SYNTHESIS AND CHEMISTRY OF (TRIALKYLsILYL)VINYLKETENES

by

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To my family
SYNTHESIS AND CHEMISTRY OF (TRIALKYLSSILYL)VINYLKETENES

by

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ABSTRACT

The properties of silylketenes differ dramatically from those of ketenes. New strategies for the synthesis of (trialkylsilyl)vinylketenes ("TAS-vinylketenes") were explored. These robust vinylketenes undergo highly regioselective [4+2] cycloadditions in which the ketene carbonyl dominates in controlling the regiochemical course of the reaction. TAS-Vinylketenes have been shown to undergo Diels-Alder reactions with activated olefinic and acetylenic dienophiles. These vinylketenes also participate in a hetero [4+2] version of the reaction in which carbonyl and imino dienophiles react with TAS-vinylketenes to afford substituted (δ)-lactones and lactams. TAS-Vinylketenes also react in a [4+1] annulation to afford cyclopentenones.

Thesis supervisor: Rick L. Danheiser
Title: Professor of Chemistry
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PART I

Synthesis and Chemistry of (Trialkylsilyl)vinylketenes
CHAPTER 1

INTRODUCTION AND BACKGROUND: VINYLKETENES AND (TRIALKYLSILYL)KETENES

Introduction

The utility of ketenes in organic synthesis is well-established.\(^1\) Studies in the laboratory of Staudinger\(^2\) nearly one hundred years ago led to the first general methods for the synthesis of alkyl- and arylketenes. Staudinger also examined the participation of ketenes in addition reactions with nucleophiles as well as their dimerization and polymerization reactions. Since his pioneering work, ketene chemistry has flourished and now includes studies in theoretical, mechanistic, and synthetic areas.

Vinylketenes (\(\alpha,\beta\)-unsaturated alkenylketenes) were believed to be intermediates in chemical reactions as early as 1941.\(^3\) Although these ketenes are difficult to isolate, a variety of methods exist for generating them in situ for use in synthetic reactions. Vinylketenes have the capacity to function as versatile four-carbon building blocks for the assembly of a variety of carbocyclic systems. [2+2] Cycloadditions of vinylketenes are especially valuable transformations which can serve as triggering steps for pericyclic cascades leading to the formation of six- and eight-membered carbocyclic compounds (vide infra).

My research has focused on the chemistry of (trialkylsilyl)vinylketenes (“TAS-vinylketenes”). We expected that these compounds would be more stable than vinylketenes, allowing them to express their underlying reactivity as electron-rich conjugated dienes and participate as four-carbon components in Diels-Alder and related cycloadditions. As background to our work, this chapter includes a review of the synthesis and reactions of vinylketenes, followed by a discussion of silylketenes, including their properties, common

methods of preparation, and utility in organic synthesis. The remaining chapters will detail our investigations of the synthesis and reactions of TAS-vinylketenes.

Generation of Vinylketenes

Three synthetically significant methods for the generation of vinylketenes have been reported to date: (1) the dehydrohalogenation of α,β-unsaturated acid chlorides, (2) the electrocyclic ring opening of cyclobutenones, and (3) the photochemical Wolff rearrangement of α,β-unsaturated diazo ketones. In addition, several other methods have been used to prepare particular vinylketenes. Most vinylketenes cannot be isolated due to their tendency to dimerize and polymerize, and therefore are usually generated in situ and immediately reacted with a ketenophile.

Dehydrohalogenation of acid chlorides has been used as a method for the generation of vinylketenes since 1966 when Payne first discovered that reaction of 3-methyl-2-butenoyl chloride with trimethylamine forms isopropenylketene. Although this ketene itself is unstable, it can be trapped by reaction with ethyl vinyl ether or isolated as the ketene dimer. In subsequent years, a variety of vinylketenes have been prepared via the dehydrohalogenation method including the isolable vinylketene 2 which Wuest found could be purified by distillation (24 °C, 0.01 mm Hg, eq 1).

\[
\begin{align*}
\text{O} & \quad \text{Cl} \\
\text{O} & \quad \text{C} \\
\text{Et}_3\text{N} & \quad \text{160 °C, 8h} \\
\text{benzene} & \quad \text{sealed tube} \\
\text{62%} & \quad \text{2}
\end{align*}
\]

(1)

One major drawback of the dehydrohalogenation route to vinylketenes is the production of an amine hydrochloride byproduct which is known to catalyze the polymerization of ketenes. In addition, this salt can cause isomerization of the β,γ-double bonds of 2-vinylcyclobutanones (products of [2+2] reactions of vinylketenes with olefins) into conjugation with the carbonyl group.

The electrocyclic ring opening of cyclobutenones is a second general method for the synthesis of vinylketenes. This process can occur under either thermal or photochemical conditions. In 1956, Jenny and Roberts discovered that heating optically active 2,4-dichloro-3-phenylcyclobutenone results in racemization (eq 2). They proposed that this reaction involves reversible formation of chloroketenes via electrocyclic ring opening of the cyclobutenone. In the presence of ethanol the ketene can be trapped as the ethyl ester, providing evidence in support of a vinylketene intermediate.

\[
\begin{array}{c}
\text{Ph} \\
\text{Cl} \quad \text{O} \\
\text{C} \quad \text{Cl} \\
\text{H} \\
\text{3} \\
\end{array} \xleftarrow{\text{CHCl}_3 \ 100 \degree C} \quad \begin{array}{c}
\text{Ph} \\
\text{Cl} \quad \text{C} \quad \text{O} \\
\text{Cl} \quad \text{H} \\
\text{4} \\
\end{array} \xrightarrow{\text{EtOH}} \quad \begin{array}{c}
\text{EtOH} \\
\text{Ph} \quad \text{Cl} \quad \text{O} \\
\text{Et} \\
\text{H} \\
\text{5} \\
\end{array}
\]

(2)

Photochemical conditions can also effect the electrocyclic cleavage of cyclobutenones. For example, methylprenylketene is generated via the photochemically induced electrocyclic

---


ring opening of 2,4,4-trimethylcyclobutenone. This vinylketene then undergoes \([2+2]\) cycloaddition with ethyl vinyl ether to afford a mixture of stereoisomeric cyclobutenones (eq 3). One advantage of this route is that vinylketenes can be generated at room temperature. In our laboratory, Kollol Pal studied the generation of vinylketenes by irradiation of cyclobutenones and in fact was able to observe the formation of several vinylketenes in good yield by \(^1\)H NMR spectroscopy.\(^{10} \)

![Image](image_url)

The advantages of the electrocyclic ring opening for the generation of vinylketenes are clear. This mild, efficient method produces no amine salt that can cause undesirable side reactions. Also, because this is an intramolecular process requiring no reagents, the vinylketene can be generated in very low concentration thus reducing the rate of dimerization.

A third method for the generation of ketenes, the photochemical Wolff rearrangement of \(\alpha,\beta\)-unsaturated diazo ketones, is useful for two reasons: the reaction can be run at room temperature, and the only byproduct is nitrogen.\(^{11} \) In 1964, Roedig reported that irradiation of diazo ketone 10 results in formation of vinylketene intermediate 11 which can be trapped by reaction with \(N\)-(phenyl)benzaldimine to afford \(\beta\)-lactam 12 (eq 4).\(^{12} \) We have investigated the generation of vinyl- and arylketene intermediates via the photochemical Wolff rearrangement of \(\alpha\)-diazo ketones in the context of the aromatic annulation strategy developed in our laboratory.\(^{13} \)

---

Another method for the generation of vinylketenes involves the photolysis or thermolysis of alkenylcarbene metal complexes. In this process, metal-ketene complexation suppresses undesired side reactions such as dimerization. These metal-ketene complexes can undergo nucleophilic addition, cycloaddition with alkenes, and intramolecular cyclization. For example, reaction of cobalt complex 13 and 3-hexyne at 25 °C results in the formation of cobalt-vinylketene complex 14, addition of sodium methoxide then yields ester 15 in 54% yield (eq 5).

In summary, three synthetically significant methods for the generation of vinylketenes have found use in recent years: (1) the dehydrohalogenation of acid chlorides, (2) the electrocyclic ring opening of cyclobutenones, and (3) the photo Wolff rearrangement of...

unsaturated \(\alpha\)-diazo ketones. Other pyrolytic and thermolytic methods also can be used for the preparation of specific ketenes.\(^\text{16}\)

**Reactions of Vinylketenes**

Vinylketenes participate in a variety of reactions including nucleophilic addition and \([2+2]\) and \([4+2]\) cycloadditions. A brief summary of these reactions follows.

Nucleophilic addition of water, alcohols, amines, and carboxylic acids to vinylketenes affords acids, esters, amides, and anhydrides. Nucleophiles trap vinylketenes very efficiently, and this process is often cited as evidence that a ketene was generated in a reaction. For example, in our laboratory Kollol Pal confirmed the intermediacy of a vinylketene generated by the electrocyclic ring opening of 2,3-dimethylcyclobutenone by carrying out the reaction in the presence of \(t\)-butylamine to afford amides 17 and 18 (eq 6).

![Equation 6](image)

Vinylketenes have found their greatest utility reacting with alkenes and alkynes in \([2+2]\) cycloadditions leading to 2-vinylcyclobutanones and -cyclobutenones.\(^\text{17,18}\) In particular, our research group has extensively employed these cycloadditions as triggering steps for pericyclic cascades that lead to the formation of 3-cyclohexenols, cyclooctadienones, and highly substituted phenolic compounds (Scheme 1). In these reactions, vinylketenes function as electron-deficient \(2\pi\) components in the key \([2+2]\) cycloaddition step.

---

16. See ref 1a, pp 52-149.
17. For examples, see refs 5d,h,i,j, 8f, and 13.
Scheme 1 outlines three strategies for the synthesis of carbocyclic compounds developed in our laboratory based on vinylketenes. The first strategy (pathway a) provides a method for the synthesis of substituted 3-cyclohexenols. In this annulation, generation of the vinylketene by dehydrohalogenation of an α,β-unsaturated acid chloride followed by a [2+2] cycloaddition with an electron-rich alkene affords a 2-vinylcyclobutanone intermediate. Addition of a nucleophile with subsequent alkoxy-accelerated [1,3] sigmatropic rearrangement then yields a 3-cyclohexenol.

Pathway b illustrates a [4+4] strategy for the synthesis of eight-membered carbocycles. In this method, generation of the vinylketene occurs by either 1,4-dehydrohalogenation of an acid chloride or the thermal electrocyclic ring opening of a cyclobutenone. [2+2] Cycloaddition of the vinylketene with a 1,3-diene yields a 2,3-divinylcyclobutanone intermediate. Subsequent [3,3] sigmatropic rearrangement results in formation of the 2,6-cyclooctadienone.

The aromatic annulation strategy described in pathway c is a powerful method for the preparation of highly substituted phenolic compounds. We have demonstrated the utility of this strategy by developing direct synthetic routes to a variety of natural products, including
Dan Shen diterpenoid quinones,\textsuperscript{19} maesanin,\textsuperscript{20} aegyptinones A and B,\textsuperscript{21} salvilenone,\textsuperscript{22} and bergapten.\textsuperscript{23} Irradiation of an $\alpha$-diazoketone triggers a photochemical Wolff rearrangement to produce a vinylketene which then reacts with an acetylene in a regiospecific [2+2] cycloaddition. Continued irradiation or thermolysis effect the $4\pi$ electrocyclic opening of the resulting 4-vinylcyclobutenone generating a dienylketene. The penultimate $6\pi$ electrocyclization is followed by tautomerization to yield the aromatic product.

Although vinylketenes have a proclivity to undergo [2+2] cycloadditions, a few examples of direct [4+2] cycloadditions of these compounds do exist,\textsuperscript{24} including cases involving dimerization of vinylketenes. For example, reaction of two molecules of vinylketene 19 affords the $\alpha$-pyrones 20 and 21 resulting from a [4+2] cycloaddition (eq 7).\textsuperscript{5d}

Generating vinylketenes in low concentrations in the presence of an excess of ketenophile helps to prevent this undesired dimerization.

As summarized above, vinylketenes have been well-documented as intermediates in a variety of reactions and their participation in [2+2] cycloadditions has been extensively exploited in organic synthesis. If this normal reaction pathway could be suppressed, vinylketenes might express their underlying reactivity as electron-rich conjugated dienes for other useful transformation.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{reaction_diagram.png}
\caption{Reaction scheme for the formation of $\alpha$-pyrones 20 and 21 from vinylketene 19.}
\end{figure}

\textsuperscript{23} Danheiser, R. L.; Trova, M. P. \textit{Synlett} 1995, 573.
that most other ketenes, we hypothesized that silylvinylketenes might exhibit the stability of 
silylketenes, thus reducing their eagerness to participate in [2+2] reactions. In order to 
understand the basis for this hypothesis, it is first necessary to review the synthesis and 
chemistry of (trialkylsilyl)ketenes.

(Trialkylsilyl)ketenes

Silylketenes\(^{25}\) exhibit completely different properties from most other ketenes. The 
remarkably stable parent compound (trimethylsilyl)ketene\(^{25}\) can be stored at room 
temperature for several years without decomposition. In fact, this TAS-ketene can even be 
purified by distillation at 82 °C. As will become apparent later in this chapter, TAS-ketenes 
resist dimerization and undergo reactions at a much slower rate than their alkylketene 
counterparts.

The silyl substituent has an extraordinary ability to stabilize ketenes and suppress their 
natural tendency to dimerize and undergo [2+2] cycloadditions. Originally, TAS-ketenes 
were believed to exist as a tautomeric mixture of (trimethylsilyl)ketene and 
trimethylsilyloxyacetylene, accounting for their unusual stability. Spectroscopic studies later 
showed that this was not true and that only the ketene structure is present.

Currently, the amazing stability of TAS-ketenes is believed to result from 
hyperconjugative electron \(\sigma-\pi\) donation from the C-Si bond into the in-plane carbonyl \(\pi^*\)-
orbital, a reasonable supposition considering that the power of the C-Si bond as a 
hyperconjugative electron donor has been well documented.\(^{27}\) Also, Tidwell has proposed 
that the stability of TAS-ketenes is due to the electron-releasing ability of the electropositive

25. For a review on silylketenes, see: Pommier, A.; Kocienski, P.; Pons, J.-M. J. Chem. Soc., Perkin 
Trans. 1 1998, 2105.
26. Loebach, J. L.; Danheiser, R. L. In Encyclopedia of Reagents for Organic Synthesis; Paquette, L. A., 
27. For a discussion, see: (a) Patai, S. The Chemistry of Organic Silicon Compounds; Patai, S., Rappoport, Z., 
York, 1982; Vol. 2, pp 1-203.
silicon group, allowing for σ donation. The carbonyl group is rendered less electrophilic and, as a result, less reactive toward nucleophilic addition reactions and cycloadditions.  

![Diagram of trimethylsilyl group attached to the C-2 of a ketene](image)

A trimethylsilyl group attached to the C-2 of a ketene results in an upfield shift of the 13C NMR resonance of C-1 as a result of partial sp character at C-1, providing some evidence for silicon acting as a σ–π donor in (trialkylsilyl)ketenes. The phenomenon of σ–π donation by silicon is well documented in other areas of silicon chemistry.

Alternatively, Runge has suggested that TAS-ketene stability is due to back-donation from the ketene π-system to the d-orbitals of the silicon atom, resulting in a partial Si-C double bond. Any major contribution by such a resonance form (see below) should result in a longer C-C bond and shorter C-O bond. Ab initio molecular orbital calculations confirmed that the C=O and C=C bond lengths of (trimethylsilyl)ketene are almost the same as the C=O and C=C bonds of methylketene and therefore Runge’s proposed structures probably do not contribute significantly to TAS-ketene stability.

![Diagram of resonance forms of (trimethylsilyl)ketene](image)

**Generation of (Trialkylsilyl)ketenes**

Silylketenes have been prepared by a wide variety of methods including the thermolysis of alkoxyalkynes, dehydration of silylacetic acids, Wolff rearrangement of α-diazo ketones, electrocyclic ring opening of cyclobutenediones, and reaction of lithiated

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silyldiazomethane with carbon monoxide. Shchekovskaya achieved the first synthesis of (trimethylsilyl)ketene in 1965 by pyrolysis of an alkoxy(trialkylsilyl)acetylene, the most commonly used procedure for the preparation of TAS-ketenes to date. Heating ethoxy(trimethylsilyl)ethyne 22 at 120 °C results in liberation of ethylene, affording ketene 23 in 90% yield (eq 8). Initially, Shchukovskaya believed that the mechanism of the reaction proceeds via an isomerization, but in 1975 Ruden reported that the reaction actually occurs via a retro-ene 6-membered transition state.

\[
\begin{align*}
\text{Me}_3\text{Si} & \equiv \text{OEt} & 120^\circ\text{C} & \xrightarrow{} \text{Me}_3\text{Si} \equiv \text{O} \\
\text{Me}_3\text{Si} & \equiv \text{O} & \xrightarrow{-\text{C}_2\text{H}_4} & \text{Me}_3\text{Si} \equiv \text{C}=\text{O} (8)
\end{align*}
\]

Subsequent studies have shown that (trimethylsilyl)ketene (23) can be generated at lower temperatures by the thermal decomposition of t-butoxy(trimethylsilyl)ethyne 24. Heating alkyne 24 at temperatures as low as 50 °C resulted in the slow elimination of 2-methylpropene. Nearly instantaneous conversion to (trimethylsilyl)ketene occurs at higher temperatures (100-110 °C). The large t-butoxy group shields the triple bond and helps to prevent side reactions (such as polymerization and nucleophile attack) that commonly occur when the silylketene is generated from the less hindered ethoxy derivative 22. Therefore, preparation of silylketenes from 24 can occur in the presence of nucleophiles which subsequently react with the ketene. For example, (trimethylsilyl)ketene (generated by pyrolysis of 24) in the presence of diphenylamine, afforded amide 25 in quantitative yield (eq 9). Unfortunately, the t-butoxy derivative 24 requires several steps to prepare whereas a one-step procedure yields ethoxy derivative 22 from commercially available ethoxyacetylene.

---

Substituted (trialkylsilyl)ketenes can be prepared by a related method, the thermal rearrangement of trialkylsilyloxyacetylenes. Treatment of 1-methoxy-3-methyl-1-butyne with trimethylsilyl iodide affords intermediate 1-(trimethylsilyloxy)-3-methyl-1-butyne. Rearrangement to the corresponding isopropyl-substituted ketene occurs at room temperature (eq 10). Synthesis of the parent (trimethylsilyl)ketene can occur via a similar rearrangement in which reaction of ketene, trimethylsilyl triflate, and triethylamine affords (trimethylsilyloxy)acetylene as an intermediate which undergoes 1,3-silicon transfer at room temperature to afford (trimethylsilyl)ketene in 63% yield.

Lutsenko reported another pyrolytic method for the generation of (TAS)ketenes. Heating (triethylsilyl)acetic anhydride affords (triethylsilyl)ketene in 80% yield (eq 11). Condensation of two molecules of (triethylsilyl)acetic acid produces the necessary anhydride. The requisite silylacetic acids can presumably be prepared in one step by the conversion of acetic acid to the dianion by treatment with LDA followed by silylation with two equivalents of the desired silyl chloride. Dehydrohalogenation of acid chlorides also forms TAS-ketenes, but this method generally gives only low yields of the desired product.
In 1989, Olah reported an efficient preparation of silylketenes by the dehydration of silyl acetic acids.\textsuperscript{38} Treatment of commercially available (trimethylsilyl)acetic acid 31 with dicyclohexylcarbodiimide (DCC) in the presence of catalytic triethylamine affords (trimethylsilyl)ketene in 63\% yield (eq 12). However, all attempts in our laboratory to accomplish the synthesis of (trimethylsilyl)ketene according to this procedure have thus far been unsuccessful. Other (TAS)acetic acid precursors for this new approach to TAS-ketenes can be prepared as mentioned above.

\begin{equation}
\text{Me}_3\text{Si} \backslash \text{O} \backslash \text{Me}_3\text{Si} \xrightarrow{\Delta} \text{Me}_3\text{Si} \backslash \text{C}=\text{O} \quad \text{(11)}
\end{equation}

In 1985, Maas reported an extremely facile synthesis of TAS-ketenes by the Wolff rearrangement of \( \alpha \)-silyl-\( \alpha \)-diazo ketones under photochemical conditions or with transition metal catalysis.\textsuperscript{39} Irradiation of \( \alpha \)-diazo ketone 32 affords silylketene 33 in 94\% yield (eq 13). Alternatively, treatment of 32 with copper triflate (4 mol\% in benzene, 20 \( ^\circ \)C) results in Wolff rearrangement, producing the desired ketene 33 in 93\% yield. The requisite \( \alpha \)-silyl-\( \alpha \)-diazo ketone can be prepared via silylation of an \( \alpha \)-diazo ketone, thus allowing access to a variety of aryl- and alkyl-substituted silylketenes.

\begin{equation}
\text{Me}_3\text{Si} \backslash \text{C}=\text{O} \quad \text{(12)}
\end{equation}

In recent years, Tidwell has done extensive studies on the preparation of bis(trialkylsilyl)ketenes via the electrocyclic ring opening of cyclobutenediones under both thermal and photochemical conditions. Reaction of bis(t-butyldimethyl-silyl)acetylene with dichloroketene (generated from trichloroacetyl chloride with zinc-copper couple) affords dichlorocyclobutenone. Hydrolysis with concentrated sulfuric acid yields the cyclobutenedione which undergoes a facile electrocyclic ring opening to produce bisketene in excellent yield (Scheme 2).

Scheme 2

Recently, Murai reported a remarkably efficient route to bis(silyl)- and stannyl(silyl)ketenes by the reaction of lithiated (trimethylsilyl)diazomethane with carbon monoxide, followed by trapping with a silyl chloride, silyl triflate, or stannyl chloride. Thus, treatment of (trimethylsilyl)diazomethane with n-butyllithium followed by exposure to carbon monoxide (1 atm) affords acyllithium intermediate 39. Extrusion of dinitrogen produces the lithiated silylketene 40 which is trapped with triethylsilyl trifluoromethanesulfonate to produce the bis(silyl)ketene 41 in 85% yield. Efforts to trap lithiated silylketene 40 with alkyl halides or a proton source were unsuccessful.

Scheme 3

Reactions of (Trialkylsilyl)ketenes

Silylketenes undergo a diverse assortment of reactions and the rich area of silylketene chemistry has been extensively investigated. The remainder of this chapter will briefly summarize the participation of TAS-ketenes in nucleophilic addition reactions as well as [2+2] and [4+2] cycloadditions. Also, the formation of allenes, cyclopropanones, and cyclobutanones from TAS-ketenes will be reviewed.

(1) Nucleophilic Addition

TAS-Ketenes readily undergo nucleophilic addition with a variety of compounds including water, alcohols, amines, and certain carbon nucleophiles. Hydration of

(trimethylsilyl)ketene under neutral conditions occurs at a significantly slower rate than the addition of water to comparable alkylketenes. However, under acidic or basic conditions, the rate of silylketene hydration is faster than that of alkylketenes. This interesting rate difference is believed to result from silicon's unique ability to stabilize both a negative charge \( \alpha \) to the silicon (basic hydration conditions) and to stabilize a positive charge \( \beta \) to the silicon (acidic hydration conditions).

