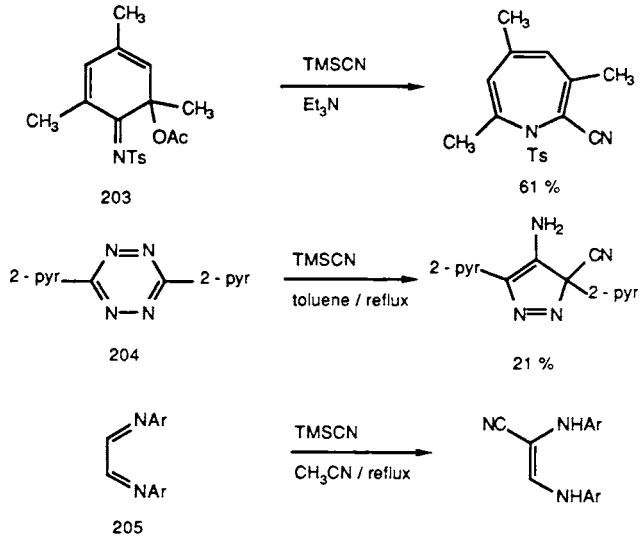
201 (X = NR, S, O)

Cyanosilylation of imines by **1** is currently utilized fairly extensively and even routinely[483] in synthesis. Syntheses conducted in the patent literature employing the reaction have been directed toward the preparation of cyanoazabicyclohexane plant sterilants,[484] imidazopyrrolopyridine herbicides,[485] 3-halovinylglycine antibacterial agents,[486] and bicyclic lactam cholecystokinin antagonists.[487]

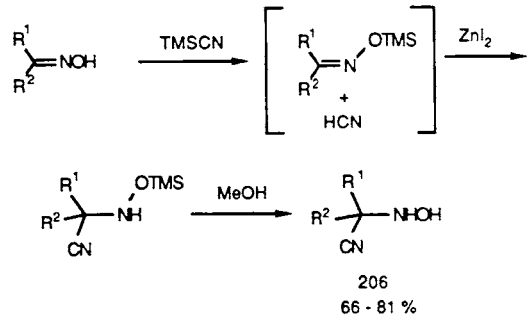
The reaction has also been employed to intercept imines formed *in situ* in an overall transformation of secondary amines to α-cyanoamines.[488] The secondary amine was dehydrogenated with phenylselenic anhydride, and the resultant imine, e.g. **202**, reacted with **1**.



Imine cyanosilylation has been found to give rise to a number of unexpected, rearranged products with iminocyclohexadienyl acetates **203**,[489] 1,2,4,5-tetrazines **204**,[490] and 1,4-diaza-1,3-butadienes **205**.[491]

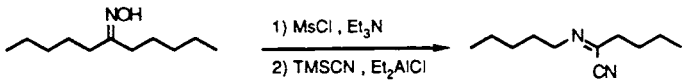


Oximes and Derivatives. Cyanosilylation of oximes was first reported by Ojima and co-workers.[475,492] Reaction of oximes with TMSCN in the presence of zinc iodide gave N-trimethylsilyloxy-α-aminonitriles in high yield. These compounds could be isolated but were generally treated with methanol to yield N-hydroxy-α-aminonitriles **206**. Reaction was thought to take place by initial silylation of the



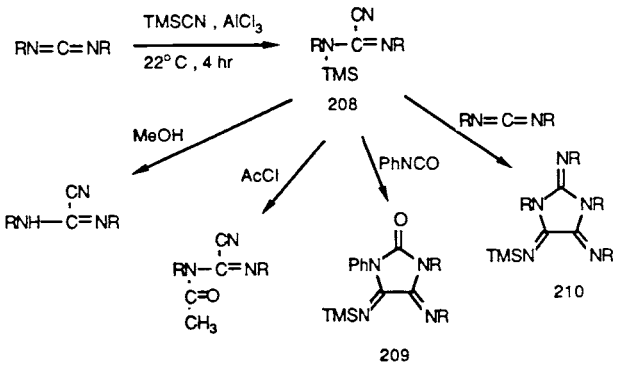
206
66 - 81 %

hydroxy group followed by addition of the hydrogen cyanide generated in the process to the C=N bond. An interesting modification of the reaction was developed by Maruoka et al.[493] When the hydroxy group was transformed into a better leaving group such as a mesylate, action of **1** and diethylaluminum chloride on the oxime derivative promoted Beckmann rearrangements which provided high yields of iminonitriles, e.g. **207**.



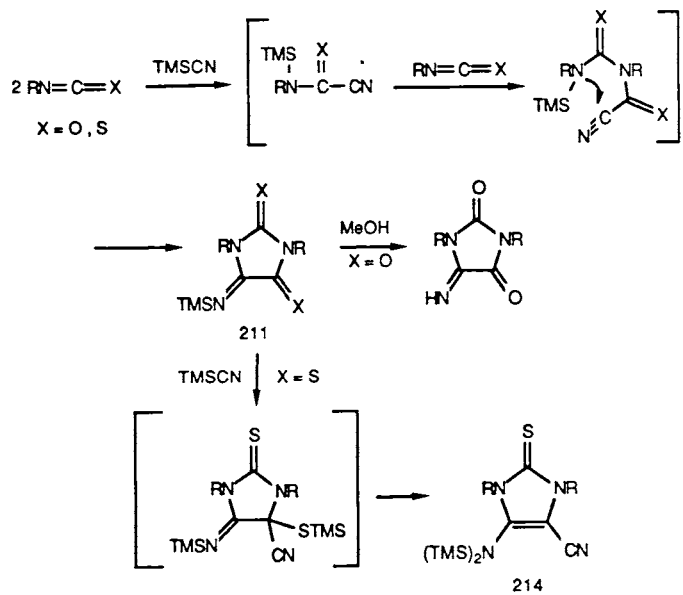
91 % 207

Carbodiimides. The reaction of **1** with carbodiimides in the presence of a catalytic amount of aluminum chloride has been shown to lead to the formation of the corresponding 1 : 1 adducts **208** in 84–96% yield at room temperature.[494–496] The reaction took place even in the absence of catalyst under more severe conditions, e.g., 190°C for 24 h. In some instances, the 1 : 1 adducts were stable enough



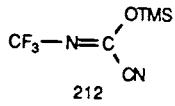
to be vacuum distilled, but generally the adducts were converted into more stable products by hydrolysis or acetylation. Cycloaddition reactions of the 1 : 1 adducts with isocyanates and carbodiimides were also examined, leading to the corresponding diazolidine heterocycles **209** and **210**, respectively.

Isocyanates and Isothiocyanates. The reaction of TMSCN with several aromatic isocyanates was reported by Ojima and Inaba[497] in 1974. This study was subsequently extended to aliphatic isocyanates[498] and to isothiocyanates.[496,499] The authors proposed initial cyanosilylation of the C=N bond (Scheme 7). The initial adduct, however, was very reactive and engaged in further reactions. With isocyanates and a 2 : 1 isocyanate : **1** stoichiometry, high yields (79–94%) of iminodiazolidinediones (**211**, X = O) were obtained. Only with tosyl isocyanate, presumably because of decreased nucleophilicity of the nitrogen, was a 1 : 1 adduct able to be isolated. In a full paper more complete details of the reactions were given.[496] Attempts to isolate 1 : 1 adducts by employing large excesses of **1** were unsuccessful, with the exception of the tosyl isocyanate reaction which provided the 1 : 1 adduct in 95% yield. The structure of this adduct was assigned largely on an intuitive basis. The inability of the electron attracting N-tosyl derivative to engage in further reaction seemed to support cyanosilylation of C=N rather than C=O. An infrared absorption at 1610 cm^{-1} was attributed to C=O, but the absorption might equally well be assigned to a C=N group that would remain after cyanosilylation of C=O.



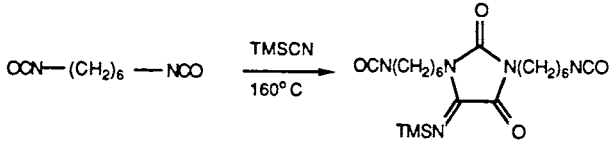
Scheme 7.

Lutz and Sundermeyer[500] reported the reaction of trifluoromethyl isocyanate with **1**. As with tosyl isocyanate, trifluoromethyl isocyanate formed an isolable 1:1 adduct when equimolar reactants and reaction temperatures less than 50°C were employed. When two-fold stoichiometry of the isocyanate and higher temperatures were utilized, a 5-iminodiazolidinedione product analogous to those reported by Ojima et al.,[496] was formed. Lutz and Sundermeyer assigned structure **212** to the 1 : 1 adduct, resulting from cyanosilylation of the C=O group, largely on the basis of spectral characteristics, e.g., 1650 cm^{-1} for infrared absorption for the C=N group.



212

Whether initial cyanosilylation of C=N or C=O takes place with isocyanates cannot be ascertained from subsequent reactions of the adducts. Either 1 : 1 addition product would yield the same 1 : 2 adduct with additional isocyanate. From a bond-energy standpoint, however, it would seem that cyanosilylation of C=O would be favored because of the substantially greater bond strength of Si–O (129 kcal/mole) compared to Si–N (105 kcal/mole).[446]



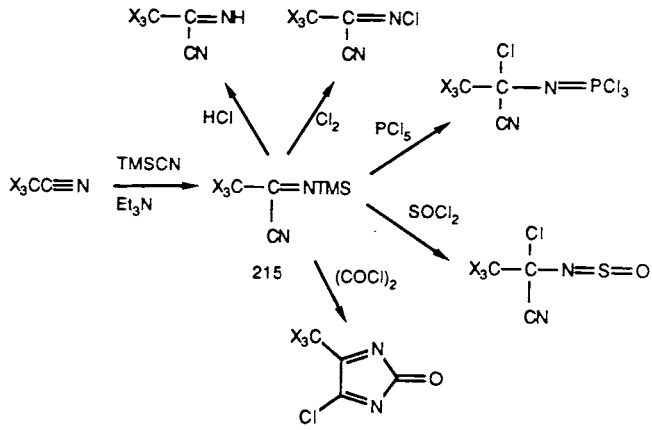
213

The reaction to form 1 : 2 adducts has been effectively utilized industrially to prepare unusual diisocyanate monomers **213**.[501]

The reaction of **1** and isothiocyanates proceeded to a slightly different type of reaction product than those obtained with isocyanates and carbodiimides.[496,499] The 4-thione group in intermediate **211** (X = S) was apparently subject to nucleophilic attack by another molecule of **1**. The resultant silylated cyanohydrin underwent sigmatropic extrusion of sulfur to form the 4-cyano derivative **214** (R = CH_3) in 54% yield (Scheme 7).

3.5.2. Carbon–Nitrogen Triple Bonds

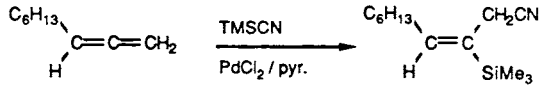
Electrophilic activation was found to be necessary in order for TMSCN to add to nitrile functional groups. Trichloroacetonitrile and trifluoroacetonitrile reacted with **1** in the presence of triethylamine to give the cyanosilylated adducts **215** in 72% and 60% yields, respectively.[502] The adducts were further subjected to several interesting reactions.



3.6. Cyanosilylation of Carbon–Carbon Multiple Bonds

3.6.1. Allenes

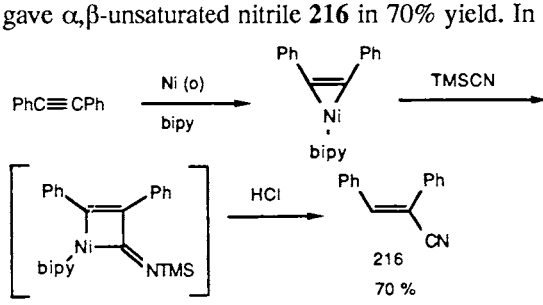
Allenes have been reported to react with TMSCN in the presence of palladium or nickel catalysts and organic bases such as pyridine.[503] With the allenes examined, the trimethylsilyl group always added to the central carbon atom, and the cyano group was introduced on the least substituted carbon terminus. The vinyl silanes thus produced were chiefly E-stereoisomers.



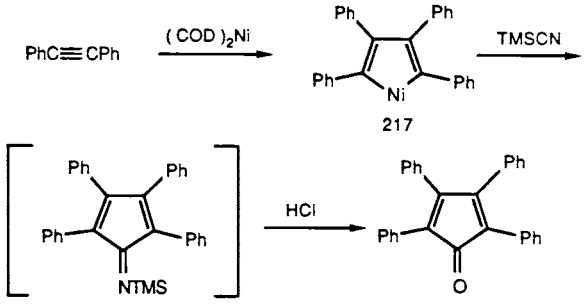
66 % (E / Z = 95 / 5)

3.6.2. Alkynes

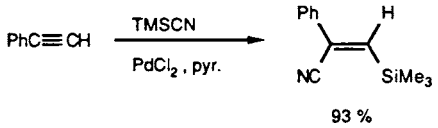
Alkynes have also been found to require complexation with nickel or palladium before reaction with **1** can occur. The nature of the reaction product was reported by Eisch and co-workers[504] to depend strongly on whether electron-donor ligands were present on the catalyst. Reaction of diphenylacetylene and nickel(0) in THF with 2,2'-bipyridine, a strong donor ligand, gave rise to a complex which when reacted with **1** gave α,β-unsaturated nitrile **216** in 70% yield. In the absence of



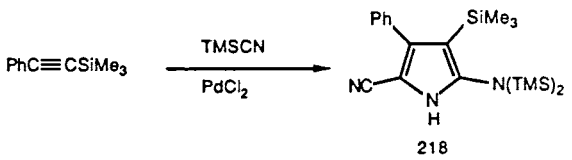
strong donor ligands as with bis(1,5-cyclooctadiene)nickel(0), for example, the nickelacyclobutenimine intermediate depicted above gave way to a nickelole intermediate **217**. Now reaction with **1** followed by protodenickelation gave tetracyclone in 50% yield. In both of these reactions, **1** was proposed to react in its isonitrile form.

