I. New Methodology for the Generation and Cycloadditions of Thio-Substituted Ketenes
II. A Synthetic Approach to the Taxol A-Ring

by
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To My Mother and Father
for their Love and Support
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Michael David Lawlor

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ABSTRACT

Part I:

A ketene cycloaddition strategy has been developed for the synthesis of α-thiocyclobutanones and -butenones. The reaction proceeds by the rhodium-catalyzed rearrangement of α-diazo thiol esters to thio-substituted ketenes, which then undergo [2 + 2] cycloaddition reactions with a vide variety of activated and unactivated alkenes and alkynes. The versatility of the product α-thiocyclobutanones as valuable synthetic intermediates has been explored with reactions such as sulfide reduction, regioselective alkylation, sulfide oxidation and Pummerer rearrangement, and ring expansion. Studies have also begun involving the application of this methodology to solid-phase combinatorial chemistry for the immediate purpose of synthesizing a library of support-bound α-thiocyclobutenones. These compounds would ultimately serve as key components in an aromatic annulation strategy for the preparation of a library of highly substituted phenol derivatives.

Part II:

A highly convergent route was designed for the synthesis of a Taxol A-ring synthon based on a key cyclohexa-2,4-dienone intermediate, which was envisioned to arise from a variant of an aromatic annulation reaction developed in these laboratories. This version of the annulation involves the reaction of 4,4-dimethylcyclobutenone derivatives with silyloxyacetylenes. The preparation of these precursors and model studies on the annulation reaction to provide cyclohexa-2,4-dienones are described.

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

New Methodology for the Generation and Cycloadditions of Thio-substituted Ketenes
CHAPTER 1

Introduction and Background

We have discovered a new method for the synthesis of \( \alpha \)-thiocyclobutanones which entails the rhodium-catalyzed transformation of \( \alpha \)-diazothiol esters to thio-substituted ketenes, and their cycloaddition reactions with alkenes and alkynes to generate \( \alpha \)-thiocyclobutanones and -cyclobutenones. Little work has been reported with these types of cyclobutanones due to the lack of suitable methods for their preparation, but we feel that they possess great potential as versatile synthetic intermediates. Before detailing the mechanism and promising scope of this new reaction (Chapters 2 and 3), a discussion of the standard methods for the preparation of cyclobutanones and cyclobutenones and their utility as synthetic intermediates is presented to put our new methodology into context.

Cyclobutanones and Cyclobutenones as Synthetic Intermediates

Small ring compounds are ubiquitous in the field of organic chemistry. Naturally occurring \( \beta \)-lactams such as penicillin and cephalosporin have attracted much attention as antibiotics and have spawned a whole new field of \( \beta \)-lactam research to develop even better drugs. Other naturally occurring small ring compounds, such as the pinenes, have been widely used as synthetic building blocks. Cyclobutanones and cyclobutenones constitute another important class of small ring compounds, even though few are known to exist in nature. These readily available four-membered ring ketones are remarkably versatile synthetic intermediates.\(^{1,2}\)

In many instances, cyclobutanones exhibit a higher degree of reactivity than larger ring ketones. This property is attributed to the large deviation from the ideal tetrahedral carbon-carbon bond angle, which results in a considerable ring strain of ca. 25 kcal/mol.\(^3\)
A summary of the impressive spectrum of cyclobutanone reactivity is depicted in Scheme 1. The high electrophilicity of the carbonyl carbon atom is exploited in most of these transformations, including the ring enlargement reactions. Baeyer-Villiger oxidation affords γ-butyrolactones, key structural units in many natural products. Similarly, diazo compound-mediated one-carbon homologation gives cyclopentanones, while Beckmann rearrangement provides γ-lactam derivatives. Preparation of five-membered rings represents perhaps the most useful role of cyclobutanones as synthetic intermediates.

Depending on ring substitution, addition of nucleophiles to cyclobutanones gives one of several possible products. Ring contraction of α-halocyclobutanones under Favorisii rearrangement conditions provides a facile pathway to cyclopropanecarboxylic acid derivatives. When the C-2 carbon atom is sufficiently substituted with anion stabilizing groups, ring opening occurs. Finally, transformation to other cyclobutane derivatives is readily effected by addition of nucleophiles to the carbonyl group of cyclobutanones (not pictured).

Scheme 1

Many naturally occurring sesquiterpene-γ-lactones have been targets of synthetic chemists due to their antitumor activity. This biological activity arises from the structural element α-methylene-γ-butyrolactone. Grieco and Hiroi reported the preparation of α-methylene-γ-butyrolactone 2 in four steps from cyclobutanone 1. The first step involves
Baeyer-Villiger oxidation of the four-membered ring, which proceeds regioselectively in good yield.\(^4\)

\[
\begin{align*}
\text{1) } & \text{H}_2\text{O}_2, \text{AcOH (90\%) } \\
\text{2) } & \text{Dihydropyran, H}^+ \text{ (quant.)} \\
\text{3) } & \text{LDA, CH}_2\text{O (80\%)} \\
\text{4) } & \text{MsCl, pyridine (71\%)} \\
\end{align*}
\]

\[1\] THPO

Regioselectivity is often a concern when attempting a ring enlargement reaction of a cyclobutanone derivative. Experiments with the 11-norprostaglandin derivative 3 illustrate the limitations of diazomethane for this transformation (eq 2).\(^5\) Greene and co-workers devised a method for the synthesis of 2,3-disubstituted cyclopentanone 8 based on the antimony-catalyzed ethyl diazoacetate addition to cyclobutanone 6, in which migration of the less substituted carbon atom occurs almost exclusively (eq 3).\(^6\)

\[
\begin{align*}
\text{3} & \xrightarrow{\text{CH}_2\text{N}_2} \text{4 (50\%)} \quad + \quad \text{5 (25\%)} \\
\end{align*}
\]

\[2\]

\[
\begin{align*}
\text{6} & \xrightarrow{\text{BO, Me}_2\text{O}_2, -78 \text{ °C}} \text{7} \\
\text{7} & \xrightarrow{\text{DME, H}_2\text{O, reflux}} \text{8 (63\%)} \\
\end{align*}
\]

\[3\]
The use of α-halocyclobutanones provides another popular means of avoiding regiochemical ambiguity in ring expansion reactions. The electron withdrawing effect of halogen substituents precludes diazo carbon insertion on the halogen-substituted side of the carbonyl group. This approach was exemplified with the synthesis of the racemic aglycon acetate of loganine (11), an important compound in alkaloid biosynthesis.\(^7\)

\[
\begin{align*}
\text{Me}_2\text{Si} & \quad \text{CH}_3\text{CHN}_2 \\
\text{Cl} & \quad \text{quant.} \\
\text{O} & \quad \text{Me}_2\text{Si} \\
\text{Cl} & \quad \text{O} \\
\text{CO}_2\text{Me} & \quad \text{OH} \\
\end{align*}
\]

The Favorskii rearrangement of α-halocyclobutanones has found industrial application in the synthesis of the carboxylic acid portion of chrysanthemates and pyrethroids which display high insecticidal activity. The racemic chrysanthemic acid 14 was prepared in one step from α-chlorocyclobutanones 12 and 13 as shown in eq 5.\(^8\) Dihalovinyl-substituted cyclopropanecarboxylic acids such as 16, readily available using a similar reaction sequence, are precursors to some of the most active pyrethroids (eq 6).\(^9-12\)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{NaOH} \\
\text{CO}_2\text{H} & \quad 88\% \\
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad 1) \text{NaOH, 20 °C} \\
\text{CO}_2\text{H} & \quad 2) \text{NaOH, 90 °C} \\
\text{cis:trans > 4:1} & \quad 89\% \\
\end{align*}
\]
Other reactions of α-halocyclobutanones which compete with Favorstkii rearrangement are cine-substitution and ring opening. In general, cine-substitution refers to the nucleophilic substitution reaction of 2-halogenocyclobutanones of type 17, in which the new substituent is attached at C-4. Two possible mechanisms have been suggested for this reaction (Scheme 2). In path a, enolate formation results in bicyclobutanone intermediate 18 after expulsion of the halogen via internal displacement. Alternatively, the product could arise through an enol/ion pair mechanism via intermediates 19, 20, and 21 (path b). This transformation has been applied to the synthesis of tropolones, many of which show antibacterial and fungicidal activity. A general approach reported by H. C. Stevens proceeds by initial cine-substitution of dichlorocyclobutanone 23 by acetate ion to generate intermediate 24; this compound then undergoes fragmentation to form the tropolone 25 (eq 7). 15

Scheme 2
Cyclobutanones are ideal intermediates for the conversion of olefins to the corresponding vicinally disubstituted saturated compounds. The double bond is first subjected to a [2 + 2] cycloaddition reaction with a ketene. Nucleophilic cleavage of the resulting cyclobutanone provides vicinally disubstituted products in a regio- and stereoselective fashion. This methodology was utilized in the synthesis of multifidene (28), a component of a Mediterranean brown alga. The key step involves ring cleavage of dichlorocyclobutanone 26 to afford the ester 27 exclusively as the cis-isomer (eq 8).\textsuperscript{14,15}

![Chemical Structure](image)

\textsuperscript{(8)}

In the absence of sufficient anion stabilizing substituents \textit{alpha} to the carbonyl group, addition of nucleophiles readily produces tertiary alcohols. A reduction in angle strain accompanies the hybridization change of the carbonyl carbon atom from sp\textsuperscript{2} to sp\textsuperscript{3}. Many interesting cyclobutanols have been prepared in this manner, such as the antibacterial agent 31. Addition of a Reformatsky reagent to cyclobutanone 29 gave a mixture of diastereomeric alcohols, with 30 predominating in a 9:1 ratio. Deprotection and coupling of the amine with Boc-(S)-valine completed the synthesis of the target molecule (eq 9).\textsuperscript{16,17}

![Chemical Structure](image)

\textsuperscript{(9)}
Cyclobutenones undergo reversible electrocyclic ring opening to vinylketenes under the proper thermal or photochemical conditions. The reactivity of these vinylketenes represents the primary synthetic application of cyclobutenones. In particular, the \([2 + 2]\) cycloaddition with alkenes and alkynes has been exploited to provide various products depending on the reaction conditions and the substitution pattern of the cyclobutenone (Scheme 3).

Scheme 3

If \(R^3\) is an allyl group, a facile intramolecular cycloaddition occurs to provide fused cyclobutanones (34). In these laboratories, a two-step sequence to provide cyclohexenols was developed. Intermolecular \([2 + 2]\) cycloaddition occurs readily with alkenes substituted with an electron-donating group. Treatment of the resulting
vinylcyclobutanones (36) with an appropriate nucleophile induces [1,3] sigmatropic rearrangement to provide the products (37). Eight-membered carbocyclic compounds were also prepared by a [4 + 4] annulation approach in which the vinylketene was generated in the presence of a diene.\textsuperscript{20} In these cases, [2 + 2] cycloaddition followed by [3,3] sigmatropic rearrangement (Cope rearrangement) affords the products (35). Smith and Hoehn first demonstrated that 4,4-diphenyl-substituted cyclobutenones (32, R\textsuperscript{3} = R\textsuperscript{4} = Ph) rearrange quantitatively to \(\alpha\)-naphthols (38). The product is formed by electrocyclic ring closure and tautomeration of the arylvinylketene 39, generated by electrocyclic ring opening of the starting cyclobutene (Figure 1).\textsuperscript{21,22}

\textbf{Figure 1}

\[
\begin{align*}
\text{39} & \quad \begin{array}{c}
\text{Ph} \\
\text{R}^1 \\
\text{R}^2
\end{array} \\
\text{40} & \quad \begin{array}{c}
\text{R}^3 \\
\text{R}^1 \\
\text{R}^2
\end{array}
\end{align*}
\]

Smith and Hoehn's \(\alpha\)-naphthol synthesis, along with similar examples of the electrocyclic closure of dienylketenes,\textsuperscript{23,24} laid the groundwork for the development of the aromatic annulation reaction developed in these laboratories. We saw the opportunity to generate a series of dienylketenes (40, Figure 1), the reactive structural unit in 39, from the electrocyclic ring opening of vinylcyclobutenones. These compounds were prepared in turn by the [2 + 2] cycloaddition of vinylketenes with heterosubstituted acetylenes (Scheme 3). The vinylketene was generated by thermolysis or photolysis of a cyclobutenone derivative in the "first generation" version of the reaction. This strategy was extremely effective for the preparation of highly substituted phenols (41) and was used as a key step in the synthesis of several natural products.\textsuperscript{25}

Liebeskind and Moore independently reported the synthesis of highly substituted quinones through the intermediacy of vinylketenes. By taking advantage of the availability
of squaric acid esters, compounds of type 42 and 44 were readily prepared. Thermolysis of these aryl- and alkynylcyclobutenenones generated vinylketenes, which cyclized to the hydroquinones (eq 9).\textsuperscript{26,27} Air oxidation gave the observed products (43). Moore also found that cyclopentenediones were formed from alkynylcyclobutenones 44 depending on the electronic nature of the substituent R (eq 10).\textsuperscript{28}

\[
\text{MeO} \quad \text{Me} \quad \text{O} \\
\text{MeO} \quad \text{Ph} \\
42 \\
\text{1) } 160^\circ\text{C, xylene} \\
\text{2) air} \\
\downarrow 72\% \\
\text{MeO} \quad \text{Me} \quad \text{O} \\
\text{MeO} \\
43
\]

\[
\text{MeO} \quad \text{MeO} \\
\text{MeO} \quad \text{SiMe}_3 \\
\text{44} \\
\text{135}^\circ\text{C, } p\text{-xylene} \\
\downarrow \\
\frac{1}{2} \text{R} \quad \text{R} \\
\frac{45}{46} \\
\text{R} = \text{CH}_2\text{OSiMe}_3 \\
\text{R} = \text{Ph} \\
\text{R} = \text{CO}_2\text{Et} \\
80\% \\
13\% \\
---}