Other oxygen nucleophiles also react at a much faster rate with alkylketenes than with TAS-ketenes. However, under appropriate conditions, simple alcohols do add to (trimethylsilyl)ketene to afford esters in excellent yield. Alcohols also combine with the more hindered (\( t \)-butyldimethylsilyl)ketene, although at a slightly reduced rate. TAS-Ketenes react with sterically hindered alcohols very slowly unless a Lewis acid that can catalyze the reaction is present. For example (eq 14), addition of \( n \)-butanol to TMS-ketene occurs rapidly at \(-10^\circ C\), but reaction of \( t \)-butanol with 23 is much slower (CCl₄, 48 h, rt, 80%) unless catalyzed by a Lewis acid (BF₃-OEt₂, 5 min, rt, 93%).

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{O} \\
\text{Ot-Bu} & \quad \text{BF}_3\text{-OEt} \\
\text{rt} & \quad 5 \text{ min} \\
\end{align*}
\]

\[\rightarrow\]

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{O} \\
\text{C}=\text{O} & \quad \text{H} \\
\text{C}=\text{O} & \quad \text{H} \\
\text{Me}_3\text{Si} & \quad \text{O} \\
\text{On-Bu} & \quad \text{Ot-Bu} \\
\end{align*}
\]

Zinc halides effectively catalyze the addition of alcohols to (trimethylsilyl)ketenes. Many functional groups tolerate the presence of this mild Lewis acid, including carbonyl groups, acetics, olefins, and epoxides that would be sensitive to other Lewis acids such as BF₃-OEt₂. Kita has thus found that zinc chloride catalyzes the addition of \( \alpha \)-hydroxy ketones

to (trimethylsilyl)ketene to afford functionalized α-silylacetates (eq 15), compounds that are
difficult to prepare by traditional methods. Yamamoto reported that a naturally occurring
lipase isolated from Rhizopus japonicus also catalyzes this transformation.47

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{C} = \text{O} \quad \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array} \\
\text{H} \quad \text{Me}
\end{align*}
\]

As mentioned earlier, TAS-ketenes react rapidly with amines to form amides.48
Ruden reported the quantitative conversion of (trimethylsilyl)ketene to the corresponding
amide 46 upon addition of diisopropylamine at room temperature (eq 16).31 Bromine also
adds to (trimethylsilyl)ketene to produce bromo(trimethylsilyl)acetylbromide.30 In addition,
alkoxy(tributyl)tins combine with TAS-ketenes to afford α-stannyl esters.49

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{C} = \text{O} \quad \begin{array}{c}
\text{i-Pr}_2\text{NH} \\
\text{CCl}_4
\end{array} \\
\text{H} \quad \text{Me}
\end{align*}
\]

Taylor reported a convenient one-pot preparation of coumarins based on the addition
of salicylaldehyde salts to TAS-ketenes.50 Condensation of o-acyl phenol 47 with ketene 23
affords α-silylcarboxylate 48, and subsequent cyclization and elimination yields coumarin 49
in 92% yield (eq 17).

The addition of carbon nucleophiles to TAS-ketenes has also received considerable attention. Organolithium reagents add to substituted TAS-ketenes; subsequent addition of acid results in formation of a ketone, whereas treatment with a trialkylsilyl chloride affords a silyl enol ether. For example, treatment of bis(trimethylsilyl)ketene with n-butyllithium followed by acidic workup affords ketone 51. Alternatively, addition of n-butyllithium to ketene 52 followed by trapping with trimethylchlorosilane produces the vinyl silyl ether 53 as a single stereoisomer (eq 18).

When a TAS-ketene containing a proton at C2 is treated with strongly basic organolithium reagents, only proton abstraction results (no nucleophilic addition is observed). Kita reported that the resulting lithiated silylketene can react with a (trialkylsilyl)chloride at low temperature to afford bis(trialkylsilyl)ketenes in excellent yield. In the presence of a less basic organocerium reagent, nucleophilic addition to TAS-ketenes

occurs, forming an enolate. For example, addition of BuCeCl₂ to \((t\text{-butyldimethylsilyl})\text{ketene}\) affords enolate which can be trapped with either aqueous ammonium chloride or an alkyl halide to afford 56 and 57 (eq 19).

![Chemical Reaction Diagram](image)

Enamines can react as ketenophiles, combining with silylketenes to form 1,3-diones. For example, Shioiri reported that addition of enamine 58 to \((t\text{-butyldimethylsilyl})\text{ketene}\) 54 at room temperature followed by hydrolysis of the imine during silica gel chromatography affords dione 59 in 70% yield (eq 20).

![Chemical Reaction Diagram](image)

(2) Cycloadditions of TAS-Ketenes

Because of the stabilizing effect of silicon substituents on ketenes, TAS-ketenes undergo [2+2] cycloadditions only with very reactive, electron-rich olefins. In 1974, Zaitseva reported the addition of 1,1-diethoxyethene to (trimethylsilyl)ketene to afford the [2+2] cycloadduct. Brady later reported that (trimethylsilyl)ketene reacts with tetramethoxyethene

---

to form cyclobutanone 61. Treatment of ketene 23 with the bulkier alkene 62 results only in addition to the ketene (without subsequent ring closure) to yield acyclic ester 63 (eq 21).

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} \\
\text{Me}_3\text{Si} & \quad \text{C}=\text{O} \\
& \quad \text{H} \\
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OSiMe}_3 \\
\text{Me}_3\text{Si} & \quad \text{OSiMe}_3
\end{align*}
\]

90 °C 2 h 

65%

95%

In 1975, Zaitseva reported the first [2+2] cycloaddition of a TAS-ketene and an aldehyde. Reaction of (trimethylsilyl)ketene with benzaldehyde in the presence of BF₃·OEt₂ affords a 2:1 mixture of cis- and trans-4-phenyl-3-trimethylsilyloxetan-2-one (64) in 65% yield (eq 22). Due to the decreased reactivity of TAS-ketenes in [2+2] cycloadditions, these reactions usually require catalysis by Lewis acids. Since Zaitseva’s discovery, this [2+2] approach has become a common method for the synthesis of β-lactones. Recent developments in the area of oxetanone synthesis include the use of bulky Lewis acids for preparation of exclusively cis-substituted β-lactones and chiral Lewis acids for the formation of enantiomERICALLY enriched products. Silylketenes do not participate in [2+2] reactions with ketones.

61. For a review on the synthesis of β-lactones via the [2+2] reaction of TAS-ketenes and carbonyl compounds, see ref 25 and references cited therein.
Although the well-known Staudinger reaction of ketenes and imines is an extremely useful method for the synthesis of β-lactams, few examples of silylketene participation in this type of reaction have been reported.\textsuperscript{64} In 1976, Brady reported the first \([2+2]\) reaction of a TAS-ketene with an imine. Reaction of bromo(trimethylsilyl)ketene \textsuperscript{66} (generated in situ by dehydrohalogenation of \textsuperscript{65}) with \(N\)-(\textit{t}-butyl)benzaldimine provided β-lactam \textsuperscript{67} in 56\% yield (eq 23).\textsuperscript{64a}

![Chemical structure](image)

\[ \text{Me}_3\text{Si} = \text{C}=\text{O} \]

\textsuperscript{65}

\[ \text{Me}_3\text{Si} = \text{C}=\text{O} \]

\textsuperscript{66}

\[ \text{Me}_3\text{Si} = \text{C}=\text{O} \]

\textsuperscript{67}

Schubert later reported the reaction of ethoxy(triphenylsilyl)ketene \textsuperscript{69} (generated in situ from metal complex \textsuperscript{68}) with \(N\)-(methyl)benzaldimine which produces a 74:16 mixture of \textit{cis} and \textit{trans}-substituted β-lactams \textsuperscript{70} and \textsuperscript{71} (eq 24).\textsuperscript{64b} At about the same time, Zaitseva reported that (trimethylsilyl)ketene reacts with \(N\)-alkylsulfonyl chloralimines.\textsuperscript{64c}

Usually TAS-ketenes do not participate in formal [4+2] cycloaddition reactions, but a few examples have been reported. Shioiri recently described the reaction of \((t\text{-butyldimethylsilyl})\)ketene with an electron-rich 1,3-diene.\(^{65}\) Experimental evidence was obtained suggesting that this reaction proceeds via a stepwise mechanism. Thus, addition of diene 72 to ketene 54 affords a betaine intermediate (73) that can be trapped as the ester 74 by addition of water. Increasing the time or temperature of the reaction results in cyclization to afford the dihydropyranone 75 which subsequently isomerizes to pyranone 76 (Scheme 4).

**Scheme 4**

---

In 1996, Aoyama and Shioiri reported another example of a TAS-ketene undergoing a [4+2] cycloaddition.\textsuperscript{66} Reaction of (trimethylsilyl)ketene with acylisocyanate 77 affords the [4+2] adduct, 78. Subsequent reaction with dimethylacetylene dicarboxylate and expulsion of carbon dioxide then yields 2-pyridone 79 in nearly quantitative yield in an extremely efficient one-pot procedure (eq 25).

\begin{equation}
\begin{array}{c}
\text{R} \quad \text{N=C=O} \\
\text{77} \\
\end{array} + \begin{array}{c}
\text{Me}_3\text{Si} \quad \text{C=O} \\
\text{H} \quad \text{23} \\
\end{array} \xrightarrow{o\text{-dichlorobenzene}} \text{reflu}x \quad 3 \text{ h} \xrightarrow{\text{DMAD}} \begin{array}{c}
\text{CO}_2\text{Me} \quad \text{CO}_2\text{Me} \\
\text{79} \\
\end{array} 99\% \end{equation}

(3) Formation of Allenes, Cyclopropanones, and Cyclobutanones

Olefination of (trimethylsilyl)ketene with stabilized phosphorus ylides has been used for the preparation of allenes.\textsuperscript{67} For example, reaction of ylide 80 with (trimethylsilyl)ketene at -5 °C affords allenic ester 81 in 85% yield (eq 26). Reaction of (trimethylsilyl)ketene with \textit{unstabilized} phosphorus ylides results only in formation of complex mixtures of products. Combination of a variety of phosphorus ylides (such as Ph$_3$P=C(Ph)(Et)) with \textit{bis}(trialkylsilyl)ketenes gives reasonable yields of silylallenes.

Silyl-substituted ketenimines can also be prepared using organophosphorous chemistry. Barbaro and co-workers described the reaction of (trimethylsilyl)ketene with [bis(trimethylsilyl)methylimino]triphenylphosphorane 82 at room temperature, affording ketenimine 83 in moderate yield (eq 27).68 Another aza-Wittig-type reaction serves as a key step in Molina’s total synthesis of aaptamine in which treatment of a functionalized iminophosphorane with (trimethylsilyl)ketene affords a silylketenimine intermediate.69

Zaitseva found that reaction of TAS-ketenes with diazomethane produces cyclopropanones or cyclobutanones.70 The outcome of the reaction depends greatly on the amount of diazomethane used. Treatment of (trimethylsilyl)ketene with one equivalent of diazomethane at 130 °C results in exclusive formation of 2-(trimethylsilyl)-cyclopropanone 84. The cyclopropanone product can react with a second equivalent of diazomethane to afford the ring expansion products 85 and 86 as a mixture of isomers. The cyclobutanones can be obtained directly by treatment of 23 with two equivalents of diazomethane at −78 °C (Scheme 5).

Scheme 5

(Trimethylsilyl)diazomethane also combines with TAS-ketenes in [2+1] cycloadditions. Brady reported that (diethylmethylosilyl)ketene 87 reacts smoothly with TMS-diazomethane to afford exclusively the cis-substituted cyclopropanone 88 (eq 28). Reaction of TMS-diazomethane with (trimethylsilyl)ketene and other (trimethylsilyl)arylketenes have also been reported. Concurrent with our work (see Chapter 5), Tidwell reported the [4+1] reaction of bis(trialkylsilylketenes) with TMS-diazomethane. This reaction will be discussed in detail in Chapter 5.

Our laboratory reported the first synthesis and isolation of a silylvinylketene several years ago. Since then, we have been interested in developing new routes to substituted TAS-vinylketenes and systematically investigating their utility in organic synthesis.

discusses new approaches for the synthesis TAS-vinylketenes, and Chapters 3-5 present our results on TAS-vinylketene reactivity in [4+2] and [4+1] cycloadditions.
CHAPTER 2
SYNTHETIC APPROACHES TO SUBSTITUTED TAS-VINYLKETENES

Synthesis of (Trimethylsilyl)vinylketene by Dehydrohalogenation

One of the most widely used methods for the preparation of TAS-vinylketenes involves the dehydrohalogenation of acid chlorides. Indeed, this approach has been used for the synthesis of vinylketenes as discussed in Chapter 1. Several years ago our laboratory reported the first synthesis of (trimethylsilyl)vinylketene (92) by this method, according to the route outlined in Scheme 6.\(^\text{73}\) Treatment of 1-(trimethylsilyl)propyne (89)\(^\text{74}\) with diisobutylaluminum hydride and methyllithium affords a vinylalanate intermediate\(^\text{75}\) that subsequently reacts with carbon dioxide to form (Z)-2-(trimethylsilyl)-2-butenoic acid (90). The potassium salt of 90 reacts with oxalyl chloride to afford acid chloride 91 that is used in the next step without purification. Addition of 91 to a pentane solution of triethylamine followed by heating at reflux (15 to 24 h) yields (trimethylsilyl)ketene. Purification by distillation (25 °C, 1 mmHg) affords the ketene (92) as a yellow-green liquid (Scheme 6). (Trimethylsilyl)vinylketene is moderately stable and can be stored in solution at 0 °C for 1-2 weeks without appreciable decomposition.

Scheme 6

![Scheme 6: Synthesis of (Trimethylsilyl)vinylketene](image)

Unfortunately, the limited thermal stability of this vinylketene restricts the scope of its reactions. We expected that substituted TAS-vinylketenes would be more stable. Unfortunately, although dehydrohalogenation of the α,β-unsaturated chloride 91 provides convenient access to (trimethylsilyl)vinylketene, this strategy is not well-suited for the synthesis of more highly substituted TAS-ketenes. In some cases the requisite precursors are not available, and regiochemical ambiguities can arise in dehydrohalogenation (1,4-elimination) reactions involving β,β-disubstituted-α,β-unsaturated carboxylic acid derivatives (eq 29).

\[
\begin{array}{c}
\text{Cl} \quad \text{Cl} \\
\text{Cl} \quad \text{Cl}
\end{array} \quad \text{R}_3\text{Si} \quad \text{C} \quad \text{R}_3\text{Si} \quad \text{C} \quad \text{R}_3\text{Si} \quad \text{C} \\
\text{R}^1 \quad \text{R}^2 \\
\text{R}^1 \quad \text{R}^2
\end{array}
\]

(29)

Recent studies in our laboratory have demonstrated that the photochemical Wolff rearrangement provides an efficient method for the synthesis of vinylketenes.\textsuperscript{13} In these transformations, the vinylketene is not isolated, but is trapped in situ with an alkyne, initiating a cascade of pericyclic reactions leading ultimately to the formation of a highly substituted aromatic system. Maas and co-workers have shown that saturated TAS-ketenes can be generated in a similar fashion by the Wolff rearrangement of α-silyl-α-diazo ketones.\textsuperscript{39} The efficiency of these processes suggested that the rearrangement of α'-silyl-α'-diazo-α,β-unsaturated ketones (94) might provide the basis for a new route to TAS-vinylketenes (eq 30).

\[
\begin{array}{c}
\text{O} \quad \text{N}_2 \\
\text{O} \quad \text{N}_2
\end{array} \quad \text{R}_3\text{SiOTf} \quad \text{i-Pr}_2\text{EtN} \quad \text{R}_3\text{Si} \quad \text{C} \quad \text{R}_3\text{Si} \quad \text{C} \quad \text{R}_3\text{Si} \quad \text{C} \\
\text{R}^1 \quad \text{R}^2 \\
\text{R}^1 \quad \text{R}^2
\end{array}
\]

(30)
Synthesis of Substituted TAS-Vinylketenes by Photochemical Wolff Rearrangement

The requisite α-diazo ketone precursors (93) were all prepared using the "detrifluoroacetylativ" diazo transfer strategy previously developed in our laboratory. Thus, treatment of methyl ketone 96 with 1.1 equivalents of lithium hexamethyldisilazide in THF at −78 °C produces a lithium enolate, which is acylated by exposure to 1.2 equivalents of trifluoroethyl trifluoroacetate at −78 °C. Treatment of the resulting α-trifluoroacetyl ketone (97) with 1.5 equiv of MsN₃ in the presence of 1.0 equivalents of water and 1.5 equivalents of Et₃N in acetonitrile (25 °C, 4 h) affords the desired diazo ketone 98 in 75-79% yield after chromatographic purification (eq 31). It should be noted that α'-diazo-α,β-unsaturated ketones generally cannot be prepared by addition of diazomethane to acyl chlorides because of competing side reactions involving dipolar cycloadditions to the conjugated double bond.

\[
\begin{align*}
\text{O} & \quad \text{1. 1 equiv LiHMDS} \\
\text{THF, -78 °C} & \quad \text{O} \quad \text{1.5 equiv MsN₃} \\
\text{2. 1.2 equiv TFETFA} & \quad \text{CF₃} \quad \text{1.0 equiv H₂O} \\
\text{-78 °C, 5-10 min} & \quad \text{1.5 equiv Et₃N} \\
\text{96} & \quad \text{97} \quad \text{98} \\
\end{align*}
\]

75-79%

Silylation of the diazo ketones was accomplished using a modification of the method of Mass and co-workers. In this procedure, diazo ketones are treated with a silyl triflate reagent and diisopropylethylamine to afford the α-silyl-α-diazo ketone. As reported by Maas, the silylated α-diazo ketones have a tendency to undergo protodesilylation during their preparation and isolation caused by the presence of acidic trialkylammonium triflate byproducts. Jennifer Loebach of our laboratory found that this problem can be minimized by employing a solvent system consisting of equal parts Et₂O and hexane. The ammonium

78. See ref 39 and the following: Bruckmann, R.; Maas, G. Chem. Ber. 1987, 120, 635.
salts have reduced solubility in this medium, and the desired silylation products are obtained in 10-30% higher yield as compared to reaction in Et₂O alone. A variety of α'-trialkylsilyl-α'-diazoo-α,β-enones can be prepared in good yield by employing this protocol (Scheme 7). Diazoketones 100-102 were isolated as yellow to orange oils that can be stored in solution at 0 °C for several days without significant decomposition. Because a wider range of silyl chloride reagents are available as compared to silyl triflates, we briefly examined the suitability of silyl chlorides as substitutes for triflates in the silylation reaction. As a model case, the reaction of chlorotriethylsilane with diazo ketone 98 was examined under the standard silylation conditions (1.0 equiv i-Pr₂EtN, Et₂O:hexane, 0 °C to rt). Unfortunately, this reaction afforded none of the desired product even after stirring for several days at room temperature. Apparently, silyl chlorides are insufficiently reactive to effect the desired transformation.

Scheme 7

\[
\begin{array}{ccc}
\text{R}^1\text{R}^2\text{SiOTf, i-Pr}_2\text{EtN} & \text{Et}_2\text{O-hexane} & 0^\circ\text{C to rt} \\
\text{R}^1\text{R}^2 = \text{(CH}_2\text{)}_4 & \text{R}^3 = \text{(i-Pr)}_3 & \text{100} & 75\% \\
\text{98} & \text{R}^1 = \text{R}^2 = \text{CH}_3 & \text{R}^3 = \text{(i-Pr)}_3 & \text{101} & 86-89\% \\
\text{98} & \text{R}^1 = \text{R}^2 = \text{CH}_3 & \text{R}^3 = \text{Et}_3 & \text{102} & 70-84\% \\
\end{array}
\]

Recently we have been interested in preparing TAS-vinylketenes with alkoxy- or phenyl-substituted silyl groups. We anticipated that these particular silyl groups would permit useful synthetic transformations following cycloaddition. The silyl triflates necessary for the synthesis of these desirable TAS-vinylketenes were not readily available. However, these highly reactive and extremely moisture sensitive compounds have been prepared previously by treatment of the requisite silyl chloride with triflic acid\(^{80}\) or by reaction of the silyl chloride with silver triflate.\(^{81}\) Alternatively, treatment of an aryl- or allylsilane with triflic acid results

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in displacement of the phenyl or allyl group, affording a silyl triflate product.\textsuperscript{82} We first prepared an aryl-substituted silyl triflate using the strategy outlined in eq 32. Reaction of dichlorodiphenylsilane with 2.4 equivalents of ethylmagnesium bromide afforded the desired silane 103 in excellent yield,\textsuperscript{83} and addition of an equimolar amount of triflic acid then generated the desired silyl triflate 104 and benzene, which can be removed by distillation. The crude triflate reagent (104) was used for silylation reactions without further purification.

\[
\begin{align*}
\text{Ph}_2\text{SiCl}_2 & \xrightarrow{\text{2.4 equiv EtMgBr, Et}_2\text{O, reflux 4 h}} \text{Ph}_2\text{SiEt}_2 & \xrightarrow{1.0 \text{ equiv TfOH}} \text{PhEt}_2\text{SiOTf} \\
& & \text{PhH}
\end{align*}
\]

(32)

Reaction of diazo ketone 98 with approximately one equivalent of the unpurified diethyl(phenyl)silyl trifluoromethanesulfonate 104 under the standard silylation conditions affords the desired silyl diazo ketone 105 in 56-74\% yield (eq 33, not optimized).

\[
\begin{align*}
\text{PhEt}_2\text{SiOTf, i-Pr}_2\text{EtN} & \xrightarrow{\text{N}_2} \text{Et}_2\text{O-hexane} \ x 0 \text{°C to rt, 1-2 h}} \text{PhSiEt}_2\text{Ph}
\end{align*}
\]

(33)

Unfortunately, synthesis of the alkoxy-substituted silyl triflate 107 was not straightforward (Scheme 8). Dichlorodiethylsilane, when treated with isopropanol in refluxing benzene, affords the alkoxy silyl chloride 106 in 75\% yield after distillation.\textsuperscript{84} (Chloride 106, as expected, was not sufficiently reactive to effect silylation of diazo ketone 98). Reaction of chloride 106 with silver triflate afforded a mixture of products that could not be separated by distillation. By a second route, dichlorodiethylsilane reacts with two equivalents of silver triflate to afford the ditriflate 107 in 61\% yield after distillation.

Unfortunately, subsequent treatment with isopropanol and base afforded a mixture of products that decomposed upon attempted distillation.

Scheme 8

An alternate route to 107 which was not investigated experimentally is outlined in eq 34. Treatment of dichlorodiethylsilane with an equimolar amount of isopropanol followed by addition of allylmagnesium bromide was expected to afford intermediate 109, and subsequent displacement of the allyl group with triflic acid was then anticipated to produce the desired compound 107.