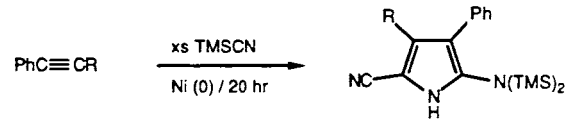


Palladium(II) chloride was later reported by Chatani and Hanafusa[505,506] to effectively cyanosilylate arylacetylenes by *cis*-addition. The regiochemistry of the addition was always such that the trimethylsilyl group was added to the unsubstituted terminus of the arylacetylene to provide (Z)-β-cyano-β-arylalkenylsilanes, in excellent yields in some cases.

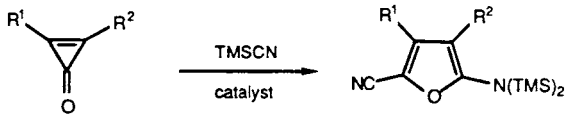


The reaction was subsequently examined with disubstituted alkynes in the absence of solvent by two research groups employing both palladium and nickel catalysts. Kusuomoto et al.[507] examined the interaction of silylated alkynes such as 2-phenyl-1-(trimethylsilyl)ethyne with **1** and palladium (II) chloride at 120°C for 9 h. Upon workup, pyrrole **218** was isolated in 84% yield. Similarly, Chatani and co-workers[508,509] reported pyrrole products (52–88%) to result from the reaction of both arylacetylenes and diarylacetylenes with excess **1** employing catalysts such as palladium chloride/pyridine and nickel(0) catalysts. A mechanism has not yet been proposed for the formation of these pyrroles or for the formation of the analogous furans **219** obtained from cyclopropenones.[510]





R = Ph , 87 % ; R = H ,58 %

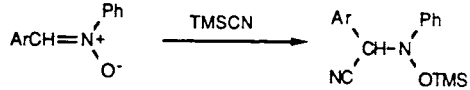


219

3.7. Cyanosilylation of Dipolar Compounds

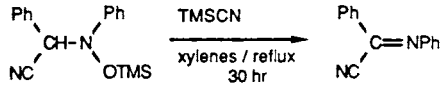
3.7.1. Nitrones

The original report of the reaction of a nitrone and TMSCN was that of Tsuge et al.[511] These workers reported that aldonitrones reacted with **1** in refluxing benzene solution to form high yields (>95%) of the corresponding 1,3-cyanosily-



220

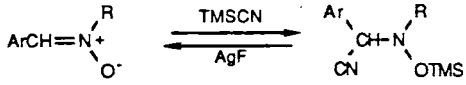
lated products **220**. Of the four aldonitrones examined, crystalline 1,3-cyanosilylated products resulted in every case. The products were desilylated upon treatment with hydrochloric acid in ethanol affording the corresponding N-hydroxy-α-aminonitriles in good yield. It was also observed that the cyanosilylated adducts were thermally unstable upon extended exposure to high temperatures, and among the decomposition products was the iminonitrile resulting from 1,2-elimination of trimethylsilanol. The reaction did not work with ketonitrones, however, which gave no reaction in refluxing benzene and products of radical disproportionation at 120°C in the absence of solvent.



75 %

The above report by Tsuge et al.[511] seems to have been overlooked by subsequent workers.[512–514] The elimination of trimethylsilanol from cyanosilylated aldonitrone products was shown to be base-catalyzed.[512] Yields of between

70–90% of iminonitriles were obtained at room temperature in the presence of triethylamine. Cyanosilylation was also shown to be an effective blocking procedure with aldonitrones, the nitrone being regenerated quantitatively upon reaction with silver fluoride.[514]

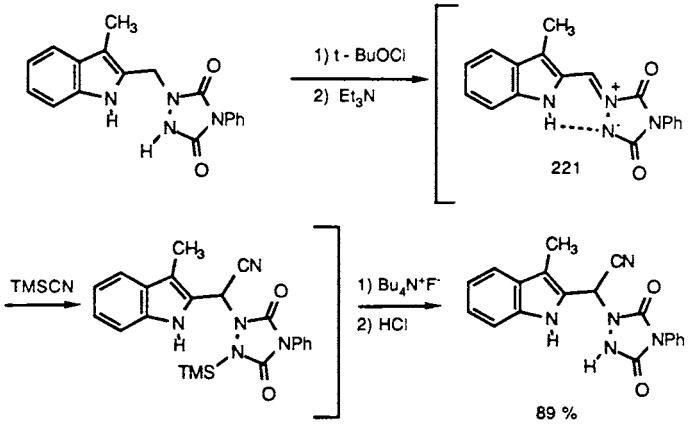


3.7.2. Nitrile Oxides

Acetonitrile oxide was reported to react with several organosilicon reagents, among them TMSCN, to form the corresponding 1,3-adducts.[515] IR, ^{1}H, and ^{13}C NMR were reported on the cyanosilylated product.

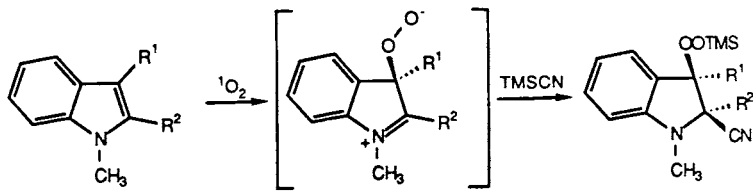
3.7.3. Iminium Imides

A report dealing with nucleophilic additions to triazolinedione ylides can be considered to involve 1,3-cyanosilylation of an iminium imide intermediate **221**, followed by desilylation with fluoride ion.[516]



3.7.4. Other Dipolar Compounds

Cyanotrimethylsilane has been proposed to be an excellent trapping agent for dipolar peroxide intermediates, e.g. **222**.[517a] Other photooxygenation intermediates were similarly trapped. Cyanosilylation of furan photooxygenation products, however, did not appear to involve zwitterionic intermediates.[517b]

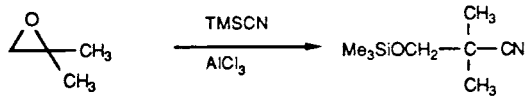


222

3.8. Strained Heterocyclic Compounds

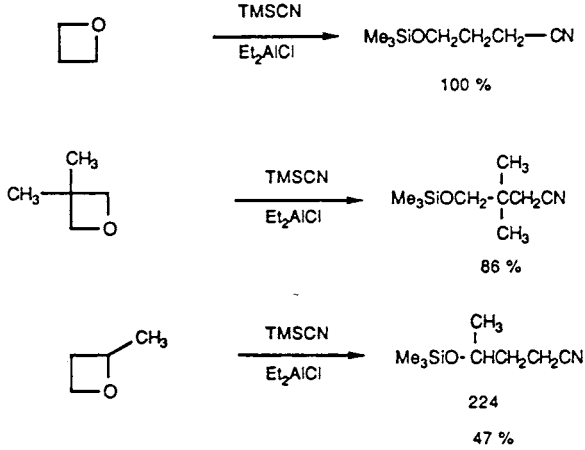
3.8.1. Oxiranes and Oxetanes

Catalysis using Aluminum Lewis Acids. Ring-opening addition of cyanotrimethylsilane (**1**) to oxiranes was first reported by Lidy and Sundermeyer in 1973.[240] They reported 75–93% yields of 2-(trimethylsilyloxy)ethyl nitriles from the aluminum chloride catalyzed addition of **1** to oxiranes. With 2,2-dimethyloxirane, the reaction was reported to take place regiospecifically, producing adduct **223** in which the nitrile group had added to the most substituted carbon of the oxirane.

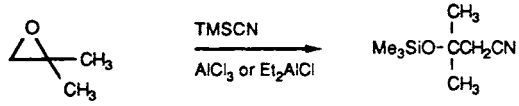


223

The reaction was later extended to oxetanes by Mullis and Weber[518] using diethylaluminum chloride instead of aluminum chloride; no reaction took place in the absence of a catalyst. The authors observed high yields of 3-(trimethyl-

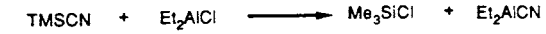


silyloxy)propyl nitriles by reaction of **1** with oxetane and 3,3-dimethyloxetane, but 2-methyloxetane provided the unexpected product **224** in which the regiospecificity of the reaction was opposite to that predicted by Lidy and Sundermeyer.[240] In an effort to resolve this apparent discrepancy, Mullis and Weber[518] examined the reaction of **1** and 2,2-dimethyloxirane employing both aluminum chloride and diethylaluminum chloride catalysts. In both instances, 2,2-dimethyl-3-[(trimethylsilyl)oxy]propionitrile **225** was isolated, i.e., the addition product in which the nitrile function had added to the least substituted carbon of the oxirane—the opposite regiochemistry of that reported by Lidy and Sundermeyer.[240]

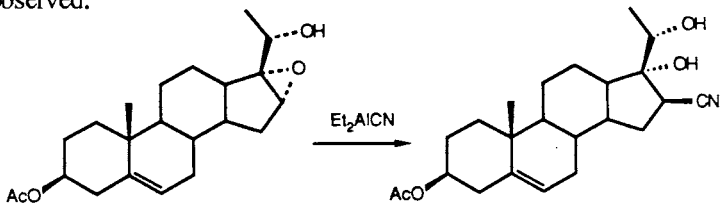


225

Mullis and Weber[518] further reported that 1 itself reacted with diethylaluminum chloride to give chlorotrimethylsilane and diethylaluminum cyanide, the latter of which had earlier been reported to react with oxiranes.[519] In the one case studied

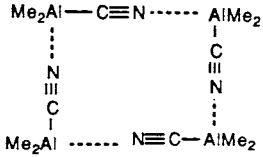


where regiochemical differences could arise, the regiochemistry in which the nitrile moiety was introduced on the least substituted carbon of the oxirane reactant had been observed.[519]



The observed C-nucleophilicity of diethylaluminum cyanide, as later proposed by Spessard et al.[520] to explain differences between aluminum Lewis acid catalysts and others *vide infra*, can be accounted for by HSAB theory. The "hard" nitrogen end of cyanide ion complexes with the "hard" aluminum ion, leaving the "soft" carbon end to attack the relatively "soft" oxirane carbon. Spessard proposed that diethylaluminum cyanide could actually be written as the isonitrile structure **226.** Some support for this kind of arrangement is derived from the reported tetrameric solution structure **227** of dimethylaluminum cyanide.[521]

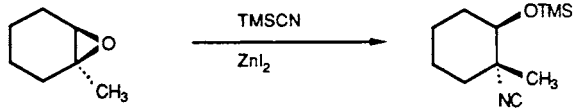
226



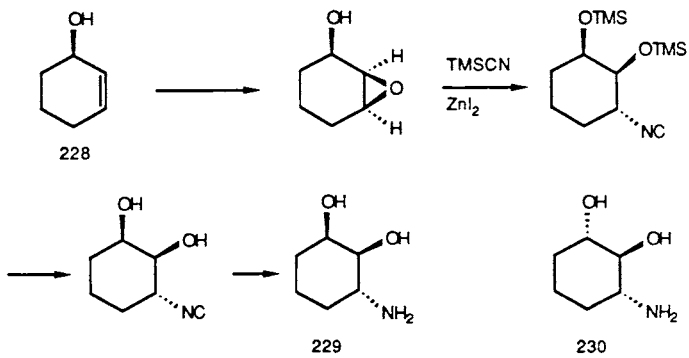
227

Concerning the utilization of the aluminum Lewis acid catalyzed reaction in additional syntheses, a highly efficient asymmetric sythesis of α-amino-β-hydroxyacids employing diethylaluminum chloride catalyzed addition of **1** to oxirane intermediates has been reported.[522] The aluminum chloride catalyzed reaction has also recently been extended to the regioselective synthesis of cyanodeoxy sugars in which a considerable directing effect was shown by neighboring hydroxyl groups.[523]

Catalysis using Zinc Lewis Acids. The discovery that the nature of the addition products of TMSCN with oxiranes was very much dependent on the Lewis acid catalyst was independently reported by Gassman and Guggenheim (using zinc iodide)[524] and by Spessard et al.[520] (employing zinc chloride). Utilization of the zinc(II) catalysts provided 2-(trimethylsilyloxy)ethyl *isonitrile* products instead of the corresponding *nitrile* products obtained with the aluminum catalysts. Furthermore, the regiochemistry of the zinc-catalyzed reaction was opposite to that observed with aluminum, in that the isonitrile function was attached to the most highly substituted carbon of the oxirane reactant.

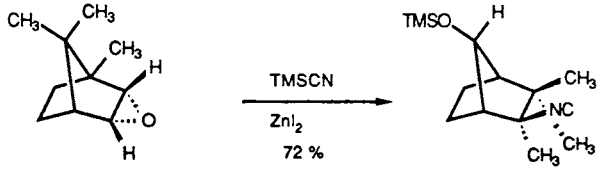


The zinc(II) catalyzed reaction of **1** with oxiranes has provided high-yield syntheses of 2-(trimethylsilyloxy)ethyl isonitriles[525] which have been used as valuable intermediates for the synthesis of 2-hydroxyethyl amines via hydrolysis,[524] of oxazolines by treatment with palladium chloride,[524] and of the corresponding N-methylamine compounds via reduction.[520] The reaction was also extended to the synthesis of compounds in which three contiguous chiral centers have been established.[526] For example, cyclohexenol **228** was converted into amine **229** in an overall 61% yield from the oxirane intermediate; in a similar fashion, the epimer of **228** provided amine **230** in 70% yield.



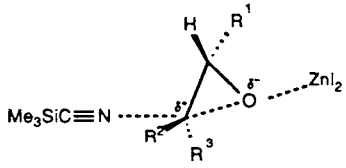
The zinc(II) catalyzed reaction has also been extended to oxetanes.[527,528] High yields of 3-(trimethylsilyloxy)propyl isonitriles resulted which, of course, could readily be converted into useful 3-aminoalcohols. The reaction was again shown to be regiospecific; in all cases the isonitrile function was attached to the most electropositive α-carbon center of the starting oxetane.