\text{R} \\
\frac{52\%}{43\%}

\textbf{Cyclobutanone Synthesis}

The most widely used method for the synthesis of cyclobutanones and cyclobutenones is the [2 + 2] cycloaddition of ketenes with alkenes and alkynes.\textsuperscript{29} The mechanism of ketene cycloadditions has been the topic of much debate and has been used to explain its special features. For instance, in most cases the geometry of the alkene is transferred to the stereochemistry of the product; this fact has often been viewed as support for a concerted mechanism. This stereospecificity allows the preparation of \textit{cis-} and \textit{trans-} substituted cyclobutanones (eq 11 and 12).\textsuperscript{30}
The "endo effect" is a hallmark of the [2 + 2] cycloaddition reactions of ketenes.\textsuperscript{31} This term refers to the experimental trend in which the bulkiest substituent on the ketene ends up on the most sterically hindered face of the cyclobutanone. The larger the difference in bulk of the two substituents on the ketene, the larger the effect. When cyclic olefins are used as ketenophiles, the larger ketene substituent is found in the \textit{endo} position (the concave face) of the bicyclic cycloadducts. This \textit{endo}-selectivity is usually very high with cyclopentadiene cycloadducts, but it is often less pronounced with other cyclic olefins. This preference is rationalized by an orthogonal approach of the reactants in preparation for bond formation, with the smaller ketene substituent projecting toward the alkene (Scheme 4). In agreement with the orbital symmetry rules of Woodward and Hoffmann,\textsuperscript{32} the ketene acts as the antarafacial partner (bond formation on different sides of the π bond), while the alkene serves as the suprafacial component (bond formation on the same side of the π bond) (Scheme 4). This transition state geometry also explains the higher reactivity of \textit{cis}-over \textit{trans}-olefins. It should be noted, however, that a stepwise mechanism is not ruled out by any of these observations. In addition, Rey and co-workers showed by epimerization studies that, due to the preferred puckered conformation of the cyclobutanone ring, the \textit{endo}-configuration is often the more thermodynamically stable isomer in 7-monosubstituted bicyclo[3.2.0]hept-2-en-6-ones (Figure 2).\textsuperscript{33}
The regioselectivity of ketene cycloaddition reactions is also quite remarkable. Frontier molecular orbital theory predicts that for this $[\pi^2S + \pi^2a]$ process, initial bond formation occurs between the carbon atom of the olefin or alkyne with the highest HOMO coefficient and the carbon atom of the ketene having the highest LUMO coefficient.$^{34}$ This analysis often corresponds to bond formation between the most nucleophilic carbon atom of the ketenophile and the central carbon atom of the ketene. Accordingly, electron donating alkene and alkyne substituents are usually found at C-3 of the resulting cycloadducts (eq 13 and 14).$^{23,35}$
Ketenes are known to react periselectively with conjugated dienes to afford [2 + 2] cycloadducts. A recent report by Yamabe and co-workers claims that ketenes act as dienophiles in a Diels-Alder reaction with dienes.\textsuperscript{36} Frontier molecular orbital interactions and ab initio calculations for the [4 + 2] and [2 + 2] cycloadditions of ketene with cyclopentadiene favor the former pathway, in which the C=O bond of ketene reacts as the dienophile. To account for the experimentally observed [2 + 2] cycloaddition products, a [3,3] sigmatropic rearrangement (Claisen rearrangement) of the [4 +2] adduct was proposed. The hypothesis was tested by low temperature NMR spectroscopy experiments on the reaction of diphenylketene with cyclopentadiene (Scheme 5). At -30 °C, [4 + 2] adduct \textgamma-methylenedioxydihydropyranyl 53 was detected; elevation of the reaction temperature led to formation of the cyclobutanone 54. While 54 may be formed by the [3,3] sigmatropic rearrangement of Diels-Alder adduct 53, it is also possible that the [4 + 2] cycloaddition is reversible, and a standard [2 + 2] pathway accounts for cyclobutanone formation. In addition, the results at of this low temperature experiment does not necessarily translate to the higher temperatures, 25 °C and above, at which most ketene cycloadditions are conducted.
Scheme 5

While the selectivity of the ketene [2 + 2] cycloaddition reaction assures its importance as a route to cyclobutanones and cyclobutenones, it does suffer the disadvantage of a relatively limited scope. Unactivated alkenes and alkynes are often poor components in the reaction, such that ketene, alkyl-, and arylketenes generally react in good yields only with activated π bonds. As a result, substitution patterns of the resulting cycloadducts are limited (eq 15).

\[
\begin{align*}
\text{X, Y = H, alkyl, aryl} & & \text{Z = OR, NR}_2, \text{SR, Ar, vinyl} \\
\end{align*}
\]

Just as heteroatom donating groups increase the ketenophilicity of π bonds, the reactivity of the ketene is enhanced by electron withdrawing substituents.\textsuperscript{3,7} Dichloroketene\textsuperscript{38} reacts well with many types of unactivated multiple bonds. Like most ketenes, dichloroketene is usually prepared in situ in the presence of a ketenophile. While the method of dehydrohalogenation of acid halides with tertiary amine bases has been utilized for this purpose,\textsuperscript{13,39} the triethylamine hydrochloride byproduct promotes the decomposition of dichloroketene at a rate comparable to its [2 + 2] cycloaddition reaction with unactivated olefins and alkynes. Another method for ketene generation, the zinc-mediated dehalogenation of α-halo acid halides,\textsuperscript{40} suffered from a similar limitation due to the zinc chloride byproduct until Hassner and Krepski introduced the addition of phosphorous oxychloride as a zinc chloride complexing agent.\textsuperscript{41} This advance paved the
way for the development of dichloroketene as a powerful tool for the production of [2 + 2] cycloadducts with unactivated alkenes and alkynes. Dimethoxyethane has also been shown to function as an effective zinc chloride sequestering agent.42

Dichloroketene is often employed as a ketene equivalent (Scheme 6). Due to its increased scope of reactivity, a far wider range of cyclobutanones and cyclobutenones are available than with ketene itself. Dechlorination of the 4,4-dichlorocyclobutanones (55) by zinc in acetic acid or tributyltin hydride affords unsubstituted cyclobutanones (56) in near quantitative yields, identical in structure with those that would be obtained from the cycloaddition of ketene with the same olefin.38

Scheme 6
References

(25) See Chapter 3 in Part II of this thesis for a discussion of this chemistry.
(31) For a discussion, see: (a) Ref. 29c. (b) Ref. 29b, pp 459-536. (c) Ref. 29a, pp 163-166.
(37) These electronic effects are also explained by frontier molecular orbital theory, see Ref. 34b. See also (a) Ref. 29b, pp 13-18. (b) Ref. 29c.
CHAPTER 2

Rhodium-Catalyzed [2 + 2] Cycloaddition of $\alpha$-Diazotiothiol Esters

A Serendipitous Discovery

During the course of a study aimed at the synthesis of $\beta$-lactones from the reaction of thiol esters with ketones and aldehydes,$^1$ cyclopropane thiol ester 58 was required as a starting material. It was determined that the most direct route for the preparation of this compound would involve a cyclopropanation reaction of $\alpha$-diazothiol ester 57 with 4-phenyl-1-butene. We chose rhodium(II) acetate, frequently used for cyclopropanation reactions, as the catalyst for this transformation. The reaction proceeded smoothly to provide one major product as a mixture of stereoisomers. Upon examination of spectral data, however, formation of the desired cyclopropane was ruled out. The unsubstituted cyclopropane thiol ester, previously prepared in our laboratories, shows characteristic $^1$H NMR spectrum peaks at ca. 1.0 ppm corresponding to the ring methylene protons, and an IR stretch at 1680 cm$^{-1}$. Peaks in the $^1$H NMR spectrum of the product of the reaction of 57 were further downfield, and the IR spectrum showed a carbonyl stretching frequency at 1780 cm$^{-1}$. Quite surprisingly, this rhodium-catalyzed reaction had provided an entirely different product which was identified as $\alpha$-thiocyclobutanone 59.$^*$ No trace of the expected cyclopropane product was detected.

---

$^*$ The author gratefully acknowledges the contributions of Thomas Lee to this project. Thomas was responsible for recognizing and correctly identifying this unexpected product, as well as conducting many of the initial studies of the rhodium-catalyzed [2 + 2] cycloaddition reaction chemistry of $\alpha$-diazothiol esters.
Scheme 7

To account for this intriguing result, we propose an unprecedented Wolff-type rearrangement of the α-diazo thiol ester to generate a thio-substituted ketene (62), which then undergoes a [2 + 2] cycloaddition reaction with the alkene to provide the observed product (eq 16). The reaction most likely proceeds by initial formation of rhodium carbenoid species 60. The exact nature of the remaining steps is speculative but may involve the sulfur ylide intermediate 61. Subsequent mechanistic experiments, which will be discussed in more detail below, support the crucial role of rhodium in this reaction. To the best of our knowledge, this discovery marks the first documented metal-assisted rearrangement of an α-diazo thiol ester.

\[
\begin{align*}
\text{ArS}^\cdot \text{C}^\cdot \text{O}^\cdot \text{N}_2 & \rightarrow \text{ArS}^\cdot \text{C}^\cdot \text{O}^\cdot \text{Rhl}_n & \rightarrow \left[ \begin{array}{c} \text{ArS}^\cdot \text{C}^\cdot \text{O}^\cdot \text{H}^+ \\ \text{ArS}^\cdot \text{H} \end{array} \right] & \rightarrow \text{ArS}^\cdot \text{C}^\cdot \text{C}^\cdot \text{O}^\cdot \\
57 & \rightarrow 60 & 61 & 62 \\
\end{align*}
\]

(16)

Synthetic Transformations of α-Diazo Carbonyl Compounds

The Wolff rearrangement of α-diazo ketones is well studied and widely used in organic synthesis.\(^2\) Wolff rearrangements can be induced photochemically, catalytically
with metal salts, or thermally. An important application of the Wolff rearrangement is in the Arndt-Eistert synthesis, an efficient method for the homologation of carboxylic acids. With cyclic ketones, this process has been used to induce ring contraction, primarily of five and six-membered ring systems.\textsuperscript{2d,2a} The photochemical Wolff rearrangement has also been used as a tool for generating ketenes. In the Danheiser laboratories, a "second generation" version of the aromatic annulation reaction (see Part II) has been developed, in which the only change in the cascade of pericyclic reactions is that the vinylketene is formed via a photo-Wolff rearrangement of an $\alpha,\beta$-unsaturated-$\alpha'$-diao ketone 63 (eq 17).\textsuperscript{3}

\begin{equation}
\text{R}_2\text{C}=\text{O} \rightarrow \text{R}_1\text{C}^\text{=}\text{O} + \text{R}_4^\text{=C}=\text{X} \rightarrow \text{R}_1\text{R}_2\text{R}_3\text{R}_4\text{OH}
\end{equation}

(17)

The transition metal-catalyzed decomposition of diazocarbonyl compounds is one of the most rapidly expanding areas of research in recent years.\textsuperscript{4} The coordinative unsaturation at the metal center allows it to react as an electrophile with diazo compounds. Electrophilic addition followed by loss of dinitrogen produces the metal-stabilized carbene 64. Reaction with an electron-rich substrate (a cyclopropanation reaction with an alkene is depicted as an example) regenerates the metal complex and completes the catalytic cycle (Figure 3). While some transition metals such as silver(I) catalyze the Wolff rearrangement of diazocarbonyl compounds, other metals such as palladium, rhodium, and copper induce entirely different reactivity. The transient metal-bound carbene species (metal carbenoid) 64 believed to be formed with these metals is stabilized and therefore less prone to undergo Wolff rearrangement. Instead, alternative pathways such as cyclopropanation, insertion, and ylide formation predominate. The inter- and intramolecular cyclopropanation of
alkenes\textsuperscript{4a,4c,4e} and intramolecular C-H insertion\textsuperscript{4b,4d} with alkyl diazoacetates have been extensively employed in the synthesis of natural products.

Figure 3\textsuperscript{4e}

Examples of the use of $\alpha$-diazo thiol esters as reactive intermediates are sparse, and all involve the photo-Wolff rearrangement. In the early 1970s, at a time when the photochemistry of $\alpha$-diazo esters was attracting considerable attention, Hixson and Hixson investigated the Wolff rearrangement of $S$-methyl diazothioacetate for possible application as a route to enzyme labeling agents.\textsuperscript{5} Photolysis of 65 in methanol at 310-380 nm afforded the homologated ester product 68 in excellent yield (Scheme 8). The intermediacy of ketene 67 derived from a Wolff rearrangement was proposed to account for this result.