With efficient routes to a variety of α-trialkylsilyl-α-diazo ketones in hand, we were able to carry out a systematic investigation of their conversion to the desired TAS-vinylketenes. Initial studies by Loebach found that Wolff rearrangement occurred upon irradiation at 300 nm using a Rayonet RPR-100 photochemical reactor at 30-35 °C (Scheme 9). Better yields were obtained in the synthesis of more highly substituted vinylketenes, possibly because of the greater stability of the diazo ketone precursors.
TAS-Vinylketenes exhibit a number of interesting spectral characteristics. The following page outlines the spectral features of the diethyl(phenyl)silyl-substituted ketene 113 (Figure 1). The IR spectrum of TAS-vinylketene 113 shows the expected strong diagnostic stretch near 2100 cm\(^{-1}\) resulting from the symmetric stretching modes of the ketene backbone (C=C=O). The \(^1\)H NMR spectrum is relatively uninformative because TAS-vinylketenes do not contain a proton on the ketene double bond that would be diagnostic of the structure. However, the \(^{13}\)C NMR spectrum has two notable features. As expected, the C-1 (C=C=O) carbons of TAS-vinylketenes are extensively deshielded and give a low field signal near 185 ppm. The C-2 carbon (C=C=O) exhibits an unusually high field signal near 20 ppm, resulting from contribution of the resonance structure illustrated below.
Figure 1. Spectral Characteristics of
(E)-2-(1-Methyl-1-propenyl)-2-(diethyl(phenyl)silyl)ketene (113)

IR (film): 3360, 2440, and 2060 cm⁻¹

¹H NMR (500 MHz, CDCl₃):
7.53-7.57 (m, 2H) 0.90-1.04 (m)
7.32-7.39 (m, 3H)
1.80 (s) 4.96 (q, J = 6.8 Hz)
4.15 (d, J = 6.8 Hz)

¹³C NMR (125 MHz, CDCl₃):
136.2, 135.1, 130.1, 128.6
Maas previously reported the application of the transition-metal catalyzed Wolff rearrangement for the preparation of saturated alkyl(TAS)ketenes, and we hoped that this method might be applicable for the synthesis of TAS-vinylketenes. Treatment of silylated α-diazo ketone 100 with a 0.04 to 0.2 equivalents of CuOTf results in formation of the desired ketene 110 (eq 35). Unfortunately, the yield of this reaction (22-26%) compares poorly with the excellent yield (89%) obtained by the photochemically induced Wolff rearrangement of the same diazo ketone, and this method was not pursued further.

\[
\text{cat. CuOTf (i-Pr)\textsubscript{3}Si} \quad \text{C} = \text{O} \\
\text{benzene} \quad \text{rt, 1-2.5 h (35)} \\
\begin{array}{c}
\text{(i-Pr)\textsubscript{3}Si} \\
\end{array}
\]

Substituted TAS-vinylketenes are remarkably robust compounds, in dramatic contrast to typical vinylketenes. The triisopropyl derivative (111) was recovered unchanged after heating in C\textsubscript{6}D\textsubscript{6} at 80 °C for four days, although some decomposition of the (triethylsilyl)vinylketene 112 was observed after heating at this temperature for 10 h. Also notable is the observation that these ketenes can be purified by conventional silica gel chromatography without any detectable decomposition.

We were interested in preparing 3-alkoxy-substituted TAS-vinylketenes because these electron-rich compounds are expected to exhibit increased reactivity in cycloaddition reactions. As discussed earlier, TAS-vinylketenes are easily prepared by the photochemically induced Wolff rearrangement of α'-trialkylsilyl-α'-diazo-α,β-enones. We expected that application of this protocol to α-alkoxy-α'-trialkylsilyl-α'-diazo-α,β-enones might provide a route to the desired alkoxy-substituted vinylketenes.

Dr. Yutaka Ukaji of our laboratory investigated this approach as outlined in Scheme 10. Lithiation of 3,4-dihydro-2\(H\)-pyran (114) with n-butyllithium followed by treatment with \(N,N\)-dimethylacetamide afforded the α,β-unsaturated methyl ketone 115 as previously reported by Boeckman. Application of our standard diazo transfer conditions provided
diazo ketone 116 in moderate yield. Subsequent silylation with triisopropylsilyl trifluoromethanesulfonate in the presence of diisopropylethylamine provided silyl diazo ketone 117 in 58% yield after purification by silica gel chromatography. Unfortunately, irradiation of 117 in a degassed benzene solution yielded none of the desired ketene 118. It is possible that alkoxy-substituted TAS-vinylketene 118 is an exceptionally sensitive compound and may have formed under the photochemical conditions and then decomposed or polymerized.

Scheme 10

\[ \text{Scheme 10} \]

Synthesis of Substituted TAS-Vinylketenes by Electrocylic Cleavage of Cyclobutenones

In our previous studies on the application of vinylketenes in annulation routes to six- and eight-membered rings, our laboratory has shown that the electrocyclic ring opening of cyclobutenones provides an especially attractive method for the generation of these reactive species. It therefore appeared likely that 2-trialkylsilylcyclobutenones might afford TAS-vinylketenes in good yield upon heating. Advantages of this method include the fact that no byproducts are formed and the reaction is reversible. In fact, Tidwell has recently shown that

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silylated bisketenes can be generated in a similar fashion by the thermal or photochemical ring opening of cyclobutenediones (see Scheme 2).

Our plan for the preparation of cyclobutenone precursors to TAS-vinylketenes called for the [2+2] cycloaddition of dichloroketene with an activated alkyne followed by reductive dechlorination. It is important to note that in order to obtain the requisite 2-silyl substituted cyclobutenone, the alkyne must contain a donating substituent (such as an alkoxy or phenyl group) to direct the regiochemical course of the reaction. In the case of (trialkylsilyl)acetylenes with only alkyl substituents, mixtures of regioisomeric cycloadducts are generally obtained. Earlier, in attempts to prepare (trimethylsilyl)vinylketene via this method, Sard discovered that the [2+2] cycloaddition of (trimethylsilyl)acetylene with dichloroketene affords almost exclusively the undesired β-silylcyclobutenone 120 (eq 36).87

Scheme 11 outlines the application of this strategy to the synthesis of TAS-vinylketene 127. Addition of dichloroketene to the phenyl-substituted (trialkylsilyl)acetylenes 121 and 122 provides the desired dichlorocyclobutenones 123 and 124 in high yield. The structure of compound 124 (a single regioisomer as determined by 300 MHz $^1$H NMR analysis) was assigned based on the known powerful directing effect of phenyl groups in the [2+2] cycloadditions of ketenes and also by knowledge of the $^{13}$C NMR spectrum of the previously characterized cyclobutenone 123 (Figure 2).86

---

Dechlorination of 4,4-dichlorocyclobutenones does not proceed smoothly under conventional conditions, but can be accomplished in good yield by employing the protocol developed independently in our laboratory\(^8\) and that of Dreiding.\(^9\) Upon heating in benzene at 60 °C for 4.5 h, 125 undergoes smooth conversion to the desired TAS-vinylketene 127. As expected, this (trimethylsilyl)vinylnketene proved less stable to chromatography than the triethyl- and triisopropylsilyl derivatives 110-112 and could only be obtained in 37% yield after purification on Florisil. For this reason, it ultimately proved advantageous to generate the ketenes from cyclobutenones 125 and 126 in situ for various cycloadditions rather than to subject these sensitive compounds to isolation and purification. Chapters 3 and 4 discuss the “in situ generation” of TAS-vinylketenes from cyclobutenones 125 and 126 in detail.

Interestingly, in several reactions where cyclobutenone 125 was heated at elevated temperatures (110-150 °C), a butenolide side product was isolated. We believe that this byproduct results from reaction of TAS-vinylketene 127 with diradical oxygen. A related reaction of oxygen with a bisketene has been previously reported by Tidwell, and a similar mechanism may be operative in our examples. Scheme 12 outlines the mechanism we propose for formation of butenolide byproduct 129. Addition of oxygen to ketene 127 followed by reaction with a second ketene molecule affords diradical intermediate 128. After intersystem crossing, 128 can undergo cyclization to afford two molecules of butenolide 129. After bubbling air through a refluxing toluene solution of cyclobutenone 125 for 18 h, the butenolide (129) was isolated in 42% yield following purification by silica gel chromatography.

Scheme 12

A variety of spectral data was collected and analyzed in order to substantiate the structural assignment of 129. The $^1$H NMR spectrum exhibits a singlet at 4.94 ppm corresponding to the two C-5 protons on the butenolide ring. The IR spectrum of 129 shows a strong carbonyl stretching frequency at 1745 cm$^{-1}$ indicative of the $\alpha,\beta$-unsaturated lactone. Further proof for the structure of 129 was obtained from a $^{13}$C NMR DEPT experiment. The

C-5 carbon appears as a methylene group at a characteristic resonance of 73.7 ppm. Also, the carbonyl resonance is observed at 176.9 ppm and the two butenolide alkenyl carbons appear at 174.0 ppm (C-4) and 133.4 ppm (C-3). The C-4 carbon is deshielded by conjugation with the carbonyl group and therefore appears downfield in the $^{13}$C NMR spectrum.

We have shown that TAS-vinylketenes form easily by the electrocyclic ring opening of 2-silylcyclobutenones and we therefore believed it would be possible to access alkoxy-substituted TAS-vinylketenes (131) by this method (Scheme 13). One factor motivating our interest in alkoxy-substituted TAS-cyclobutenones is the potential utility of these compounds as synthetic intermediates. Addition of $\text{R}^-$ to the carbonyl of 130 followed by hydrolysis should provide an avenue to a wide array of substituted cyclobutanones (132) that could then undergo electrocyclic ring opening to TAS-vinylketenes (133). Three methods were explored for the formation of the requisite 3-alkoxy-2-(trialkylsilyl)cyclobutenones.

Scheme 13

The first method we investigated involved the [2+2] cycloaddition of dichloroketene with an alkoxy silane (eq 37). (Trimethylsilyl)ethoxyacetylene (22) underwent smooth [2+2] cycloaddition with dichloroketene (generated via dehalogenation of trichloroacetyl chloride) to afford the desired cyclobutenone 134 in excellent yield. The next step in our scheme required the reductive dechlorination of a 4,4-dichlorocyclobutenone, which is considerably more difficult than in the case of the corresponding saturated derivatives, though it can be accomplished using procedures developed independently in our laboratory and that of Dreiding (vide supra). Unfortunately, the reductive dechlorination of 134 was unsuccessful.

using the standard conditions and we were forced to abandon this approach. We suspect that zinc coordination to the neighboring ethoxy group may prevent the desired reductive dechlorination from occurring.

Zaitseva has reported that reaction of TAS-ketenes with ketene acetals affords 3,3-dialkoxy-2-(trialkylsilyl)cyclobutanones in 48-49% yield. Our second strategy for the synthesis of 3-alkoxy-2-(trialkylsilyl)cyclobutenones was based on this precedent. We anticipated that cyclobutanone 140 produced by the Zaitseva reaction might undergo elimination in the presence of ZnCl₂ to give the desired 2-silylcyclobutenone 141 (Scheme 14). We hoped that the regiochemistry of this elimination reaction could be controlled by employing the procedure of Scheeren which allowed him to regioselectively deprotonate cyclobutanone 136 at the more hindered position. Scheeren found that situ trapping with (trimethylsilyl)chloride affords silyl enol ether 137, while without ZnCl₂, the alternative isomer 138 is isolated (eq 38). In our case, in the absence of a trapping agent, we expected to observe elimination of ethoxide to provide the desired cyclobutenone 141 upon treatment of 140 with Et₃N-ZnCl₂.

Scheme 14
Zaitseva reported the preparation of our target intermediate (140) in 48% yield via the reaction of diethylketene acetal (139, synthesized by dehydrobromination of bromoacetaldehyde diethylacetal in t-BuOK/t-BuOH)\textsuperscript{92} and (triethylsilyl)ketene without solvent at 80 °C. Unfortunately, in our hands, attempts to repeat Zaitseva’s procedure afforded none of the desired product 140. The reaction was attempted using freshly distilled reagents, and a variety of solvents, temperatures, and reaction times were investigated, but in no case could [2+2] cycloadduct be detected by \textsuperscript{1}H NMR. We have been unable to account for these results.

Our third method investigated the generation of alkoxy-substituted TAS-vinylketenes from squaric acid derivatives (Scheme 15). Liebeskind has extensively studied the chemistry of squaric acid and its derivatives, reporting that addition of organolithium reagents to diisopropylsquarate followed by treatment with catalytic amounts of acid is the best available procedure for the preparation of squaric acid derivatives.\textsuperscript{93} We found that reaction of diisopropyl squarate (142) with dimethylphenylsilyllithium in THF at −78 °C followed by treatment with concentrated aqueous HCl affords silyl-substituted cyclobutendione 144 in 84-86% yield.

Liebeskind also reported that selective reduction of the more reactive carbonyl group of squaric acid derivatives occurs smoothly upon addition of lithium tri-(tert-butoxy)aluminum hydride at reduced temperatures.\textsuperscript{94} We studied the reduction of cyclobutenedione 144 with a variety of hydride reagents, as summarized in Table 1. Of the reagents investigated, only the lithium tri-(t-butoxy)aluminum hydride successfully reduced cyclobutenedione 144, but the reaction required a large excess of the hydride reagent (entry 6). Although this route appeared feasible, we were discouraged by the multiple steps required to access the desired cyclobutenone intermediate and therefore this route was not studied further.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2 equiv i-Bu₂AlH, CH₂Cl₂, -78 °C, 1 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>1.2 equiv Li s-Bu₂BH, THF, 0 °C, 5 min</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>1.6 equiv NaBH₄, i-PrOH, rt, 5 min</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>1.2 equiv LiAl(t-BuO)₃H, THF, 0 °C to rt, 2 days</td>
<td>No reaction observed</td>
</tr>
<tr>
<td>5</td>
<td>2.3 equiv LiAl(t-BuO)₃H, THF, -78 °C to rt, 2 days</td>
<td>No reaction observed</td>
</tr>
<tr>
<td>6</td>
<td>5.0 equiv LiAl(t-BuO)₃H, THF, -40 °C, 45 min</td>
<td>~30%</td>
</tr>
<tr>
<td>7</td>
<td>1.2 equiv Red-Al, Et₂O, 0 °C, 2 h</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Alternative Routes to TAS-Vinylketenes: Preliminary Studies

Currently in our laboratory, Kevin Shea is investigating the preparation of TAS-vinyl- and alkynylketenes via the cross coupling reactions of stannyl- and halo(silylketenes) as outlined in Scheme 16. Murai previously reported a synthesis of tributylstannyl(trimethylsilyl)ketene 146 from (trimethylsilyl)diazomethane as discussed in Chapter 1. We expect that ketene 146 may undergo Stille-type reactions with alkenyl- and alkynyl halides. Alternatively, reaction of bromo(trialkylsilyl)ketenes⁶₄ᵃ (148) with alkenyl- or alkynylstannanes should afford unsaturated ketene products as well. This method would allow efficient access to a wide array of unsaturated TAS-ketenes (147), including the elusive TAS-alkynylketenes.
We have developed efficient methods for the synthesis of TAS-vinylketene and continue to investigate new, improved routes to these compounds. In what kind of synthetically significant reactions do these novel compounds participate? The remainder of this thesis explores this provocative question. Chapters 3 and 4 detail the [4+2] cycloadditions of TAS-vinylketenes, and Chapter 5 presents the application of these compounds in a novel [4+1] annulation strategy for the synthesis of cyclopentenones.
CHAPTER 3

APPLICATION OF TAS-VINYLKETENES AS DIENES IN THE DIELS-ALDER
REACTION: SYNTHESIS OF CARBOCYCLIC COMPOUNDS

Substituted cyclohexenones are important synthetic targets and are most commonly prepared via the Robinson annulation. In recent years, considerable research has been directed toward the development of alternative routes to cyclohexenones based on the Diels-Alder reaction. Most of these methods have been based on the application of highly functionalized dienes as 4π components, and depending on the choice of diene, routes to cyclohexenones with electron-withdrawing groups at C-4, C-5, and C-6 are now available.

Danishefsky has developed an elegant route to cyclohexenones in which oxygen substituted dienes participate in [4+2] cycloadditions with electron-deficient dienophiles. The oxygen substituents impart a high degree of reactivity and regiospecificity on the dienes which combine with activated dienophiles to produce cyclohexene intermediates. Subsequent treatment of the enol ether with acid hydrolyzes the vinylogous hemiketal to produce substituted cyclohexenones. Note that this methodology produces cyclohexenones in which the dienophile activating (W) group ends up at the C-4 position of the cyclohexenone ring.

Even moderately reactive dienophiles undergo cycloadditions with these unhindered, electron-rich dienes. For example, 2-methylcyclohexenone reacts with Danishefsky’s diene at 200 °C to afford the substituted cyclohexanone intermediate 151. Exposure of the reaction mixture to a 3:1 THF:0.005 N HCl solution then produces the cis-fused cyclohexenone 152 in

95. Portions of this chapter are published in ref 79b.
47% yield (eq 39). Subsequently, Danishefsky reported the synthesis of chiral 1-alkoxy-3-trimethylsilyloxy-1,3-dienes for asymmetric Diels-Alder reactions.\textsuperscript{98,99} In a related method, Rawal has reported that chiral 1-amino-3-silyloxy-1,3-dienes participate in Diels-Alder reactions with \(\alpha,\beta\)-unsaturated aldehydes and esters to afford substituted cyclohexenones in high ee.\textsuperscript{100}

\[
\begin{align*}
\text{Me}_3\text{SiO} & \xrightleftharpoons[200 \degree C, 20 \text{ h}]{\text{xylene}} \text{Me}_3\text{SiO} \\
149 & \quad + \quad \text{OMe} \\
\quad + \quad 150 & \quad \xrightarrow{\text{HCl}} \text{MeO} \\
151 & \quad \downarrow \\
152 & \quad \text{MeO} \\
\end{align*}
\]

Trost has investigated a novel Diels-Alder approach for the preparation of cyclohexenones in which 2-alkoxy-3-thio-substituted dienes undergo [4+2] cycloadditions with electron-poor dienophiles to afford cycloadducts that can be converted to cyclohexenones by enol ether hydrolysis, oxidation of the sulfide to a sulfoxide, and thermal elimination. This methodology generates cyclohexenones in which the dienophile W-group is ultimately found at the C-5 position of the new ring.\textsuperscript{101} Trost has employed this approach for the synthesis of carvone (156) as illustrated in Scheme 17.

Scheme 17

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{PhS} & \quad \text{PhS} \\
\text{153} & \quad \text{154} \\
\longrightarrow & \quad \text{\text{75\%}} \\
\text{MeO} & \quad \text{MeO} \\
\text{PhS} & \quad \text{PhS} \\
\text{155} & \quad (4:1 \text{ regioisomers}) \\
\end{align*}
\]

1) \(\text{Ph}_3\text{P}=\text{CH}_2, \text{THF}\)  
2) \(\text{HClO}_4, \text{aq CH}_3\text{CN}\)  
3) \(\text{NaH}, \text{MeI, THF}\)  
4) \(\text{mCPBA}\)  
5) \((\text{MeO})_3\text{P}, \Delta\)

\text{carvone} \ 156

A third objective of interest in this area of Diels-Alder based cyclohexenone synthesis has been the development of vinylketene \textit{equivalents} capable of participating as diene components in [4+2] cycloadditions. In contrast to the Diels-Alder strategies summarized above, these reactions would produce cyclohexenones in which the dienophile W-group would appear at the C-6 position of the new cyclohexenone ring. Unfortunately, the tendency of vinylketenes to form only [2+2] cycloadducts with alkenes (eq 40) and the intrinsic instability of these ketenes generally precludes their direct use as [4+2] enophiles, as discussed in Chapter 1.\textsuperscript{24}
Vinylketene acetals have found use as vinylketene surrogates; however, the scope of this methodology is somewhat limited because of the sensitivity of these compounds and the fact that the s-cis conformation required for cycloaddition is usually disfavored in these Z-substituted dienes. Substitution by an electron-donating alkoxy- or silyloxy-group at C-3 dramatically increases the reactivity of vinylketene acetals, and these activated dienes readily participate in [4+2] cycloadditions with a variety of dienophiles.\textsuperscript{16,102} For example, the oxygenated diene 157 combines rapidly with dimethylacetylene dicarboxylate (DMAD) in refluxing benzene to afford substituted phenol 159 in 89% yield (eq 41).

\begin{equation}
\text{OMe} \quad \text{CO}_2 \text{Me} \quad \text{O} \quad \text{Me}_3 \text{SiO} \quad \text{CO}_2 \text{Me} \\
\text{157} \quad \text{158} \quad \text{benzene} \quad 80 \degree \text{C} \quad 30 \text{min} \quad \text{89\%} \quad \text{HO} \quad \text{CO}_2 \text{Me} \quad \text{CO}_2 \text{Me} \quad \text{159}
\end{equation}

In 1980, our laboratory reported that (trimethylsilyl)vinylketene participates as a reactive enophile in [4+2] cycloadditions with standard electron-deficient Diels-Alder dienes. This chemistry is summarized later in this section. Several years later, Ghosez reported that N-silylated silylvinylketenimines can function in a similar manner as vinylketene equivalents in Diels-Alder reactions with olefinic and acetylenic dienophiles.\textsuperscript{103} In an example of this interesting cycloaddition, ketenimine 160 combines smoothly with methyl acrylate at 150 \degree C, and subsequent protodesilylation with potassium fluoride in refluxing methanol yields dihydroaniline 162 (eq 42). Hydrolysis to the cyclohexenone 163 can then be effected using 1.2 N HCl. Ketenimine 160 also reacts in [4+2] cycloadditions with methyl crotonate, various acetylenic esters, and napthoquinones.

\textsuperscript{102} Savard, J.; Brassard, P. \textit{Tetrahedron} 1984, 40, 3455. \\
[4+2] Cycloadditions of TAS-Vinylketenes

Several years ago, our laboratory reported the first synthesis and isolation of (trimethylsilyl)vinylketene (92). As expected, 92 fails to engage in typical ketene [2+2] cycloadditions and instead participates as a diene component in [4+2] cycloadditions with electron-deficient alkenes and alkynes. The ketene carbonyl group is predicted to donate electron density into the diene system (see resonance hybrid, below), activating this system for [4+2] cycloadditions with standard electron-deficient dienophiles.

The trimethylsilyl group confers only a weak directing effect on Diels-Alder reactions of 1- and 2-(trimethylsilyl)-1,3-dienes and is not expected to contribute significantly to the regiochemical course of TAS-vinylketene reactions. As mentioned above, the carbonyl oxygen of the vinylketene is predicted to function as an electron-donor substituent and

therefore is expected to control the regiochemical outcome of these cycloadditions. In fact, early experiments by Howard Sard in our laboratory confirmed the expectation that \([4+2]\) cycloadditions with TAS-vinylketenes would be highly regioselective.\(^73\) For example, methyl propiolate (164) reacts smoothly with (trimethylsilyl)vinylketene (92) to afford 3-(trimethylsilyl)salicylate (165) as a single regioisomer (eq 43). Note also that the cycloadduct undergoes facile protodesilylation when treated with trifluoroacetic acid at room temperature to yield 166.

(Trimethylsilyl)vinylketene also reacts with olefins such as diethyl fumarate and \(N\)-phenylmaleimide to afford cyclohexenones. Unfortunately, the scope of these reactions is restricted by the limited thermal stability of this vinylketene (which begins to decompose at temperatures above 95 °C), and ketene 92 does not undergo cycloadditions with less reactive dienophiles in satisfactory yield.