Mechanistically, the zinc catalyzed ring opening addition of **1** to oxiranes and oxetanes perhaps can best be described as involving an S_N2 process in which considerable positive charge is developed in the transition state. Support for the S_N2 nature of the reaction is the *trans* stereochemistry of the addition observed in virtually all cases. A further indication that the process is largely S_N2 comes from the observation that *t*-butylcyanodimethysilane reacted 10–20 times slower than did **1**, presumably because of steric crowding in the transition state.[529] That considerable positive charge is developed in the transition state was indicated by the observed regiospecificity in which the isonitrile moiety became attached to the α-carbon atom of the oxirane/oxetane that could best support a positive charge. Also, methyl-substituted oxiranes have been reported to react faster than unsubstituted oxiranes,[524] and certain oxirane reactants which would be particularly prone to rearrange if carbocationic intermediates were involved did in fact provide rearranged products. Thus, the tricyclic oxirane **231** provided approximately 90% rearranged products with the major product being **232**.[530] A useful way of picturing



231 232

the transition state is structure **233** proposed by Utimoto et al.[531] An obvious piece of missing information relevant to discussions of mechanism and transition state structure, however, is a determination of the rate equation for the reaction.



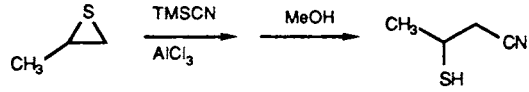
233

Catalysis using Other Lewis Acids. Palladium cyanide, stannous chloride, and trimethylgallium have been reported to catalyze ring opening of oxiranes by TMSCN to afford 2-(trimethylsilyloxy)ethyl isonitrile products in high yield, with the palladium and gallium catalyzed reactions proceeding under milder conditions than those with the zinc catalysts.[531] Boron trifluoride etherate catalyzed the

reaction of **1** with certain anhydro sugars to provide excellent yields (after hydrolysis) of the corresponding hydroxy nitrile derivatives, although certain ketal functions, notably benzylidene ketals, apparently interferred with the normal addition to the oxirane in some instances.[164] Lanthanide compounds such as $SmCl_3$, $CeCl_3$, and $LnCl_3$ catalyzed ring-opening to the corresponding cyano alcohol derivatives in good to excellent yield.[532] Titanium tetraisopropoxide has been shown to be only moderately effective as a catalyst for adding **1** to 2,3-epoxy alcohols to provide cyano alcohol products.[533]

3.8.2. Thiiranes

In analogous fashion with oxirane reactants and aluminum catalysts, aluminum chloride catalyzed reaction of TMSCN with 2-methylthiirane provided the corresponding β-mercapto nitrile **234** in which the cyano group had added to the least substituted carbon atom of the heterocycle.[534] Zinc chloride, zinc bromide, and titanium tetrachloride were ineffective as catalysts. The reaction was apparently of limited scope, since polymerization rather than addition was observed with cyclohexene thiirane.

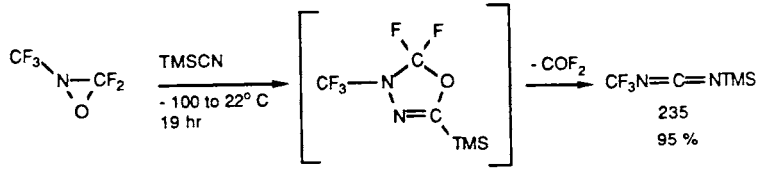


234

43 %

3.8.3. Oxaziridines

Reaction of **1** with 2-(trifluoromethyl)-3,3-difluorooxaziridine resulted in a high yield of 1-(trifluoromethyl)-3-(trimethylsilyl)carbodiimide **235**.[535] The reaction was proposed to take place only with fluorinated oxaziridines and involved cycloaddition followed by rearrangement with loss of COF_2.



235

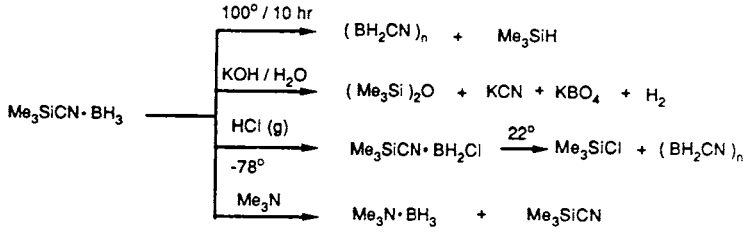
95 %

4.0. CYANATIONS

4.1. Substitution Reactions

4.1.1. Substitution on Elements Other Than Carbon

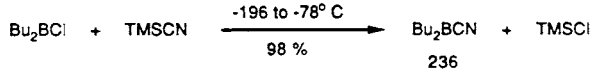
Group III Elements. Many of the early reactions of TMSCN and boron

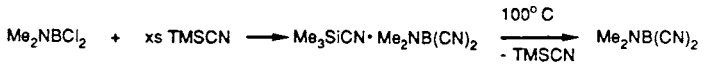


Scheme 8.

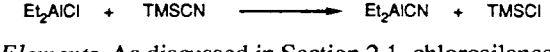
compounds actually originated in Germany during World War II.[536,537] Reaction of **1** and diborane provided a white solid which melted at 69°C and possessed a **1**: BH_3 ratio of 1.03.[20] A summary of the reactions of the adduct is given in Scheme 8, where $(BH_2CN)_n$ is a polymeric product of undetermined structure.

Trimethylborane reacted with **1** and provided a white solid, presumably an adduct as above, although the solid could not be characterized.[538] Adducts with 1 : 1 stoichiometry were also formed with boron halides, but they were much less thermally stable than the borane adduct.[539] Di-*n*-butylboron chloride reacted metathetically with **1** at low temperature to give **236** as a colorless, viscous liquid that was highly aggregated.[540] The reaction of dimethylaminoboron dichloride and an excess of **1** provided a relatively stable adduct; dimethylaminoboron dicyanide could be obtained in pure form by heating the adduct at 100°C.[541]

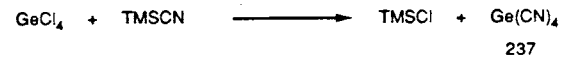




Reaction of either diethylaluminum chloride[518] or triethylaluminum[542] with TMSCN has been shown to provide diethylaluminum cyanide, the latter proceeding in 85% yield at room temperature. These results are pertinent to earlier discussion of the reactions of **1** with enones (see Section 3.2.2.) and oxiranes (see Section 3.8.).



Group IV Elements. As discussed in Section 2.1, chlorosilanes react with **1** by chloride-cyanide interchange to produce new cyanosilanes and TMCS. Germanium halides similarly exchange halogen for cyanide. This reaction has been used to prepare tetracyanogermanium **237**,[19] dicyanodimethylgermanium,[29] and germanium(II) cyanide from germanium(II) fluoride.[543]

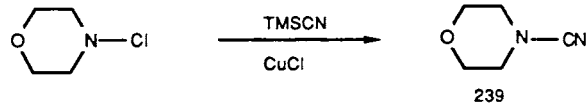


Whereas dimethyltin dichloride was readily converted to the corresponding dicyanide,[29] tin tetrachloride was reported to react with **1** to form product **238** resulting from initial addition followed by substitution of chloride.[544]

$$SnCl_4 + TMSCN \longrightarrow [SnCl_4(TMSCN)_2] \xrightarrow{-TMSCl} SnCl_3CN(TMSCN)$$

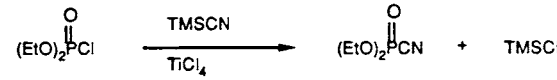
238

Group V Elements. N-Halogenated compounds are N-cyanated by the action of TMSCN. Thus, N-chloromorpholine and **1** gave N-cyanomorpholine **239** in 50%



239

yield.[545] Phosphorous halides also readily exchanged cyanide with **1**.[19,546,547] With certain phosphorous halides, titanium tetrachloride and other Lewis acids



were shown to be effective catalysts by increasing the electrophilicity of the phosphorous.[548–552] Likewise, halide salts of arsenic, antimony, and bismuth formed the corresponding cyanides **240** upon reaction with **1**.[19]

$$MCl_3 + TMSCN \longrightarrow M(CN)_3 + TMSCl$$

M = As, Sb, and Bi — **240**

Group VI Elements. Elemental sulfur has been reported to react with TMSCN to form trimethylsilyl isothiocyanate,[18,59] and certain disulfide linkages were cleaved to the corresponding thiocyanates with **1**.[553]

Sulfur halides readily exchange cyanide with **1**, and many sulfur-halogen compounds with varying sulfur oxidation states have been examined. Thus, reactions of **1** with several kinds of sulfenyl halides and related compounds have been studied, including Cl_3C-SCl,[240] RSCl,[554] ArSCl,[548,554] R_FSCl,[555] $(RO)_2P(O)$-SCl,[556–559] SCl_2,[142,560,561] S_2Cl_2,[142,562] and $(SCN)_2$.[562] Perhaps the most generally useful report of the reactions of sulfenyl chlorides with **1** is that by Harpp and co-workers.[554] High yields (70–94%) of thiocyanates **241** were obtained at room temperature by dropwise addition of **1** to sulfenyl chlorides in very dry acetonitrile.

$$RSCl + TMSCN \longrightarrow RSCN + TMSCl$$

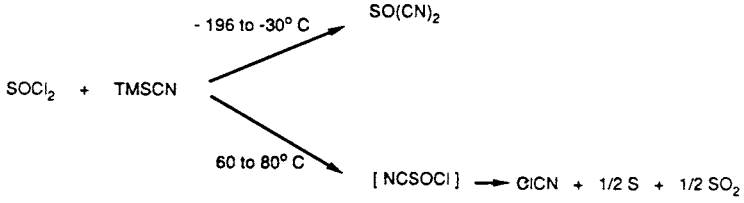
241

$$ArSOCH_3 + TMSCN \longrightarrow ArSCN + (CH_3)_3SiOCH_3$$

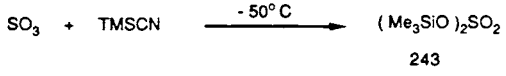
242

Harpp et al.[563] have also shown that alkyl arenesulfenates **242** react with **1** in a similar fashion.

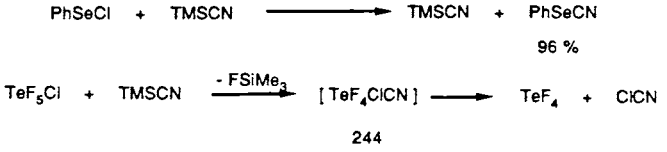
Sulfur(IV)- and sulfur(VI)-halogen compounds also undergo reaction with TMSCN. Thionyl chloride reacted with **1** to provide thionyl cyanide when the reaction was conducted in the cold,[560] while cyanogen chloride was produced at



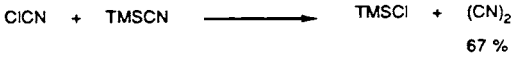
elevated temperatures.[548] Sulfuryl chloride also gave cyanogen chloride when reacted with **1** at 60–80°C.[548] Sulfur trioxide provided bis(trimethylsilyl)sulfate **243** in 72% yield.[562]



Benzeneselenenyl chloride reacted with TMSCN to give phenyl selenocyanate in high yield,[564,565] while tellurium chloride pentafluoride was proposed to react with **1** to form an intermediate cyanated substitution product **244** that decomposed to give cyanogen chloride and tellurium tetrafluoride.[566]

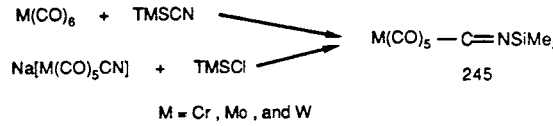


Group VII Elements. Chlorine and bromine reacted with TMSCN to provide the corresponding chlorotrimethylsilanes and bromotrimethylsilanes.[545] A variation of this reaction involving interaction with cyanogen chloride was shown to be a viable method for the preparation of dicyanogen.[567]

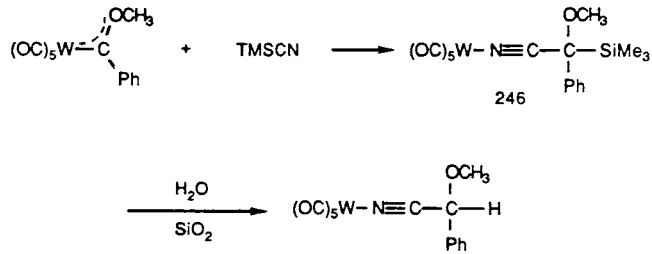


Transition Metals. In general, transition metal complexes react with the isonitrile form of TMSCN resulting in displacement of a ligand and formation of metal–carbon bonds. Thus, titanium complexes were observed to form Ti–C bonds rather than the stronger Ti–N bonds.[568] Similarly, Group VIB metal carbonyl compounds reacted with **1** in its isonitrile form, producing complexes **245**.[26] These

complexes were also shown to be available via silylation of the corresponding sodium salts.[569]

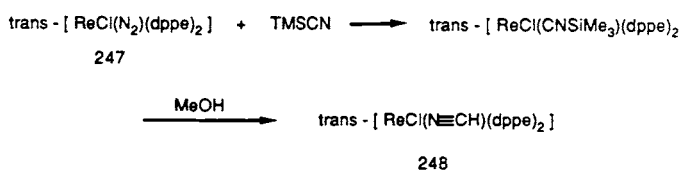


Displacement of nitrogen from tungsten and molybdenum complexes by **1**, followed by methanolysis, resulted in the first incorporation into a metal complex of the aminocarbyne group, CNH_2.[570] Reaction of pentacarbonyl[methoxy-(phenyl)carbene]tungsten with TMSCN resulted in coupled insertion product **246**; subsequent replacement of the trimethysilyl group by hydrogen was effected by wet silica gel.[571]



Reaction of TMSCN and pentacarbonyliron resulted in displacement of CO by the isonitrile form of **1** in a reaction similar to that noted above.[58,117,572]

Addition of **1** to rhenium complex **247** provided the corresponding isonitrile complex. Methanolysis was facile, generating complex **248** containing the HCN ligand.[570]

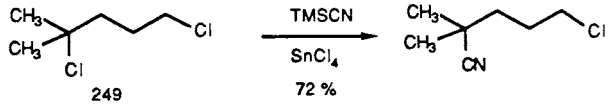


Finally, silver and mercuric oxides also have been reported to undergo exchange reactions with **1**, leading to the corresponding transition-metal cyanides.[18,58]

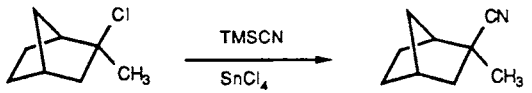
4.1.2. Substitutions on Carbon

Halide Substitutions. Halide substitutions at carbonyl carbon, i.e., the conversion of acyl halides into acyl cyanides, are very facile and were discussed for mechanistic reasons under cyanosilylations in Section 3.3.2. Cyanation of tertiary

alkyl halides, on the other hand, has been a long-standing problem in organic synthesis. Elimination competes with substitution when using cyanide ion, while N-alkylation and the Ritter reaction often occur under S_N1 conditions. Reetz and Chatziiosifidis,[573,574] however, observed some rather remarkable reactions of tertiary alkyl chlorides and TMSCN. In the presence of stannic chloride, only tertiary chloride and not primary chloride was replaced by nitrile in dichloride **249**, and exo-2-chloro-2-methylnorbornane was converted into the exo-nitrile **250** with 100% stereoselectivity.