This high yielding, clean reaction contrasts with the analogous reactions of $\alpha$-diazo esters and amides, which often give a significant amount of byproducts from carbene insertion reactions under typical Wolff rearrangement conditions.\textsuperscript{2a}
Scheme 8

![Chemical Structures]

In another study, Georgian and coworkers studied the competitive Wolff rearrangement of unsymmetrically substituted 2-diazo-1,3-dicarbonyl compounds of type 69 (Scheme 9). In all cases, products derived from exclusive sulfur migration were isolated. The intermediacy of thio-substituted ketene species 72 was postulated based on the isolation of α-carbomethoxy acids (74) upon the addition of water to the reaction mixture. Further evidence was garnered from the production of β-lactam 73 when the photolysis was conducted in the presence of N-benzyldieneaniline. In all cases, products derived from exclusive sulfur migration were isolated. To explain this remarkable selectivity, sulfonium ylide 71 was postulated as a precursor to the ketene 72. Considering these two studies, it is possible that our rhodium-catalyzed decomposition of α-diazo thiol esters shares a common intermediate with the photo-Wolff rearrangement of similar substrates.
Scheme 9

The chemistry of the rhodium-catalyzed decomposition of α-diazo thiol esters has been neglected thus far, and our proposed reaction pathway represents a useful addition to the chemistry of diazocarbonyl compounds. More interesting to us, however, is the attractiveness of this methodology to the rich field of ketene chemistry. There were several reasons for choosing to conduct a systematic investigation of this reaction. Perhaps the most striking feature was the remarkable facility of the cycloaddition reaction with the unactivated alkene, 3-phenyl-1-butene. Normally, only highly activated ketenes such as dichloroketene (see Chapter 1) react this readily with simple olefins. If this reaction proved to be general, it could serve as a complement to dichloroketene chemistry. In fact, the expected versatility of the product α-thiocylobutanones promised to afford certain advantages over dichlorocyclobutanones. Finally, the mild, catalytic conditions of the reaction and ease of preparation of the starting materials were appealing in terms of the scope and practicality of the reaction.

Preparation of α-Diazo Thiol Esters

Four α-diazo thiol esters were prepared in order to study the ramifications of varying the electronic and steric character of the thiol component on the course of the
reaction. Of the numerous methods available for the preparation of \( \alpha \)-diazocarbonyl compounds,\textsuperscript{2b} we chose to employ the detrifluoroacetylation diazo transfer reaction developed in our laboratories for the synthesis of these intermediates.\textsuperscript{7} This reaction involves acylation of the lithium enolate of the thiol ester with trifluoroethyl trifluoroacetate. The \( \beta \)-dicarbonyl intermediate is isolated but not purified, and treated as a solution in acetonitrile at room temperature with triethylamine and water followed by a solution of methanesulfonyl azide in acetonitrile. The \( \alpha \)-diazot thiols (79, 57, 80, and 81) were isolated in good yield after column chromatography (eq 18). \( S \)-Mesityl-\( \alpha \)-diazot thiol ester 57 is a solid and can be stored indefinitely at 0 °C. On the other hand, \( S \)-phenyl-\( \alpha \)-diazot thiol ester 79 decomposed slowly upon storage and was usually repurified immediately before use.

\[
\text{RS}CH_3 \xrightarrow{1.05 \text{ equiv LiHMDS}} \text{RS} \equiv \text{N}_2
\]

\( \begin{align*}
75 \quad R &= \text{Ph} \\
76 \quad R &= \text{Mesityl} \\
77 \quad R &= \rho \text{-OCH}_3 \text{Ph} \\
78 \quad R &= t\text{-Bu}
\end{align*} \)

\begin{align*}
\text{THF, 0 °C, 30 min} \\
1.2 \text{ equiv CF}_3\text{CO}_2\text{CH}_2\text{CF}_3 \\
-78 °C, 10 \text{ min; } 1.5 \text{ equiv CH}_3\text{SO}_2\text{N}_3 \\
1.5 \text{ equiv NEt}_3 \\
1.0 \text{ equiv H}_2\text{O, CH}_3\text{CN} \\
\text{rt, 2.5 h}
\end{align*}

\( \alpha \)-diazot thiol ester  \\ Yield (%)  \\
79 \quad R &= \text{Ph} \\
57 \quad R &= \text{Mesityl} \\
80 \quad R &= \rho \text{-OCH}_3 \text{Ph} \\
81 \quad R &= t\text{-Bu}
\]

Thiol esters are readily prepared by coupling thiols with carboxylic acids and their derivatives.\textsuperscript{8} Substrates 75-77 were synthesized in ca. 95% yield by the reaction of acetyl chloride with the appropriate thiol.\textsuperscript{*} In an unoptimized procedure, the hindered \( t \)-butylthiol gave 78 in only 10% yield. In the case of 76 and 77, preparation of the thiols was also required. For example, \( S \)-mesityl thioacetate (76) was synthesized in two steps from 2-mesitylenesulfonyl chloride (eq 19). Reduction with zinc amalgam afforded the thiol,\textsuperscript{9,10}

\* \( S \)-Phenyl thioacetate is commercially available.
which was acylated with acetyl chloride in the presence of pyridine to provide the desired product in excellent yield.

Scope of the Cycloaddition Reaction

In the course of optimizing the cycloaddition reaction conditions, several variables were kept relatively constant. The concentrations of the reaction mixtures with respect to the diazo thiol esters were maintained at ca. 0.1-0.2 M. We reasoned that performing the reactions at higher concentrations could facilitate side reactions such as ketene dimerization and polymerization. In addition, the ketenophiles were employed in large excess (5-10 equiv) to allow rapid trapping of the ketene, a standard tactic in [2 + 2] cycloaddition reactions. Finally, except for some experimentation with copper(I) and copper(II) trifluoromethansulfonate catalysts, rhodium(II) acetate was used exclusively due to its effectiveness and availability. The reactions were typically carried out using as little as 2 mole percent of the catalyst.

A standard set of conditions was developed for the cycloaddition reaction which proved to be quite general for a wide variety of ketenophilic partners. A solution of the diazo thiol ester in dichloroethane or dichloromethane was added slowly, over approximately three hours, via syringe pump to a refluxing solution of the ketenophile and a catalytic amount of rhodium(II) acetate in the same solvent. Faster rates of addition led to decreased product yields. We were pleased to find that alkenes and alkynes spanning a wide range of substituent patterns are suitable partners in the cycloaddition reaction and allow the preparation of an array of $\alpha$-thiocyclobutanones and -butenones in moderate to
good yields (Tables 1 and 2). All products were purified by column chromatography on silica gel and may be stored indefinitely at 0 °C.

Several important points are evident from the tabulated results. The promising reactivity displayed in the initial case (Scheme 7, and entry 8 in Table 1) was followed up by the success of the cycloaddition with several unactivated π bonds (entries 1-3, 6-9, and 10,11 in Table 1, 1-3 in Table 2). Regarding the choice of the diazo thiol ester, the cleanest reactions and highest yields were obtained with the mesityl substrate. This difference in reactivity is illustrated by comparison of entries 7 and 8, and entries 9 and 10 in Table 1, in addition to entries 1 and 2 in Table 2. Especially with the less reactive ketene cycloaddition partners, acyclic terminal olefins and unactivated alkynes, the S-mesityl diazo thiol ester (57) is clearly a superior substrate. This trend may imply a steric effect; use of the bulky sulfide may better shield the intermediate ketene from undesired side reactions which compete with the desired [2 + 2] cycloaddition, such as dimerization and polymerization, or nucleophilic addition of the sulfur atom of the product cyclobutanone to the ketene. Alternatively, the bulky mesityl substituent may force the intermediate ketene to adopt a nonplanar conformation (Figure 4), thus minimizing π-donation from the sulfur atom and the aromatic ring and creating a more reactive ketene. As a result of its superior reactivity, reactions with the S-mesityl diazo thiol ester 57 were run in dichloromethane at lower temperatures (40 °C), while the other diazo thiol esters required the higher reaction temperatures afforded by dichloroethane (83 °C). With the more reactive ketenophiles, however, nearly identical results are obtained using either α-diazo thiol ester 57 or 79 (entries 1 and 2, entries 5 and 6 in Table 1). In these cases, we recommend the use of the thiophenol-derived reagent 79 because it is more readily available.

Figure 4
<table>
<thead>
<tr>
<th>entry</th>
<th>alkene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>diazo thiol ester</th>
<th>cyclobutanone&lt;sup&gt;d&lt;/sup&gt;</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>methylenecyclohexane</td>
<td>79</td>
<td><img src="image1.png" alt="Image" /></td>
<td>73-78</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>methylenecyclohexane</td>
<td>57</td>
<td><img src="image2.png" alt="Image" /></td>
<td>78-81</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>methylenecyclohexane</td>
<td>81</td>
<td><img src="image3.png" alt="Image" /></td>
<td>37</td>
</tr>
<tr>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>methylenecyclohexane</td>
<td>80</td>
<td><img src="image4.png" alt="Image" /></td>
<td>69</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>cyclopentadiene</td>
<td>79</td>
<td><img src="image5.png" alt="Image" /></td>
<td>90-96</td>
</tr>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>cyclopentadiene</td>
<td>57</td>
<td><img src="image6.png" alt="Image" /></td>
<td>92</td>
</tr>
<tr>
<td>7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4-phenyl-1-butene</td>
<td>79</td>
<td><img src="image7.png" alt="Image" /></td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reagents: 8<sup>a</sup> endo-SPh, 8<sup>b</sup> exo-SPh, 86<sup>a/b</sup> = 5-11:1

<sup>d</sup> Reagents: 87<sup>a/b</sup> endo-SPh, 87<sup>a/b</sup> exo-SPh, 87<sup>a/b</sup> = 98:2

<sup>b</sup> Reagents: 88<sup>a</sup> trans, 88<sup>b</sup> cis, 88<sup>a/b</sup> = 3:1
Table 1 continued.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene or imine&lt;sup&gt;a&lt;/sup&gt;</th>
<th>diazo thiol ester</th>
<th>cyclobutanone or β-lactam&lt;sup&gt;d&lt;/sup&gt;</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4-phenyl-1-butene</td>
<td>57</td>
<td>[Image]</td>
<td></td>
</tr>
<tr>
<td>9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2-methyl-4-phenyl-1-butene</td>
<td>79</td>
<td>[Image]</td>
<td></td>
</tr>
<tr>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2-methyl-4-phenyl-1-butene</td>
<td>57</td>
<td>[Image]</td>
<td></td>
</tr>
<tr>
<td>11&lt;sup&gt;c&lt;/sup&gt;</td>
<td>indene</td>
<td>79</td>
<td>[Image]</td>
<td></td>
</tr>
<tr>
<td>12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>indene</td>
<td>57</td>
<td>[Image]</td>
<td></td>
</tr>
<tr>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N-benzylideneaniline</td>
<td>79</td>
<td>[Image]</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 10 equiv of alkene was employed in entries 6, 7, and 8. 5 equiv was used in all other runs. 3.5 equiv of imine was used in entry 13. <sup>b</sup> Reaction conducted in dichloromethane at 40 °C. <sup>c</sup> Reaction conducted in dichloroethane at 83 °C. <sup>d</sup> Ar = 2,4,6-trimethylphenyl (mesityl).
Table 2. Preparation of Cyclobutenones from α-Diazo Thiol Esters

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne&lt;sup&gt;a&lt;/sup&gt;</th>
<th>diazo thiol ester</th>
<th>cyclobutene&lt;sup&gt;d&lt;/sup&gt;</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4-octyne</td>
<td>79</td>
<td><img src="image1" alt="Diagram" /></td>
<td>14</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4-octyne</td>
<td>57</td>
<td><img src="image2" alt="Diagram" /></td>
<td>38</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1-phenyl-1-propyne</td>
<td>57</td>
<td><img src="image3" alt="Diagram" /></td>
<td>50</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1-methoxy-1-propyne</td>
<td>79</td>
<td><img src="image4" alt="Diagram" /></td>
<td>72</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1-methoxy-1-propyne</td>
<td>57</td>
<td><img src="image5" alt="Diagram" /></td>
<td>71-92</td>
</tr>
</tbody>
</table>

<sup>a</sup> 5 equiv of acetylene was employed in entries 1-3. 3.5 equiv was used in entries 4 and 5. <sup>b</sup> Reaction conducted in dichloromethane at 40 °C. <sup>c</sup> Reaction conducted in dichloroethane at 83 °C. <sup>d</sup> Ar = 2,4,6-trimethylphenyl (mesityl).

The use of diazo thiol ester 81 (R = t-Bu) was abandoned early in the studies (entry 3 in Table 1). It was perceived that the sulfur atom of this alkyl thiol ester would be more electron-donating and therefore aid in the rearrangement, but perhaps this same characteristic decreased the [2 + 2] cycloaddition reactivity of the resulting thio-substituted ketene to the benefit of competing side reactions. Likewise, the presence of an electron-
donating substituent on the phenyl ring (diazo thiol ester 80) (entry 4 in Table 1) resulted in a slightly lower yield of product.

Finally, a distinguishing characteristic of ketene [2 + 2] cycloaddition reactions is borne out with our results, as evidenced by the excellent *endo* selectivity with cis-1,2-disubstituted olefins\textsuperscript{11} seen in entries 5, 6, 11 and 12 in Table 1. \(^1\)H NMR spectrum coupling constants between the C-7 proton and the C-1 ring junction proton in these types of bicyclic cyclobutanones are diagnostic; C-7 \(\text{exo}\)-protons exhibit larger coupling constants (6.3-10.5 Hz) than C-7 \(\text{endo}\)-protons (2.4-5.0 Hz). This trend is also observed for vicinal protons of monocyclic cyclobutanones (Figure 5).\textsuperscript{12-14} However, the splitting patterns of 86a were too complex to allow this type of analysis, so the stereochemical assignment for this case was made by indirect means. Ghosez also synthesized cyclobutanone 86a by the [2 + 2] cycloaddition reaction of (phenylthio)ketene, prepared by the dehydrohalogenation of phenylthioacetyl chloride, with cyclopentadiene.\textsuperscript{15} Ghosez claimed that the \(\text{endo}\)-thiophenyl configuration in cycloadduct 86a was assigned based on detailed spectral analysis but did not include details. We followed Ghosez's procedure to generate a compound which matched 86a by \(^1\)H NMR spectral analysis, thus completing its indirect stereochemical assignment.