Originally, substituted TAS-vinylketenes were not available by the dehydrohalogenation route. However, development of the photo Wolff rearrangement of \(\alpha\)-silyl-\(\alpha\)-diazo ketones made the more robust, substituted ketenes available. We expected that these derivatives would engage in \([4+2]\) cycloadditions with a broader range of substrates than (trimethylsilyl)ketene, providing a useful synthetic route to highly substituted cyclohexenones and phenols. We therefore undertook a systematic investigation of Diels-Alder reactions of these substituted TAS-vinylketenes, focusing on the scope and
stereochemical course of the process. Initial experiments by Jennifer Loebach of our laboratory confirmed the feasibility of these reactions and, subsequently, my research goal has been to extend the scope of this interesting methodology by investigating the use of different substituted TAS-vinylketenes, other reactive dienophile partners (including heterodienophiles, see Chapter 4), and Lewis acid catalysts.

The relative reactivity of different TAS-vinylketenes was explored initially by examining their cycloadditions with the reactive dienophile, dimethyl acetylenedicarboxylate (DMAD). In a typical reaction, a degassed toluene solution of TAS-vinylketene 111 and 1.0 equiv of DMAD was heated at 150 °C for 16 h in a threaded Pyrex tube sealed with a Teflon cap. Concentration and purification by chromatography on silica gel provided the expected phenol 167 in nearly quantitative yield (eq 44). Protodesilylation of this cycloadduct proceeded readily (80% yield) upon exposure to 20 equiv of TFA in dichloromethane at room temperature for 2 h.

Interestingly, cycloaddition with the corresponding triethylsilyl derivative 112 afforded a mixture of products tentatively assigned as the silyl ether 169 and phenol 170 (eq 45). In this case, the acidity of the phenolic product apparently promotes desilylation of the cycloadduct at the elevated reaction temperature. This process is not as facile in the case of the triisopropylsilyl derivative 111 because of the steric bulk of the silyl group.
Further experiments investigated by Loebach confirmed that a wide range of substituted TAS-vinylketenes would react with DMAD. As discussed in Chapter 2, cyclobutenones undergo 4π-electrocyclic ring opening to afford TAS-vinylketenes. We were interested in using this method to generate ketenes in situ from cyclobutenones for reaction with DMAD. As illustrated in eq 46, heating 2-silylcyclobutenones 125 and 126 in toluene at reflux in the presence of DMAD affords phenols 171 and 172 in good yield. Presumably, cyclobutenones 125 and 126 undergo an in situ electrocyclic ring opening to generate TAS-vinylketenes which then react in [4+2] cycloadditions. Lower yields of the desired phenols were obtained when the reactions were conducted at higher temperatures and butenolide side products were isolated (see Chapter 2 for a discussion). It is interesting to note that in both cases, none of the rearranged products (akin to 169 and 170) were observed.

The scope of TAS-vinylketene cycloadditions encompasses other reactive dienophiles such as ethyl cyanoacrylate, nitroethylene, and cyanoallene. Since ethyl cyanoacrylate bears two electron-withdrawing groups, the cycloadditions of this dienophile were not informative with regard to the stereochemical course of the Diels-Alder reactions of TAS-vinylketenes. Simple acrylate derivatives proved insufficiently reactive, so we turned our attention to reactions of nitroalkenes. TAS-Vinylketene 111 combines with nitroethylene in a regioselective Diels-Alder reaction, but because of the high acidity of the doubly activated α'}
proton in the cycloadduct, the product is expected to undergo equilibration. Therefore, the identity of the major product does not necessarily provide insight into the stereochemical course of the cycloaddition stop. No such ambiguity is associated with the reaction of 2-nitropropene with ketene 111 (eq 47), and indeed this cycloaddition produces a single cycloadduct in 35% yield whose structure was established by Loebach as 174 by analysis of $^1$H NMR coupling constant data and an NOE study.

$$
\begin{align*}
\text{toluene} & \quad \text{reflux 116 h} \\
111 & \quad 173 \\
\rightarrow & \quad 35\% \\
174
\end{align*}
$$

This result indicates that as in other Diels-Alder reactions, cycloadditions involving TAS-vinylketenes follow the Alder endo rule and prefer transition states in which the dienophile activating group adopts an endo orientation (175) relative to the diene system (eq 48). Disappointingly, vinylketene 111 failed to react with less reactive dienophiles such as N-phenylmaleimide and chloroacrylonitrile; in each case, complex mixtures of products were obtained.

$$
\begin{align*}
O_2N & \quad \text{endo} \\
175 & \quad 174 \\
\end{align*}
$$

Other work by Loebach established that monoactivated allenes are excellent partners for [4+2] cycloadditions with TAS-vinylketenes, providing access to phenolic products that could otherwise be produced only by cycloadditions with less reactive acetylene dienophiles. For example, addition of cyanoallene to TAS-vinylketene 111 in toluene at 150 °C gave a single product in good yield, which NOE studies revealed to be not the expected $o$-(triisopropylsilyl)phenol, but rather the isomeric silyl ether 178 (Scheme 18). Isomerization
of the presumed initial cycloadduct 175 to 178 may proceed via the intermediacy of the \( \alpha \)-silyl ketone 177. 1,3-Silyl shifts of \( \alpha \)-silyl ketones to form silyl enol ethers are well-known processes.\(^\text{105}\)

**Scheme 18**

\[
\begin{array}{c}
\text{(i-Pr)}_3\text{Si} \quad \text{C}=\text{O} \\
\text{[4+2]} \quad \text{cycloaddition} \\
\begin{array}{c}
\text{H}_2\text{C}=\text{C}=\text{C}=: \text{CN} \\
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\text{(i-Pr)}_3\text{Si} \quad \text{C}=\text{O} \\
\text{[4+2]} \quad \text{cycloaddition} \\
\begin{array}{c}
\text{H}_2\text{C}=\text{C}=\text{C}=: \text{CN} \\
\end{array}
\end{array}
\]

We anticipated that other reactive allenes might also participate in cycloadditions with TAS-vinylketenes and so we next examined the reaction of acetylallene with the vinylketene generated in situ by electrocyclic ring opening of 125. Thus, a degassed toluene solution of acetylallene (179) and cyclobutenone 125 was heated at reflux for 20 h, and the desired cycloadduct was isolated in 37-45% yield (eq 49). None of the silyloxy product resulting from 1,3-silyl rearrangement was observed as in the cyanoallene case. Disappointingly, reaction of acetylallene with the triisopropylsilyl-substituted ketene 111 led to even lower yields (25-26%) of the phenolic product.

The acetylallene for this study was prepared in two steps by the method of Buono (eq 50).\textsuperscript{106} First, reaction of 2,4-pentanedione 182 with triphenylphosphine-bromine in dichloromethane affords a mixture of (E/Z)-2-bromo-4-oxo-2-pentene 183 and a triphenylphosphine oxide hydrobromide salt, which is precipitated by the addition of ether. After concentration of the filtrate, the resulting vinyl bromide 183 is used directly in the next step without further purification. Dehydrobromination of 183 occurs upon treatment with triethylamine in ether. The solvent is removed by distillation and pure acetylallene (179) is isolated in 59-65% yield following careful distillation at reduced pressure. The colorless liquid (bp 62 °C, 80 mmHg) polymerizes readily and must be stored over a small amount of hydroquinone to inhibit this undesired reaction.

Rigby has reported the application of the [4+2] cycloadditions of vinyl isocyanates and benzyne\textsuperscript{107} as a useful method for the preparation of phenanthridinones (eq 51).\textsuperscript{108} We expected that this highly reactive acetylene species might react with TAS-vinylketenes in good yield to afford interesting polycyclic products.


Benzyne can be generated by a variety of methods. Rigby obtained the best results with Diels-Alder reactions of vinyl isocyanates when the benzyne was generated by Pb(OAc)$_4$ oxidative decomposition of 1-aminobenzotriazole (184). With this method for benzyne preparation, reaction can occur over a broad range of temperatures (-78 °C to 55 °C). However, side reactions sometimes occur in the presence of the lead tetraacetate, a powerful oxidizing agent, and acetic acid is a byproduct of the reaction. Generation of benzyne with lead tetraacetate is believed to proceed through a nitrene intermediate (188, eq 52). Fragmentation of the ortho-fused benzene derivative expels two molecules of nitrogen, lead diacetate, and acetic acid, none of which compete for benzyne.

1-Aminobenzotriazole (184) is commercially available but is quite expensive, so for our study this benzyne precursor was prepared by amination of benzotriazole according to the procedure of Campbell and Rees (eq 53). Thus, treatment of triazole 189 with hydroxylamine-$\alpha$-sulfonic acid in aqueous potassium hydroxide affords 1-aminobenzotriazole in 13% yield (lit. 38%).

Unfortunately, attempted reaction of TAS-vinylketene 190 with benzyne (generated as described above by the lead tetraacetate method) led only to unreacted starting material and the benzyne dimer biphenylene (192, eq 54). Apparently, reaction of TAS-vinylketenes with benzyne occurs more slowly than benzyne dimerization.

In an attempt to expand the scope of the [4+2] cycloadditions of TAS-vinylketenes to include dienophiles of low reactivity, the application of Lewis acids as catalysts for the reaction was examined. It should be noted that Lewis acids have found considerable use as catalysts for [2+2] cycloadditions of TAS-ketenes with aldehydes.\(^{110}\) Unfortunately, attempts to promote the cycloaddition of vinylketene 111 with methyl acrylate or DMAD using either Me\(_2\)AlCl or BF\(_3\)-OEt\(_2\) at various temperatures proved unsuccessful (see Table 2). In all cases, extensive decomposition of 111 was observed and none of the desired cycloadduct was detected.

\(^{110}\) See ref 58 and the following: Brady, W. T.; Saidi, K. *J. Org. Chem.* 1979, 44, 733.
Table 2  Attempted Lewis Acid Catalysis of Diels-Alder Cycloadditions of TAS-Vinylketenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketene</th>
<th>Dienophile</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>111</td>
<td>DMAD</td>
<td>1.0 equiv Me₂AlCl&lt;sub&gt;2&lt;/sub&gt;, 0 °C to rt</td>
<td>rapid decomposition of the ketene</td>
</tr>
<tr>
<td>2</td>
<td>111</td>
<td>DMAD</td>
<td>1.0 equiv Me₂AlCl&lt;sub&gt;2&lt;/sub&gt;, -78 °C to rt</td>
<td>rapid decomposition of the ketene</td>
</tr>
<tr>
<td>3</td>
<td>111</td>
<td>DMAD</td>
<td>0.1 equiv BF₃·OEt₂, CH₂Cl₂, 0 °C to rt</td>
<td>rapid decomposition of the ketene</td>
</tr>
<tr>
<td>4</td>
<td>111</td>
<td>DMAD</td>
<td>0.1 equiv BF₃·OEt₂, CH₂Cl₂, -78 °C to rt</td>
<td>rapid decomposition of the ketene</td>
</tr>
<tr>
<td>5</td>
<td>methyl acrylate</td>
<td>1.0 equiv Me₂AlCl&lt;sub&gt;2&lt;/sub&gt;, CH₂Cl₂, 0 °C</td>
<td>rapid decomposition of the ketene</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>methyl acrylate</td>
<td>0.1 equiv BF₃·OEt₂, CH₂Cl₂, 0 °C</td>
<td>rapid decomposition of the ketene</td>
<td></td>
</tr>
</tbody>
</table>

TAS-vinylketenes bearing electron-donating substituents are expected to exhibit increased reactivity in [4+2] cycloadditions, expanding the scope of this methodology to include less activated dienophiles. Our initial attempts to prepare 3-alkoxy TAS-vinylketenes have thus far been unsuccessful (as discussed in Chapter 2), however, further studies are planned to explore this important area.

We have shown that TAS-vinylketenes undergo highly regioselective [4+2] cycloadditions with reactive olefinic and acetylenic dienophiles to produce highly substituted cyclohexenones and phenols. The ketene carbonyl dominates in controlling the regiochemical course of the reaction and the stereochemical course of these cycloadditions follows the Alder
endo rule. The syntheses of oxygen and nitrogen heterocycles via the hetero Diels-Alder reactions of TAS-vinylketenes is described in Chapter 4.
CHAPTER 4
APPLICATION OF TAS-VINYLKETENES AS DIENES IN THE DIELS-ALDER REACTION: SYNTHESIS OF HETEROCYCLIC COMPOUNDS

The hetero Diels-Alder reaction is an extremely important method for the synthesis of heterocyclic compounds.\(^\text{111}\) A wide variety of heterodienophiles participate in [4+2] cycloadditions, including carbonyl compounds, imines, iminium salts, and azo- and nitroso compounds. This methodology often allows the rapid construction of complex molecules from simple starting materials and has been applied for the synthesis of many heterocyclic natural products. In recent years, asymmetric versions of hetero Diels-Alder reactions have also been reported.

As discussed in the preceding chapter, we have shown that TAS-vinylketenes take part in [4+2] cycloadditions with olefins and acetylenes, and we anticipated that carbonyl compounds and imines might also function as dienophiles providing efficient routes to interesting heterocycles. This chapter describes the results of our investigation of the hetero Diels-Alder reactions of TAS-vinylketenes, including a discussion of the scope, stereochemical course, and mechanism of the process.

Diels-Alder Reactions with Carbonyl Dienophiles: Background

In 1949, Gresham and Stedman reported the first example of the oxa Diels-Alder reaction of a carbonyl dienophile with a conjugated diene.\(^\text{112}\) Specifically, heating 2,4-dimethyl-1,3-butadiene and formaldehyde affords 5,6-dihydropyran 194 in 60% yield (eq 55). Unfortunately, similar reactions of diene 193 with higher aldehydes leads only to low yields of products.

---

Later findings confirmed that simple 1,3-dienes react best with electron-deficient carbonyl compounds. For example, diethyl oxomalonate (196) combines with 2-methyl-1,3-butadiene to afford the pyran cycloadduct 197 in 80% yield (eq 56). Less reactive carbonyl compounds will participate in [4+2] cycloadditions in the presence of Lewis acid catalysts or under the application of high pressure.

Vinylketene equivalents such as 198 have been shown to undergo Lewis-acid catalyzed Diels-Alder reactions with aldehydes. For example, as illustrated in eq 57, electron-rich diene 198 and amino aldehyde 199 combine in the presence of diethylaluminum chloride to afford a 92:8 mixture of lactones 200 and 201.

---

Diels-Alder Reactions of TAS-Vinylketenes with Carbonyl Dienophiles

We anticipated that TAS-vinylketenes would participate in oxa Diels-Alder reactions with activated carbonyl compounds to afford $\alpha,\beta$-unsaturated $\delta$-valerolactones. The proposed oxa Diels-Alder reaction of TAS-vinylketenes was initially investigated by examining cycloadditions with the highly reactive and commercially available oxadienophile diethyl oxomalonate. In a typical reaction, an acetonitrile solution of silylketene 111 and 1.5 equiv of diethyl oxomalonate (196) was heated at reflux for 15 minutes. Concentration and purification by chromatography on silica gel afforded the desired $\alpha,\beta$-unsaturated $\delta$-valerolactone 202 in 94% yield (eq 58). As shown in previous studies (Chapter 3), the ketene carbonyl functions as an electron-donor substituent and directs the regiochemical course of the reaction.

\[
\begin{align*}
\text{(i-Pr)}_3\text{Si} & \quad \text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \\
\text{reflux} & \quad 15 \text{ min} \\
\text{111} & \quad \text{196} \\
\quad & \quad 94\% \\
\text{202}
\end{align*}
\]

$^1$H NMR spectral data supports the structural assignment for compound 202 and includes a diagnostic resonance at 3.21 ppm (quartet) that corresponds to proton $H_a$ on the lactone ring. The IR spectrum contains a strong carbonyl stretching frequency at 1715 cm$^{-1}$ due to the lactone carbonyl. In addition, the $^{13}$C NMR spectrum exhibits characteristic resonances for the $\alpha,\beta$-unsaturated lactone carbonyl carbon at 168.9 ppm, two alkenyl carbons (166.6 and 122.0 ppm), and the C-2 carbon at 85.0 ppm.

The reaction of oxomalonate 196 with the cyclohexenyl TAS-ketene 110 also proceeds smoothly to afford lactone 203 in 77% yield (eq 59). With this more sterically hindered ketene, the reaction rate is slower and requires two hours in refluxing acetonitrile to reach completion.

TAS-Vinylketenes generated by the electrocyclic ring opening of cyclobutenones also participate in oxa Diels-Alder reactions. For example, addition of oxomalonate 196 to a refluxing acetonitrile solution of cyclobutenone 126 affords the predicted cycloadduct 205 in excellent yield (eq 60).

As expected, unactivated carbonyl compounds such as pivaldehyde do not participate in cycloaddition reactions with TAS-vinylketenes. Lewis acids have found considerable use as catalysts for [2+2] cycloadditions of TAS-ketenes with aldehydes and we hoped that Lewis acids might promote the oxa Diels-Alder reaction of TAS-vinylketenes. Unfortunately, attempts to promote the cycloaddition of vinylketene 111 with pivaldehyde using ZnCl$_2$ proved unsuccessful, resulting only in slow decomposition of the ketene; none of the desired cycloadduct was observed. Previous attempts to catalyze Diels-Alder reactions of TAS-vinylketenes with other Lewis acids gave similarly disappointing results (see Chapter 3).

Finding effective conditions for protodesilylation of the lactone cycloadducts required a substantial amount of investigation. A variety of acidic conditions were explored for the protodesilylation of lactone 202 (Table 3), but none resulted in clean removal of the triisopropylsilyl group. However, protodesilylation of the triethylsilyl derivative 205 proceeds more easily. Thus, treatment of lactone 205 with 5 equivalents of methanesulfonic acid in refluxing dichloromethane affords the desired lactone 206 in quantitative yield (entry 6, eq 61).
Protodesilylation of α-Silylcyclopentenones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lactone</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>202</td>
<td>20 equiv TFA, CH₂Cl₂, rt, 48 h</td>
<td>no reaction, recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>starting material in 88% yield</td>
</tr>
<tr>
<td>2</td>
<td>202</td>
<td>15 equiv MsOH, MeOH, rt, 24 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>202</td>
<td>5 equiv TBAF, THF, rt, 1 h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>205</td>
<td>20 equiv TFA, CH₂Cl₂, rt, 5 days</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>205</td>
<td>1 equiv TBAF, THF, rt, 30 min</td>
<td>complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>205</td>
<td>5 equiv MsOH, CH₂Cl₂, reflux, 15 h</td>
<td>100%</td>
</tr>
</tbody>
</table>

Cycloadditions with Imino Dienophiles: Background

In addition to carbonyl compounds, we were also interested in exploring the utility of imines as dienophiles in [4+2] cycloadditions with TAS-vinylketenes. An enormous amount of research has been devoted to the study of electron-deficient imines such as N-sulfonyl and N-acylimines as well as iminium salts as dienophiles in the Diels-Alder reaction. These [4+2] cycloadditions comprise an important strategy for the synthesis of nitrogen heterocycles.

Neutral imines generally react in [4+2] cycloadditions only with highly activated dienes in the presence of a Lewis acid catalyst. Grieco has demonstrated that iminium salts react with dienes in intermolecular [4+2] cycloadditions.¹¹⁵ The iminium salts are generated in aqueous solution by the reaction of a primary amine with aqueous formaldehyde or by the

reaction of an aldehyde with an ammonium chloride solution. Unfortunately, iminium ions derived from higher aldehydes are generally much less reactive.

Unactivated imines were of particular interest to our group as heterodienophiles for Diels-Alder reactions with TAS-vinylketenes. Simple, uncharged imines are usually not reactive as heterodienophiles in Diels-Alder cycloadditions unless partnered with reactive, electron-rich dienes in the presence of a Lewis acid. For example, Brassard's oxygenated diene 198 (a vinylketene equivalent) combines with chiral imine 207 with the aid of a Lewis acid to form the lactam 208 in good yield (eq 62).

\[
\begin{align*}
198 & \quad + \quad 207 \\
\text{Et}_2\text{AlCl} & \quad CH_2Cl_2 \\
-78 \degree C \text{ to rt} & \quad \rightarrow \\
84\% & \quad 95\% \text{ d.e.} \\
208
\end{align*}
\]

Danishefsky employed the imino Diels-Alder reaction as a key step in the total synthesis of ipalbidine (Scheme 19). Reaction of vinylketene equivalent 210 with 1-pyrroline in the presence of BF$_3$-OEt$_2$ affords the lactam intermediate 212. Reduction of the lactam carbonyl and subsequent dehydration provides ipalbidine (213) in 78\% yield.

We envisioned that the [4+2] cycloadditions of TAS-vinylketenes with imines might provide another direct route to substituted 5,6-dihydro-2(1H)-pyridones (α,β-unsaturated δ-valerolactones).

It is well known that imines of the type R₂C=NH are generally not stable. Benzophenone imine (Ph₂C=NH), however, is stable and is commercially available, and we hoped that this ketimine would react in [4+2] cycloadditions with TAS-vinylketenes. Unfortunately, when ketene 111 was heated with benzophenone imine in refluxing acetonitrile, only a complex mixture of inseparable products was obtained and none of the desired lactam cycloadduct could be observed in the ¹H NMR spectrum.

Unlike N-H substituted imines, N-(trimethylsilyl)imines are quite stable under anhydrous conditions. These imines are easily prepared and some can even be purified by distillation at reduced pressure. Note that the cycloadduct derived from an N-(trimethylsilyl)imine is expected to undergo protodesilylation under very mild conditions (e.g. aqueous workup or silica gel chromatography) to afford the same products that would have resulted from cycloaddition of the unstable imines of the type R₂C=NH.

Few examples of [4+2] cycloadditions of N-(trimethylsilyl)imines have been reported to date. Barluengas has reported that N-(trimethylsilyl)imines react as dienophiles in ZnCl₂ -
catalyzed [4+2] cycloadditions with 2-amino-1,3-dienes to afford tetrahydropyridones and 4-piperidinones.\textsuperscript{119} For example, reaction of \( N \)-(trimethylsilyl)benzaldehyde \( 215 \) with the electron-rich chiral diene \( 214 \) affords enamine \( 216 \) which is converted on silica gel to the enantiomerically enriched tetrahydropyridone \( 217 \) (eq 63). As suggested above, in these reactions \( N \)-silylimines function as masked forms of the elusive imines of ammonia. Most imines that are not substituted at nitrogen rapidly trimerize to the corresponding triazines.

\[
\begin{align*}
\text{OMe} & \quad \text{ZnCl}_2 & \quad \text{THF} & \quad 1) \text{NaHCO}_3 & \quad 2) \text{SiO}_2 \\
214 & \quad 215 & \quad 216 & \quad 70\% & \quad 82\% \text{ e.e.} \\
\text{OMe} & \quad \text{NH} & \quad \text{Ph} & \quad \text{Ph} & \quad 217
\end{align*}
\]

The reaction of imines with ketenes has been exploited extensively for the synthesis of \( \beta \)-lactams in the well known Staudinger reaction. \( N \)-(Trimethylsilyl)imines have also been employed as participants in these [2+2] cycloadditions. In 1977, Birkofer described that addition of \( N \)-(trimethylsilyl)benzophenone imine to diphenylketene affords the acyclic intermediate \( 220 \) in quantitative yield; none of the \( \beta \)-lactam product was observed (Scheme 20). Heating \( N \)-(trimethylsilyl)benzaldimine with diphenylketene at 160 °C and subsequent hydrolysis of the \( N \)-trimethylsilyl group provides \( \beta \)-lactam \( 222 \) in poor yield.\textsuperscript{120}

Panunzio reported that the [2+2] cycloadditions of ketenes (generated in situ from an acid chloride) with N-(trimethylsilyl)imines is a useful method for the direct preparation of N-H substituted azetidinones. For example, reaction of N-(trimethylsilyl)imine 224 with the ketene derived from acid chloride 225 affords the acyclic azadiene intermediate 226 which can be observed by analysis of the crude reaction mixture. Upon heating in refluxing toluene for 6 h, cyclization occurs to afford exclusively the trans-substituted β-lactams 227 and 228 in 59% yield as a 80/20 mixture of the anti and syn isomers (Scheme 21).¹²¹

Panunzio found that syn selectivity can be obtained in the [2+2] cycloadditions of N-(trimethylsilyl)imines with ketenes by appending an alkoxy substituent on the ketene. For example, reaction of imine 215 with the ketene derived from acid chloride 229 affords the cis-substituted β-lactam 231 in 81% yield.\textsuperscript{122} Panunzio postulates that the cis-diastereoselectivity results from the formation of a weak electrostatic bond between the imine carbon and the ether oxygen. This interaction stabilizes the azadiene intermediate 230. A similar electrostatic interaction had previously been proposed in an example of the classical Staudinger reaction of an alkoxy-substituted ketene with an N-alkyl imine.\textsuperscript{123}

Imino Diels-Alder Reactions with TAS-Vinylketenes

We anticipated that N-(trimethylsilyl)imines might participate as dienophiles in Diels-Alder reactions. Described in the following section is our systematic investigation of the imino Diels-Alder reactions of TAS-vinylketenes, including our studies of the scope, stereochemical course, and mechanism of the process.