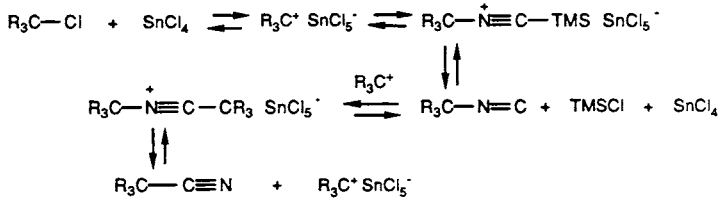
249



250

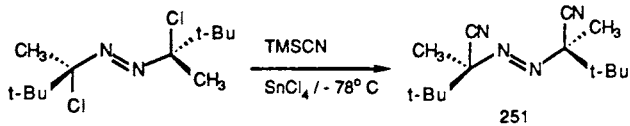
Reetz and co-workers[575] later explored these observations in greater detail in order to optimize conditions and determine a reaction mechanism. The reaction was extended to many other tertiary alkyl halides and was found to fail only when electron-withdrawing groups were present on the carbon bearing the halogen. Optimal conditions to achieve >80% conversions to nitrile products involved use of 25 mol % stannic chloride at room temperature for about 36 h. The proposed mechanism, for which considerable support was provided, involved a cationic chain mechanism as shown in Scheme 9. A key intermediate in the mechanism is the isonitrile, which could be detected under certain conditions. Stannic chloride was shown to catalyze the isonitrile to nitrile rearrangement.

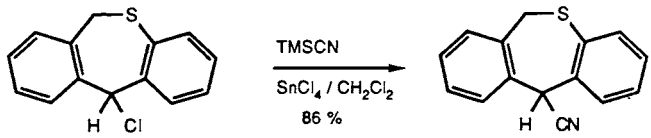
More recently, the above method has been applied to a stereospecific synthesis of α,α′-dicyanoazoalkanes (e.g., **251**),[576] 6,11-dihydrodibenzo[b,e]thiepin-11-carbonitrile **252**,[577] and N-(α-cyanobenzyl)benzimidoyl chloride **253**.[578] Also, the

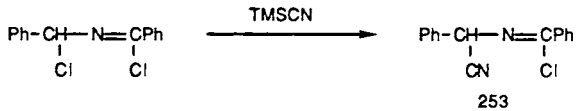


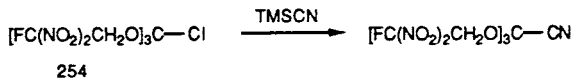
Scheme 9.

corresponding nitrile-for-chloride substitution products were obtained from halo ethers such as **254**[579,580] and from α-halo thioethers,[581] with no competitive displacement of an ether group being observed (see *Ether Substitutions* below). No catalyst was employed in the former reactions.[579–580]

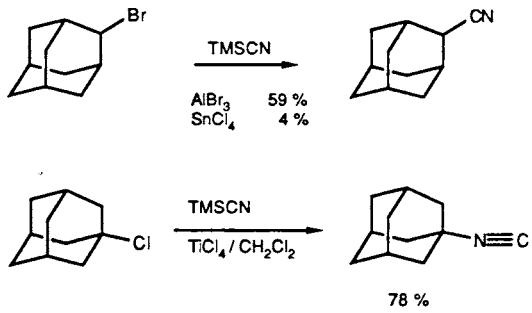




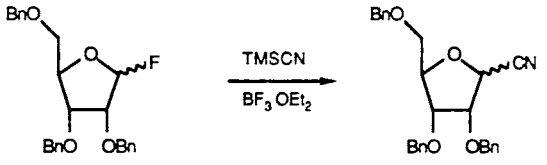




Olah and co-workers[582] have shown that with adamantyl halides higher concentrations of stannic chloride and refluxing conditions result in improved yields of the corresponding nitriles. Aluminum bromide also effectively catalyzed the reaction in certain instances when stannic chloride did not. In contrast, Sasaki and co-workers[583] had reported earlier that 1-adamantyl chloride was converted into the isonitrile in 78% yield by treatment with **1** and titanium tetrachloride. This latter report has not been elaborated in subsequent literature.



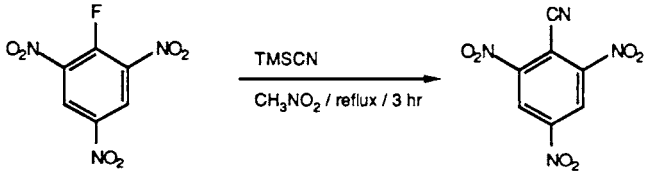
Fluoride displacement from glycosyl fluoride derivatives by TMSCN in the presence of boron trifluoride etherate has been observed.[584,585] Furanosyl fluorides reacted non-stereospecifically, providing equal quantities of α- and β-anomeric nitriles **255**. Pyranosyl fluorides, however, reacted more stereoselectively. In one report,[584] the reaction provided a 90% overall yield with a 3 : 1 α : β-anomer ratio; in the other report,[585] in which isocyanide products were isolated under certain conditions, only the α-isomer **256** was obtained (85% yield).



255

256
predominantly

Nucleophilic aromatic substitution reactions in which TMSCN is the cyanide source were first reported by Chaykovsky and Adolph.[586] Aromatic fluorides which possessed multiple, powerful electron-withdrawing groups gave aromatic cyanides when reacted with **1**. Thus, picryl fluoride gave picryl cyanide **257** in 75% yield when refluxed with **1** in nitromethane solution. Picryl chloride, however, was unreactive. The importance of multiple electron-withdrawing groups was indicated



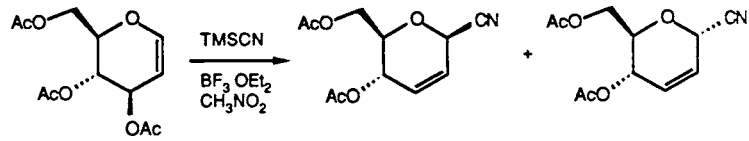
257

by the observation of only a 26% yield of nitrile from 2,4-dinitrofluorobenzene and no reaction with 2-nitrofluorobenzene.

Aromatic cyanation has been extended to aryl iodides (aryl chlorides and bromides were unreactive) by the use of a palladium(0) catalyst. Under these conditions, electron-withdrawing groups were unnecessary.[587] With **1** as the cyanating agent, refluxing iodobenzene with tetrakis(triphenylphosphine)palladium in triethylamine solvent provided benzonitrile in 88% yield. The reaction

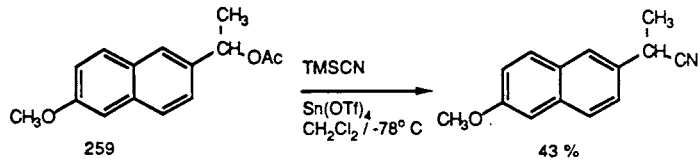
was shown to tolerate a variety of substituents on the ring including methyl, chloro, bromo, methoxy, and carbomethoxy.

Carboxylate Substitutions. Replacement of acetate by cyanide with TMSCN as the cyanide source was reported by De Las Heras and co- workers[588] to occur in a series of acetylated glucals by an S_N2'-like process. 3,4,6-Tri-O-acetyl-D-glucal **258** gave the two 2,3-unsaturated pyranosyl cyanide α- and β-anomers in 57% and 42% yields, respectively, when reacted with **1** in the presence of boron trifluoride etherate.



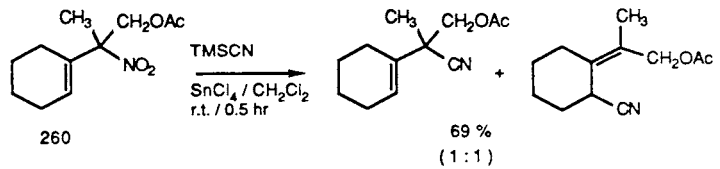
258

Substitution of nitrile for acetate in more conventional alkyl acetates such as **259** has been reported to occur in moderate yield.[589]



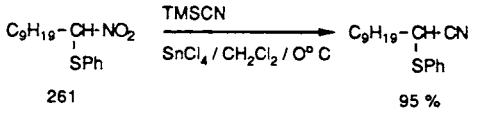
259 43 %

Nitro Substitutions. The nitro group was shown to be effectively replaced by nitrile in a Lewis acid catalyzed reaction with **1**, provided the nitro group occupied an allylic or benzylic position.[590] Although this reaction took place readily under mild conditions and was tolerant of other functional groups such as ester, nitrile, and carbomethoxy, an unfortunate aspect was poor regiochemical control as indicated with allylic nitro compound **260**. A low yield (27%) of cyanated product was observed with the one benzylic nitro compound examined.



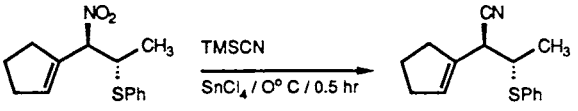
260 69 % (1 : 1)

Substitution of nitro by cyano in α-nitro sulfides proceeded very readily and in excellent yield.[591] The reaction of **1** with sulfide **261** was complete in 20 min at 0°C when a full equivalent of stannic chloride was employed. The reaction was proposed to proceed via an S_N1 mechanism involving thio-stabilized carbocationic intermediates. Extension of the reaction to β-nitro sulfides clearly demonstrated participation of the β-phenylthio group and that episulfonium ion intermediates were involved.[592] Because of this type of intermediate, regiochemical control was



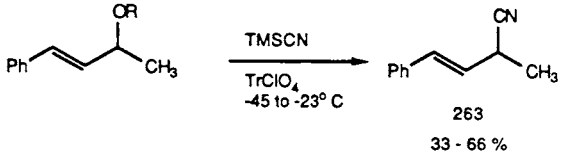
261 95 %

often poor, although an exception was seen with compound **262.** The anti isomers were reported to react faster than the syn isomers in all cases studied. In fact, only the anti isomer was consumed when a 1 : 1 mixture of the syn and anti β-nitro sulfides **262** were allowed to react for 5 min; the syn β-nitro sulfide was recovered unchanged.

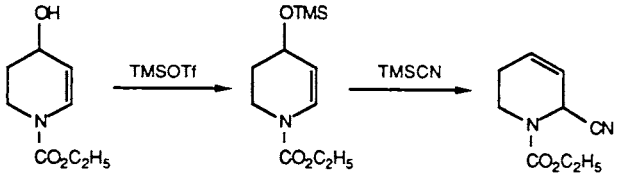


262 (anti) 80 % (100 % anti)

Ether Substitutions. Substitution of an ether group by a cyano group upon reaction with TMSCN requires activation of the ether function. The ring strain present in small ring heterocycles such as oxiranes and oxetanes apparently provides enough activation to allow these compounds to react readily with **1** in the presence of Lewis acids (see Section 3.8). Allylic ethers are also suitably activated, and have been reported to react with **1** in the presence of trityl perchlorate affording β,γ-unsaturated nitriles such as **263** in moderate to good yields.[593] Kozikowski and Park[594] reported the S_N2' displacement of allylic silyl ether **264.**



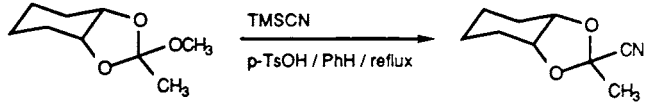
263
33 - 66 %



264 70 %

A final activated ether that is reactive with **1** and is cyanated under proper catalytic conditions is the ketal. The remainder of this section is devoted to the large body of literature describing reactions of ketals and related derivatives with **1.**

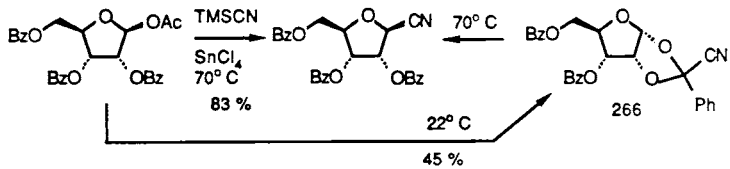
The ability of TMSCN to react with ketals and replace one of the ether functions with a nitrile group was originally reported by Becsi and Zbiral[595] in a study examining cyclic orthoesters. Three orthoesters derived from *cis*- and *trans*-1,2-cyclohexanediols were examined, among them orthoester **265**. The methoxy groups were replaced with excellent selectivity (no ring opening) in 90, 70, and 84% yields; in some instances, *p*-toluenesulfonic acid was employed as a catalyst.