**Figure 5**

\[
\begin{align*}
\text{J}_{1,7,\text{cis}} &= 9 \text{ Hz} \\
\text{J}_{1,7,\text{trans}} &= 3.1 \text{ Hz} \\
\text{J}_{2,3,\text{cis}} &\approx 9-10 \text{ Hz} \\
\text{J}_{2,3,\text{trans}} &\approx 3 \text{ Hz}
\end{align*}
\]

The coupling patterns of the indene adducts (91 and 92, entries 11 and 12) are not as complex. With the aid of homonuclear decoupling \(^1\)H NMR experiments, we determined that for cycloadduct 91, \(J_{2,3} = 9.0 \text{ Hz}\), while for 92, \(J_{2,3} = 9.4 \text{ Hz}\). These large coupling constants are indicative of vicinal ring protons in the *cis* configuration, and
thus an *endo*-aryltio disposition (Figure 6). The major product in entry 8 was assigned as *trans*-2,3 cyclobutanone 59a based on a coupling constant of 6.8 Hz, while for the minor isomer 59b, $J = 9.5$ Hz. The same preference exists in the formation of *S*-phenylthiocyclobutanones 88a and 88b (entry 7). The product distributions in these two examples are contrary to those which are predicted by a concerted transition state analysis and appear to support the argument that the relative thermodynamic stability of the products plays a role in the stereochemical outcome of ketene [2 + 2] cycloaddition reactions (see Chapter 1). In fact, exposure of a 3.5:1 mixture of 59a and 59b to 1.1 equiv of lithium methoxide in methanol at 25 °C for 11 h led to an increase in the ratio to 9.4:1 in favor of 59a. This equilibration experiment shows that the thermodynamically more stable cyclobutanone (59a) is the major product of the cycloaddition reaction in this case, and also lends support to the *trans*-stereochemical assignment. Finally, analogous to cyclobutanones, the reported coupling constant range for monocyclic 3,4-disubstituted $\beta$-lactams is 1.5-2.8 Hz for *trans*-isomers and 4.5-5.9 Hz for *cis*-isomers. In accordance with this data, *trans*-*$\beta$-lactam 93 (entry 13) was identified based on a coupling constant of 2.5 Hz between the ring protons.

**Figure 6**

![Diagram of molecules 91 and 92 with coupling constants](image)

The regiochemistry of the [2 + 2] cycloadditions is consistent with the frontier molecular orbital considerations previously described. In the case of the cyclobutanone products, confirmation is straightforward based on analysis of coupling patterns in the $^1$H NMR spectrum. This process is also useful in the case of cyclobutenones 94, 95, and 96 (entries 3, 4, and 5, Table 2); small homoallylic couplings are observed between the C-4
protons and the methyl groups. This characteristic is not anticipated for the regioisomeric cyclobutenones.

The yields of cycloadducts with unactivated alkenes rivals that of dichloroketene. For example, the 2,2-dichloro analog of 82 was synthesized in 55% yield by the dehydrohalogenation of trichloroacetetyl chloride in the presence of methylenecyclohexane. The results with unactivated alkynes were not quite as promising. The dialkyl-substituted acetylene in entry 2 (Table 2) resulted in a disappointingly low yield of cyclobutenone 95, and terminal acetylenes such as phenylacetylene gave only complex product mixtures (not listed). In contrast, dichloroacetene generated by the zinc dehalogenation method afforded products with these alkynes in yields of 73% (two step yield after dechlorination) and 75-87%, respectively. 18

Mechanism of the Cycloaddition Reaction

The exact mechanism of this transformation remains speculative. Clearly, the four-membered ring products are derived from a cycloaddition reaction from some sort of ketene species. The proposed catalytic role of rhodium was verified by conducting the reaction in the absence of catalyst. Thus, the conditions of entry 1 in Table 1 (refluxing dichloroethane) without rhodium(II) acetate led to a substantially lower cyclobutanone yield of 31%. A thermal Wolff rearrangement is likely operating in this case.

A photochemical variant of this reaction was also investigated. Photolysis of a solution of diazo thiol ester 79 and methylenecyclohexane in benzene at 300 nm led to polymeric products with no detectable trace of cyclobutanone by 1H NMR analysis. The results of Hixson and Hixson and Georgian and coworkers 5,6 suggest that photo-Wolff rearrangement of α-diazo thiol esters is a facile process. This may be true; however, unlike nucleophilic trapping with alcohols, water, or imines, our experiment indicated that [2 + 2] cycloaddition under these conditions is not so straightforward.
There are few literature examples of thio-substituted ketenes as partners in [2 + 2] cycloaddition reactions.\textsuperscript{19} To the best of our knowledge, there has been only one report of the cycloaddition reaction of (phenylthio)ketene with cyclopentadiene, but a yield was not given.\textsuperscript{15} In addition, cycloadditions of this ketene with unactivated olefins have not been reported. In order to create a benchmark with which to compare our system, we decided to generate (phenylthio)ketene by a standard procedure, the dehydrohalogenation of acid chlorides, and test its reactivity.\textsuperscript{20} In the event, treatment of a solution of one equivalent of phenylthioacetyl chloride and five equivalents of cyclopentadiene in diethyl ether with a solution of one equivalent of triethylamine in diethyl ether over 4.5 h, followed by stirring at 25 °C for 24 h resulted in a meager 13% yield of cyclobutanone after purification. This experiment revealed the sluggish rate of cycloaddition of the ketene intermediate even in the presence of an excellent ketenophile. Similarly, less than 5% of the cycloadduct was obtained with ten equivalents of 4-phenyl-1-butene in refluxing dichloroethane (83 °C).

The ultimate failure of the photochemical and thermal methods of generation to afford cycloadducts of (phenylthio)ketene necessitates further consideration of the reaction mechanism and the nature of the ketene intermediate. These results follow theoretical predictions of the influence of substituents on ketene reactivity. As a general rule, electropositive ketene substituents decrease their reactivity in cycloaddition reactions by raising the energy of the LUMO, while electronegative groups have the opposite effect.\textsuperscript{11} Dichloroketene, for example, is extremely reactive even with unactivated π bonds (see Chapter 1). Thio-substituted ketenes are predicted from isodesmic energy calculations to have reasonable stability, and thus be less reactive. A crucial question must therefore be addressed: what makes the α-diazo thiol ester-derived cycloadducts so accessible?

One possibility to explain the unusual reactivity of our ketene species can be formulated by an examination of the catalytic nature of the reaction. The α-diazo thiol esters are added very slowly to a solution of the catalyst and ketenophile and are
presumably transformed very rapidly to the ketene species via the rhodium carbenoid.* Assuming that the intermediate ketenes react immediately after formation, it may be assumed that no more than two mole percent of ketene is present at any one time in the reaction mixture. With the large excess of ketenophile present, the [2 + 2] cycloaddition pathway may dominate over side reactions. This explanation cannot be ruled out by our dehydrohalogenation experiment, in which the acid chloride was introduced slowly to the reaction mixture, because the issue is clouded by variables such as the triethylamine hydrochloride byproduct and an unknown rate of ketene formation.

Another hypothesis deals with the nature of the intermediate ketene species. Hegedus has reported the formation of cyclobutanones and β-lactams by the photolytic reactions of chromium "Fischer" carbene complexes with alkenes and imines, respectively (Scheme 10).21-24† The cycloaddition products parallel those of free ketenes with respect to regio- and stereoselectivity. In considering the possible intermediacy of ketenes in this novel transformation, Hegedus realized that the reactions were free of the usual problems associated with free ketene cycloadditions, such as the formation of dimerization and polymerization products. In addition, better reactivity and higher yields were observed. As a consequence, he proposed photolytically generated chromium-ketene complexes as the reactive species.

---

* The reaction mixtures are cooled and worked up immediately after completion of diazo thiol ester addition; see Experimental Section for details.
† The author would like to thank Professor Scott Virgil for extremely helpful discussions of this work.
The first step of the mechanism was suggested to involve a photochemically driven insertion of carbon monoxide into the metal-carbon double bond to produce ketene complex 100. This intermediate could not be observed spectroscopically but was postulated based on its subsequent reactions. The metallacyclopropane is only reactive towards nucleophilic reagents and fails to undergo typical ketene/olefin cycloaddition reactions. Therefore, 100 must rearrange to some other species, perhaps a metal-ketene complex such as 101.25

It is possible that a similar role played by the rhodium metal accounts for the reactivity in our case. In this scenario, following rhodium carbenoid formation and sulfur migration, the rhodium remains complexed to the thio-substituted ketene (see eq 16, page 19). This discrete intermediate would possess enhanced reactivity in [2 + 2] cycloaddition reactions due to the reduced electron density of the ketene π system. After reaction of this complex with a ketenophile, the free rhodium(II) would be returned to the catalytic cycle. Transition metal-ketene complexes of iridium, another Group VIIIIB element, have recently been proposed.

Switching to a different catalyst may provide some information regarding our proposed interaction of rhodium with the ketene. The only catalyst modifications that we have attempted thus far were to use copper(I) and copper(II) trifluoromethanesulfonate
(triflate) catalysts, which are commonly used in cyclopropanation reactions of diazocarbonyl compounds. These experiments resulted in the formation of several unidentified byproducts along with a trace of the desired cyclobutanone. The electronic character of the current system would be severely altered by employing rhodium(II) trifluoroacetate. Following our revised mechanism, this more electrophilic catalyst would produce an even more reactive ketene. As a result, product yields may improve, especially with less ketenophilic alkenes and alkynes.
References

(8) See ref. 1 and references cited therein.
(11) For a discussion and references, see Chapter 1.
(20) For references, see Chapter 3 in Part II of this thesis.
CHAPTER 3

\textit{\alpha-}\text{Thiocyclobutanones as Synthetic Intermediates}

\textbf{Overview}

A major factor motivating our interest in the $[2 + 2]$ cycloaddition reaction chemistry of thio-substituted ketenes has been the potential of the product \textit{\alpha-}\text{thiocyclobutanones as synthetic intermediates}. The transformations which were envisioned for this class of molecules are shown in Scheme 11.

\textbf{Scheme 11}

\begin{center}
\begin{tikzpicture}
    \node (104) at (0,0) {$\begin{array}{c}
        \text{\textbf{104}} \\
        \text{SPh}
    \end{array}$};
    \node (105) at (4,0) {$\begin{array}{c}
        \text{\textbf{105}}
    \end{array}$};
    \node (106) at (4,2) {$\begin{array}{c}
        \text{\textbf{106}} \\
        \text{SPh}
    \end{array}$};
    \node (107) at (8,0) {$\begin{array}{c}
        \text{\textbf{107}}
    \end{array}$};
    \node (108) at (0,-2) {$\begin{array}{c}
        \text{\textbf{108}} \\
        \text{R = Me, Ac}
    \end{array}$};
    \draw (104) -- (105) node [midway, above] {reduction};
    \draw (104) -- (106) node [midway, above] {alkylation};
    \draw (106) -- (107) node [midway, above] {reduction};
    \draw (108) -- (109) node [midway, above] {reduction};
    \draw (104) -- (108) node [midway, above] {Pummerer};
\end{tikzpicture}
\end{center}

Reduction of the carbon-sulfur bond provides \textit{\alpha-}\text{unsubstituted cyclobutanones (105)}. Because our methodology allows the preparation of \textit{\alpha-}\text{thiocyclobutanones (104)} from unactivated alkenes that do not react with ketene itself, this sequence can thus be used to access cyclobutanones which are not available directly from $[2 + 2]$ cycloaddition reactions. Our \textit{\alpha-}\text{thiocyclobutanones are analogous to dichlorocyclobutanones for this
purpose; however, additional reactions of this system promised to extend its utility to include the synthesis of molecules which are not readily available by dichloroketene methodology.

Selective alkylation of the sulfur-substituted carbon atom of \( \alpha \)-thiocyclobutanones (104) was expected to provide disubstituted cyclobutanones 106. Reduction of these tertiary sulfides should give \( \alpha \)-alkylcyclobutanones 107. This three step sequence from the \( \alpha \)-diazothiol ester marks a synthetic equivalent for monoalkylketenes. Another useful pathway begins with oxidation of the sulfide to the sulfoxide, followed by Pummerer rearrangement to generate \( O,S \)-acetals 108. Reduction of the carbon-sulfur bond in 108 should provide \( \alpha \)-acetoxyacyclobutanones 109. This series of reactions represents a synthetic equivalent for acetoxyketenes. All of these transformations demonstrate the unique reactivity of \( \alpha \)-thiocyclobutanones imparted by the presence of the sulfur substituent, and they may also be used as substrates for the multitude of general cyclobutanone reactions described in Chapter 1. Clearly, \( \alpha \)-thiocyclobutanones possess the potential to supplant dichlorocyclobutanones as the most accessible and versatile class of cyclobutanones.

**Reduction of \( \alpha \)-Thiocyclobutanones**

A wide variety of reagents are available for reduction of the carbon-sulfur bond, including Raney nickel, nickel boride, metal complex reducing agents, zinc in acidic media, tributyltin hydride, and alkali metals.\(^1\) The choice of reagent depends on factors such as the reactivity of the substrate and the chemoselectivity that is required by the presence of other reducible functional groups in the molecule. With \( \alpha \)-thiocyclobutanones, we anticipated facile desulfurization due to the adjacent carbonyl group, which would stabilize any carbanionic or radical intermediates. As a result, we avoided harsher, less selective reagents such as Raney nickel in favor of two mild, experimentally simple procedures.
Tributyltin hydride is a very effective reagent for the selective desulfurization of unsymmetrical sulfides. The reduction is a free radical process, usually initiated by 2,2'-azobis(isobutyronitrile) (AIBN). The reaction proceeds by homolytic substitution at sulfur in unsymmetrical sulfide 110 by tributyltin radical (111). Either carbon-sulfur bond may be cleaved, giving rise to two possible products after chain propagation by abstraction of a hydrogen atom from tributyltin hydride (Scheme 12).