Reactions with N-(Trimethylsilyl)benzaldimine

To test the feasibility of the proposed silylimine [4+2] cycloadditions, we initially examined the reaction of TAS-vinylketenes with the easily prepared N-(trimethylsilyl)benzaldimine. To our immense delight, we found that the combination of silylketene 111 and 1.5 equivalents of imine 215 in refluxing acetonitrile provides the desired cycloadduct (tentatively assigned as the N-silyl isomer 232) and no catalyst is needed to promote the reaction! The bond to silicon is easily hydrolyzed from the crude product 232 during purification on silica gel to afford lactam 233 in excellent yield (eq 65). Similarly, in subsequent cases, protodesilylation of the initial crude products occurs during silica gel chromatography.
The $N$-(trimethylsilyl)benzaldehyde substrate (215) was prepared using the procedure of Hart (eq 66). Thus, treatment of benzaldehyde with lithium hexamethyldisilylamide in hexane affords the desired silyl imine 215 in 90% yield (lit. 89%) after distillation at reduced pressure. This yellow liquid can be stored at 0 °C indefinitely under anhydrous conditions. Note that this reaction proceeds via a heteroatom variant of the Peterson olefination, presumably via the four-membered transition state 234.

$\text{PhCHO} + \text{Me}_3\text{SiLi} \rightarrow \text{Ph} = \text{N}(-\text{SiMe}_3)_2$  \hspace{1cm} (66)

$^{1}H$ NMR spectral data supports the structural assignment of compound 233, including a resonance at 4.77 ppm due to the C-6 proton and a multiplet at 2.21 ppm corresponding to the C-5 proton. The N-H proton is observed as a broad singlet at 5.51 ppm. These assignments are consistent with data previously reported by Marson for the related lactam 235 in which the C-5 and 6 substituents are trans rather than cis (Figure 3).114

Proof of the cis-stereochemistry of 233 was obtained from $^1$H NMR coupling constant data and an NOE study (Figure 4). The proton at C-6 ($H_a$) is assigned to be on the same side of the ring as proton $H_b$ due to the observed equatorial-axial coupling constant ($J_{ab} = 3.6$ Hz). Also, irradiation of $H_a$ results in a 9% enhancement of $H_b$, providing further confirmation that $H_a$ and $H_b$ are on the same side of the ring. Although the trans isomer was not available for comparison of NOE data, later NOE studies on an analogous compound support this assignment.
The same cycloaddition was run with 1.0 equiv of imine 215 rather than 1.5 equiv as in eq 65. However, in this case the time for the reaction to reach completion increased from 1.5 h to 3 h and the yield decreased slightly to 72%. Therefore, in most of the [4+2] cycloadditions examined subsequently, a slight excess of imine was employed.

The rate of the [4+2] reaction was found to be noticeably faster in acetonitrile than in toluene. Reactions in toluene were only approximately 50% complete by TLC analysis after the same period of time in which the acetonitrile based reactions were finished. This increase in rate in the more polar solvent suggests that the mechanism of the reaction proceeds via a transition state involving more charge separation than the ground state (vide infra). We later discovered that the hetero Diels-Alder reactions of TAS-vinylketenes proceed rapidly and at a lower temperature in the absence of solvent. For example, ketene 112 combines with imine 215 (1.5 equiv) at room temperature in two hours (no solvent) to afford the cis-substituted lactam 236 in 76% yield (eq 67). Again, an NOE study confirmed the cis assignment of the substituents on this triethylsilyl-substituted lactam: irradiation of the C-6 proton resulted in a 6% enhancement of the neighboring C-5 proton.

\[
\begin{align*}
\text{Et}_3\text{Si} & \quad \text{C}=\text{O} \\
\text{112} & \quad \text{N}\text{SiMe}_3 \\
\text{Ph} & \quad \text{H} \\
\text{no solvent} & \quad \text{rt} \quad 2\text{ h} \\
\text{SiO}_2 & \quad \text{76\%} \\
\text{Et}_3\text{Si} & \quad \text{O} \\
\text{236} \\
\end{align*}
\]

The Diels-Alder reactions of N-(trimethylsilyl)benzaldimine and two other TAS-vinylketenes were explored. Silylketene 110 undergoes cycloaddition with imine 215 to afford the exo-substituted product 237 (as identified by an NOE study) in 91% yield (eq 68). Irradiation of the C-1 proton (Ha) results in no enhancement of the C-8a proton (Hb). However, one C-8 proton (Hc) exhibits a 7% enhancement, confirming the trans assignment of lactam 237 (Figure 5).
Assuming that these reactions follow a concerted cycloaddition mechanism, it would appear that the steric effect of the cyclohexenyl substituent in ketene 110 leads to a preference for the transition state in which the phenyl group is exo (238, eq 69), whereas the less hindered ketenes 111 and 112 prefer the transition state in which this group has the endo orientation.
[4+2] Cycloaddition of silylimine 215 with the TAS-vinylketene generated via in situ
electrocyclic ring opening of cyclobutenone 126 also was successful and afforded the lactone
239 in 84% yield after purification by column chromatography (eq 70).

\[
\begin{align*}
\text{Et}_3\text{Si} & \quad \text{O} \\
\text{Ph} & \quad \text{N} \quad \text{SiMe}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{CN} & \quad \text{reflux 45 min;} \\
\text{SiO}_2 & \quad 84\%
\end{align*}
\]

\[
\begin{align*}
\text{Et}_3\text{Si} & \quad \text{O} \\
\text{Ph} & \quad \text{N} \quad \text{Ph}
\end{align*}
\]

\[
(70)
\]

(2) Reactions with N-(Trimethylsilyl)cinnamaldimine

Clearly, the imino Diels-Alder reactions of TAS-vinylketenes have a broad scope with
respect to the ketene. We next were interested in investigating the scope of the reaction with
regard to imino dienophiles. We began this study with a reaction of a vinyl-substituted imine,
N-(trimethylsilyl)cinnamaldimine (240), which was prepared according to the procedure of
Colvin.\textsuperscript{125} Treatment of commercially available (and pleasantly aromatic) cinnamaldehyde
with LiHMDS followed by trapping with chlorotrimethylsilane affords imine 240 as a yellow
liquid in 59% yield (lit. 95%) after distillation at reduced pressure.

Reaction of TAS-vinylketenes 111 and 110 with aldimine 240 occurs almost
instantaneously at room temperature. Under these solvent-free conditions, the cycloadducts
241 and 242 were obtained in 78% and 73% yield, respectively (Scheme 22).

Scheme 22

![Scheme 22](image)

Support for the sterochemical assignments for the *cis* isomer 241 and the *trans* isomer 242 was obtained by NOE experiments. Irradiation of the C-6 proton (H<sub>a</sub>) of 241 resulted in a 9% enhancement of the corresponding C-5 proton (H<sub>b</sub>), indicating that the two protons have a *cis* orientation. However, irradiation of the C-1 proton (H<sub>a</sub>) of 242 resulted in no enhancement of the C-8a proton (H<sub>b</sub>) and instead showed an 8% enhancement of H<sub>c</sub>, thereby indicating that the lactam ring is *trans*-substituted (Figure 6).

Figure 6

![Figure 6](image)
(3) Reactions with N-(Silyl)ketimines

To further investigate the scope of this interesting cycloaddition, we next turned our attention from aldimines to ketimines. Would this class of more highly substituted imines be effective partners for cycloadditions with TAS-vinylketenes? We first undertook a study of the reaction of TAS-vinylketenes with N-(trimethylsilyl)benzophenone imine (219), prepared via the procedure of Rochow.\textsuperscript{126} Addition of benzonitrile to an ethereal solution of phenyllithium and subsequent treatment with chlorotrimethylsilane affords the N-silyl imine 219 in 77% yield (lit. 55%) after purification by distillation at reduced pressure (eq 71).

\[
\begin{align*}
\text{Ph\text{-C\equiv N}} & \quad \text{PhLi, Et}_2\text{O} \quad \text{rt} \quad 15 \text{ min;} \\
\text{Me}_3\text{SiCl} & \quad \text{rt} \quad 22 \text{ h} \\
\text{243} & \quad 77\% \\
\text{219}
\end{align*}
\]

We were delighted to discover that ketimine 219 reacts with ketene 111 to afford the lactam 244 in 79% yield (eq 72). This cycloaddition proceeds at a significantly slower rate (refluxing CH\textsubscript{3}CN, 18 h) than the comparable reaction with aldimine 215 (refluxing CH\textsubscript{3}CN, 15 min), probably due to the increased steric demands of 219.

The cyclohexenyl-substituted ketene 110 also combines smoothly with imine 219 (refluxing acetonitrile, 24 h) to provide the desired lactam 245 in 66% yield (eq 73).

\[
\begin{align*}
\text{(i-Pr)_3\text{Si}} & \quad \text{C=O} \\
\text{111} & \quad \text{Me}_3\text{Si} \quad \text{N} \\
\text{219} & \quad \text{CH}_3\text{CN} \quad \text{reflux} \quad 18 \text{ h;} \\
\text{244}
\end{align*}
\]

Silylketenimines were also studied as potential heterodienophiles in Diels-Alder reactions with TAS-vinylketenes. Silylketenimines 247 and 249 were prepared by the method of Watt. Thus, treatment of the requisite nitrile with lithium diisopropylamide and subsequent trapping with t-butyldimethylchlorosilane affords the ketenimine products in excellent yields (Scheme 23). Unfortunately, reaction of these imines with ketene 111 afforded only a complex mixture of products.

Scheme 23

(4) Reaction with Alkyl-Substituted N-(Silyl)Imines

In all successful cases thus far, the azadienophile component has had one or more stabilizing phenyl substitutents. We next investigated the reaction of TAS-vinylketenes with alkyl-subsituted N-silylimines, which are notably less stable than the aromatic-substituted derivatives. In 1987, Cainelli reported the preparation of enolizable N-(trimethylsilyl)imines
which must be generated and trapped in situ at temperatures of $-30 \, ^\circ\text{C}$ or below.\textsuperscript{128} For example, addition of isobutyraldehyde to a $-30 \, ^\circ\text{C}$ solution of LiHMDS generates $N$-(trimethylsilyl)isobutyraldimine (250, eq 74).

\[
\begin{align*}
\text{CHO} & \quad \text{LiHMDS} \\
\text{THF} & \quad -40 \, ^\circ\text{C} \\
\rightarrow & \quad N\text{-SiMe}_3
\end{align*}
\]

(74)

Attempts to use this procedure for in situ reactions with TAS-vinylketenes led to disappointing results. Generation of the imine by the aforementioned procedure and subsequent addition of ketene 111 at $-78 \, ^\circ\text{C}$ followed by slow warming to room temperature afforded a complex mixture of inseparable products. At low temperatures, the vinylketene and imine probably do not undergo cycloaddition and as the temperature increases, the imine likely isomerizes to the more stable enamine which may react with the ketene by alternative pathways initiated by nucleophilic addition.

In contrast to this result, we have found that nonenolizable alkyl-substituted imines serve as good partners for [4+2] cycloadditions with TAS-vinylketenes. Reaction of pivaldehyde with LiHMDS at ambient temperature affords $N$-(trimethylsilyl)pivaldimine 251\textsuperscript{115} in 46-48% yield after distillation at reduced pressure. Treatment of ketene 110 with imine 251 using our standard cycloaddition conditions (CH\textsubscript{3}CN, reflux, 24 h) afforded none of the desired lactam product. However, heating the reaction mixture in a sealed tube at 110 $^\circ\text{C}$ for 90 h did provide the desired cycloadduct in 56% yield (eq 75). This imine appears to slowly decompose at these elevated temperatures, and therefore it was necessary to utilize three equivalents of the dienophile which were added in two portions of 1.5 equiv each.

Not surprisingly, the combination of hindered ketene 110 with the sterically encumbered imine 251 results in formation of the trans-substituted product. This stereochemistry was confirmed by an NOE study in which irradiation of the C-1 proton (Hₐ) results in a 5% enhancement of one C-8 proton (Hₖ). No enhancement of the C-8a proton (Hₐ) is observed, confirming the trans assignment (Figure 7).

Figure 7

(5) Reactions with N-Alkyl-Substituted Imines

We next chose to study the cycloadditions of N-alkyl imines and TAS-vinylketenes. This class of imines is generally prepared by addition of an amine to an aldehyde or ketone. For example, treatment of benzaldehyde with methylamine in refluxing benzene with water separation via a Dean-Stark trap provides N-methyl benzaldimine (253) in 89% yield (lit. 87-95%, eq 76).129

Reaction of ketene 111 with N-alkyl imine 253 does proceed successfully, but affords an inseparable 3:1 mixture of diastereomeric lactams 254 and 255 in 71% yield (eq 73).

SYBYL Calculations of the ground state energy of the cis and trans-substituted lactams 254 and 255 were performed in an attempt to determine which conformational isomer has a lower ground state energy for each product. For the modeling studies, the triisopropylsilyl group of lactams 254 and 255 was replaced with a proton in order to simplify the calculations and because the silyl group probably does not significantly influence the difference in ground state energies of lactams 254 and 255. These molecular modeling studies indicate that for the cis-substituted lactam, it is conformer 255a (with the phenyl group in the equatorial position) which is the thermodynamically most stable conformation. The difference in energy between 255a and 255b \((\Delta G = 1.46 \text{ kcal/mol})\) should result in approximately a 90:10 ratio of conformational isomers. The trans-substituted lactam 254 slightly favors a conformation in which the phenyl group adopts an equatorial position (254a). The small difference in energy between 254a and 254b \((\Delta G = 0.388 \text{ kcal/mol})\) indicates that compound 254 exists as approximately a 2:1 ratio of conformational isomers 254a and 254b.
The identity of the major cycloadduct was confirmed by an NOE study (Figure 8). Irradiation of the C-5 methyl group of the major isomer (254, favored conformation shown) results in a 5% enhancement of the proton at C-6, confirming that these two groups reside on the same side of the ring (trans-substituted). However, irradiation of the C-6 proton (Ha) of the minor isomer gives a 7% enhancement of the C-5 proton (Hb). Thus, the minor isomer does in fact have both protons on the same side of the ring (cis-substituted). Although no enhancement of Ha is expected upon irradiation of the C-5 methyl group, a 3% enhancement is in fact observed, but this value is not considered to be a significant NOE enhancement.

**Figure 8**
In order to determine experimentally which isomer is the thermodynamically favored product, we investigated the base-induced isomerization of the mixture of products. Thus, treatment of the 75:25 (trans:cis) mixture of isomers 254 and 255 with potassium t-butoxide in t-butanol results in isomerization to provide predominately the cis-substituted isomer in a 72:28 cis:trans ratio (eq 78), indicating that the cis isomer is the thermodynamically favored product in agreement with our molecular modeling calculations. In fact, based on the calculated difference in energies between 254a and 255a (ΔG = 0.754) we would predict to observe a similar ratio of approximately 75:25.

\[
\begin{align*}
(\text{t-Pr})_3\text{Si} & & (\text{t-Pr})_3\text{Si} \\
\text{O} & & \text{O} \\
\text{NCH}_3 & & \text{NCH}_3 \\
\text{Ph} & & \text{Ph} \\
\text{254} & & \text{255}
\end{align*}
\]

\[
\text{KOt-Bu} \xrightarrow{\text{t-BuOH}} \text{254 + 255} \quad (78)
\]

75:25

Unfortunately, other more hindered alkyl-substituted imines did not participate in [4+2] cycloadditions with TAS-vinylketenes. For example, reaction of ketene 111 with enantiomerically enriched imine 258 (prepared from benzaldehyde and (S)-α-methylbenzylamine) at 125 to 150 °C afforded mostly unreacted ketene and imine starting materials. None of the desired cycloadduct was observed by 'H NMR. Reaction of 2-phenyl-1-pyrroline 259\textsuperscript{130} with ketene 111 (CH\textsubscript{3}CN, 110 °C, 35 h) also gave disappointing results, providing a complex mixture of products.

\[
\begin{align*}
\text{Ph} & & \text{N} & & \text{H} \\
\text{258} & & \text{Ph} \\
\text{Ph} & & \text{Ph} & & \text{N} \\
\text{259}
\end{align*}
\]

\textsuperscript{130} A sample of this imine was kindly provided by Marcus Hansen. For details on the preparation of this compound, see: Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Maryanoff, B. E. \textit{Organic Syntheses} 1997, 75, pp 215-222.
(6) Cycloadditions with Other Azadienophiles

In the next phase of our study, we turned our attention to investigating electron-rich and electron-deficient imine derivatives as partners in Diels-Alder reactions with TAS-vinylketenes. First, electron-rich heteroatom-substituted imines such as amidines were studied. Visiting scientist Iwao Okamoto examined the [4+2] cycloadditions of these nucleophilic imines without success. For example, treatment of ketene 111 with amidine 260 at room temperature resulted in some disappearance of the starting material but no cycloadduct could be observed by $^1$H NMR (eq 79). Preliminary experiments have been carried out to survey the possible utility of other azadienophiles, however these compounds (shown in Figure 9) also resulted in no reaction with ketene 111.

![Chemical structure](image)

Figure 9

Electron-deficient imine derivatives also do not participate in [4+2] cycloadditions with TAS-vinylketenes. Addition of glyoxylate 268 to ketene 111 in refluxing acetonitrile for 22 h afforded none of the desired product. Preparation of this imine was accomplished by a two-step procedure as described by Colvin (Scheme 24). First, silylation of glycine methyl ester hydrochloride by treatment with base and then a silyl chloride affords the $N$-silylamine 266. Subsequent chlorination of 266 with $t$-butyl hypochlorite followed by base induced elimination forms the imine 268.
Mechanism of Imino Diels-Alder Reactions

What is the mechanism of the Diels-Alder reaction of TAS-vinylketenes and imines? One can envision alternate pathways ranging from a Diels-Alder concerted mechanism to a true stepwise process, as illustrated in Scheme 25. In the stepwise process, the imine would first add to the ketene to afford an acyclic intermediate that would then undergo electrocyclic closure to afford the lactam.

Scheme 25
Marson has reported a convenient method for the formation of the 5,6-dihydro-2(1H)-pyridone ring system by a [5+1] condensation of a 3-alkenamide with an aldehyde or ketone that occurs via an intermediate similar to the one proposed above for the stepwise mechanism for the [4+2] cycloaddition. For example, amide 269 and benzaldehyde combine in the presence of polyphosphoric ester (PPE) to form intermediate 270 which cyclizes to afford exclusively the trans-substituted lactam 235 in 63% yield (eq 80). Recall that our related [4+2] cycloaddition of ketene 111 with imine 215 affords only the cis-substituted product 233.

\[
\begin{align*}
\text{NH}_2 & \quad \text{O-P} \\
\text{269} & \quad \text{PPE} \\
\text{O} & \quad \text{25 \degree C} \quad \text{24 h} \\
\text{35 \degree C} & \quad \text{270} \\
\text{235} & \quad \text{473}
\end{align*}
\]

With respect to the stepwise mechanism (which would involve nucleophilic attack of the imine on the ketene), it is important to note that amines are much more nucleophilic than imines. In order to examine whether a stepwise mechanism is feasible, we first studied the nucleophilic addition of amines to (TAS)ketenes. We found that diethylamine adds rapidly to (triisopropylsilyl)ketene at room temperature (CH₃CN, 20 min). TAS-Vinylketenes also react quickly with diethylamine, however the rate of this addition is slower than the addition of amine with TAS-ketenes. For example, TAS-vinylketene 112 reacts with diethylamine in acetonitrile when heated at 50 °C for 20 min to afford a mixture of isomers (271-273) that result from nucleophilic addition of the amine to the TAS-vinylketene (eq 81). Because nucleophilic addition to TAS-vinylketenes does occur under conditions comparable to those employed in our imine cycloadditions, we cannot immediately rule out the possibility of a stepwise mechanism in the [4+2] cycloaddition in which the imine would act as a nucleophile and attack the ketene, followed by cyclization in a second step.

Also relevant to the mechanism question are the [2+2] cycloadditions of ketenes with imines. It is well-established that alkyl- and aryl-ketenes react with imines to form β-lactams in a process commonly known as the Staudinger reaction. In a typical example, acid chloride 274 undergoes in situ dehydrohalogenation to form methylketene which subsequently reacts with imine 275 to afford the cis-substituted β-lactam 276 in good yield (eq 82). The stereochemical outcome of these [2+2] cycloadditions is sometimes difficult to predict and depends greatly on the structure of the imine and ketene, the solvent, base, mode of ketene generation, and temperature as well as other factors.

The Bose reaction, a variation of the Staudinger reaction in which an aminoketene reacts with an imine, affords 3-amino-substituted β-lactams. For example, combination of an amino-substituted ketene (generated in situ from anhydride 277) reacts with imine 278 in a [2+2] cycloaddition to form 3-amino-2-azetidinone 280 after hydrolysis (eq 83).

---


The mechanism of these important [2+2] cycloadditions has been the subject of intense scrutiny and the reactions are generally believed to proceed via a stepwise mechanism. In fact, experiments have been reported in which the intermediate zwitterion was trapped with ethanol. The substituents on the ketene presumably determine the direction of attack by the imine based on steric considerations. Because the trans conformation of the imine is preferred, formation of the zwitterionic intermediate and subsequent conrotatory ring closure generally affords the cis-substituted β-lactams.