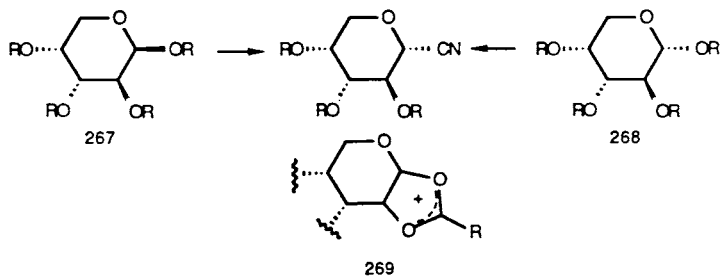
265 70 %

The reaction was extended to simple ketals by Utimoto and co-workers.[596] Treatment of the ketal with **1** in the presence of boron trifluoride etherate or stannous chloride resulted in 64–97% yields of α-alkoxynitriles.

Application of the reaction to carbohydrate derivatives was reported simultaneously by Utimoto and Horiie[597] and by De Las Heras, and Fernández-Resa[598] In these systems, the more reactive derivatives were those in which the ketal function contained a replaceable carboalkoxy group at carbon-1 of a pyranose or furanose ring. Utimoto and Horiie obtained an excellent yield of a furanosyl cyanide when the corresponding acetate was heated at 70°C with **1** and stannous chloride. Allowing the reaction to stir at room temperature, however, produced a 1,2-O-(1-cyanobenzylidene)ribofuranose product **266** which was converted into the furanosyl cyanide on warming.



De Las Heras et al.[598] reported that boron trifluoride etherate catalyst and nitromethane solvent provided improved yields. They also isolated dioxolane structures similar to Utimoto's above which were indicative of participation by the neighboring 2-O-acyl group. Isolation of the dioxolanes plus the observation that both pyranosyl acetate anomers **267** and **268** gave the same pyranosyl cyanide led



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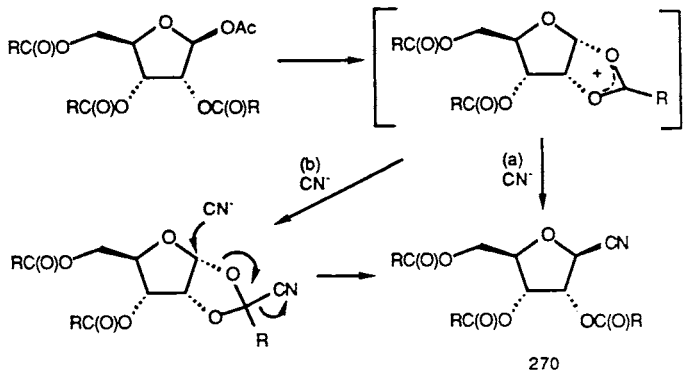


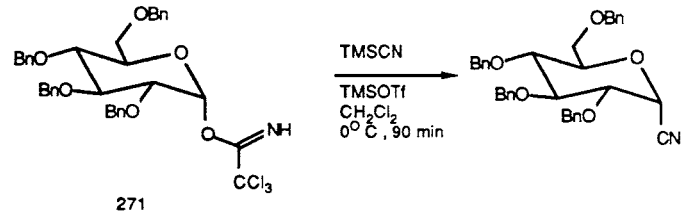
270

Scheme 10.

the authors to propose that the reaction involved acyloxonium ion intermediates such as structure **269.**

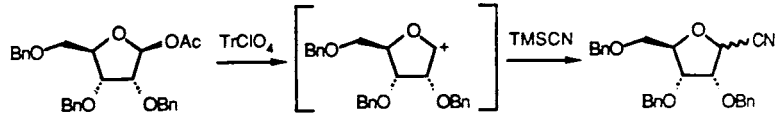
Reetz and co-workers, in a study of the cyanation of simple α-acetoxy ethers, obtained a 98% yield of a ribofuranosyl cyanide using stannic chloride in methylene chloride at room temperature.[575] These workers proposed that neighboring group participation was probably responsible for the retention of configuration observed in the reaction. Utimoto et al.[194] proposed the detailed mechanism shown in Scheme 10 involving neighboring group participation by the 2-O-acyl group and acyloxonium ion formation; retention of configuration was accomplished by a double inversion at C–1. Product **270** was proposed to be formed either directly (path *a*) or from the 1,2-O-(1-cyanoalkylidene) intermediate (path *b*).

More recent reports of cyanations of O,O-ketals of carbohydrate derivatives have appeared in which the stereochemical outcome has not been explained and may not be easily rationalized by the steps in Scheme 10. The trichloroacetimidate derivative **271** provided only the α-nitrile product in 87% yield.[599,600]

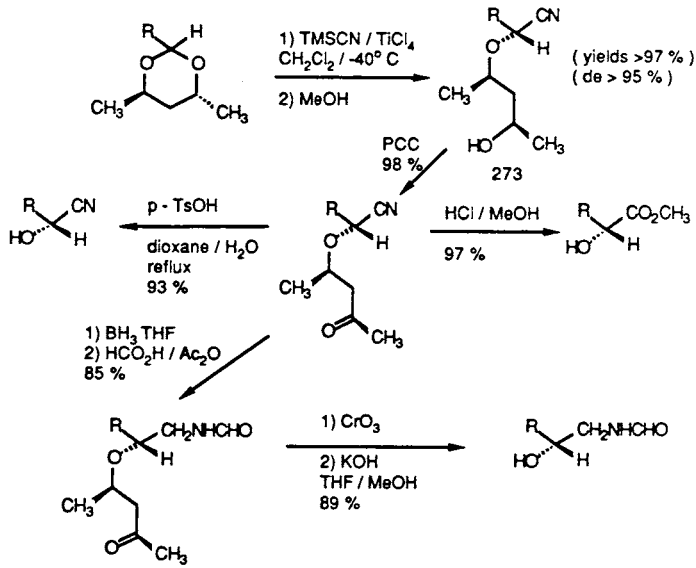


271

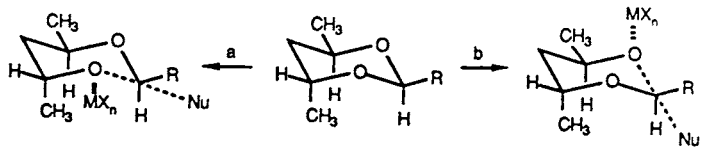
Also relevant are studies employing trityl perchlorate as catalyst.[601,602] When the reaction of acetate **272** with TMSCN was conducted in dimethoxyethane, an α/β ratio of 63/37 was observed (97% yield). When the reaction was conducted in diethyl ether, however, an α/β ratio of 93/7 was obtained (93% yield).



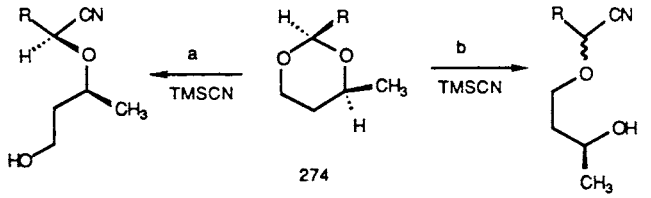
Utilization of the cyanation reaction of O,O-ketals in asymmetric synthesis was first developed by Johnson and co-workers.[603,604] A series of chiral ketals, readily available from aldehydes and (R,R)- or (S,S)-pentane-2,4-diols, provided cyanohydrin ethers **273** upon treatment with **1** and titanium tetrachloride. These chiral cyanohydrin ethers were further converted into optically activecyanohydrins, β-aminoalcohols, and α-hydroxyesters with ee's of 90+%. Predominant formation of one diastereomer upon reaction with **1** was explained as originating from cleavage of the C–O bond which minimizes a 1,3-diaxial H/Me



interaction. In path *a*, the 1,3-H/Me interaction is lessened because of bond lengthening; this is not the case with path *b*.



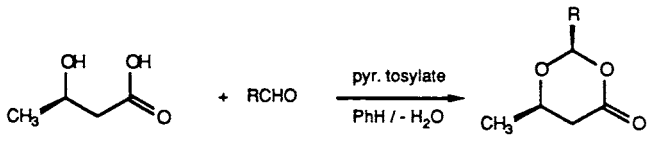
Ketals **274** derived from 1,3-diols having a single chiral center were also examined.[604] Here the resultant adduct could be either a primary (path *a*) or a secondary (path *b*) alcohol. The cyanation reaction was found to be extremely



274

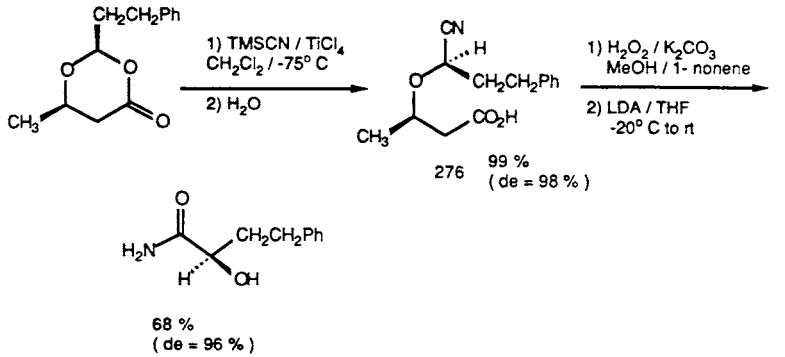
sensitive to conditions, providing 1 : 1 to 99 : 1 mixtures of primary : secondary alcohol products depending on rates of addition of reagents and reaction temperature. Optical yields varied; in one procedure a 71% ee was obtained from a ketal which was derived from an alcohol of 80% optical purity.

Seebach et al.[605] made an advancement in asymmetric syntheses of this kind utilizing 1,3-dioxan-4-ones **275** as chiral substrates. These 1,3-dioxanones offer



275

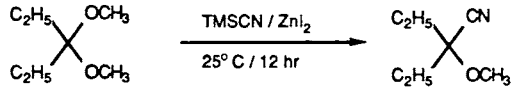
several advantages: 1) the ketal oxygens are of vastly different nucleofugacities; 2) both enantiomers of 3-hydroxybutanoic acid are available and inexpensive; 3) the preparation of compounds **275** proceeds in 70–90% yield, providing a 9 : 1 *cis* : *trans* mixture from which pure cis may be obtained by recrystallization; and 4) removal of the chiral "auxillary" after ring opening requires a simple β-elimination. Reaction with TMSCN in the presence of titanium tetrachloride provided the optically active cyanohydrin derivatives, e.g., **276.**



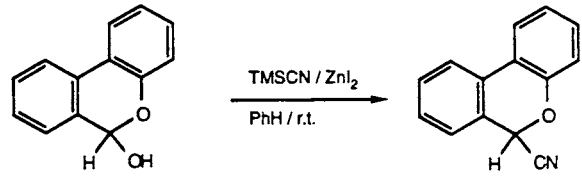
276 99 % (de = 98 %)

68 % (de = 96 %)

Kirchmeyer et al.[606] extended the reaction to ketals derived from ketones, obtaining product yields of 63–87%.



The cyanation reaction was first applied to α-ketols in a synthesis of 6H-dibenzo[b,d]pyran-6-carboxylic acid derivatives.[607] Reaction of 6H-dibenzo[b,d]pyran-6-ol, for example, with **1** and zinc iodide provided the corresponding nitrile **277** in 90% yield. By contrast, α-ketol **278** yielded only the corresponding silyl ketal; no cyanated product was detected.[229]



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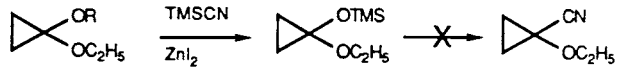
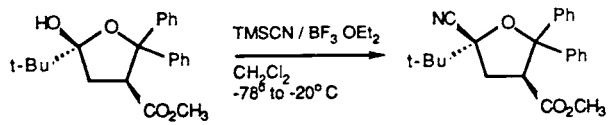


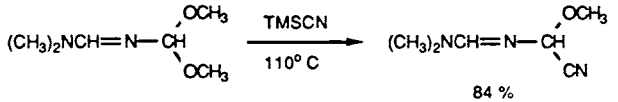
The cyanation of γ-lactols with TMSCN was found to be stereoselective, with cyanation of lactol **279** being one of the more stereoselective reactions investigated.[608] The reaction was proposed to involve oxonium ions formed by com-



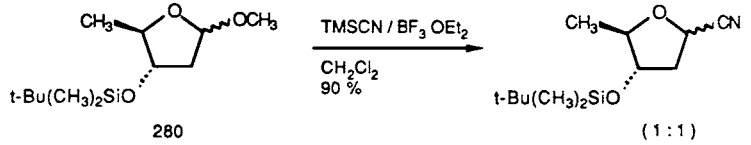
plexation with the Lewis acid catalyst followed by addition of the nucleophile from the more accessible side, leading to the observed product. More recently, it was shown that use of *t*-butylcyanodimethylsilane rather than **1** resulted in increased diastereoselectivities.[609]

The cyanation of ketals has been extended effectively to a series of formamidine

derivatives.[610] Reaction took place in the absence of catalyst at elevated temperature.

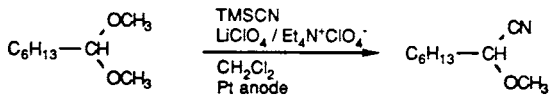


Another development that has refined the cyanation procedure is a recent report which disclosed that boron trifluoride etherate provided no detectable ring opening with cyclic ketals, e.g., **280**.[611] Utimoto et al.[194] had earlier shown that stannic chloride caused significant ring opening to occur.



280 (1 : 1)

Electrogenerated acids have been utilized to catalyze the cyanation reaction.[158,612,613] In one example, heptanal dimethyl ketal and TMSCN were electrolyzed in methylene chloride using platinum electrodes in an undivided cell. On workup, the cyanated product **281** was obtained in 89% yield. The nature of the supporting electrolyte was important as lithium tetrafluoroborate or tetraethylammonium tosylate gave no product.