Scheme 12

The reduction of phenyl alkyl sulfides (R = alkyl, R₁ = phenyl) proceeds smoothly to give hydrocarbons 112 and phenyl tributyltin sulfide 113 by selective cleavage of the alkyl-sulfur bond (eq 20). The ease of reduction parallels the stabilities of the carbon radical intermediates formed. For example, when R = t-butyl, the reaction is complete in 50 min. On the other hand, attempted reduction of ethyl phenyl sulfide, proceeding through the less stable ethyl radical, results in the recovery of 65% of the starting material after 65 h. The phenyl tributyltin sulfide byproducts did not compete with the starting sulfides for reaction with the tributyltin radical species.

Bu₃SnH + PhSR → RH + Bu₃SnPh (20)

<table>
<thead>
<tr>
<th>R</th>
<th>rxn time (h)</th>
<th>% unreacted PhSR</th>
<th>% yield Bu₃SnPh</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃Ph</td>
<td>0.25</td>
<td>0</td>
<td>89</td>
</tr>
<tr>
<td>t-Bu</td>
<td>0.8</td>
<td>0</td>
<td>62</td>
</tr>
<tr>
<td>s-Pr</td>
<td>110</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>Et</td>
<td>65</td>
<td>65</td>
<td>35</td>
</tr>
</tbody>
</table>

We expected that this mild, selective procedure would be ideal for the reduction of the alkyl carbon-sulfur bond of α-thiocyclobutanones. Cycloadducts 91 and 92 were
chosen as model substrates based on considerations of product volatility and ease of isolation. Sulfide 91 was reduced cleanly within 1 h by 1.2 equiv of tributyltin hydride and catalytic AIBN to provide the expected cyclobutanone 112 in 89% yield after purification by silica gel chromatography (eq 21). The reaction conditions were optimal when a solution of tributyltin hydride and AIBN in toluene was added slowly over ca. 30 min to a refluxing solution of the sulfide in toluene. Reduction of α-mesitylthiocyclobutanone 92 required the addition of an extra 0.5 equiv of tributyltin hydride (along with an additional 0.05 equiv of AIBN) in order to go to completion, but product 112 was isolated in nearly quantitative yield (eq 21).

\[
\begin{array}{cccc}
\text{R} & \text{equiv Bu}_3\text{SnH} & \text{equiv AIBN} & \text{yield (\%)} \\
\text{Ph (91)} & 1.2 & 0.10 & 89 \\
\text{Mesityl (92)} & 1.7 & 0.15 & 98 \\
\end{array}
\]

The tributyltin hydride-mediated reduction was very effective, but in order to ensure the broad applicability of this methodology, we developed another protocol as well. Zinc in acetic acid has been used for the generation of acetophenones from the corresponding (methylsulfinyl)acetophenones, but these rather acidic conditions may compromise other acid-labile functional groups. Holton reported a modification of this reagent system for the reduction of α-phenylthio and α-phenylsulfinyl ketones and esters. By using activated zinc in a mixture of tetrahydrofuran and saturated aqueous ammonium chloride at 25 °C, the carbon-sulfur bond was cleaved from substrates such as 115 (eq 22). These conditions were mild enough to avoid competing ester hydrolysis, migration of acid-sensitive olefins, or reduction of α,β-unsaturated ketones in other substrates.
The mechanism of this and other zinc-mediated reductions has been proposed to begin with electron donation to the carbonyl group. The intermediate radical (118) decomposes by cleavage of the C-Z bond to form stabilized radical 119 (Scheme 13).  

Scheme 13

Following Holton's conditions, treatment of 91 with 50 equiv of activated zinc dust in a 1:1 THF/aq saturated ammonium chloride mixture at 25 °C resulted in ca. 50% conversion to product (eq 23, Table 3). By heating the reaction mixture to reflux under these conditions (oil bath ~70 °C), clean reduction was observed within 18 h. Further experimentation was aimed at optimizing the amount of zinc dust required for the reaction to proceed to completion. At least 20 equiv of zinc dust was required to obtain reasonable conversion, resulting in an 84% yield of reduced product along with ca. 5% of unreacted sulfide (entry 5). A run using 25 equiv of zinc dust displayed near complete consumption of the α-thiocyclobutanone, but an artificially low yield was obtained due to loss of product.
from repeated concentrations (entry 6).* As in the tin hydride studies, the α-
mesitylthiocyclobutanone 92 was also reduced under these conditions (entry 7). The best
runs are listed in entries 6 and 7, but the reaction times are unoptimized.

![Chemical structure](image)


table 3. Reduction of α-Thiocyclobutanones with Zinc

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>equiv Zn</th>
<th>temp</th>
<th>time (h)</th>
<th>yield and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>50</td>
<td>25°C</td>
<td>48</td>
<td>ca. 1:1 product/sm</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>50</td>
<td>reflux</td>
<td>18</td>
<td>TLC scale: no sm, pure product by GC analysis</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>10</td>
<td>reflux</td>
<td>19</td>
<td>~6:1 product/sm</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>15</td>
<td>reflux</td>
<td>19</td>
<td>~16:1 product/sm</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>20</td>
<td>reflux</td>
<td>25</td>
<td>84%, ~5% sm</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>25</td>
<td>reflux</td>
<td>66</td>
<td>68%&lt;sup&gt;a&lt;/sup&gt;, no sm</td>
</tr>
<tr>
<td>7</td>
<td>Ar</td>
<td>25</td>
<td>reflux</td>
<td>42</td>
<td>93%&lt;sup&gt;b&lt;/sup&gt;, no sm</td>
</tr>
</tbody>
</table>

<sup>a</sup> Significant amount of product may have been lost during concentration.  <sup>b</sup> Yield estimated by NMR.

Tertiary sulfides (see below) were also reduced using the standard tributyltin
hydride conditions. Cyclobutanone 122 was not an ideal substrate due to the volatility of
the product 123; despite careful workup and isolation, only a moderate yield of 7-
methylcyclobutanone 123 was isolated. This case demonstrates that the reaction is effected
at lower temperatures. Interestingly, the reduction proceeded stereoselectively with
hydrogen atom addition occurring almost exclusively from the convex face of the molecule

* Several filtration steps were attempted in an unsatisfactory effort to remove the zinc chloride byproduct. After aqueous workup, column chromatography allowed the separation of the product from the residual solids.
(eq 24). The methyl signals of the two isomers are easily distinguished in the $^1$H NMR spectrum, with the *endo*-methyl appearing further upfield. Both C-7 epimers of 123 have previously been prepared and characterized. Brady and coworkers reported the resonance of the *endo*-methyl as a doublet at 0.99 ppm in the $^1$H NMR spectrum.\(^6\) Dreiding and coworkers completed both assignments, listing the *exo*-methyl as a doublet at 1.26 ppm and the *endo*-methyl as a doublet at 0.99 ppm.\(^7\) Our major reduction product exhibited a methyl doublet at 1.01 ppm, thus confirming its C-7 *endo*-methyl stereochemistry. A small amount (ca. 10:1) of the other isomer was present in the $^1$H NMR spectrum. This stereochemical outcome is consistent with the corresponding reduction of 7-halobicyclo[3.2.0]hept-2-en-6-ones.\(^8\)

\[
\begin{array}{c}
\text{122} \quad \text{SPh} \\
\text{123} \quad \text{CH}_3 \\
\end{array}
\]

1.2 equiv Bu$_3$SnH  
0.1 equiv AIBN  
benzene, reflux, 1 h  
58% 

\[
\begin{array}{c}
\text{123a} \quad \text{CH}_3 \\
\text{123b} \\
\end{array}
\]

\sim 10:1

Substrate 124 provided a much more accurate assessment of the efficiency of tertiary sulfide reduction. Subjecting 124 to the standard tributyltin hydride conditions gave a good yield of $\alpha$-benzylcyclobutanone 125. The reaction was not as selective as that of 122; the product was formed as a ca. 7:1 mixture of C-7 epimers. Based on the structural assignment of 123, we assume that the major product in this case also exhibits the *endo*-methyl configuration (eq 25). Our synthesis of $\alpha$-alkylcyclobutanones such as 123 and 125 represents an improvement over dichlorocyclobutanone methodology and provides access to a wide range of cyclobutanones which in the past have been difficult to prepare.
Another mild, zinc-mediated reduction of α-phenylthioketones involves the use of a zinc/trimethylsilyl chloride reagent combination as illustrated with the desulfurization of tertiary sulfide 126 (eq 26).\textsuperscript{9} This reaction proceeds more smoothly in moist ether (commercially available, undistilled), suggesting that zinc chloride or some other hydrolysis product may aid in the transformation. Using this procedure, the reduction of sulfide 91 was examined; however, these reactions were not as clean as the runs using the Holton protocol, so this chemistry was not pursued.

Finally, the reduction of α-thiocyclobutanones with nickel boride was investigated. Nickel and cobalt borides are prepared by reduction of the respective metal(II) salts with sodium borohydride, usually in alcohol or aqueous solutions.\textsuperscript{10,11} Due to a rapid loss of activity, the reagents are generated in the presence of the organosulfur compound to be reduced. Nickel boride was not selective enough in our system, resulting in a mixture of the desulfurization products and other byproducts, one of which appeared to be the alcohol derived from carbonyl reduction.

Having worked out two successful procedures for the desulfurization of α-thiocyclobutanones, we turned our attention to the analogous reaction with α-thiocyclobutenones. Cleavage of carbon-heteroatom bonds at C-4 of cyclobutenones is a
delicate task due to the formation of destabilized intermediates which possess
cyclobutadienoid antiaromatic character with a variety of reducing agents. The use of zinc
metal has been investigated because the intermediate zinc enolate retains substantial
carbanionic character at C-4. However, Hassner and Dillon were unable to reduce 4,4-
dichlorocyclobutenone derivatives using standard zinc metal and tributyltin hydride
conditions for the dechlorination of 4,4-dichlorocyclobutanones. A protocol was
subsequently developed in our laboratories to effect this transformation and provide access
to non-halogenated cyclobutenone derivatives in good yields and with minimal cine-
rearrangement, double bond isomerization, and partially reduced byproducts. The
reductions were carried out at 25 °C in alcoholic solvents in the presence of 5 equiv of
acetic acid and 5 equiv of a tertiary amine such as tetramethylethylenediamine (TMEDA)

We attempted the reduction of α-thiocyclobutenone 96 using both of our protocols
for the cyclobutanone desulfurization. In each case, many products were formed by TLC
analysis along with unreacted starting material. This behavior mimicked that of
dichlorocyclobutenones. We have not yet applied the Zn/AcOH/TMEDA conditions to our
α-thiocyclobutenones.

Regioselective Alkylation of α-Thiocyclobutanones

Because of the stabilizing effect of the sulfur substituent, β-ketosulfides can be
selectively deprotonated and alkylated at the sulfur-substituted carbon atom. Coates and
coworkers studied the alkylation of α-phenylthioketones and -aldehydes. They
determined that the phenylthio group increased the acidity of 2-phenylthiocyclohexanone by
at least 3 pKa units by measuring the position of equilibrium established between the
lithium enolates of cyclohexanone and 2-phenylthiocyclohexanone by trapping with
trimethylsilyl chloride. In the alkylation studies, 2-phenylthiocyclohexanone (128) was
treated with sodium or potassium hydride in tetrahydrofuran followed by the addition of
alkyl or allyl halides to afford exclusively alkylation products such as 129 (eq 27).
\[
\begin{align*}
\text{Alkylation Conditions} & \quad \text{Yield (\%)} \\
\text{NaH, THF, 80 °C, 2h;} & \quad 93 \\
2 \text{ equiv CH}_3I, 0 ^\circ \text{C, 2 h} & \\
\text{KH, THF, 25 °C, 5 min;} & \quad 91 \\
1.6 \text{ equiv n-Bul, 25 °C, 24 h} &
\end{align*}
\]

An \(\alpha\)-thiocyclobutanone identical to one of our substrates was included in this study. Treatment of 86 (stereochemistry not specified) with lithium diisopropylamide in tetrahydrofuran followed by addition of methyl iodide gave a 76\% yield of cyclobutanone 122 as a single regioisomer and a 2:1 mixture of epimers (eq 28). Coates and coworkers further demonstrated the utility of these alkylated \(\alpha\)-phenylthioketones with a reduction-alkylation sequence. For example, treatment of 122 with lithium in liquid ammonia generated the corresponding enolate which was alkylated by treatment with methyl iodide (Scheme 14). This protocol would add to the scope of our chemistry by allowing thio-substituted ketenes to serve as synthetic equivalents for dialkylketenes.

Scheme 14

Cohen and coworkers have also taken advantage of the increased acidity of the thiophenyl-substituted carbon atom for the monoalkylation of the parent 2-phenylthiocyclobutanone.\(^\text{15}\) Treatment of 104 with potassium \(t\)-butoxide in \(N,N\)-dimethylformamide (DMF) followed by addition of methyl or \(n\)-butyl iodide gave
monoalkylated products 106. Desulfurization via reductive lithiation with lithium 1-dimethylaminonaphthalenide (LDMAN) provided the 2-alkylcyclobutanones 107 (Scheme 15). In both of these studies, no competing α'-alkylation was reported.

Scheme 15

We chose substrates 82 and 86 for our alkylation studies. Due to the steric demands of the α-disubstituted enolate of 82, we reasoned that appropriate conditions for this substrate would be generally applicable. The enolate of 86 is less hindered and would allow a stereochemical analysis of the alkylation.