As mentioned previously, [2+2] cycloadditions of ketenes and N-(trimethylsilyl)imines are known to proceed via a stepwise mechanism because often the acyclic intermediate can be observed spectroscopically or, in some cases, isolated. In these examples, addition of a TAS-ketene to an imine first generates a characterizable acyclic intermediate that, upon heating, cyclizes to an azetidinone. Surprisingly, no reactions of (trialkylsilyl)ketenes with N-(trimethylsilyl)imines have been reported to date. We believed that the rate of such a reaction would provide an important value for comparison with our [4+2] cycloadditions of (trialkylsilyl)vinylketenes with N-(trimethylsilyl)imines. In fact, we found that heating (triisopropylsilyl)ketene (281) with N-(trimethylsilyl)benzaldimine 215 at 70 °C resulted in slow reaction and was only approximately 30% complete (by TLC analysis) after 3 days. However, when the reaction temperature was increased to 140 °C for 3 h, we were able to isolate the [2+2] adduct 283 in 72% yield (eq 84).
Presumably, this [2+2] reaction proceeds by a stepwise mechanism as do known reactions of TAS-imines with ketenes. The initially formed \textit{trans,cis}-witterionic compound isomerizes to zwitterionic intermediate 282 which then undergoes conrotatory ring closure to afford the \textit{trans}-substituted \(\beta\)-lactam 283. Since the conrotatory ring closure in this cycloaddition affords the \textit{trans}-substituted \(\beta\)-lactam, we would expect (and in fact do observe) formation of the \textit{cis}-substituted product from the disrotatory ring closure in the \([4+2]\) cycloaddition of ketene 111 with imine 215 (eq 65).

Because the \([4+2]\) cycloadditions of imines with TAS-vinylketenes are much faster than the related stepwise \([2+2]\) cycloaddition of imines with TAS-ketenes it is possible that the TAS-vinylketene reactions are proceeding via a completely different mechanism, a concerted process. As noted earlier, the reactions proceed at a faster rate in polar than in non-polar solvents, and thus the reaction would follow an \textit{asynchronous} concerted mechanism in which a significant separation of charge occurs in the transition state (Figure 10). This charged intermediate would be stabilized by the presence of a polar solvent.

\textbf{Figure 10}

![Figure 10](image)

Further investigations are underway in our laboratory to determine the mechanism of the \([4+2]\) cycloaddition and to explain the interesting stereochemical observations made in the studies described in this chapter.

\textbf{Protodesilylation of Lactam Cycloadducts}

Multiple attempts were made to protodesilylate the triisopropylsilyl-substituted lactams 233 and 252 (Table 4). Although some of these conditions effectively removed the triisopropylsilyl group, the desired product could not be isolated in >95% purity (entries 1, 5, 6).

Table 4  Protodesilylation of (Triisopropylsilyl)-Substituted Lactams

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycloadduct</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>233</td>
<td>20 equiv TFA CH₂Cl₂, rt 20 h</td>
<td>complete conversion to 246, &lt;95% purity</td>
</tr>
<tr>
<td>2</td>
<td>233</td>
<td>5 equiv TBAF THF, reflux 1 h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>233</td>
<td>1.1 equiv CsF CH₃CN, reflux 20 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>233</td>
<td>20 equiv MsOH MeOH, reflux 4 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>233</td>
<td>20 equiv MsOH CH₂Cl₂, reflux 1.5 h</td>
<td>complete conversion to 246, &lt;95% purity</td>
</tr>
<tr>
<td>6</td>
<td>233</td>
<td>5 equiv MsOH CH₂Cl₂, reflux 17 h</td>
<td>complete conversion to 246, &lt;95% purity</td>
</tr>
<tr>
<td>7</td>
<td>252</td>
<td>10% aq. HCl THF, rt 2 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>252</td>
<td>oxalic acid MeOH, rt 22 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>9</td>
<td>252</td>
<td>1.1 AlCl₃ CH₂Cl₂, rt</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

Table 5 details our attempts to protodesilylate the triethylsilyl-substituted lactams 239 and 236 which cleaved more readily than the triisopropylsilyl derivatives. Clean removal of the triethylsilyl-group can be accomplished by treatment with 5 equiv of methanesulfonic acid in refluxing dichloromethane (entries 3 and 4, eq 85).

Table 5  Protodesilylation of (Triethylsilyl)-Substituted Lactams

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycloadduct</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>239</td>
<td>20 equiv TFA CH₂Cl₂, rt 25h</td>
<td>14% yield; 239 was recovered in 86% yield</td>
</tr>
<tr>
<td>2</td>
<td>239</td>
<td>5 equiv TBAF THF, rt 3 days</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>239</td>
<td>5 equiv MsOH CH₂Cl₂, reflux 4 h</td>
<td>55% yield of 245</td>
</tr>
<tr>
<td>4</td>
<td>236</td>
<td>5 equiv MsOH CH₂Cl₂, reflux 6 h</td>
<td>83% yield of 285</td>
</tr>
</tbody>
</table>
Conclusion

We have shown that TAS-vinylketenes participate in oxa and imino Diels-Alder reactions with a variety of heterodienophiles. As shown in previous work, the ketene carbonyl dominates in controlling the regiochemical course of these reactions. Particularly interesting is the stereochemical course of these cycloadditions: with less hindered dienes the endo product is obtained and with more bulky vinylketenes the exo product forms. Investigations are ongoing to determine whether the mechanism of the imino [4+2] cycloadditions proceeds via a stepwise mechanism or an asynchronous concerted transition state which is stabilized in the presence of a polar solvent. Overall, we have shown that TAS-vinylketenes function as interesting four-carbon dienes in Diels-Alder cycloadditions to afford α,β-unsaturated δ-valerolactones and -lactams.
CHAPTER 5

TAS-VINYLKETENES AS FOUR-CARBON COMPONENTS
IN A NEW [4+1] ANNULATION STRATEGY

Introduction

The invention of new methods for the construction of five-membered rings continues to be a problem of considerable importance in organic synthesis. Many biologically active natural products incorporate a cyclopentenone ring as a major structural feature and cyclopentyl systems serve as valuable synthetic intermediates in routes to many classes of compounds. Five-membered rings can be synthesized by a variety of different methods, including the Nazarov cyclization, the Pauson-Khand cyclization of olefins with alkynes, [3+2] coupling reactions, the [3+2] annulation, intramolecular aldol condensations, and vinylcarbene insertion into C-H bonds. Only a few [4+1] annulation strategies have been reported to date, one example being the methodology base on oxyanion and carbanion-accelerated vinylcyclopropane rearrangements developed in our laboratory.

This chapter outlines our work on the stereoselective [4+1] annulation strategy for the synthesis of...
substituted cyclopentenones based on the reaction of TAS-vinylketenes with nucleophilic “carbenoid” reagents such as sulfur ylides and diazo compounds (eq 86).\textsuperscript{144}

\[
\begin{align*}
\text{R}_3\text{Si} & \quad \text{C}^=\text{O} \\
\text{R}^1 & \quad \text{R}^2 \\
+ & \quad \text{\textbullet} \text{C}^L & \quad \text{R}^3 \\
\text{L} & \quad \text{R}^4 \\
\rightarrow & \quad \text{R}_3\text{Si} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4
\end{align*}
\]

(L = leaving group)

\[ (86) \]

[4+1] Annulations with Sulfur Ylides and Diazocompounds

Our plan for the application of TAS-vinylketenes to the synthesis of five-membered rings called for their reaction with nucleophilic carbenoid reagents to generate dienolate species that would then cyclize to the desired cyclopentenones. Several classes of carbanionic nucleophiles are known to add smoothly to simple silylketenes (including (trimethylsilyl)ketene itself),\textsuperscript{145} and we therefore anticipated that TAS-vinylketenes would participate in the proposed [4+1] annulation provided that carbenoid reagents of suitable reactivity could be identified.

Among the several classes of carbenoid reagents we have examined, sulfur ylides\textsuperscript{146} and diazo compounds have thus far proved most effective for the desired [4+1] annulation. Concurrently with our studies, Tidwell has found that diazo compounds add to silylated bisketenes in a related process to produce cyclopentene-1,3-diones and 5-methylene-2(5H)-furanones.\textsuperscript{147} As illustrated in eq 87, reaction of bisketene 286 with diazomethane affords a mixture of dione 287 (22%) and furanone 288 (63%). Reactions of bisketene 286 with (trimethylsilyl)diazomethane and phenylidiazomethane (PhCHN\textsubscript{2}) provide only substituted cyclopentene-1,3-dione products.

\textsuperscript{145} For examples, see refs 31, 52, and 55.
Jennifer Loebach of our laboratory initially investigated the new [4+1] annulation strategy of TAS-vinylketenes with sulfur ylides and diazomethane compounds (Table 6). In a typical reaction, addition of 1.05 equiv of dimethylsulfonium methyldide to ketene 111 in 1:1 THF-DMSO at 0-25 °C for 1.5 h gives the desired cyclopentenone 289 in 75% yield after chromatographic purification (entry 1). Dimethyloxosulfonium methyldide also combines with 111 to produce cyclopentenone 289, though in lower yield (entry 2). Diazomethane reacts with TAS-vinylketene 111 in a similar fashion to afford the cyclopentenone product in excellent yield (entry 3). Protodesilylation of annulation product 289 was readily achieved by exposure to methanesulfonic acid in methanol at 25 °C for 3 h to afford 3,4-dimethylcyclopentenone in 95% yield (eq 88).

**Table 6**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbenoid reagent</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>@Me₂S=C=CH₂</td>
<td>1:1 THF-DMSO 0 to 25 °C 1.5 h</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>@OII Me₂S=C=CH₂</td>
<td>1:1 THF-DMSO 0 to 25 °C 1.5 h</td>
<td>43%</td>
</tr>
<tr>
<td>3</td>
<td>CH₂N₂</td>
<td>CH₂Cl₂ -120 to 25 °C 3 h</td>
<td>96%</td>
</tr>
</tbody>
</table>
Optimizing conditions for the addition of the analogous isopropyl sulfur ylide proved to be nontrivial. Initially, reaction of diphenylsulfonium isopropylide (291) with ketene 111 was attempted using our standard conditions (0 °C to rt, 1 h) and resulted in formation of the desired product, but the cyclopentenone 292 could not be isolated in >95% purity. Attempts to protodesilylate the crude product and then isolate and purify the resulting 3,4,5,5-tetramethylcyclopentenone also were unsuccessful. Effective removal of the triisopropylsilyl group from cyclopentenone 292 occurs in the presence of 5 equiv of TBAF (refluxing THF, 3 h) but, unfortunately, the desired product is not stable to silica gel purification and also could not be isolated in >95% purity. Therefore, we returned to the [4+1] annulation step in an attempt to obtain pure cyclopentenone 292 directly. It occurred to us that the isopropylide 291 is probably less stable than the methylide derivative previously studied (Table 7, entry 1). In fact, when ylide 291 was generated at a lower temperature (-20 °C versus 0 °C) smooth reaction with TAS-vinylketene 111 ensued to afford the desired cyclopentenone 292 in 57% yield after chromatographic purification (eq 89).

Diphenylisopropyl sulfonium fluoroborate (the precursor to ylide 291) was prepared by the method of Nadeau. Reaction of diphenyl sulfide and isopropyl iodide in the presence of silver fluoroborate (0 °C to rt, 2.5 h) afforded 18-31% yield (lit. 55%) of the ylide precursor 295 as a crystalline white solid.148 Treatment of this sulfonium salt with t-BuLi in a

50% THF-DMSO solution at -20 °C provides the bright yellow ylide 291 which must be used immediately to avoid decomposition (eq 90).

\[
\begin{align*}
\text{Ph}_2\text{S} + \text{I} & \xrightarrow{\text{AgBF}_4} \text{Ph}_2\text{S}\text{BF}_4^+ \\
0 \text{ °C to rt} & \xrightarrow{\text{n-BuLi}} \text{THF} -20 \text{ °C} \\
293 & \xrightarrow{\text{Ph}_2\text{S}\text{BF}_4^+} 295 \xrightarrow{\text{n-BuLi}} \text{THF} -20 \text{ °C} \\
293 & \xrightarrow{\text{Ph}_2\text{S}\text{BF}_4^+} 295 \xrightarrow{\text{n-BuLi}} \text{THF} -20 \text{ °C} \\
295 & \xrightarrow{\text{Ph}_2\text{S}\text{BF}_4^+} 296
\end{align*}
\] (90)

Commercially available (trimethylsilyl)diazomethane\textsuperscript{149} also reacts with TAS-vinylketene 111 to afford the trans-substituted cyclopentenone 296 (eq 91). However, all attempts to employ higher diazoalkanes and substituted TMS-diazomethanes in the [4+1] annulation have been unsuccessful; in each case no significant reaction occurred and the TAS-vinylketene was recovered unchanged. Fortunately, substituted sulfur ylides are more nucleophilic and do react with TAS-vinylketenes in the desired fashion, providing access to highly substituted cyclopentenones in good yield.

Scheme 26 outlines several alternative pathways to account for the mechanistic course of our [4+1] annulation. Addition of a carbenoid reagent to the vinylketene should be highly stereoselective due to the shielding effect of the bulky trialkylsilyl group and should result in the formation of the (Z)-enolate 297. Cyclization of this intermediate could produce the five-membered ring product directly, although the planar structure of the dienolate system in 297 may not allow it to achieve an arrangement in which the π electrons are suitably situated for direct backside displacement of the leaving group. An alternative pathway involves ionization to produce the 2-oxidopentadienylic cation 298, which can then undergo

conrotatory $4\pi$ electrocyclic closure to generate the cyclopentenone product. Pentadienyl cation electrocyclic ring closures are involved in the mechanism of the Nazarov cyclization,\textsuperscript{150} and epoxidation of vinylallenes produces cyclopentenones via electrocyclization of $2$-oxidopentadienylic cations analogous to $298$.\textsuperscript{151} A similar mechanism is believed to occur in the biosynthetic pathway for prostanoid synthesis by marine organisms in which conversion of an allene oxide intermediate ($300$) to the cyclopentenone product ($302$) occurs via a $4\pi$ electrocyclic closure of pentadienyl cation $301$ (Scheme 27). A third pathway, proceeding via the cyclopropanone intermediate $299$ (either formed by direct internal displacement or ionization and subsequent electrocyclic closure), cannot be excluded, particularly in view of the finding that diazomethane adds to (trimethylsilyl)ketene to generate (trimethylsilyl)-cyclopropanone in good yield.\textsuperscript{70}

\textbf{Scheme 26}

\begin{center}
\includegraphics[width=\textwidth]{scheme26.png}
\end{center}

\textsuperscript{150} For a review, see ref 137b.
A notable feature of annulations involving substituted carbenoid reagents is the exclusive formation of trans-4,5-substituted cyclopentenones. The stereochemical outcome of the reactions of substituted sulfur ylides and diazo compounds is consistent with a mechanism involving stereospecific conrotatory electrocyclic ring closure if one assumes that ionization of the initial dienolate intermediate occurs to generate a 2-oxidopentadienylic cation 298 with the C-1 substituent cis to the oxygen atom to minimize nonbonded interactions. If a mechanism involving concerted electrocyclization is indeed operative, then [4+1] annulations beginning with TAS-vinylketenes with Z-substituted alkenyl groups should afford cis-4,5-substituted cyclopentenones. Studies are underway in our laboratory to test this hypothesis.

Loebach found that both α-halocarbanions and “nitrenoid” equivalents (such as mesyl azide) were ineffective as reagents for [4+1] annulations with TAS-vinylketenes. The following sections describe other potential carbenoid reagents we explored to expand the utility of this interesting annulation process.

\[ \text{[4+1] Annulation with Acetylides} \]

In 1994, Jacobi reported the synthesis of methylenecyclopentenones in three steps from enones via cyclization of an intermediate enynone with catalysis by α-tocopherol
(vitamin E).\footnote{152} For example, enynone 304 (prepared from 303 as outlined in Scheme 28) underwent cyclization to methylenecyclopentenone 306 upon heating at 125 °C in the presence of a catalytic amount of Vitamin E. The enynones do not undergo cyclization in the absence of a catalyst and the mechanism of the reaction is believed to proceed by a reductive radical cyclization.

**Scheme 28**

We hoped that acetylides might function as carbenoid reagents in [4+1] annulations with TAS-vinylketenes to afford methylenecyclopentenones (309) in a single step. Nucleophilic addition of an acetylide to the ketene carbonyl could afford intermediate 308 which might then undergo cyclization to the cyclopentenone 309 (eq 92).

Thus, treatment of ketene 111 with phenylacetylide 310 at \(-78 \, ^\circ C\) followed by slow warming to \(-5 \, ^\circ C\), addition of 1 equiv of BHT, and then heating at 50 °C for 35 min affords

the cyclopentenone 311 in 69-75% yield after chromatographic purification (eq 93). Unfortunately, without addition of BHT the reaction gives only poor yields of the desired cycloadduct. Therefore, the reaction probably proceeds via a radical mechanism (as described by Jacobi) rather than by a carbanionic sequence of addition/cyclization in which the acetylide functions as a carbenoid reagent. Other acetylides (such as trimethylsilylacetylide and $^\text{-C=CH}$) add to TAS-vinylketene 111, but only uncyclized addition products were observed to form in these reactions by $^1$H NMR spectroscopy.

$$\text{(i-Pr)$_3$Si} \text{C}^\equiv \text{O} \quad \text{310} \quad \begin{array}{c} -78 ^\circ \text{C to rt} \\ 2 \text{h} \\ \text{BHT} \end{array} \quad \rightarrow \quad \text{(i-Pr)$_3$Si} \text{C}^\equiv \text{Ph} \quad \text{311} \quad \begin{array}{c} \text{69-75%} \end{array}$$

**Samarium Iodide-Mediated [4+1] Annulations**

Previous work by Loebach established that $\alpha$-halocarbanions were ineffective as carbenoid reagents in the [4+1] annulation. Recently, Inanaga reported that coupling of carbonyl compounds with diiodomethane aided by SmI$_2$ affords iodohydrins. For example, reaction of benzylacetone (312) with diiodomethane in the presence of SmI$_2$ (room temperature, 3 min) affords the iodo alcohol 313 in 96% yield (eq 94).

$$\text{Ph} \quad \text{312} \quad \begin{array}{c} + \quad \text{Sml}_2 \\ \text{THF rt} \\ 3 \text{ min} \\ 96\% \end{array} \quad \text{Ph} \quad \text{313} \quad \begin{array}{c} \text{OH} \\
\text{CH}_2\text{I} \end{array}$$

We hoped to employ a similar procedure for a [4+1] annulation with TAS-vinylketenes to afford cyclopentenones (eq 95). Unfortunately, however, no observable reaction occurred upon treatment of a THF solution of ketene 111 and diiodomethane with SmI$_2$. 

108
Synthetic Elaboration of Cyclopentenones

As mentioned previously, silylcyclopentenone 289 can be protodesilylated in the presence of methanesulfonic acid. We were interested in investigating other possible synthetic transformations of the silyl group such as conversion to a halide which would provide access to useful synthetic intermediates for cross-coupling and other reactions.

Negishi previously reported that trimethylsilyl-substituted cyclopentenones can be converted to the α-bromo enones by treatment with N-bromosuccinimide.153 For example, treatment of bicycle 315 with 2.5 equiv of NBS in DMF affords the bromo-substituted compound 316 in 75% yield (eq 96).

![Chemical reaction diagram showing the conversion of 315 to 316](image)

We anticipated that this transformation would occur at an extremely slow rate for triisopropylsilyl-substituted cyclopentenones such as 289 as a result of steric hindrance. However, in preliminary studies we found that the less-hindered triethylsilyl-substituted cyclopentenone 317 does undergo conversion to the bromo-substituted compound when treated with 3.5 equiv of N-bromosuccinimide in DMF (room temperature, 54 h), affording the cyclopentenone 318 in 51% yield (eq 97). Not surprisingly, reaction with this triethylsilyl compound occurs at a significantly slower rate than with the less hindered triisopropylsilyl-substituted cyclopentenone 289. Other conditions for more efficient conversion of our annulation products to vinyl bromides and iodides are under investigation in our laboratory.

Confirmation of the structural assignment of bromo cyclopentenone 318 was made by analogy to previously reported spectroscopic data. As expected, the triethylsilyl resonances of 317 do not appear in the $^1$H NMR spectrum of 318. Also, the $^{13}$C NMR spectrum of bromo cyclopentenone 318 exhibits similar resonances as reported for bromo cyclopentenone 316 (Scheme 29).

Scheme 29

Vollhardt reported that iodine monochloride (ICl)\textsuperscript{154} effectively cleaves carbon-silicon bonds to produce the corresponding iodo compound. For example, treatment of trimethylsilyl-substituted 319 with 2 equiv of iodine monochloride in carbon tetrachloride yields the diiodo derivative 320 in 94% yield (eq 98).\textsuperscript{155} Presumably, iodination of the

silicon-substituted double bond affords a β-silicon stabilized cation. Subsequent cleavage of the silicon group by attack with chloride generates the iodo alkene 320.

\[
\text{319} \quad \xrightarrow{2 \text{ equiv } \text{ICl}} \quad \text{320} \quad 94\%
\]

Preliminary small-scale studies for the iodination of triethyilsilyl-substituted cyclopentenones utilizing similar conditions gave promising results. Treatment of cyclopentenone 317 with 2 equiv of iodine monochloride (room temperature, 40 h) affords the iodocyclopentenone 321 in ~55% yield (not optimized, eq 99).

\[
\text{317} \quad \xrightarrow{2 \text{ equiv } \text{ICl}} \quad \text{321} \quad \text{rt} \ 40 \text{ h}
\]

We envision that TAS-cyclopentenones could also undergo another interesting transformation, the Tamao/Fleming cleavage of an alkoxy-substituted silyl compound to afford a hydroxyl group.\(^\text{156}\) Organosilyl groups bearing at least one electronegative substituent have been widely used as synthetic equivalents of the hydroxy group. However, successful conversion of a vinylsilane to the enol occurs only with specifically substituted silicon groups. Currently, we are working to develop synthetic routes to TAS-vinylketenes that contain the proper type of silyl group for this transformation. This methodology could potentially be applied to the total synthesis of the natural product terpestacin (323) which exhibits potential anti HIV activity (eq 100).\(^\text{157}\)


Summary

We have described herein new, efficient routes to substituted TAS-vinylketenes via the electrocyclic ring opening of cyclobutenones and the photochemical Wolff rearrangement of α-silyl-α-diazo enones. TAS-Vinylketenes are reactive as four-carbon building blocks in organic synthesis and behave as dienes in Diels-Alder reactions with reactive dienophiles, activated carbonyl compounds, and imines. These ketenes also participate in [4+1] cycloadditions with carbenoid reagents to form cyclopentenones. We are continuing to explore promising new synthetic applications of TAS-vinylketenes for the total synthesis of natural products and investigations are ongoing in our laboratory to develop other new, efficient routes to these useful synthetic intermediates.
PART II

Experimental Section
General Procedures

All reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon. Reactions were stirred magnetically unless otherwise indicated except sealed tube reactions, which were not stirred. Air- and moisture-sensitive liquids and solutions were transferred via syringe or cannula into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by using a Büchi evaporator at ca. 20 mmHg unless otherwise indicated.

Materials

Commercial grade reagents and solvents were used without further purification except as indicated below.