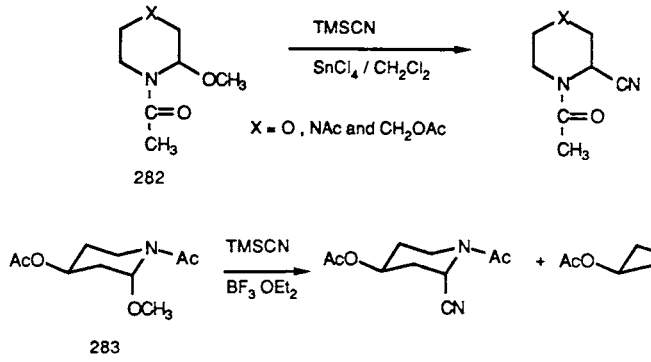


281

The cyanation of O,O-ketals by TMSCN has been extensively utilized in synthesis. Reports include a stereoselective synthesis of aspternic acid;[614] preparations of 5-O-benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl cyanide, and the corresponding O-2,3-carbonate and O-2,3-benzeneboronate derivatives;[615] the preparation of 2-β-ribofuranosylselenazole-4-carboxamide;[616] the preparation of pharmacologically active secondary amines;[617] the synthesis of 5,6-diphenyl-2-methylene-1,4-dioxane-3-one;[618] and the synthesis of pleuromutilin[619].

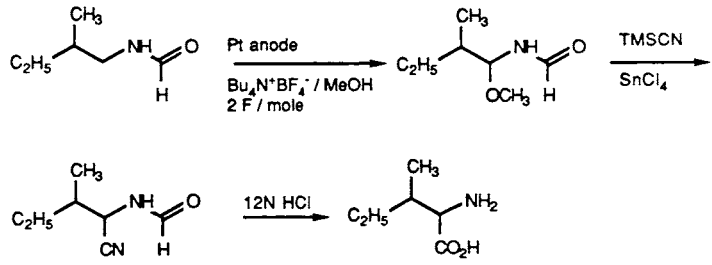
The cyanation of O,N-ketals using TMSCN and a Lewis acid was originally reported by Asher et al.[620] Piperidine, morpholine, and piperazine heterocycles **282** which contained an α-methoxy group underwent cyanation in high yield upon treatment with **1** and stannic chloride. *Trans*-N-acetyl-2-methoxy-4-acetoxy-

piperidine **283** provided an equal mixture of the two nitriles, indicating that the reaction was not stereospecific.

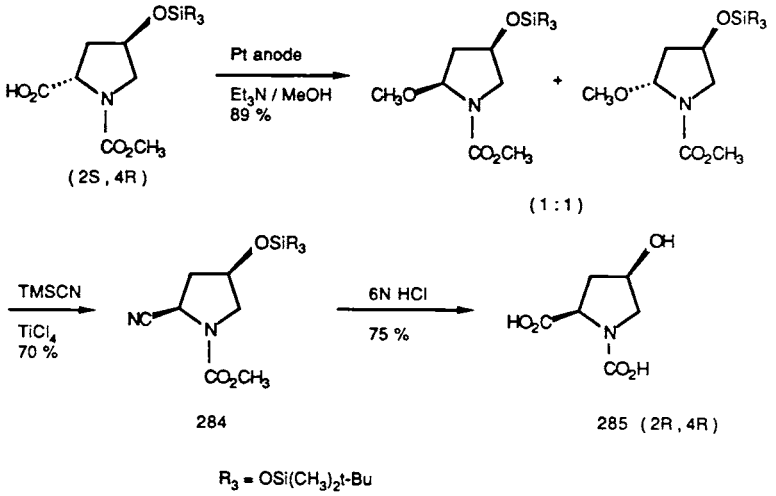


An emphasis of the Anteunis group has been to utilize this cyanation reaction as a key step in the overall transformation of primary amines into aminoacids.[621] This transformation, outlined in Scheme 11, involves anodic oxidation of a protected primary amine to introduce an α-methoxy group, substitution of the methoxy group by cyano using **1**, and hydrolysis to the aminoacid.

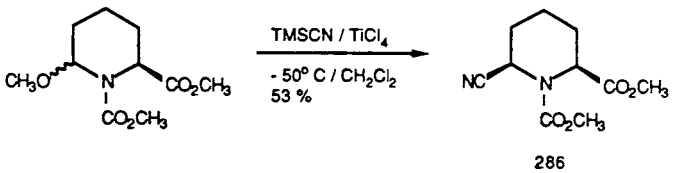
Aminoacids have in turn been anodically oxidized in methanol to replace carboxyl with methoxy. These O,N-ketal derivatives were then reacted with **1** to introduce the nitrile functional group.[622,623] Titanium tetrachloride was utilized as the catalyst, and high diastereoselectivities (>90%) were observed. For example, (2S,4R)-hydroxyproline, after O-silylation, was anodically oxidized to a 1 : 1 mixture of the O,N-ketals. The (2R,4R)-isomer **284** was essentially the only cyanation product of this mixture, however, as subsequently indicated by hydrolysis to aminoacid **285**. The overall displacement of methoxy by nitrile resulted in exclusively a *cis* configuration between the 2-cyano and 4-hydroxy groups.



Scheme 11.

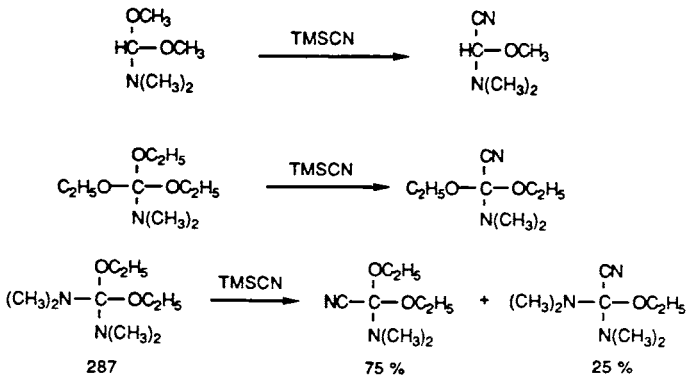


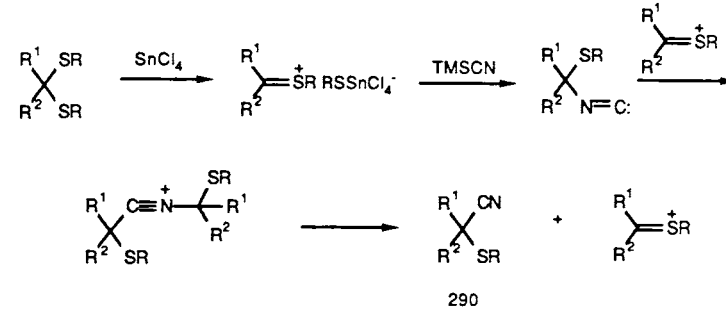
The *cis* configuration was also observed with products from reactions of **1** and 2-methoxy-6-substituted piperidines. An α-methoxy piperidine derivative of unspecified stereochemistry with regard to the methoxy group gave only the *cis* substitution product **286** when treated with **1** and titanium tetrachloride.[624]



286

The cyanation reaction was applied to various orthoester and orthocarbonate derivatives by Kantlehner and co-workers.[625] In most instances, the ether function was replaced by nitrile; only with the orthocarbonate derivative **287** was the N-substituent replaced and then not exclusively.

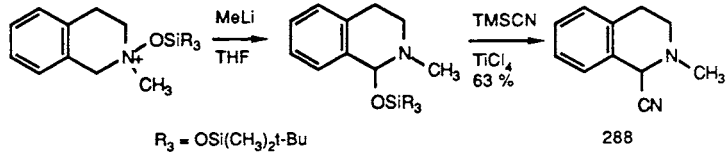




290

Scheme 12.

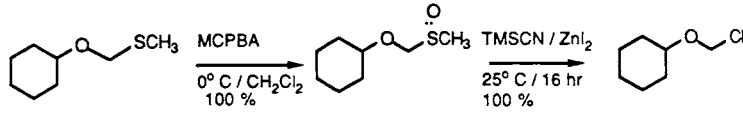
The silyloxy moiety was shown to be a useful leaving group in the preparation of nitrile **288**.[626]



R_3 = $OSi(CH_3)_2t$-Bu 288

The cyanation of O,N-ketals has also been applied in the syntheses of 2-cyano indoles,[627] 3-cyanobenzoxazines,[628,629] 6-α-cyanopenicillins,[630] N-1-cyano-2,2,2-trifluoroethyl-N-alkyl-anilines,[631] and biotin[632].

O,S-Ketals were reported to be unreactive with TMSCN in the presence of stannic chloride.[633] When the thio group was oxidized to sulfoxide, however, reaction took place very cleanly. Thus, methylthiomethyl cyclohexyl ether was transformed into cyanomethyl cyclohexyl ether **289** in quantitiative yield.



289

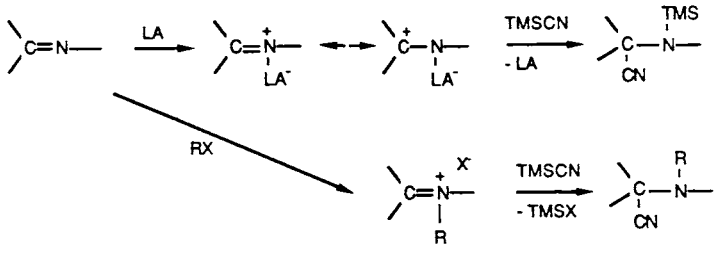
S,S-Ketals were smoothly cyanated by **1** in the presence of stannic chloride.[634] The yields of α-cyanosulfides **290** obtained were generally in the range of 80–95%. The proposed mechanism was analogous to that proposed for the cyanation of alkyl halides (Scheme 12).

4.2. Addition Reactions

4.2.1. Iminium Salts

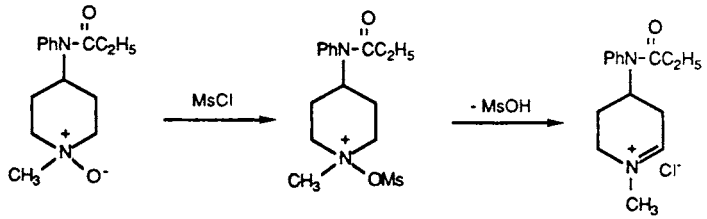
As discussed in Section 3.5.1, imines react with TMSCN when complexed by

a Lewis acid (LA) to provide the cyanosilylated adducts. Iminium salts **291** are already activated towards nucleophilic attack and, while cyanosilylation is not possible, cyanation can readily occur.



291

Reports of the reaction of **1** and iminium salts that are not part of an aromatic heterocyclic ring are relatively rare. Essawi and Portoghese[635] examined the reaction of **1** with the iminium salt **292** derived from an N-methylpiperidine-N-oxide/mesyl chloride adduct. The stereospecificity observed in the aminonitrile.



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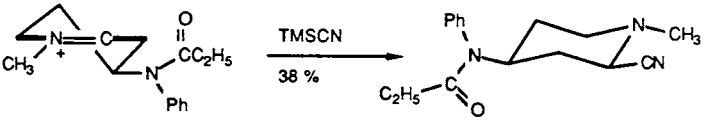
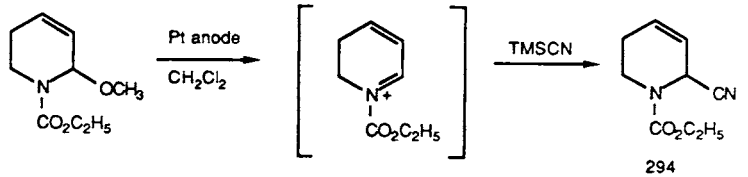
addition product **293** was surprising and was attributed to kinetic factors, with reaction occurring from a chairlike transition state without steric interference from the 4-substituent.



292 **293**

One other example with nonaromatic iminium groups was reported by Torii and co-workers.[636] Employing electrogenerated acid as the catalyst to form the iminium salt intermediate, reaction with **1** provided the 2-cyanopiperidine **294** in 50% yield.



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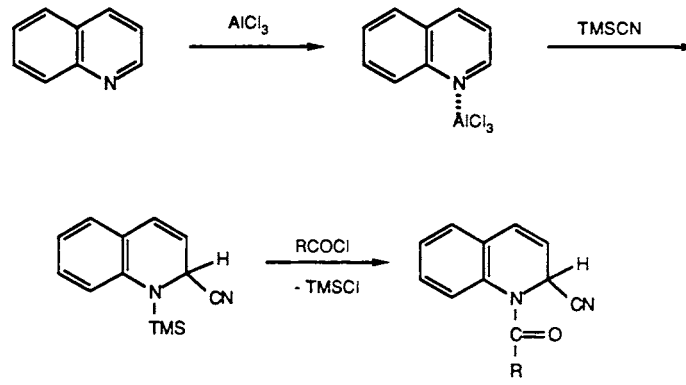
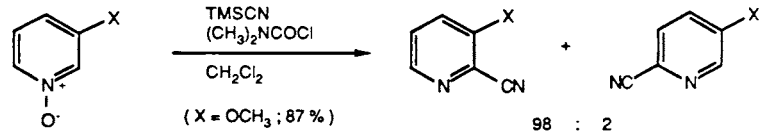


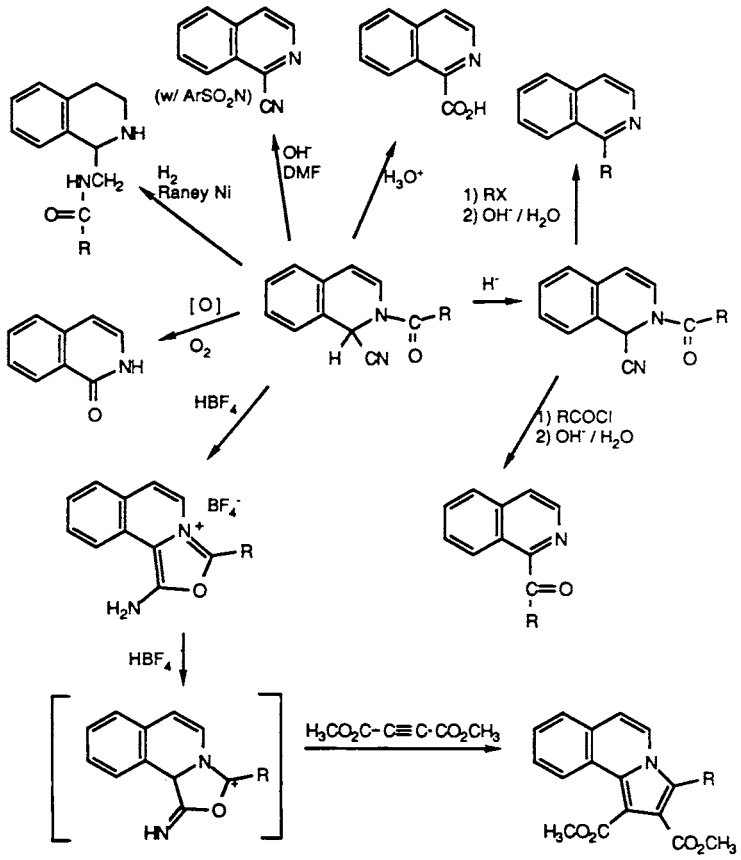
Scheme 13.