Lithium and potassium enolates of α-thiocyclobutanone 82 were regioselectively alkylated with the activated alkyl halide methyl iodide (eq 28, Table 4). Initially, we chose weaker alkoxide bases due to the success of Cohen's studies. Use of potassium t-butoxide in DMF led to a ca. 1.6:1 ratio of C-alkylation product to a byproduct which we characterized as O-alkylated compound 132 (entry 1, see Figure 6). This assignment was based on the presence of two singlets at 3.93 and 2.38 ppm in the 1H NMR spectrum of the product mixture. By employing a less electropositive metal and a less polar solvent, enolate reactivity was tailored to afford an 18:1 ratio of the C- to O-alkylation product (entry 3). However, these reaction conditions resulted in a greater amount of recovered starting material. This problem was ultimately circumvented by using a larger excess of methyl iodide to drive the reaction to completion. The optimized reaction conditions involved the addition of a solution of 80 in THF to a solution of lithium t-butoxide in THF at 0 °C. After 30 min, the alkylating agent was added, and the reaction mixture was stirred at 25 °C until the starting material was consumed, as determined by TLC. The best runs are shown in entries 5 and 6. Another unidentified byproduct, corresponding to a singlet at
3.20 ppm, was formed in most of the runs in small amounts and was not separable from the alkylation product.

Lithium hexamethyldisilazide (LiHMDS) was also tested as a base for the alkylation of $\alpha$-thiocyclobutanone 82 (entries 7 and 8). While product distributions similar to that obtained in the lithium $t$-butoxide experiments were observed by TLC and $^1$H NMR analysis, these runs did not proceed to completion. Perhaps a slightly larger excess of the base would be beneficial in these cases.

$$
\begin{align*}
\text{82} & \quad \text{O} \\
\text{SPh} & \quad \text{CH}_3 \\
\text{131} & \quad \text{O} \\
\text{SPh} & \\
\end{align*}
$$
Table 4. Alkylation of α-Thiocyclobutanone 82 with Methyl Iodide

<table>
<thead>
<tr>
<th>entry</th>
<th>base, equiv</th>
<th>solvent</th>
<th>equiv MeI</th>
<th>rxn temp (°C)</th>
<th>rxn time (h)</th>
<th>C to O ratio</th>
<th>yield and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOt-Bu, 1.05</td>
<td>DMF</td>
<td>1.4</td>
<td>-40 to 25</td>
<td>0.5</td>
<td>1.6:1</td>
<td>~22% remaining sm</td>
</tr>
<tr>
<td>2</td>
<td>KOt-Bu, 1.2</td>
<td>THF</td>
<td>1.4</td>
<td>-40 to 25</td>
<td>1.5</td>
<td>2.8:1</td>
<td>~17% remaining sm</td>
</tr>
<tr>
<td>3</td>
<td>LiOrBu, 1.2</td>
<td>THF</td>
<td>1.4</td>
<td>-40 to 25</td>
<td>24</td>
<td>18:1</td>
<td>~35% remaining sm</td>
</tr>
<tr>
<td>4</td>
<td>LiOrBu, 1.2</td>
<td>THF</td>
<td>2.0</td>
<td>0 to 25</td>
<td>24</td>
<td>16:1</td>
<td>~24% remaining sm</td>
</tr>
<tr>
<td>5a</td>
<td>LiOrBu, 1.3</td>
<td>THF</td>
<td>4.0</td>
<td>0 to 25</td>
<td>44</td>
<td>24:1</td>
<td>69% no sm</td>
</tr>
<tr>
<td>6</td>
<td>LiOrBu, 1.2</td>
<td>THF</td>
<td>4.0</td>
<td>0 to 25</td>
<td>26</td>
<td>26:1</td>
<td>77% ~92% pure</td>
</tr>
<tr>
<td>7</td>
<td>LiHMDS, 1.05</td>
<td>THF</td>
<td>4.0</td>
<td>0 to 25</td>
<td>42</td>
<td></td>
<td>remaining sm same product distribution</td>
</tr>
<tr>
<td>8</td>
<td>LiHMDS, 1.10</td>
<td>THF</td>
<td>4.0</td>
<td>0 to 25</td>
<td>49</td>
<td></td>
<td>no improvement over entry 7</td>
</tr>
</tbody>
</table>

* Small scale run using only 34 mg of 82.

A similar trend was observed with cyclopentadiene adduct 86 (eq 29, Table 5). Poor selectivity for C-alkylation was observed using potassium enolates in THF and DMF (entries 1 and 2). A comparison of these two runs indicated that by switching to a less polar solvent, the reaction was slower; but surprisingly, more of the major byproduct was formed in the process. This compound was originally believed to be the O-alkylation product 133 (Figure 7) based on the presence of a singlet at 3.72 ppm in the ^1H NMR spectrum. After separation by column chromatography, further analysis of this byproduct by IR spectroscopy produced a surprising finding. Strong and medium intensity bands were observed in the carbonyl region at 1720 and 1770 cm⁻¹, respectively. The true identity of this byproduct is therefore subject to question. Other small singlets are present.
in this downfield region of the $^1$H NMR spectrum as well and may be due to $O$-alkylation. In contrast to the spiro adduct, all of these reactions showed complete consumption of the cyclobutanone.

**Figure 7**

![Chemical Structures](image)

The optimized conditions for substrate 82 turned out to be ideal for 86 as well. The methylated $\alpha$-thiocyclobutanone 122 was isolated in 87% yield under these conditions as a 12:1 mixture of endo-methyl to exo-methyl isomers (entry 7). Only trace amounts of byproducts were present in the crude reaction mixture. Efforts to increase the rate of reaction of the lithium enolate by using DMF as a cosolvent or an additive resulted in greater byproduct formation (entries 4 and 5).\(^{16}\)

\[
\begin{align*}
86 & \xrightarrow{\text{C-7 epimer}} \quad 122b \\
122a & \quad R = \text{CH}_3 \\
124a & \quad R = \text{CH}_2\text{Ph}
\end{align*}
\]

The stereochemical result was consistent with the reduction studies, in which the hydrogen atom was introduced from the convex face of the the molecule to provide the endo-alkylcyclobutanones (see eq 24 and 25). This assignment was confirmed indirectly based on previously reported data for this compound. Ghosez and co-workers prepared 122b by the [$2 + 2$] cycloaddition of methyl(phenylthio)ketene, prepared by the dehydrohalogenation of (phenylthio)acetyl chloride, with cyclopentadiene (eq 30).\(^{17}\) No spectral data were reported, but Ghosez confirmed the endo-methyl configuration of the adduct by X-ray crystallographic analysis and stated that the assignment was consistent
with the ketene "endo effect" (see Chapter 1). Agawa had previously prepared the same compound by the same method but assigned the structure as the exo-methyl adduct 122a.\textsuperscript{18} They reported the $^1$H NMR chemical shift of the methyl group at 1.24 ppm. Ghosez pointed out that Agawa had made the wrong assignment at C-7, and that Agawa's group had actually synthesized 122b as well. It is therefore apparent that the endo-methyl peak resides at 1.24 ppm in the $^1$H NMR spectrum. Our major product (122a) showed a singlet at 1.48 ppm, while the minor isomer appeared at 1.25 ppm in the $^1$H NMR spectrum (matching Agawa's report). Thus, the major product of our alkylation reaction contained the exo-methyl configuration at C-7.

\[
\text{PhS} \quad \begin{array}{c}
\text{O} \\
\text{Cl}
\end{array} \quad \xrightarrow{5 \text{ equiv }} \quad \begin{array}{c}
\text{5 equiv} \\
\text{1 equiv NEt}_3 \\
\text{10 h, 25 °C} \\
86\%
\end{array} \quad \xrightarrow{122b} \quad \begin{array}{c}
\text{O} \\
\text{SPh} \\
\text{CH}_3
\end{array}
\]

(Benzy1 bromide exhibited exclusive selectivity for exo-face addition to the enolate to provide cyclobutanone 124a (eq 29), as no trace of the other isomer was detected by $^1$H NMR spectral analysis (entry 8, Table 5). Analogous to the methyl iodide runs, an inseparable byproduct was present in the $^1$H NMR spectrum, which corresponded to a singlet at 4.12 ppm.

In contrast to the results with substrate 82, lithium hexamethyldisilazide functioned as a suitable base for the alkylation of $\alpha$-thiocyclobutanone 86. A small scale trial run went to completion and gave the desired product by a very clean reaction as indicated by TLC and $^1$H NMR spectral analysis (entry 9, Table 5).
Table 5. Alkylation of α-Thiocyclobutanone 86 with Activated Alkyl Halides

<table>
<thead>
<tr>
<th>entry</th>
<th>base, equiv</th>
<th>solvent</th>
<th>alkylation agent, equiv</th>
<th>rxn temp (°C)</th>
<th>rxn time (h)</th>
<th>C to O ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOt-Bu, 1.2</td>
<td>DMF</td>
<td>MeI, 1.4</td>
<td>-40 to 25</td>
<td>0.5</td>
<td>~2:1</td>
<td>no sm</td>
</tr>
<tr>
<td>2</td>
<td>KOt-Bu, 1.2</td>
<td>THF</td>
<td>MeI, 4.0</td>
<td>0 to 25</td>
<td>45</td>
<td>~1:3</td>
<td>no sm</td>
</tr>
<tr>
<td>3</td>
<td>LiOr-Bu, 1.2</td>
<td>THF</td>
<td>MeI, 4.0</td>
<td>0 to 25</td>
<td>48</td>
<td>---</td>
<td>65%, trace byproducts</td>
</tr>
<tr>
<td>4</td>
<td>LiOr-Bu, 1.2</td>
<td>DMF</td>
<td>MeI, 4.0</td>
<td>-40 to 25</td>
<td>3</td>
<td>~10:1</td>
<td>no sm</td>
</tr>
<tr>
<td>5</td>
<td>LiOr-Bu, 1.2</td>
<td>1:1 THF/DMF</td>
<td>MeI, 4.0</td>
<td>-40 to 25</td>
<td>2</td>
<td>same as entry 4</td>
<td>same as entry 4</td>
</tr>
<tr>
<td>6</td>
<td>LiOr-Bu, 1.2</td>
<td>THF/ 3 equiv DMF</td>
<td>MeI, 3.0</td>
<td>-50 to 25</td>
<td>10</td>
<td>---</td>
<td>less byproduct than entry 5, more than entry 3</td>
</tr>
<tr>
<td>7</td>
<td>LiOr-Bu, 1.2</td>
<td>THF</td>
<td>MeI, 4.0</td>
<td>0 to 25</td>
<td>24</td>
<td>---</td>
<td>87%, 12:1 mixture of epimers, trace byproducts</td>
</tr>
<tr>
<td>8</td>
<td>LiOr-Bu, 1.2</td>
<td>THF</td>
<td>BnBr, 4.0</td>
<td>0 to 25</td>
<td>17</td>
<td>~11:1</td>
<td>86%&lt;sup&gt;b&lt;/sup&gt;, one isomer</td>
</tr>
<tr>
<td>9</td>
<td>LiHMDS, 1.05</td>
<td>THF</td>
<td>MeI, 4.0</td>
<td>0 to 25</td>
<td>19</td>
<td>---</td>
<td>small scale, clean</td>
</tr>
</tbody>
</table>

<sup>a</sup> The identity of the byproduct is in doubt, so this number represents the ratio of C-alkylation product to the major byproduct.  
<sup>b</sup> Combined yield of the C-alkylation and byproduct mixture.

Attempts to extend the scope of the alkylation to include an unactivated electrophile met with minimal success (eq 31 and 32, Table 6). In the case of methylenecyclohexane
adduct 82, alkylation with 1-iodo-3-phenylpropane (134)* gave a complex mixture of products, including O-alkylation and a significant amount of material represented by baseline TLC spots (entries 1-3). Cyclopentadiene adduct 86 gave similar results (entries 4-11). Isolation of the polar byproducts formed in entry 4 showed no incorporation of 1-iodo-3-phenylpropane. A possible explanation for these results is that some sort of ring opening reaction is taking place to give a carboxylic acid product, but this conclusion remains speculative. The use of lithium hexamethyldisilazide as the base gave nearly identical results (entry 11). In both cases, downfield (~4.0 ppm) methylene signals in the 1H NMR spectrum suggested O-alkylation product and some other byproduct, but no firm determination of the extent of C-alkylation product was feasible due to the complex 1H NMR spectral data.