(a) Distilled under argon or vacuum from calcium hydride:

- acetonitrile, benzene, dichloromethane, DMSO, diisopropylethylamine, hexane, toluene, and triethylamine

(b) Distilled under argon or vacuum from sodium benzophenone ketyl or dianion:

- tetrahydrofuran and diethyl ether

(c) Distilled under argon

- trichloroacetyl chloride

(d) Other

N-Bromosuccinimide was recrystallized from water.\(^1\) Alkyllithium reagents were titrated in tetrahydrofuran or hexane at 0 °C using 1-10-phenanthroline as an indicator.\(^2\)

Chromatography

(a) Analytical thin-layer chromatography (TLC)

Analytical thin-layer chromatography (TLC) was performed on Merck pre-coated glass-backed 0.25 mm silica gel 60-F-254 plates. Visualization of spots was effected by one or more of the following techniques: (a) ultraviolet irradiation, (b) exposure to iodine vapor,

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\(^2\) Inorganic Synthesis 1963, 7, 10.
and (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating at ca. 200 °C.

(b) *Column chromatography*

Column chromatography was performed on ICN silica gel (32-60μm).

**Instrumentation**

(a) *Melting points*

Melting points (mp) were determined with a Fischer-Johns melting point apparatus and are uncorrected.

(b) *Spectrometry*

$^1$H NMR spectra were measured with Varian XL-300 (300 MHz), Unity-300 (300 MHz), and Unity-500 (500 MHz) instruments. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the CHCl$_3$ peak at 7.26 ppm used as a standard). $^{13}$C NMR spectra were measured with Varian XL-300 (75 MHz), Unity-300 (75 MHz), and Unity-500 (125 MHz) spectrometers. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of CHCl$_3$ at 77.0 ppm used as a standard). Infrared spectra (IR) were obtained using a Perkin Elmer 1320 grating spectrophotometer.

(c) *Elemental analyses*

Robertson Laboratory, Inc. of Madison, New Jersey and E+R Microanalytical Laboratory, Inc. of Parsippany, New Jersey performed elemental analyses.
1-Diazo-1-(diethyl(phenyl)silyl)-3-methyl-3-penten-2-one (105).

A three-necked, 15-mL, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with diazoketone 98 (0.052 g, 0.419 mmol), 0.8 mL of ether, and 0.8 mL of hexane then cooled at 0 °C. Diisopropylethylamine (0.073 mL, 0.419 mmol) was added followed by diethylphenylsilyl trifluoromethanesulfonate 104 (0.130 g, 0.416 mmol). The resulting solution was stirred for 30 min and then allowed to warm to room temperature over 30 min. The reaction mixture was filtered through Celite with the aid of 5 mL of ether and concentrated at reduced pressure to give 0.129 g of a red-orange oil. Column chromatography on 3 g of silica gel (elution with 0-2.5% EtOAc-hexane) afforded 0.085 g (74%) of diazo ketone 105 as a yellow oil.

IR (film): 2950, 2060, and 1590 cm⁻¹

¹H NMR (500 MHz, CDCl₃): 7.55-7.58 (m, 2H), 7.36-7.40 (m, 3H), 6.09 (q, J = 7.0 Hz, 1H), 1.78 (s, 3H), 1.72 (d, J = 7.0 Hz, 3H), 1.09 (q, J = 5.8 Hz, 4H), and 1.05 (t, J = 5.8 Hz, 6H)

¹³C NMR (125 MHz, CDCl₃): 197.0, 137.4, 135.1, 134.4, 131.5, 130.5, 128.8, 52.3, 14.3, 13.6, 7.9, and 4.1
(E)-2-(1-Methyl-1-propenyl)-2-(diethyl(phenyl)silyl)ketene (113).

A solution of diazo ketone 105 (0.194 g, 0.677 mmol) in 6.7 mL of benzene was placed in a 25-cm vycor tube (15 mm O.D., 13 mm I.D.) fitted with a rubber septum. A second rubber septum (inverted) was secured with wire to the tube to insure a good seal and the reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, <0.05 mmHg) and then irradiated with 300 nm light for 3 h in a Rayonet reactor. Column chromatography on 10 g of silica gel (elution with hexane) provided 0.111 g (64%) of ketene 113 as a yellow oil.

IR (film): 3360, 2440, and 2060 cm⁻¹

¹H NMR (500 MHz, CDCl₃): 7.53-7.57 (m, 2H), 7.32-7.39 (m, 3H), 4.96 (q, J = 6.8 Hz, 1H), 1.80 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H), and 0.90-1.04 (m, 10H)

¹³C NMR (125 MHz, CDCl₃): 184.8, 136.2, 135.1, 130.1, 128.6, 123.8, 119.3, 25.0, 19.2, 14.6, 7.9, and 4.8
4,4-Dichloro-3-phenyl-2-(triethylsilyl)-2-cyclobutenone (124).

A 500-mL, three-necked, round-bottomed flask equipped with a rubber septum, reflux condenser, and pressure-equalizing addition funnel was charged with activated zinc\textsuperscript{159} (7.26 g, 111 mmol) and a solution of (triethylsilyl)phenylacetylene\textsuperscript{160} 122 (4.01 g, 37.0 mmol) in 80 mL of ether. The resulting solution was heated at reflux while a solution of trichloroacetyl chloride (4.2 mL, 37.0 mmol) in 125 mL of ether was added dropwise over 3 h. The reaction mixture was heated at reflux for 14 h and was then allowed to cool to room temperature and filtered. The filtrate was extracted with two 100-mL portions of saturated NaHCO\textsubscript{3}, two 100-mL portions of water, and two 100-mL portions of saturated NaCl, dried over MgSO\textsubscript{4}, filtered, and concentrated to give 6.67 g of a red-brown liquid. Column chromatography on 40 g of silica gel (elution with 0-2% ether-pentane) provided 5.55 g (92%) of cyclobutenone 124 as a yellow oil.

\begin{align*}
\text{IR (film):} & \quad 2950 \text{ and } 1770 \text{ cm}^{-1} \\
\text{\hspace{1cm} }^{1}H \text{ NMR (300 MHz, CDCl}_3\text{):} & \quad 7.91-7.94 \text{ (m, 2H), } 7.57-7.60 \text{ (m, 3H), and } 0.85-1.00 \text{ (m, 15H)} \\
\text{\hspace{1cm} }^{13}C \text{ NMR (75 MHz, CDCl}_3\text{):} & \quad 183.4, 181.9, 149.8, 133.1, 129.9, 129.7, 129.2, 91.0, 7.2, \text{ and } 3.1.
\end{align*}

3-Phenyl-2-(trimethylsilyl)-2-cyclobutenone (125).

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, 25-mL pressure-equalizing addition funnel, and argon inlet adapter was charged with zinc dust (0.626 g, 9.53 mmol), TMEDA (1.44 mL, 9.53 mmol), and 8 mL of ethanol and then cooled at 0 °C using an ice-water bath. Acetic acid (0.55 mL, 9.53 mmol) was added over 2 min, and then a solution of cyclobutenone 123 (0.463 g, 1.64 mmol) in 5 mL of ethanol was added dropwise via the addition funnel over 12 min. The reaction mixture was stirred for 15 min, and then the ice-bath was removed and the reaction mixture was stirred for 3 h at 25 °C. The resulting mixture was filtered through Celite with the aid of 80 mL of 1:1 Et₂O:pentane. The filtrate was extracted with 100 mL of 1 M aqueous HCl solution, 100 mL of water, 80 mL of saturated NaHCO₃, and 80 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.409 g of a yellow liquid. Column chromatography on 20 g of silica gel (gradient elution with 0-4% EtOAc-hexane) provided 0.257 g (74%) of 125 as a yellow oil.

**IR (film):**
- 2950 and 1785 cm⁻¹

**¹H NMR (300 MHz, CDCl₃):**
- 7.59-7.61 (m, 2H)
- 7.50-7.51 (m, 3H)
- 3.71 (s, 2H)
- 0.32 (s, 9H)

**¹³C NMR (75 MHz, CDCl₃):**
- 191.0, 176.7, 131.4, 129.2, 128.7, 128.6, 126.4, 54.6, and -1.2

**HRMS:**
- Calcd For C₁₃H₁₆OSi: 216.0970
- Found: 216.0970
3-Phenyl-2-(triethylsilyl)-2-cyclobutenone (126).

A 100-mL, 3-necked, round-bottomed flask equipped with a rubber septum, 50-mL pressure-equalizing addition funnel, and argon inlet adapter was charged with zinc dust (1.14 g, 17.5 mmol), TMEDA (2.6 mL, 17.5 mmol), and 13 mL of ethanol and then cooled at 0 °C using an ice-water bath. Acetic acid (1.00 mL, 17.5 mmol) was added over 8 min, and then a solution of cyclobutenone 124 (0.99 g, 3.0 mmol) in 16 mL of ethanol was added dropwise via the addition funnel over 1 h. The reaction mixture was stirred for 15 min, and then the ice-bath was removed and the reaction mixture was stirred for 4.5 h at room temperature. The resulting mixture was filtered through Celite with the aid of 150 mL of 1:1 Et2O:pentane. The filtrate was extracted with 50 mL of 1 M aqueous HCl solution, 50 mL of water, 40 mL of saturated NaHCO3, and 40 mL of saturated NaCl solution, dried over MgSO4, filtered, and concentrated to give 0.848 g of a yellow liquid. Column chromatography on 25 g of silica gel (gradient elution with 0-10% ether-pentane) provided 0.428 g (55%) of 126 as a yellow oil.

IR (film): 2070 and 1740 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.63-7.66 (m, 2H), 7.51-7.54 (m, 3H), 3.75 (s, 2H), 0.99 (t, J = 6.8 Hz, 9H), and 0.86 (q, J = 6.8 Hz, 6H)

¹³C NMR (75 MHz, CDCl₃): 191.5, 178.1, 147.2, 133.6, 131.4, 129.0, 128.7, 52.1, 7.4, and 3.4

HRMS: Calcd For C₁₆H₂₂OSi: 258.1440
Found: 258.1441
2-(1-Phenylethenyl)-2-(trimethylsilyl)ketene (127).

A 25-mL, two-necked, round-bottomed flask equipped with a glass stopper and reflux condenser was charged with cyclobutone 125 (0.106 g, 0.497 mmol) in 18 mL of benzene and then heated at 60 °C for 4.5 h. The resulting mixture was allowed to cool to room temperature and then concentrated to give 0.113 g of a yellow oil. Column chromatography (twice) on 2.0 g Florisil (elution with hexane) provided 0.039 g (37%) of ketene 127 as a pale yellow oil.

\[
\text{IR (film):} \quad 2080 \text{ and } 1740 \text{ cm}^{-1}
\]

\[
\text{\textsuperscript{1}H NMR (300 MHz, CDCl}3\text{):} \quad 7.41-7.43 (m, 2H), 7.30-7.40 (m, 3H), 4.98 (s, 2H), \\
\text{and } 0.28 (s, 9H)
\]

\[
\text{\textsuperscript{13}C NMR (75 MHz, CDCl}3\text{):} \quad 180.9, 142.7, 139.4, 128.3, 128.0, 126.8, 110.9, \\
26.0, \text{ and } -0.6
\]

\[
\text{HRMS:} \quad \text{Calcd For C}_{13}\text{H}_{16}\text{OSi:} \quad 216.0970 \\
\text{Found:} \quad 216.0970
\]
3-Phenyl-2-trimethylsilyl butenolide (129).

A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser was charged with cyclobutenone 125 (0.153 g, 0.703 mmol) in 30 mL of toluene. Air was bubbled through the solution at a rate of about 5 bubbles per second. The reaction mixture was heated at reflux for 18 h then cooled to room temperature and concentrated to give 0.213 g of a yellow oil. Column chromatography on 10 g of silica gel (elution with 0-10% EtOAc-hexane) afforded 0.069 g (42%) of butenolide 129 as a yellow oil.

IR (CDCl$_3$): 2950 and 1740 cm$^{-1}$

$^1$H NMR (300 MHz, CDCl$_3$): 7.45-7.46 (m, 3H), 7.29-7.44 (m, 2H), 4.93 (s, 2H), and 0.149 (s, 9H)

$^{13}$C NMR (75 MHz, CDCl$_3$): 176.9, 174.0, 133.4, 130.0, 128.5, 127.9, 127.4, 73.7, and -0.97
A 25-mL, two-necked, round-bottomed flask equipped with a glass stopper and reflux condenser was charged with a solution of cyclobutene 125 (0.109 g, 0.511 mmol), DMAD (0.063 mL, 0.511 mmol), and 7 mL of toluene. The resulting solution was heated at reflux for 42 h and then allowed to cool to room temperature. Concentration of the resulting mixture afforded 0.260 g of an orange oil. Column chromatography on 26 g of silica gel (elution with 20% EtOAc-hexane) provided 0.116 g (63%) of phenol 171 as a white solid, mp 51–52 °C.

IR (CCl₄): 1740 and 1660 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 11.21 (s, 1H), 7.33-7.35 (m, 3H), 7.22-7.24 (m, 2H), 6.79 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H), and -0.04 (s, 9H)

¹³C NMR (75 MHz, CDCl₃): 170.0, 169.4, 166.5, 156.0, 143.0, 135.1, 129.3, 128.7, 127.9, 127.8, 121.1, 106.9, 52.8, 52.5, and 0.8

HRMS: Calcd For C₁₉H₂₂O₅Si: 358.1236
     Found: 358.1235
Dimethyl 3-Hydroxy-5-phenyl-4-(triethylsilyl)phthalate (172).

A 25-mL, two-necked, round-bottomed flask equipped with a glass stopper and reflux condenser was charged with a solution of cyclobutenone 126 (0.111 g, 0.429 mmol), DMAD (0.053 mL, 0.429 mmol), and 7 mL of toluene. The resulting solution was heated at reflux for 55 h and then allowed to cool to room temperature. Concentration of the resulting mixture afforded 0.167 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 0-70% benzene-hexane) afforded 0.095 g (55%) of phenol 172 as a white solid, mp 61-61.5 °C.

IR (CCl₄): 1730 and 1660 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 11.28 (s, 1H), 7.32-7.36 (m, 5H), 6.79 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 0.78 (t, J = 7.8 Hz, 9H), and 0.48 (q, J = 7.8 Hz, 6H)

¹³C NMR (75 MHz, CDCl₃): 170.1, 169.5, 166.8, 157.2, 143.1, 135.0, 128.7, 127.8, 127.7, 127.0, 121.3, 106.6, 52.8, 52.5, 7.8 and 4.2

HRMS: Calcd For C₂₂H₂₈O₅Si: 400.1706
Found: 400.1707
3,4-Dimethyl-6-oxo-5-(triisopropylsilyl)-3,6-dihydropyran-2,2-dicarboxylic acid diethyl ester (202).

A 10-mL, two-necked, pear-shaped flask equipped with a glass stopper and a reflux condenser fitted with a rubber septum and an argon inlet needle was charged with ketene 111 (0.121 g, 0.479 mmol), diethyl ketomalonate (0.110 mL, 0.719 mmol), and 0.43 mL of acetonitrile. The reaction mixture was heated at reflux for 15 min and then cooled and concentrated at reduced pressure to give 0.280 g of a yellow liquid. Column chromatography on 14 g of silica gel (elution with 5% EtOAc-hexane) provided 0.191 g (94%) of lactone 202 as a white solid, mp 69-70 °C.

IR (CH$_2$Cl$_2$): 2930, 2860, and 1715 cm$^{-1}$

$^1$H NMR (300 MHz, CDCl$_3$): 4.21-4.36 (m, 3H), 4.04-4.36 (m, 1H), 3.21 (q, $J = 7.2$ Hz, 1H), 2.12 (s, 3H), 1.47 (sept, $J = 7.5$ Hz, 3H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.13 (d, $J = 7.0$ Hz, 3H), and 1.04 (d, $J = 7.5$ Hz, 18H)

$^{13}$C NMR (75 MHz, CDCl$_3$): 168.9, 166.6, 164.4, 163.7, 122.0, 85.0, 62.7, 62.5, 41.5, 23.3, 19.0, 14.0, 13.7, 12.9, and 12.4

Elemental Analysis:

Calcd for C$_{22}$H$_{38}$O$_6$Si: C, 61.93; H, 8.98
Found: C, 62.12; H, 9.05
3-Oxo-3,5,6,7,8,8a-hexahydro-isochromene-1,1-dicarboxylic acid diethyl ester (203).

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with ketene 110 (0.208 g, 0.679 mmol), diethyl ketomalonate (0.155 mL, 1.02 mmol), and 0.68 mL of acetonitrile. The tube was tightly sealed with a teflon cap and then heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated at reduced pressure to give 0.461 g of an yellow-orange oil. Column chromatography on 10 g of silica gel (elution with 5% EtOAc-hexane) provided 0.250 g (77 %) of lactone 203 as a white solid, mp 79-80 °C.

IR (CDCl₃): 2930, 2850, 1740 and 1710 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 4.24-4.38 (m, 3H), 4.05-4.14 (m, 1H), 3.26 (dd, J = 12.0, 3.3 Hz, 1H), 2.76 (m, 1H), 2.35 (dt, J = 12.3, 4.6 Hz, 1H), 2.10 (m, 1H), 1.82-1.91 (m, 2H), 1.54-1.67 (m, 3H), 1.46 (sept, J = 7.3 Hz, 3H), 1.32 (t, J = 7.3 Hz, 3H), 1.25 (t, J = 7.3 Hz, 3H), and 1.05 (d, J = 7.3 Hz, 18H)

¹³C NMR (125 MHz, CDCl₃): 174.1, 167.9, 165.7, 164.6, 122.0, 85.0, 63.9, 63.4, 46.8, 37.4, 31.0, 30.5, 26.2, 19.8, 14.8, 14.5, and 13.0

136
(i-Pr)_2Si

203
6-Oxo-4-phenyl-5-(triethylsilyl)-3,6-dihydropyran-2,2-dicarboxylic acid diethyl ester (205).

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with cyclobutenone 126 (0.115 g, 0.445 mmol), diethyl ketomalonate (196, 0.100 mL, 0.667 mmol), and 0.40 mL of acetonitrile. The tube was tightly sealed with a teflon cap and heated at reflux for 15 h. The reaction mixture was cooled and concentrated at reduced pressure to afford 0.250 g of a yellow oil. Column chromatography on 12 g of silica gel (elution with 10% EtOAc-hexane) provided 0.176 g (92%) of the lactone 205 as a white solid, mp 63 °C.

IR (film): 2960, 2880, 1735, and 1575 cm\(^{-1}\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.31-7.33 (m, 3H), 7.18-7.21 (m, 2H), 4.24 (q, \(J = 7.3\) Hz, 4H), 3.21 (s, 2H), 1.26 (t, \(J = 7.3\) Hz, 6H), 0.71 (t, \(J = 7.9\) Hz, 9H), and 0.34 (q, \(J = 7.8\) Hz, 6H)

\(^13\)C NMR (125 MHz, CDCl\(_3\)): 166.3, 164.6, 163.4, 139.9, 129.9, 129.5, 128.2, 127.7, 82.8, 63.1, 38.1, 13.9, 7.4 and 4.2

Elemental Analysis: Caled for C\(_{23}\)H\(_{32}\)O\(_6\)Si: C, 63.86; H, 7.46
Found: C, 63.78; H, 7.31
6-Oxo-4-phenyl-3,6-dihydropyran-2,2-dicarboxylic acid diethyl ester (206).

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with a solution of silyl lactone 205 (0.065 g, 0.151 mmol) in 0.75 mL of CH₂Cl₂. Methanesulfonic acid (0.049 mL, 0.756 mmol) was added rapidly dropwise. The tube was tightly sealed with a teflon cap and heated at reflux for 15 h. The reaction mixture was cooled, diluted with 10 mL of CH₂Cl₂, and washed with 10 mL of saturated NaHCO₃ solution, 10 mL of water, 10 mL of 10% aqueous HCl solution, and 10 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated at reduced pressure to give 0.060 g of a cloudy brown oil. Column chromatography on 14 g of silica gel (elution with 20-50% EtOAc-hexane) provided 0.048 g (100%) of the lactone 206 as a white solid, mp 68.5 °C.

IR (film): 2950, 2900, 1705, 1435, and 1360 cm⁻¹

¹H NMR (500 MHz, CDCl₃): 7.45-7.55 (m, 5H), 6.33 (s, 1H), 4.31 (q, J = 7.1 Hz, 4H), 3.48 (s, 2H), and 1.29 (t, J = 7.2 Hz, 6H)

¹³C NMR (125 MHz, CDCl₃): 165.9, 161.9, 152.3, 135.2, 131.0, 129.0, 126.1, 114.4, 82.9, 63.2, 31.1, and 13.8

Elemental Analysis: Calcd for C₁₇H₁₉O₅: C, 64.14; H, 5.70
Found: C, 64.25; H, 5.88
cis-4,5-Dimethyl-6-phenyl-3-(triisopropylsilyl)-5,6-dihydro-1H-pyridin-2-one (233).

A 10-mL, two-necked, pear-shaped flask equipped with a glass stopper and a reflux condenser fitted with a rubber septum and an argon inlet needle was charged with ketene 111 (0.134 g, 0.531 mmol), imine 215 (0.147 g, 0.829 mmol), and 0.47 mL of acetonitrile. The reaction mixture was heated at reflux for 1.5 h then cooled to room temperature and concentrated at reduced pressure to give 0.272 g of a yellow oil. Column chromatography on 27 g of silica gel (elution with 5% EtOAc-hexane) provided 0.151 g (79%) of lactam 233 as a white solid, mp 197-199 °C.

IR (CDCl$_3$): 3400, 2930, 2850, and 1625 cm$^{-1}$

$^1$H NMR (300 MHz, CDCl$_3$): 7.28-7.42 (m, 5H), 5.51 (br s, 1H), 4.77 (d, $J = 3.6$ Hz, 1H), 2.21 (m, 1H), 2.10 (s, 3H), 1.53 (sept, $J = 7.3$ Hz, 3H), 1.12 (d, $J = 5.7$ Hz, 18H), and 0.82 (d, $J = 7.1$ Hz, 3H)

$^{13}$C NMR (75 MHz, CDCl$_3$): 170.0, 165.9, 138.4, 128.5, 127.6, 126.6, 126.4, 58.1, 45.0, 23.0, 19.3, 13.0, and 11.0

Elemental Analysis: Calcd for C$_{22}$H$_{35}$NOSi: C, 73.89; H, 9.86; N, 3.92

Found: C, 73.80; H, 9.88; N, 3.84
cis-4,5-Dimethyl-6-phenyl-3-(triethylsilyl)-5,6-dihydro-1H-pyridin-2-one (236).

A 5-mL, pear-shaped flask equipped with a reflux condenser fitted with a rubber septum and an argon inlet needle was charged with ketene 111 (0.160 g, 0.761 mmol) and imine 215 (0.202 g, 1.14 mmol) then stirred at room temperature for 2 h. The resulting yellow oil was purified by column chromatography on 10 g of silica gel (elution with 0-10% EtOAc-hexane) which provided 0.182 g (76%) of lactam 236 as a white solid, mp 155 °C.

IR (CH2Cl2): 2930, 2850, and 1630 cm⁻¹

1H NMR (500 MHz, CDCl3): 7.28-7.41 (m, 5H), 5.56 (br s, 1H), 4.79 (d, J = 4.0 Hz, 1H), 2.22 (m, 1H), 2.08 (s, 3H), 0.97 (t, J = 7.8 Hz, 9H), and 0.86 (m, 9H)

13C NMR (125 MHz, CDCl3): 171.0, 167.5, 139.4, 129.3, 128.5, 127.3, 127.1, 58.9, 44.9, 22.8, 11.7, 8.5, and 5.8
trans-1-Phenyl-4-(triisopropylsilyl)-1,5,6,7,8,8a-hexahydro-2H-isoquinolin-3-one (237).