Investigations of cyanation reactions of iminium salts contained within an aromatic ring are numerous. The carbon–nitrogen double bond in these aromatic heterocycles still requires activation before reaction will occur with TMSCN, however, and this has most commonly been accomplished with an acid chloride/Lewis acid mixture, giving rise to so-called Reissert compounds (Scheme 13). The reaction is usually conducted by adding the acyl chloride to a slurry of the heterocycle, aluminum chloride, and **1** in methylene chloride. The procedure was originated by Ruchirawat and co-workers[637] but has been extended, largely by Popp and co-workers, to a wide variety of nitrogen-containing heterocycles. The Reissert compounds produced (70–90% yield) can be hydrolyzed to the corresponding carboxylic acid as is done in the classical Reissert reaction and are also valuable synthetic intermediates. Some of this chemistry is outlined in Scheme 14.[638–640]

Besides quinolines[637,641] and isoquinolines,[637,642–646] many other nitrogen heterocycles have been converted to Reissert compounds using **1** as the cyanide source. These heterocycles include ellipticines,[647–649] quinine,[647] phthalazines,[648,650–652] phenanthrolines,[653] quinazoline,[654–658] quinoxaline,[659] cinnoline,[654] pyridines,[660,661] pyrimidine,[662–664] pyridazine,[662] pyrazines,[655,665] carbolines,[666,667] phenanthridine,[644,668] benzothiazole,[669,670] benzoxazole,[669] and benzimidazole[670].

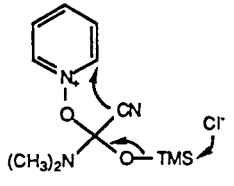
An interesting and useful variation of the Reissert chemistry, leading to high yields of aromatic nitrile products, employs aromatic N-oxides, TMSCN, and dimethylcarbamoyl chloride. This procedure was developed by Fife and provided 2-cyano derivatives in >90% yields.[671,672] The regioselectivity of the reaction was





Scheme 14.

shown to be dependent on the X substituent, with *o/p* directing substituents (in electrophilic aromatic substitutions) such as methyl, methoxy, hydroxy, and chloro leading to cyanation at the 2-positions in 90% selectivity. With *m*-directing substituents, such as cyano and carbomethoxy, cyanation took place with approximately equal selectivity at the 2- and 6-positions. The proposed mechanism is shown in Scheme 15. The lack of cyanation at the 4-position also suggested an "intramolecular delivery" of cyanide. The author proposed structures **295** and **296**



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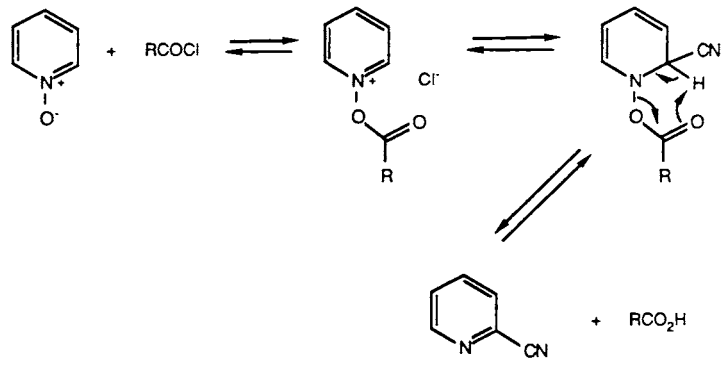
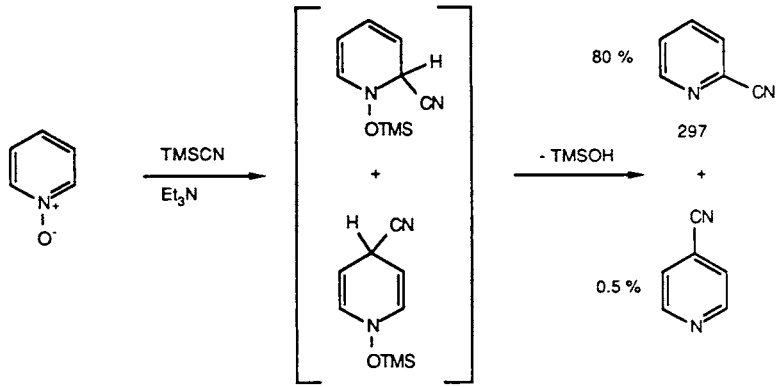


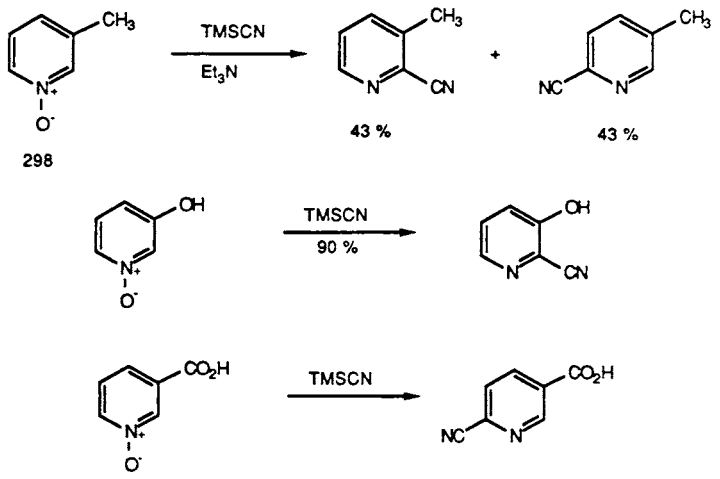
Scheme 15.

as possibilities. Fife's method has been utilized to synthesize 1-cyanoisoquinoline[673] and 6,6′-dicyano- 2,2′-dipyridylmethanol[674].

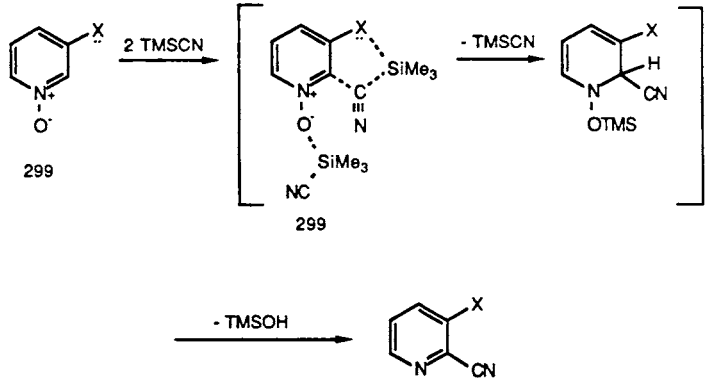
Vorbruggen and Krolikiewicz discovered that activation of aromatic N-oxides need not necessarily be accomplished using an acid chloride (or equivalent) in classical Reissert–Henze fashion.[675,676] Reaction of the N-oxide with 3–4 equivalents of TMSCN in the presence of triethylamine produced chiefly 2-cyanated products (e.g., **297**) in good-to-excellent yields. The reaction was thought to take place by cyanosilylation of the N-oxide followed by triethylamine assisted



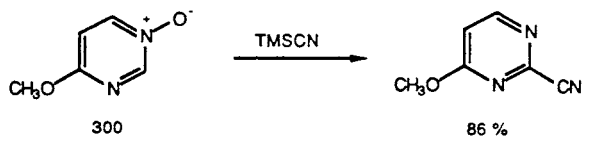
1,2-elimination of trimethylsilanol. Although the reaction was regioselective for the α-carbon positions, selective cyanation of the 2- or the 6-positions was not as easily accomplished as with Fife's method. 3-Picoline N-oxide **298**, for example, afforded a 1 : 1 mixture of the 2- and 6-cyanated products in 86% overall yield. Some substituents, however, directed the cyanation to the same ring positions that were observed with Fife's method.



Sakamoto and co-workers investigated substituent effects in pyridine N-oxides in greater detail by examining a series of 3-substituted derivatives.[677] They concluded that when the 3-substituent had an available lone pair of electrons, cyanation occurred chiefly in the 2-position. Intermediate structures such as **299** were proposed to account for this effect.



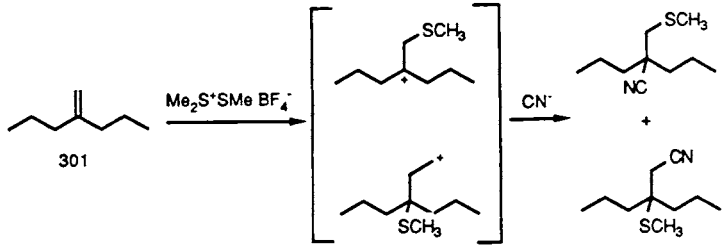
The reaction was also extended to pyrimidine N-oxides by Yamanaka et al.[678,679] In the case of 4-substituted derivatives such as **300**, the 2-position was more reactive than the 6-position, whereas with other disubstituted derivatives the 2- and 6-positions were of comparable reactivity.



The cyanation of N-oxides has been utilized to prepare substituted pyridines which are useful as anti-allergy agents.[680]

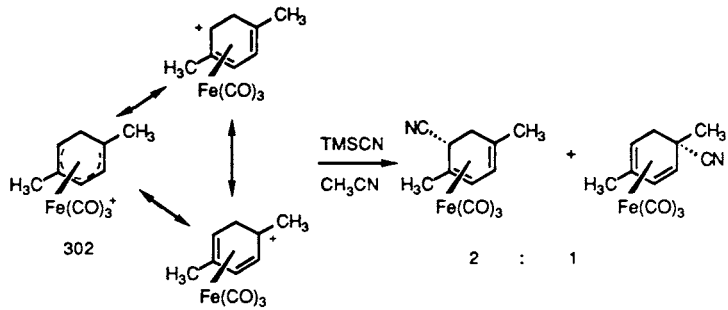
4.2.2. Carbocations

Utilization of TMSCN as a cyanide source to react with carbocations was first reported by Trost and co-workers.[681] The cyanosulfenylation of 2-propyl-1-pentene **301** using dimethyl(methylthio)sulfonium fluoborate and sodium cyanide

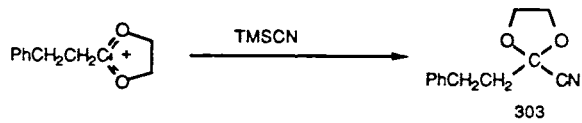


produced a 98 : 2 mixture with the major product being the anti-Markovnikov product. Because of "decreased nucleophilicity of the cyanide" with **1**, however, only a 35% yield of that cyanosulfenylated product was obtained along with 52% of the Markovnikov product.

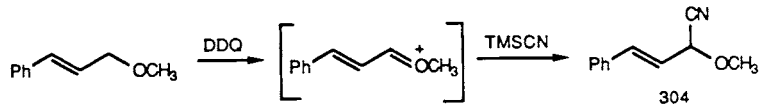
Alexander and co-workers found that cyanation of tricarbonyl(η^5-cyclohexadienyl)iron(1+) **302** using TMSCN was considerably superior in terms of yield of nitrile products to cyanations conducted with sodium cyanide or tetrabutyl ammonium cyanide.[682,683] The reaction was moderately regioselective with the secondary nitrile product (resulting from attack at the less hindered end of the dienyl system) predominating 2 to 1 over the tertiary nitrile.



Hayashi et al.[684] reported that the 1,3-dioxolan-2-ylium cation, derived from an ethylene ketal and trityl cation, afforded the corresponding nitrile **303** in 42%

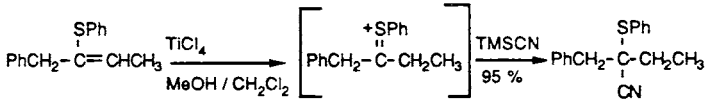


yield when reacted with **1**. These workers also investigated cyanations of alkoxy-stabilized carbocations derived from DDQ oxidation of allyl ethers.[685] For example, methyl cinnamyl ether was converted into 1-cyano- 1-methoxy-3-phenyl-2-propene **304** in 60% yield using **1** as the cyanating reagent.



304

Takeda and co-workers[686] generated thionium ions or phenylthio-stabilized carbocations *in situ* by treating alkenyl sulfides with titanium tetrachloride and an alcohol. Reaction with TMSCN resulted in cyanation of the cation and formation of the corresponding 2-(phenylthio)alkanenitriles (e.g., **305**).



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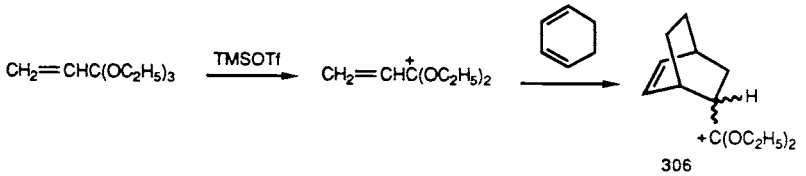
Recently, Gassman and Chavan[687] used cyanation by TMSCN to provide support for a reaction mechanism involving carbocations. Carbocation **306** was trapped in 24% yield when the reaction was conducted in the presence of **1**.