It appeared that the reaction conditions that had been so effective for activated electrophiles were incompatible with other alkyl iodides, as side reactions were occurring instead of the desired transformation. Even though more polar solvents led to less selective reactions with methyl iodide (Tables 4 and 5), we decided to conduct a thorough study of variations in the counterion, polarity, and temperature on the reactivity of the enolate of 86. The use of lithium t-butoxide in DMF gave the best result, a 48% yield of a mixture of two products in a ca. 2.7:1 ratio (entry 7). The major product appeared to be the desired cyclobutanone 136, and the minor product was indicative of O-alkylation by 1H NMR spectral analysis.† Other reaction conditions involving various combinations of lithium and

* Prepared from the commercially available bromide (Aldrich) by a standard Finkelstein procedure: 4 equiv of sodium iodide in acetone at reflux for 40 h, 97%.
† The products were not separated.
potassium enolates in THF and DMF, and different reaction temperatures, led to complex product mixtures.
<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>base, equiv</th>
<th>solvent</th>
<th>equiv</th>
<th>temp (°C)</th>
<th>rxn time (h)</th>
<th>yield and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>KOr-Bu, 1.5</td>
<td>THF</td>
<td>3.0</td>
<td>0 to 25</td>
<td>42</td>
<td>O-alk&lt;sup&gt;a&lt;/sup&gt; and other products, remaining sm</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>KOr-Bu, 1.5</td>
<td>THF</td>
<td>5.0</td>
<td>0 to 25</td>
<td>42</td>
<td>same as entry 1</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>LiOr-Bu, 1.5</td>
<td>THF</td>
<td>5.0</td>
<td>0 to 25</td>
<td>72</td>
<td>minimal O-alk., complex spectrum</td>
</tr>
<tr>
<td>4</td>
<td>86</td>
<td>LiOr-Bu, 1.5</td>
<td>THF</td>
<td>5.0</td>
<td>0 to 25</td>
<td>38</td>
<td>mostly baseline products, no sm</td>
</tr>
<tr>
<td>5</td>
<td>86</td>
<td>KiOr-Bu, 1.2</td>
<td>THF</td>
<td>5.0</td>
<td>0 to 25</td>
<td>43</td>
<td>similar to entry 4</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>KOr-Bu, 1.2</td>
<td>THF</td>
<td>5.0</td>
<td>50</td>
<td>23</td>
<td>O-alk.-type product, no baseline products</td>
</tr>
<tr>
<td>7</td>
<td>86</td>
<td>LiOr-Bu, 1.2</td>
<td>DMF</td>
<td>5.0</td>
<td>-40 to 25</td>
<td>3</td>
<td>48%, 2.7:1 mixture of C-alk. to O-alk.-type product&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>86</td>
<td>LiOr-Bu, 1.2</td>
<td>DMF</td>
<td>5.0</td>
<td>0</td>
<td>---</td>
<td>same as entry 7 by TLC</td>
</tr>
<tr>
<td>9</td>
<td>86</td>
<td>LiOr-Bu, 1.2</td>
<td>THF/3 equiv DMF</td>
<td>5.0</td>
<td>-45 to 25</td>
<td>43</td>
<td>remaining sm</td>
</tr>
<tr>
<td>10</td>
<td>86</td>
<td>LiOr-Bu, 1.2</td>
<td>THF</td>
<td>5.0</td>
<td>50</td>
<td>48</td>
<td>remaining sm</td>
</tr>
<tr>
<td>11</td>
<td>86</td>
<td>LiHMDS, 1.05</td>
<td>THF</td>
<td>4.0</td>
<td>0 to 25</td>
<td>40</td>
<td>similar to entry 4</td>
</tr>
</tbody>
</table>

<sup>a</sup> O-alk = O-alkylation

<sup>b</sup> Product ratio C-alk. to O-alk.
In summary, alkylation of α-thiocyclobutanones with activated electrophiles proceeded smoothly and regioselectively, with minor amounts of O-alkylation byproduct formation. There was no evidence in any of these reactions of alkylation at the α'-carbon atom. However, the scope of this transformation was limited to activated alkyl halides, as even the primary aliphatic iodide 1-iodo-3-phenylpropane failed to react in good yield. It appears that these α-phenylthio enolates are not very reactive towards alkylating agents, and the generation of a more "naked" enolate by varying the solvent, reaction temperature, or counterion only leads to O-alkylation and other side reactions. Even so, reduction of the available tertiary sulfides (see eq 24 and 25) provided 7-alkylcyclobutanones 123 and 125, and thus successfully illustrated the potential of this methodology as a synthetic equivalent for monoalkylketenes such as methylketene and (phenylmethyl)ketene. Presumably, α-allylcyclobutanones could also be prepared in this manner.

Oxidation of α-Thiocyclobutanones

Another possible useful synthetic transformation for our α-thiocyclobutanone system was sulfide oxidation to the sulfoxide, followed by Pummerer rearrangement to provide the α-acetoxy sulfide. As in the case of the reduction of sulfides, there are a plethora of documented reagents available for this reaction.19-21 The primary concern was over-oxidation to the sulfone, but because of their great utility in synthetic organic
chemistry, a variety of protocols exist for the selective oxidation of sulfides to sulfoxides.\textsuperscript{21}

We began our study with hydrogen peroxide, a very mild reagent promising experimental simplicity and facile product purification. Hydrogen peroxide has been reported as a selective oxidant of sulfides to sulfoxides in the presence of suitable solvents such as methanol.\textsuperscript{22} The proper choice of solvent or some other catalyst is crucial in order to speed up the otherwise extremely sluggish reaction.\textsuperscript{23} These conditions were applied successfully for the preparation of a series of dialkyl and alkyaryl sulfoxides with no trace of the corresponding sulfones (eq 33).\textsuperscript{22}

\[
\begin{array}{ccccc}
R^1\cdot S\cdot R^2 & \xrightarrow{H_2O_2, \text{MeOH}} & \overset{25 ^\circ C}{\xrightarrow{}} & \overset{O}{\xrightarrow{}} & S \cdot R^2 \\
R^1 & \xrightarrow{} & R^2 & \xrightarrow{} & \text{equiv } H_2O_2 & \text{rxn time} & \text{yield (\%)} \\
n\text{-Bu} & \xrightarrow{} & \text{Me} & \xrightarrow{} & 2 & 1 \text{ h} & 97 \\
\text{Ph} & \xrightarrow{} & \text{Me} & \xrightarrow{} & 4 & 18 \text{ h} & 91 \\
\text{Ph} & \xrightarrow{} & n\text{-Bu} & \xrightarrow{} & 4 & 75 \text{ h} & 92 \\
\end{array}
\]

When $\alpha$-thiocyclobutanone 82 was subjected to these conditions, a single product was formed. The oxidation required at least 3.5 equiv of hydrogen peroxide to consume all of the sulfide, but there was no evidence by TLC analysis of more than one compound being formed. The product was fairly clean by $^1$H NMR analysis and was carried on without purification. Curiously, this compound survived the Pummerer conditions unchanged (see below). After further consideration of some of its properties, such as a single proton singlet far downfield at 5.5 ppm in the $^1$H NMR spectrum, a much less polar $R_f$ value on TLC than would be expected for a sulfoxide, and the absence of diastereomers, we determined that the product of this hydrogen peroxide oxidation was actually the $\gamma$-
lactone, a result of Baeyer-Villiger oxidation.\textsuperscript{24} This reaction is surprisingly facile and proceeds without heating or strongly acidic catalysis, and without affecting the sulfide. The regioselectivity of the reaction is exclusive for formation of the lactone by migration of the phenylthio-substituted carbon atom (eq 34). This preference contrasts with Baeyer-Villiger oxidations of dichlorocyclobutanones (see Chapter 1) and provides an unexpected but useful entry into the chemistry of \( \alpha \)-thiocyclobutanones.

Two other reagents were found subsequently to effect the desired sulfide oxidation. Since its generality was first demonstrated by Leonard and Johnson in 1962,\textsuperscript{25} sodium periodate has been used for the selective oxidation of sulfides to sulfoxides. The reaction is typically carried out in aqueous solution; however, methanol/water solvent mixtures are efficacious when sulfide water solubility is slight. The reaction has been performed on several alkylaryl sulfides with excellent results (eq 35, 36,\textsuperscript{25} and 37\textsuperscript{26}).

\[ \text{PhSMe} \xrightarrow{\text{NaIO}_4, \text{H}_2\text{O}} \text{PhSOCH}_3 \quad 0 \degree \text{C} \quad 99\% \quad \text{(35)} \]

\[ \text{PhSCOH} \xrightarrow{\text{NaIO}_4, \text{H}_2\text{O}} \text{PhSCOCH}_2\text{OH} \quad 0 \degree \text{C} \quad 99\% \quad \text{(36)} \]

\[ \text{PhSCOH} \xrightarrow{\text{NaIO}_4, \text{EtOH/H}_2\text{O}} \text{PhSCOCH}_2\text{OH} \quad 0 \degree \text{C} \quad 99\% \quad \text{(37)} \]
Similarly, m-chloroperbenzoic acid (m-CPBA) has been utilized for the sulfide to sulfoxide transformation. By using a molar equivalent of the reagent at room temperature or below, sulfone formation can be suppressed. Ohshiro and coworkers have demonstrated that Baeyer-Villiger oxidation of a cyclobutanone derivative (138) does not compete with sulfide oxidation (eq 38).\textsuperscript{27} Agawa and coworkers also reported an example of this selectivity by synthesizing sulfoxide 140 from $\alpha$-thiocyclobutanone 122 (eq 39), an excellent precedent for test substrate 82.\textsuperscript{18}

\[
\begin{array}{c}
\text{138} \quad \text{139} \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{SPh} \quad \text{SPh} \\
\text{m-CPBA, CHCl}_3, \quad \rightarrow \quad -15^\circ C, 2 \text{ h} \\
\text{98%} \\
\end{array}
\]

\[
\begin{array}{c}
\text{122} \quad \text{140} \\
\text{CH}_3 \quad \text{H}_3\text{C} \\
\text{SPh} \quad \text{SO} \\
\text{m-CPBA, CHCl}_3, \quad \rightarrow \quad -15^\circ C, 2 \text{ h} \\
\text{94%} \\
\end{array}
\]

A summary of sulfoxide formation from $\alpha$-thiocyclobutanone 82 (eq 40) is shown in Table 7. The best conditions with sodium periodate are listed in entries 2, 5, and 7 (entry 7 is a larger scale run). A delicate balance existed between driving the reaction to completion and over-oxidation to the sulfone. For example, using 2.5 equiv of NaIO\textsubscript{4} consumed nearly all of the sulfide, but was accompanied by increased sulfone formation (entry 3). The problems with incomplete conversion may stem from limited solubility of the sulfides in the methanol/water solvent mixture. This possibility was supported by a run with the cyclopentadiene adduct (not included in Table 7), in which the sulfide crashed out of the solvent mixture, necessitating the addition of tetrahydrofuran. Even so, a significant amount of starting material remained unchanged.
*m*-CPBA oxidation yielded even better results. The reaction was complete within 1 h, yields were higher, and solubility was not an issue because the reaction was conducted in methylene chloride. Entry 9 was improved over entry 8 due to the slower addition (ca. 10 min vs 1 min) of a solution of *m*-CPBA in methylene chloride to a solution of the cyclobutanone at 0 °C. In all cases, two diastereomeric products were formed in a ratio of ca. 1.5:1.

![Chemical structure](image)

Table 7. Sulfide Oxidation of α- Thiocyclobutanone 82

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidizing agent, equiv</th>
<th>rxn temp (°C)</th>
<th>rxn time (h)</th>
<th>yield and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaIO₄, 1.1</td>
<td>25</td>
<td>21</td>
<td>~5:1 product/sm, trace sulfone</td>
</tr>
<tr>
<td>2</td>
<td>NaIO₄, 1.5</td>
<td>0 to 25</td>
<td>22</td>
<td>~6:1 product/sm, trace sulfone</td>
</tr>
<tr>
<td>3</td>
<td>NaIO₄, 2.5</td>
<td>0 to 25</td>
<td>22</td>
<td>trace sm, ~4:1 product/sulfone</td>
</tr>
<tr>
<td>4</td>
<td>NaIO₄, 1.1</td>
<td>40</td>
<td>8</td>
<td>similar to entry 2</td>
</tr>
<tr>
<td>5</td>
<td>NaIO₄, 1.5</td>
<td>25</td>
<td>22</td>
<td>75%, trace sm, sulfone</td>
</tr>
<tr>
<td>6</td>
<td>NaIO₄, 1.2</td>
<td>0 to 25</td>
<td>22</td>
<td>68%, 4.5:1 product/sm, trace sulfone</td>
</tr>
<tr>
<td>7</td>
<td>NaIO₄, 1.5</td>
<td>0 to 25</td>
<td>26</td>
<td>76%, 5.6:1 product/ sm + sulfone</td>
</tr>
<tr>
<td>8</td>
<td><em>m</em>-CPBA, 1.0</td>
<td>0</td>
<td>1</td>
<td>5.2:1 product/sm, trace sulfone</td>
</tr>
<tr>
<td>9</td>
<td><em>m</em>-CPBA, 1.0</td>
<td>0</td>
<td>1</td>
<td>88%, trace sm, no sulfone</td>
</tr>
</tbody>
</table>
Pummerer Rearrangement of α-Sulfinylcyclobutanones

The Pummerer rearrangement of sulfoxides has garnered considerable attention as a method for the preparation of α-functionalized sulfides.\textsuperscript{28} In general, the Pummerer reaction requires an electrophile to activate the sulfoxide and transform the oxygen atom into a good leaving group, a general base to remove an α-proton, and a nucleophile to be included into the final product. Acidic or basic catalysis is often used. A mechanism for the Pummerer rearrangement in the presence of acetic anhydride is depicted in Scheme 16.

The first step involves acylation of the sulfoxide oxygen to generate an acyloxy sulfoxonium salt (143). Removal of a proton from the α-carbon of 143 produces an acyl sulfoxide (144), which then eliminates acetate ion to give an α-thiocarbocation (145). In the final step, addition of acetate ion to the sulfur-stabilized carbocation completes the formation of α-functionalized sulfide 146. These $O,S$-acets are useful synthetic intermediates, primarily due to their facile hydrolysis to form aldehydes. With suitable substrates and reaction conditions, vinyl sulfides are formed by β-elimination of the cationic intermediates.

Scheme 16

\[ R = \text{S-R}^{-} + \text{R'} + \text{OAc} \]

\[ \text{AcO} \]

\[ \text{AcOH} \]

\[ \text{AcO} \]

\[ \alpha\text{-Acetoxylation is probably the most commonly encountered form of the Pummerer rearrangement, but many other nucleophiles can be introduced } \alpha \text{ to the sulfide.} \]

The thionium ion intermediates are excellent electrophiles and have been used in the realm
of natural product synthesis for inter- and intramolecular carbon-carbon bond forming reactions with double bonds, as well as aromatic and heteroaromatic systems (Scheme 17). Intramolecular heteroatom interception of the thionium ion intermediates has also been exploited for the synthesis of a variety of heterocyclic ring systems (eq 41). Recently, Padwa and co-workers have reported an elegant tandem Pummerer-Diels-Alder reaction sequence of o-benzoyl-substituted sulfoxides (150) to ultimately produce arylnaphthalene lignans (153) (Scheme 18).