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with ketene 110 (0.208 g, 0.679 mmol), imine 215 (0.184 g, 1.04 mmol), and 0.68 mL of acetonitrile. The tube was tightly sealed with a teflon cap and then heated at reflux for 25 h. The reaction mixture was cooled to room temperature and concentrated at reduced pressure to give 0.403 g of a yellow oil. Column chromatography on 14 g of silica gel (elution with 10% EtOAc-hexane) provided 0.256 g (91%) of lactam 237 as a white solid, mp 211-212 °C.

IR (CDCl₃): 3400, 2930, 2850, and 1625 cm⁻¹

¹H NMR (500 MHz, CDCl₃): 7.29-7.41 (m, 5H), 5.43 (br s, 1H), 4.79 (d, J = 5.2 Hz, 1H), 2.82 (d, J = 11.6 Hz, 1H), 2.25 (m, 2H), 2.00 (m, 1H), 1.73 (m, 1H), 1.52 (sept, J = 7.4 Hz, 3H), 1.25-1.48 (m, 4H), and 1.12 (d, J = 7.5 Hz, 18H)

¹³C NMR (75 MHz, CDCl₃): 170.5, 170.3, 138.5, 128.5, 127.7, 126.7, 123.7, 57.3, 49.2, 36.9, 30.9, 28.2, 25.9, 19.3, and 12.6

Elemental Analysis: Calcd for C₂₄H₃₇NOSi: C, 75.14; H, 9.72; N, 3.65
Found: C, 75.10; H, 10.01; N, 3.66

146
4,6-Diphenyl-3-(triethylsilyl)-5,6-dihydro-1H-pyridin-2-one (239).

A 10-mL, two-necked, pear-shaped flask equipped with a glass stopper and a reflux condenser fitted with a rubber septum and an argon inlet needle was charged with cyclobutenone 126 (0.134 g, 0.518 mmol), imine 215 (0.133 g, 0.778 mmol), and 0.47 mL of acetonitrile. The reaction mixture was heated at reflux for 45 min and then cooled and concentrated at reduced pressure to give 0.259 g of a yellow oil. Column chromatography on 25 g of silica gel (elution with 5-20% EtOAc-hexane) provided 0.157 g (84%) of lactam 239 as a white solid, mp 130-131 °C.

IR (film): 3400, 2940, 2860, 2220, and 1630 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.29-7.41 (m, 8H), 7.12-7.18 (m, 2H), 5.72 (s, 1H), 4.74 (dq, J = 5.1, 1.6 Hz, 1H), 2.80 (m, 2H), 0.81 (t, J = 7.6 Hz, 9H), and 0.43 (q, J = 7.6 Hz, 6H)

¹³C NMR (125 MHz, CDCl₃): 170.7, 162.7, 142.8, 141.6, 134.4, 129.6, 129.1, 128.9, 128.7, 128.5, 127.3, 56.0, 43.7, 8.5, and 5.2

Elemental Analysis:
Calcd for C₂₃H₂₉NO₅Si:
C, 75.98; H, 8.04; N, 3.85

Found:
C, 75.76; H, 7.99; N, 3.77
Et$_3$Si$\text{NH}$

Ph

Ph

239

149

0 1 2 3 4 5 6 7 8

0 PPM
cis-4,5-Dimethyl-6-styryl-3-(triisopropylsilyl)-5,6-dihydro-1H-pyridin-2-one (241).

A 10-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with ketene 111 (0.165 g, 0.654 mmol) and imine 240 (0.135 g, 0.654 mmol). The reaction mixture was stirred at 25 °C for 15 min and then transferred to a round-bottomed flask with 5 mL of CH₂Cl₂ and concentrated at reduced pressure to give 0.321 g of an orange oil. Column chromatography on 12 g of silica gel (elution with 0-10% EtOAc-hexane) provided 0.196 g (78%) of lactam 241 as pale yellow oily solid.

IR (film): 3160, 3040, 2900, 1625, and 1455 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.24-7.40 (m, 5H), 6.62 (d, J = 15.8 Hz, 1H), 6.16 (dd, J = 16.0, 7.8 Hz, 1H), 5.84 (br s, 1H), 4.26 (dd, J = 7.7, 3.9 Hz, 1H), 2.19 (m, 1H), 2.06 (s, 3H), 1.50 (sept, J = 7.5 Hz, 3H), 1.07 (d, J = 7.5 Hz, 18H), and 1.07 (d, J = 7.0 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃): 170.5, 166.9, 136.9, 133.6, 129.4, 128.7, 127.5, 127.2, 126.8, 56.8, 44.1, 23.6, 20.0, 13.5, and 11.7
trans-1-Styryl-4-(triisopropylsilyl)-1,5,6,7,8,8a-hexahydro-2H-isoquinolin-3-one (242).

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with ketene 110 (0.199 g, 0.649 mmol) and imine 240 (0.133 g, 0.649 mmol). The reaction mixture was stirred at 25 °C for 10 min and then transferred to a round-bottomed flask with 5 mL of CH₂Cl₂ and concentrated at reduced pressure to give 0.384 g of a yellow-orange liquid. Column chromatography on 12 g of silica gel (elution with 0-50% EtOAc-hexane) provided 0.209 g (73%) of lactam 242 as a white solid, mp 162-163 °C.

IR (film): 3400, 2930, 2860, and 1625 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.28-7.38 (m, 5H), 6.57 (d, J = 15.8 Hz, 1H), 6.20 (dd, J = 8.1, 15.8 Hz, 1H), 5.37 (br s, 1H), 4.21 (m, 1H), 2.79 (m, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 1.98 (m, 1H), 1.84 (m, 2H), 1.50 (sept, J = 7.5 Hz, 3H), and 1.09 (d, J = 7.5 Hz, 18H)

¹³C NMR (75 MHz, CDCl₃): 169.6, 169.2, 136.2, 132.6, 128.7, 128.0, 126.5, 126.4, 124.6, 55.5, 46.8, 36.3, 29.3, 28.0, 25.5, 19.4, and 12.7

Elemental Analysis: Calcd for C₂₆H₃₉NO: C, 76.23; H, 9.60; N, 3.42
Found: C, 75.97; H, 9.84; N, 3.57
4,5-Dimethyl-6,6-diphenyl-3-(triisopropylsilyl)-5,6-dihydro-1H-pyridin-2-one (244).

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with ketene 111 (0.153 g, 0.606 mmol), imine 219 (0.233 g, 0.909 mmol), and 0.60 mL of acetonitrile. The tube was tightly sealed with a teflon cap and then heated at reflux for 18 h. The reaction mixture was cooled to room temperature and concentrated at reduced pressure to give an orange oil. Column chromatography on 10 g of silica gel (elution with 0-10% EtOAc-hexane) provided 0.208 g (79%) of lactam 244 as a white solid, mp 182 °C.

IR (CDCl₃): 2930, 2850, and 1620 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.24 (m, 11 H), 3.09 (q, J = 6.9 Hz, 1H), 2.13 (s, 3H), 1.36 (sept, J = 7.5 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 7.3 Hz, 9H), and 0.82 (d, J = 7.5 Hz, 9H)

¹³C NMR (125 MHz, CDCl₃): 170.0, 165.5, 146.6, 142.6, 128.4, 128.0, 127.4, 126.9, 126.5, 126.4, 125.8, 65.0, 46.5, 23.7, 19.0, 14.0, and 12.5

Elemental Analysis: Calcd for C₂₈H₃₉NOSi: C, 77.54; H, 9.06; N, 3.23

Found: C, 77.87; H, 9.17; N, 3.32
1,1-Diphenyl-4-(triisopropylsilyl)-1,5,6,7,8,8a-hexahydro-2H-isoquinolin-3-one (245).

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with ketene 110 (0.208 g, 0.679 mmol), imine 219 (0.150 g, 0.489 mmol), and 0.49 mL of acetonitrile. The tube was tightly sealed with a teflon cap and then heated at reflux for 24 h. The reaction mixture was cooled to room temperature and concentrated at reduced pressure to give 0.342 g of a yellow-orange oil. Column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexane) provided 0.149 g (66%) of lactam 245 as a white solid, mp 237-237.5 °C.

IR (film): 3040, 2930, 2850, and 1630 cm⁻¹

¹H NMR (500 MHz, CDCl₃): 7.14-7.30 (m, 10 H), 7.03 (br s, 1H), 2.99 (dd, J = 2.4, 9.1 Hz, 1H), 2.84 (dd, J = 3.1, 11.6 Hz, 1H), 2.39 (m, 1H), 2.07 (m, 1H), 1.76 (m, 1H), 1.49 (m, 3H), 1.33 (sept, J = 7.3 Hz, 3H), 1.13 (d, J = 12.8 Hz, 1H), 0.87 (d, J = 7.3 Hz, 9H), and 0.80 (dd, J = 7.3 Hz, 9H)

¹³C NMR (75 MHz, CDCl₃): 170.4, 170.3, 146.9, 143.2, 128.3, 127.9, 127.3, 126.9, 126.6, 126.4, 125.3, 64.3, 51.1, 37.3, 31.5, 31.2, 26.5, 19.0, and 12.5

Elemental Analysis: Calcd for C₃₀H₄₁NOSi: C, 78.38; H, 9.01; N, 3.05
Found: C, 78.44; H, 9.41; N, 3.03
**trans-1-(1,1-Dimethylethyl)-4-(triisopropylsilyl)-1,5,6,7,8,8a-hexahydro-2H-isoquinolin-3-one (252).**

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with ketene 110 (0.162 g, 0.529 mmol), imine 251 (0.165 g, 1.06 mmol), and 0.53 mL of acetonitrile. The tube was tightly sealed with a teflon cap and heated at reflux for 4 h and then at 110-110 °C for 65 h. The reaction mixture was cooled to room temperature and additional imine (0.093 g, 0.53 mmol) was added then heated at 110-130 °C for 23 h. The reaction mixture was cooled to room temperature and concentrated to give 0.307 g of a yellow-gray liquid. The reaction mixture was filtered through Celite, rinsing with the aid of CH$_2$Cl$_2$ and concentrated at reduced pressure to give 0.187 g of a pale yellow solid. The solid was washed with heptane to afford 0.115 g (56%) of lactam 252 as a white solid, mp 235-237 °C.

**IR (CH$_2$Cl$_2$):** 2950, 2850, and 1630 cm$^{-1}$

**$^1$H NMR (300 MHz, CDCl$_3$):**

5.19 (br s, 1H), 3.21 (d, $J$ = 4.1 Hz, 1H), 2.72 (m, 1H), 2.25 (m, 2H), 2.00 (m, 2H), 1.80 (m, 1H), 1.47 (sept, $J$ = 7.5 Hz, 3H), 1.47 (m, 3H), 1.07 (d, $J$ = 7.1 Hz, 18H), and 1.02 (s, 9H)

**$^{13}$C NMR (125 MHz, CDCl$_3$):** 171.1, 170.4, 124.0, 60.7, 47.2, 37.2, 32.5, 30.8, 28.6, 27.3, 26.0, 19.3, and 12.6

**Elemental Analysis:**

Calcd for C$_{22}$H$_{41}$NOSi: C, 72.66; H, 11.36; N, 3.85

Found: C, 72.59; H, 11.65; N, 3.78
trans-6-Phenyl-3-(triisopropylsilyl)-1,4,5-trimethyl-5,6-dihydro-1H-pyridin-2-one (254) and cis-6-Phenyl-3-(triisopropylsilyl)-1,4,5-trimethyl-5,6-dihydro-1H-pyridin-2-one (255).

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with a solution of ketene 111 (0.069 g, 0.273 mmol), 0.27 mL of acetonitrile, and imine 253 (0.050 g, 0.410 mmol). The tube was tightly sealed with a threaded teflon cap and heated at 120 °C for 42 h. The reaction mixture was cooled and concentrated at reduced pressure to give 0.120 g of an orange oil. Column chromatography on 12 g of silica gel (elution with 5% EtOAc-hexane) afforded 0.072 g (71%) of a 3:1 mixture of lactams 254 and 255 as a pale yellow oil.

Both isomers:

IR (neat): 2940, 2850, and 1615 cm⁻¹

Major isomer (254):

\[
\begin{align*}
^{1}H \text{ NMR (300 MHz, CDCl}_3\text{):} & \quad 7.19-7.29 (m, 5H), 4.32 (d, J = 6.1 Hz, 1H), 2.90 (q, \text{ obscured by the singlet at } 2.89 \text{ ppm, } 1H), 2.89 (s, 3H), 1.92 (s, 3H), 1.54 (m, 3H), 1.06-1.13 (d, J = 7.4 Hz, 18H), \text{ and } 0.92 (d, J = 7.3 Hz, 3H) \\
^{13}C \text{ NMR (75 MHz, CDCl}_3\text{):} & \quad 168.9, 160.4, 137.2, 129.0, 128.0, 127.8, 126.1, 66.2, 40.6, 33.5, 21.7, 19.4, 19.3, \text{ and } 13.1
\end{align*}
\]

Minor isomer (255):

\[
\begin{align*}
^{1}H \text{ NMR (300 MHz, CDCl}_3\text{):} & \quad 7.19-7.29 (m, 5H), 4.19 (s, 1H), 3.03 (s, 3H), 2.35 (q, J = 7.0 Hz, 1H), 1.79 (s, 3H), 1.54 (sept, J = 7.4 Hz, 3H), 1.30 (d, J = 7.0 Hz, 3H), \text{ and } 1.00 (d, J =
\end{align*}
\]
$^{13}$C NMR (75 MHz, CDCl$_3$): 167.8, 160.9, 140.3, 128.6, 128.2, 127.4, 127.2, 66.7, 45.4, 35.1, 23.5, 19.2, 14.0, and 12.9
trans-N-(Trimethylsilyl)-4-phenyl-3-(triisopropylsilyl)-azetidin-2-one (283).

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with (triisopropylsilyl)ketene (0.063 g, 0.318 mmol) and imine 215 (0.057 g, 0.321 mmol). The tube was tightly sealed with a threaded teflon cap and then heated at 70 °C for 20 h and then at 140 °C for 3 h. The reaction mixture was cooled to give 0.117 g of an orange oil. Column chromatography on 10 g of silica gel (elution with 0-20% EtOAc-hexane) afforded 0.085 g (71%) of lactam 283 as a pale yellow oil.

IR (film): \[2930, 2850, 2230, 1710, \text{and} 1450 \text{ cm}^{-1}\]

$^1$H NMR (500 MHz, CDCl$_3$): \[7.29-7.40 \text{ (m, 5H), 4.47 (d, } J = 3.1 \text{ Hz, 1H), 3.00 (d, } J = 3.1 \text{ Hz, 1H), 1.26 (sept, } J = 7.0 \text{ Hz, 3H), 1.09 (d, } J = 7.3 \text{ Hz, 9H), and 1.05 (d, } J = 7.6 \text{ Hz, 9H), and 0.10 (s, 9H)}\]

$^{13}$C NMR (125 MHz, CDCl$_3$): \[176.3, 143.0, 129.3, 128.7, 127.2, 54.6, 52.1, 19.4, 11.1, \text{and} -0.4\]
**4,6-Diphenyl-5,6-dihydro-1H-pyridin-2-one (284)**

A flame-dried, threaded Pyrex tube (13 mm O.D., 10 mm I.D.) was charged with a solution of silyl lactam 239 (0.091 g, 0.250 mmol) in 1.01 mL of CH₂Cl₂. Methanesulfonic acid (0.081 mL, 1.25 mmol) was added. The tube was tightly sealed with a threaded teflon cap and the reaction mixture was heated at reflux for 4 h. The reaction mixture was cooled and then diluted with 10 mL of CH₂Cl₂. The organic portions were separated and washed with 10 mL of saturated NaHCO₃ solution, 10 mL of water, 10 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated at reduced pressure to give 0.095 g of a pale yellow solid. Column chromatography on 14 g of silica gel (elution with 50-100% EtOAc-hexane) afforded 0.034 g (55%) of the lactam 284 as a white solid, mp 182 °C.

**IR (CH₂Cl₂):**

3380, 3020, 2960, and 1640 cm⁻¹

**¹H NMR (500 MHz, CDCl₃):**

7.35-7.51 (m, 10H), 6.37 (s, 1H), 5.65 (br s, 1H), 4.86 (dd, J = 5.5, 11.6 Hz, 2H), and 2.96 (m, 1H)

**¹³C NMR (125 MHz, CDCl₃):**

167.5, 149.9, 141.1, 137.3, 129.6, 128.9, 128.7, 128.3, 126.4, 125.8, 118.9, 55.7, and 35.7
4,5-Dimethyl-6-phenyl-5,6-dihydro-1H-pyridin-2-one (285).

A flame-dried, 25-mL, round-bottomed flask equipped with a reflux condenser fitted with a rubber septum and argon inlet needle was charged with a solution of silyl lactam 236 (0.075 g, 0.238 mmol) in 1.2 mL of CH₂Cl₂. Methanesulfonic acid (0.077 mL, 1.19 mmol) was added and the reaction mixture was heated at reflux for 6 h. The reaction mixture was cooled, diluted with 10 mL of CH₂Cl₂, and washed with 10 mL of saturated NaHCO₃ solution, 10 mL of water, 10 mL of 10% aqueous HCl solution, 10 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated at reduced pressure to give 0.087 g of an oily yellow-brown solid. Column chromatography on 8 g of silica gel (elution with 20-100% EtOAc-hexane) afforded 0.040 g (83%) of the lactam 285 as a white solid, mp 170.5 °C.

IR (CH₂Cl₂): 3980, 2950, 1655, and 1615 cm⁻¹

¹H NMR (500 MHz, CDCl₃): 7.29-7.42 (m, 5H), 5.76 (s, 1H), 5.45 (br s, 1H), 4.90 (d, J = 4.6 Hz, 1H), 2.29 (m, 1H), 2.00 (s, 3H), and 0.80 (d, J = 7.0 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃): 168.6, 159.4, 139.2, 129.5, 128.8, 127.2, 119.6, 59.9, 41.4, 22.5, and 12.2
3,4,5,5-Tetramethyl-2-(triisopropylsilyl)cyclopent-2-en-1-one (292).

A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with a solution of ketene 111 (0.140 g, 0.554 mmol) in 5.0 mL of 50:50 THF-DMSO and cooled at -20 °C. A 15-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with diphenylisopropylsulfonium fluoroborate (0.193 g, 0.610 mmol) in 2.5 mL of THF and cooled at -78 °C with an acetone-dry ice bath. t-BuLi (1.55 M in pentane, 0.38 mL, 0.582 mmol) was added dropwise down the side of the flask over 10 sec. The resulting bright yellow ylide solution was immediately transferred via cannula over 5 min to the ketene solution, and the resulting solution was stirred for 30 min at -20 °C. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature over 3 h and then diluted with 20 mL of water. The aqueous layer was separated and extracted with three 20-mL portions of diethyl ether, and the combined organic phases were washed with 40 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.275 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-2.5% EtOAc-hexane) afforded 0.093 g (57%) of cyclopentenone 292 as a colorless oil.

IR (CDCl₃): 2960, 2940, 2860, and 1680 cm⁻¹

¹H NMR (500 MHz, CDCl₃): 2.45 (q, J = 7.3 Hz, 1H), 2.15 (s, 3H), 1.51 (s, 3H), 1.51 (sept, J = 7.6 Hz, 3H), 1.07 (d, J = 7.3 Hz, 3H), 1.05 (s, 3H), 1.04 (d, J = 7.6 Hz, 18H), and 0.94 (s, 3H)

¹³C NMR (125 MHz, CDCl₃): 217.8, 187.6, 132.2, 53.2, 47.7, 26.4, 20.5, 19.0,
18.8, 14.7, and 11.7

HRMS: Calcd for C_{18}H_{34}OSi: 294.2379
Found: 294.2378
5-(Phenylmethylene)-3,4-dimethyl-2-(triisopropylsilyl)-2-cyclopentenone (311)

A 25-mL, two-necked, round bottomed flask equipped with a glass stopper and reflux condenser was charged with phenyl acetylene (0.065 mL, 0.592 mmol) and 3 mL of THF then cooled at -78 °C. n-BuLi (2.6 M in hexane, 0.23 mL, 0.592 mmol) was added and the reaction mixture was stirred for 15 min. A solution of ketene 111 (0.136 g, 0.539 mmol) in 1 mL of THF was added dropwise via cannula to the -78 °C solution over 3 min (1 mL THF rinse). The reaction mixture was stirred at -78 °C for 1.5 h then warmed to -5 °C over 40 min. BHT (0.133 g, 0.592 mmol) was added and the solution was allowed to warm to room temperature over 15 min then heated at 50 °C for 35 min. The reaction mixture was cooled to room temperature and quenched by the addition of 10 mL of saturated NaCl solution. The organic portion was separated and the aqueous layer was extracted with two 30-mL portions of CH$_2$Cl$_2$. The organic portions were combined, dried over Na$_2$SO$_4$, filtered, and concentrated to give 0.379 g of an orange oil. Column chromatography on 25 g of silica gel (elution with 0-1% ether-pentane) afforded 0.143 g (75%) of cyclopentenone 311 as a pale yellow solid, mp 117 °C.

IR (film): 2940, 2860, and 1705 cm$^{-1}$

$^1$H NMR (300 MHz, CDCl$_3$): 7.54 (d, $J = 7.3$ Hz, 2H), 7.26-7.43 (m, 4H), 3.73 (q, $J = 7.0$ Hz, 1H), 2.29 (s, 3H), 1.61 (sept, $J = 7.5$ Hz, 3H), 1.24 (d, $J = 7.0$ Hz, 3H), and 1.09 (d, $J = 7.5$ Hz, 18H)

$^{13}$C NMR (75 MHz, CDCl$_3$): 201.5, 186.3, 139.7, 136.2, 135.2, 130.3, 129.2, 128.7, 128.6, 44.7, 18.8, 16.7, 12.0, and 11.8
2-Bromo-3,4-dimethyl-1-cyclopentenone (318)

A 25-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with silylcyclopentenone 317 (0.120 g, 0.535 mmol), N-bromosuccinimide (0.238 g, 1.34 mmol), and 1.8 mL of DMF and the solution was stirred at room temperature for 48 h. An additional portion of NBS was added (0.093 g, 0.522 mmol) and the reaction mixture was stirred for 16 h then quenched by the addition of 10 mL of a 10% aqueous HCl solution. The organic portion was separated and the aqueous portion was extracted with 3 20-mL portions of ether. The organic portions were combined and washed with 15 mL of water, 15 mL of saturated NaHCO₃ solution, 15 mL of water, and 15 mL of saturated NaCl solution, then dried over MgSO₄, filtered, and concentrated to afford 0.197 g of a red-orange liquid. Column chromatography on 10 g of silica gel (elution with 0-10% EtOAc-hexane) afforded 0.051 g (51%) of cyclopentenone 318 as a pale yellow oil.

IR (film): 2930, 1705, and 1610 cm⁻¹

¹H NMR (500 MHz, CDCl₃): 2.88 (m, 1H), 2.77 (dd, J = 18.6, 6.4 Hz, 1H), 2.15 (s, 3H), 2.14 (dd, J = 18.6, 2.2 Hz, 1H), and 1.25 (d, J = 7.0 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃): 200.4, 177.3, 122.9, 41.7, 38.3, 18.8, and 16.8