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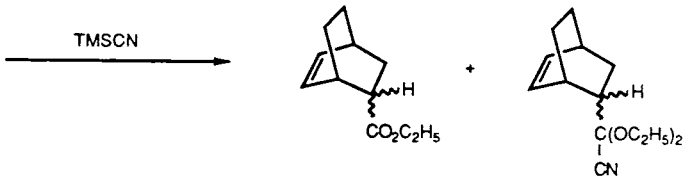


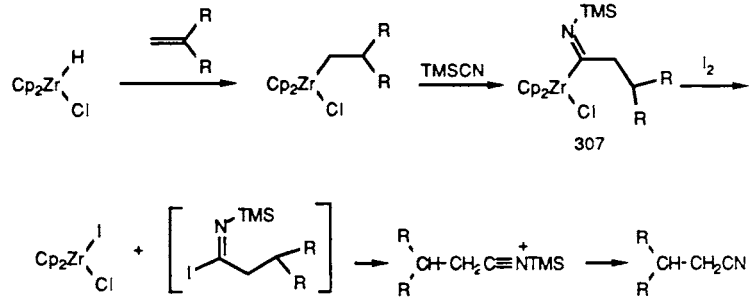
25 %
(62 % w/o TMSCN)

24 %

4.2.3. *Olefins*

A regiospecific hydrocyanation of olefins using TMSCN was reported by Buchwald and LaMaire.[688] The reaction involved hydrozirconation of the olefin, followed by sequential treatment with **1** and iodine. The reaction was proposed to take place via isonitrile insertion leading to intermediate **307**. An illustration of the

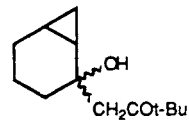
effectiveness of the hydrocyanation procedure was the conversion of 1- octene into 1-nonanitrile in 65% yield.



307

5. SILYLATIONS

Aside from early reports concerning the facile hydrolysis of cyanosilanes (i.e., silylation of water)[16,17a,18] and of reactions with Grignard reagents,[16,18,28,35] the utilization of cyanosilanes as silylating agents was overlooked for many years. This potential seems to have been first pointed out by Evans et al. in 1973 in a footnote to his paper dealing with the protection of *p*-quinones as silylated cyanohydrins.[143] The author reported that alcohols and enols were efficiently silylated with TMSCN at room temperature. Over the next few years, other reports of silylations with **1** appeared in the literature. Stork and Kraus[261] used excess **1** to simultaneously protect a secondary alcohol as the silyl ether and a ketone as the silylated cyanohydrin in a prostaglandin intermediate. House and Snoble[689] reported that although tertiary alcohol **308** resisted reaction with conventional silylating reagents, heating **308** and TMSCN in benzene and allowing HCN to escape as it was formed achieved the desired silyation (97% yield) under essentially neutral conditions. In addition, the use of TMSCN to readily silylate mercaptans and secondary amines was reported by Voronkov et al.[690]



308

It has only been quite recently, however, that a number of other groups have emphasized the oftentimes unique ability of TMSCN to silylate organic compounds under mild conditions. Mai and Patil[85] reported that a variety of alcohols, phenols, carboxylic acids, amines, and thiols were efficiently silylated with **1**, usually in isolated yields of >90%. Silylations of alcohols, phenols, and carboxylic acids with 1.2 equivalents of TMSCN in the absence of solvent were usually complete within

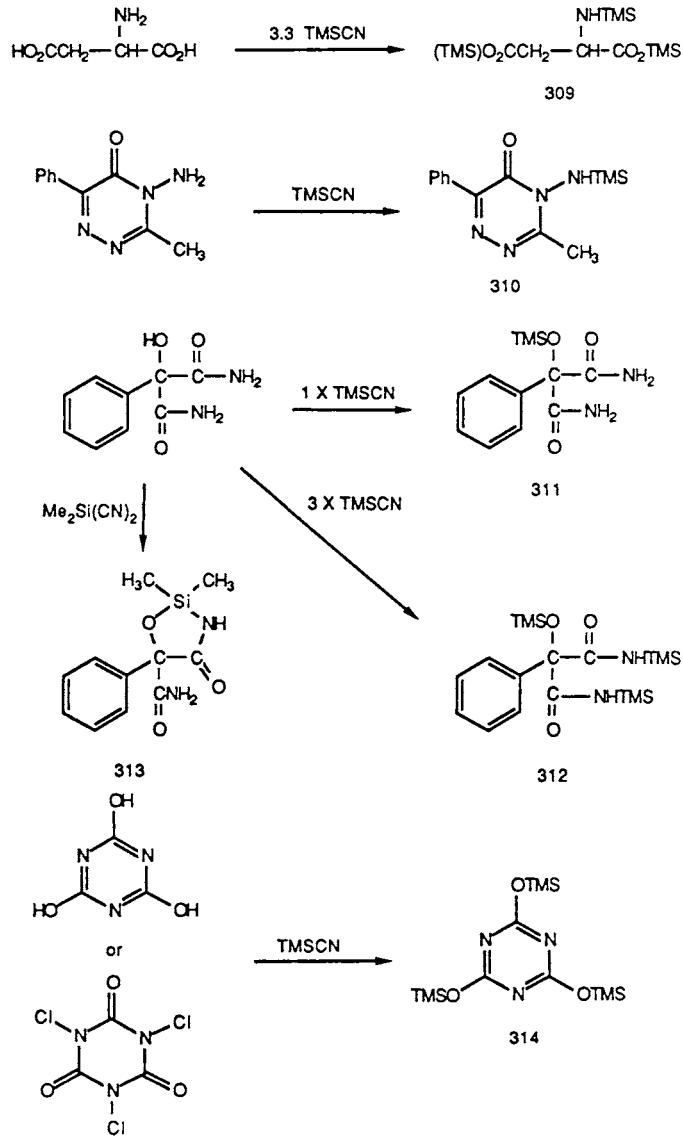
5 min; amines and thiols required heating at 70–100°C. Cyanamide, however, reacted within seconds at room temperature to yield 92% bis(trimethylsilyl)carbodiimide.[691] For the silylation of a hindered phenol, 2,6-diphenylphenol, the relative reactivities of various silylating reagents were determined to be as follows: bis(trimethylsilyl)acetamide > TMSCN > trimethylsilyl triflate ≥ bis(trimethylsilyl)sulfamide > $(Me_3Si)_2NH$ > (trimethylsilyl)-2- oxazolidinone > Me_3SiCl/Li_2S > Me_3SiCl/base. The C-silylation of various organolithium and Grignard reagents was also found to be more facile with TMSCN than with the chloride. The authors also found that hindered silyl cyanides were effective silylating reagents for alcohols, phenols, and carboxylic acids under mild and essentially neutral conditions. The reactions of tert-butyldimethylsilyl, triethylsilyl, and dimethylphenylsilyl cyanide, and dimethylsilyl, diethylsilyl, and diphenylsilyl dicyanides were investigated.

Findeisen and Fauss[692] have reported the use of TMSCN for the persilylation and consequent solubilization of difficultly soluble organic compounds. Aspartic acid, for example, was reacted with 3.3 equivalents of **1** to yield 92% of the silylated amino acid **309** which was soluble in petroleum ether. The Bayer group has also used **1** to prepare the herbicidal triazinones **310**[693] and the pesticidal malonic acid diamides **311** and **312**[388,694]. Reaction of dicyanodimethylsilane gave the cyclized derivatives **313**.[695] The silylation of both cyanuric acid and trichloroisocyanuric acid with TMSCN was reported to give tris(trimethylsilyl)cyanurate **314**.[696]

In a recent series of papers, Anteunis and co-workers[697–703] have described the advantages of the use of TMSCN for the persilylation of active hydrogen species, particularly amino acids, and their subsequent use in peptide synthesis. These advantages include:

1. extremely good "solubilizing" properties—the persilylated amino acids (or salts) and peptides are soluble in hydrocarbon solvents as well as in THF, CH_2Cl_2, EtOAc, etc.;
2. with an excess of TMSCN, any extraneous water, alcohols, or acids that are present as impurities are converted into blocked, volatile products that are easily removed by evaporation;
3. all amino acid side chain hydroxyl and thiol functionalities are blocked as their silyl ethers and thus require no other protection;
4. silylation of the amine group increases its nucleophilicity, leading to rapid reaction rates for coupling, and since it is unnecessary to add additional base to the reaction mixture, racemization of amino acids is minimized; and
5. the trimethylsilyl blocking groups may be easily removed under acidic, basic, or neutral (e.g., by hydrolysis or alcoholysis) conditions.

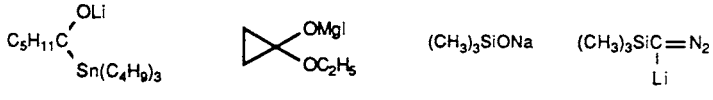
Although N,O-persilylation of amino acids for peptide synthesis is not a new technique, as Anteunis points out,[704,705] difficulties in achieving complete silyla-



tion with "classical" silylating reagents (e.g., Me_3SiCl or hexamethyldisilazane) have resulted in a de-emphasis of this technique. The advantages accrued with the use of TMSCN in peptide strategies, however, could well lead to a resurgence of interest in the silyl protecting group.

A number of other silylations with TMSCN have been reported. The lithium alkoxide **315** was successfully silylated with **1** but not with Me_3SiCl.[706] The magnesium alkoxide **316**, which yielded products of cyclopropanone alkylation

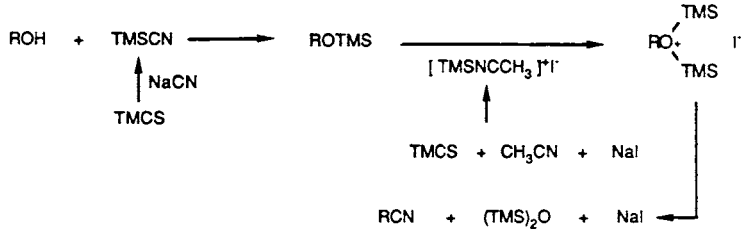
with organometallic reagents, reacted with TMSCN to yield the silyl acetal rather than the silylated cyanohydrin of cyclopropanone.[229] Sodium trimethylsilanolate **317**,[707] lithium and sodium bis(trimethylsilyl)amide,[117] and the lithium salt of trimethylsilyldiazomethane **318**[708] reacted with **1** to give products of O-, N-, and C-silylation, respectively. The reaction of TMSCN with the silanol groups of silica has also been studied.[709]



315 316 317 318

Attempts to form silylated cyanohydrins from 2,4,6-trimethylacetophenone[710] and anthrone[711] with TMSCN and a potassium cyanide/18-crown-6 complex yielded the products of enol silylation instead.

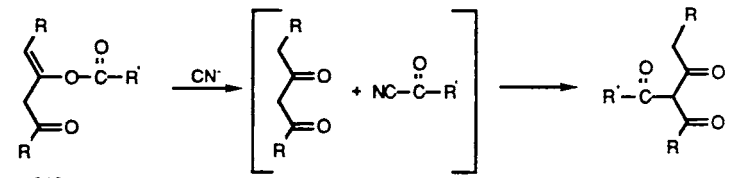
Finally, a method for the conversion of alcohols into nitriles by treatment with Me_3SiCl, NaCN, CH_3CN and a catalytic amount of NaI may involve *in situ* formation of TMSCN (see Section 2.1.) which could be the actual silylating reagent in the first step of the author's proposed mechanism.[712]



6. MISCELLANEOUS REACTIONS OF CYANOSILANES

There are a few reports in the patent literature concerning the use of TMSCN as a convenient, easily handled source of either cyanide ion or silicon in various reactions or formulations. The synthesis of tetrasubstituted silanes from halosilanes and organomagnesium reagents was reported to be more efficient if catalytic amounts of **1** or another cyanide source were added to the reaction mixture.[713] Since cyanosilanes are very efficient silylating reagents for organometallic reagents (see Section 5.), a cyanosilane formed *in situ* (see Sections 2.1. and 3.1.2.) may be the actual intermediate in this process.

The conversion of β-ketoenol esters **319** to the 2-acyl-1,3-dicarbonyl compounds **320** (intermediates in the synthesis of agricultural chemicals) was also reported to be catalyzed by cyanide ion from TMSCN or other sources.[714,715] This process may involve cleavage of **319** to the 1,3-dicarbonyl compound (or its silyl or metal enolate) which is subsequently acylated on carbon rather than on oxygen by the acylcyanide.



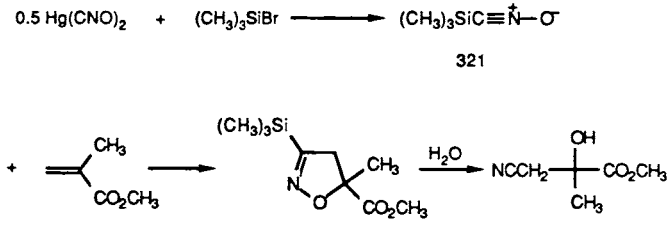
319 320

Several patents report the use of TMSCN as an additive for introducing small amounts of silanes into polymers used as photoresists.[716–718] The inclusion of silicon species was stated to make the polymers more resistant to electron beam or oxygen plasma etching.

The self-condensation of TMSCN as well as various dicyanosilanes by heating at 250°C in a bomb at very high pressures (200 atm) has been reported to produce triazines as well as higher polymers with a -[(R_3Si)C=N]- repeating unit.[719,720]

Heating TMSCN or other cyanosilanes to higher temperatures (1500°C) in a reducing atmosphere (Ar, H_2, NH_3) has been reported to yield silicon nitride/silicon carbide composite materials.[721–723] These materials have potential use as heat resistant structural elements for gas turbines and diesel engines.

Finally, the reaction of mercury fulminate with bromotrimethylsilane has been reported as a route to trimethylsilanecarbonitrile oxide **321**.[724] The nitrile oxide **321** behaves as a 1,3-dipole and participates in cycloaddition reactions with a variety of unsaturated partners, e.g., with methyl methacrylate.[724–727]



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