Scheme 17

\[ \text{PhSO}_{\text{Ph}} \xrightarrow{TFAA, \Delta} \text{PhS} \]

65% overall from sulfide

\[ \text{PhSO} \xrightarrow{\text{Ac}_2\text{O}, \text{cat. } \rho\text{-TsOH}} \]

toluene, reflux

51%

(41)
Experimentally, the Pummerer rearrangement is typically carried out by treating a sulfoxide with an excess of acetic anhydride, often with the addition of acetic acid or sodium acetate, or a catalytic acid source such as p-toluenesulfonic acid. Heat is usually required, as a result, refluxing benzene or toluene are frequently employed for the reaction. Sulfoxide 141 underwent smooth Pummerer rearrangement when subjected to standard, acid-catalyzed conditions\textsuperscript{26} to provide α-acetoxy sulfide 154 in good yield (eq 42). This chemistry provides access to functionalized cyclobutanones which are not available from dichloroketene methodology. Desulfurization of the Pummerer product 154 is expected to provide α-acetoxy cyclobutanone 155. By conducting the Pummerer reaction of 141 in an alcoholic solvent, α-alkoxy cyclobutanones should be readily available. These three-step processes from α-diazo thiol ester 79 represent synthetic equivalents for acetoxy- and alkoxyketenes. The Pummerer sequence also holds promise for the synthesis of bicyclic or tricyclic cyclobutanones by the inclusion of nucleophiles tethered to the C-2- or C-3-position of the α-thiocyclobutanones.
Ring Expansion of α-Thiocyclobutanones

The synthetic importance of the one-carbon ring expansion of cyclobutanones to cyclopentanones was stressed in Chapter 1. α,α-Dichlorocyclobutanones are typically used due to their availability and the inherent selectivity which arises from migration of the α'-carbon atom. We were curious to elucidate the behavior of α-thiocyclobutanones under some typical ring expansion conditions.

Diazocompounds have been used extensively for this purpose, reacting with ketones to produce the homologous carbonyl compounds, often accompanied by isomeric epoxides. A general mechanism for diazomethane addition to ketones is shown in Scheme 19. Lewis acids are often used to catalyze the reaction, particularly with less nucleophilic, substituted diazo compounds and less reactive ketones. Methanoi, water, and boron trifluoride etherate have been commonly employed in this capacity, and are also believed to suppress epoxide formation by tempering the nucleophilicity of the carbonyl oxygen atom (156 vs. 158). Another limitation of this methodology is that the initially formed products are capable of reacting further with the diazo compound, resulting in multiple homologations.$^{31,32}$
Migratory aptitudes in the diazoalkane ring expansion reaction are governed by electronic considerations similar to those observed in other 1,2-nucleophilic rearrangements, such that electron-withdrawing groups incorporated in \( R \) and \( R' \), located at or near C-2 of the ketone, retard migration, while electron-donating groups have the opposite effect. The migratory aptitude of the alkyl series in the diazoalkane ring expansion reaction of acyclic carbonyl compounds decreases in the order \( CH_3 \sim CH_3CH_2CH_2 > (CH_3)_2CH \sim (CH_3)_3 \).\(^{31}\) While trends are not always clearly defined due to complex mixtures of variables in many substrates, this order in the alkyl series contrasts with that frequently observed in the pinacol rearrangement and the Baeyer-Villiger reaction.

We began these studies by testing diazomethane\(^{33}\) as the ring expansion reagent. The reaction was conducted initially in the presence of methanol.\(^{34}\) We were surprised to find that under a variety of conditions, \( \alpha \)-thiocyclobutanones \( 82 \) and \( 91 \) were unaffected by diazomethane; starting materials were recovered quantitatively. Substrate \( 91 \) was tested in the event that steric congestion of the spiro cyclohexane substituents at C-3 was hindering addition to the carbonyl group of \( 82 \). Boron trifluoride etherate\(^{31,35}\) was equally ineffective in bringing about the desired transformation (eq 43, 44).
In the absence of Lewis acids, diazomethane has been reported to be unreactive with a variety of ketones, but boron trifluoride induces the reaction with many of these substrates.\(^3\)\(^6\) Perhaps in our system the role of the Lewis acid in promoting the ring expansion is hindered by competing complexation with the sulfur atom, and therefore the rate of addition to the carbonyl is not rapid enough to compete with boron trifluoride-promoted decomposition of diazomethane.\(^3\)\(^1\)

Ethyl diazoacetate has been shown to function as another effective ketone homologating agent. This diazo compound is not nucleophilic enough to add to carbonyl groups by itself, but addition can be promoted by Lewis acids such as boron trifluoride etherate,\(^3\)\(^6,\)\(^3\)\(^7\) antimony pentachloride,\(^3\)\(^8,\)\(^3\)\(^9\) and triethylxonium tetrafluoroborate.\(^3\)\(^9\) Tai and Warnhoff studied the homologation of cyclopentanone with ethyl diazoacetate in the presence of boron trifluoride etherate (eq 45).\(^3\)\(^6\)
The regiochemical issue raised by ethyl diazoacetate ring expansions has been addressed. Liu and Ogino reported the selective ring expansion of a series of bicyclo[4.2.0]octan-7-ones in fair to good yields, in which product hydrindanone carboxylates were formed exclusively or predominantly from migration of the less-substituted carbon atom (eq 46). This trend is consistent with the observations of Mock and Hartman regarding the triethylxonium ion catalyzed homologation of unsymmetrical ketones, and has also been observed with the Lewis acid-catalyzed trimethylsilyldiazomethane ketone homologation reaction.

When a solution of α-thiocyclobutanone 82 and boron trifluoride etherate in diethyl ether at 0 °C was treated with a solution of ethyl diazoacetate in diethyl ether over 10 min, smooth ring expansion occurred predominantly via migration of the less-substituted carbon atom to give spirocyclopentanone 169 in 66% yield, as a ca. 1:1 mixture of diastereomers (eq 47). The reaction was rapid but did not go to completion, even when up to 2.5 equiv of ethyl diazoacetate and boron trifluoride etherate were employed. The structure of the product was assigned based on its 1H NMR spectrum, particularly the singlets.

* Attempts to isolate product which may exist in the enol form could increase the yield.
corresponding to methine protons at C-2 of the two diastereomers. In addition, homonuclear decoupling experiments showed that an apparent triplet located at 3.3 ppm, assigned to the C-5 methine proton in one of the diastereomers, did indeed couple to the protons (2.0 - 2.5 ppm) assigned to C-4. The regioisomeric ring expansion product 170 would exhibit only doublets in the $^1$H NMR spectrum, and the decoupling experiment would have shown no correlation because the C-4 methylene protons are isolated. A minor product, assumed to be 170, was isolated along with 169, but its identity and relative abundance could not be confirmed by the $^1$H NMR spectrum. Decarboxylation of these ring expansion products would simplify the task of analyzing the $^1$H NMR spectra, and therefore facilitate a determination of the exact product ratio. The product phenylthiocyclopentanones, identical to diazomethane ring expansion products 162 and 163, should be readily available either by subjecting the $\beta$-keto esters to mild acidic conditions$^{41}$ or high temperatures.$^{39}$

![Reaction Diagram](image)

(47)

The selectivity of this ring expansion is opposite to that of the Baeyer-Villiger oxidation of $\alpha$-thiocyclobutanone 82 (see eq 34), and follows literature trends previously described. Mock and Hartman have undertaken a detailed mechanistic analysis of the triethylxoxonium catalyzed homologation of ketones with diazoacetic esters.$^{42}$ They propose that the position of insertion is not determined by the structure or electronic nature of the migrating group, but rather by the conformation of the intermediate diazonium ion (Figure 8). Conformations which minimize gauche steric repulsions will be favored, such that conventional small, medium, and large (S, M, L) group analysis rationalizes preferential migration of the least bulky group. The least congested conformation is
depicted in Figure 5, characterized by an anti-relationship between the largest substituents. Assuming an antiperiplanar transition state for the concerted nitrogen expulsion rearrangement step (eq 48), the smaller substituent R in 171 occupies the required position for migration, while the larger substituent is gauche to the departing diazonium moiety.

Figure 8

![Chemical structure](image)

Conclusion

The reactions described in this chapter illustrate the utility of α-thiocyclobutanones as versatile synthetic intermediates. Desulfurization and ring expansion reactions parallel the reactivity of dichlorocyclobutanones, but the added versatility supplied by the sulfur atom is manifested by transformations such as regioselective alkylations and Pummerer rearrangement. α-Thiocyclobutanones thus provide access to alkyl-, acetoxy-, and alkoxyketene [2 + 2] cycloaddition products which may be difficult to synthesize by other means. Armed with the wide variety of α-thiocyclobutanones which are available from this new cycloaddition methodology, this chemistry should prove to be a valuable tool in organic synthesis.
References


(5) The zinc dust was activated by washing with dilute aqueous HCl following the method of Nozoe. Holton found activated zinc to be superior to unwashed zinc dust or zinc powder. The zinc was activated and stored in a desiccator for several days without apparent loss of activity. See Tsuda, K.; Ohki, E.; Nozoe, S. J. Org. Chem. 1963, 28, 783.


CHAPTER 4

Solid-Phase Combinatorial Synthesis Applications

We have begun to apply our thio-substituted ketene [2 + 2] cycloaddition reaction methodology to the preparation of a combinatorial library of $\alpha$-thiocyclobutenones. A linker strategy has been developed and executed to anchor the diazo thiol esters to solid support. The long-term goals of this work include the investigation of the aromatic annihilation reaction of these support-bound cyclobutenones for the purpose of synthesizing a library of highly substituted phenols.

Introduction and Background

Combinatorial chemistry has emerged in recent years as one of the most active areas of scientific research. The goal of traditional organic synthesis is to produce a single, well-characterized product in high yield and purity. Combinatorial chemistry, on the other hand, abandons this approach in favor of the simultaneous, parallel creation of a large number of compounds. Frequently the goal is then to evaluate these libraries for significant and useful biological activity. The potential of this approach to impact the drug discovery process is enormous. Historically, one of the main sources of biologically active compounds for drug discovery studies has been natural products. Often these substances serve as lead compounds while hundreds to thousands of analogs are painstakingly prepared, based on structure-activity relationships, in an effort to enhance the original activity, bioavailability, and selectivity of the lead compound, and at the same time decrease its toxicity. With the advent of improved screening methods for discovering strong host-guest interactions, the need for large libraries of compounds has developed; and using combinatorial chemistry, hundreds to thousands of times more compounds can be prepared.
and screened when compared to traditional methods of organic synthesis. There is often no attempt to design an active compound when planning a combinatorial library synthesis; instead, the sheer number and variety of structures which can be prepared is relied on to produce useful compounds.

The burgeoning field of combinatorial chemistry has its roots in the pioneering work of Merrifield, who first reported solid-phase chemistry for the synthesis of peptides in 1963.\(^2\) This technique has been used extensively for the synthesis of peptides, peptidomimetics, oligonucleotides, and oligosaccharides. The solid-phase synthesis of small organic molecules was first investigated by Crowley and Rapoport\(^3\) and Leznoff\(^4\) in the mid 1970s, but until recently the use of and advances made in solid-phase combinatorial chemistry have been focused primarily on peptide synthesis.

Solid-phase synthetic strategies offer significant advantages over standard solution-phase reactions. Isolation of support-bound reaction products is accomplished simply by washing away reagents, and as a result, reactions can often be driven to completion by employing excess reagents. One notable disadvantage is that some reaction types are prohibited depending on the nature of the solid support. For instance, a Birch reduction is not feasible when using a polystyrene support; and in general, reactions involving insoluble reagents or catalysts are prohibited. Soluble polymers have been developed to circumvent these problems,\(^5\) but the wealth of publications appearing in the current literature is a testament to the expanding array of reactions which are compatible with solid-phase chemistry.

A number of general strategies have been developed for the synthesis and evaluation of combinatorial libraries on solid supports. One straightforward approach involves the synthesis of many compounds in parallel while ensuring the identity of each substrate by some means of reaction differentiation. The resulting library is termed a spatially addressable library.\(^1c\) Geysen originated this strategy with the multipin method, which was originally developed for peptide epitope mapping.\(^6,7\) Polyacrylate-grafted
polyethylene pins, derivatized with aminoalkyl groups to provide sites for substrate attachment, are placed into a supporting block such that each pin fits into a separate well of a 96-well microtiter plate. During a synthesis step, each pin can then be subjected to distinct reaction conditions. This technique utilizes readily available materials and instrumentation and is amenable to automation which was developed predominantly for high-throughput microtiter-based screening efforts. Appropriate linker groups have been appended to the pins to allow cleavage of the peptides for use in assays and for analysis of purity.

Fodor and co-workers developed a strategy based on photolithography that can be used to synthesize even larger libraries containing spatially separate compounds. A silicon wafer, functionalized with aminoalkyl or other reactive functional groups attached to the surface, serves as the solid support. The functional groups are blocked with photolabile protecting groups and are cleaved at designated regions by site-specific illumination using masks and computer microchip construction instrumentation. In the case of peptide synthesis, the deprotected sites are then coupled to similarly protected amino acids. The substrate is illuminated through a second mask, activating a different region for the next coupling step. Very large numbers of spatially addressable compounds can be created in this fashion due to the sophisticated spatial resolution of photolithography techniques.

The most popular method for generating large libraries is to employ pooling strategies, an idea introduced by Furka as the "portioning-mixing" method of peptide synthesis, and often termed the "split synthesis" strategy or the "divide, couple, and recombine" process. In contrast to the spatially addressable libraries, inseparable mixtures of compounds are prepared. The process is initiated by dividing a quantity of resin into equal-sized portions and placing them into separate reaction vessels. After a chemical transformation is carried out, the support-bound material from all of the reaction vessels is combined, mixed thoroughly, and then separated again into the requisite number of groups for the next synthetic step. If enough beads are incorporated initially, the
repetition of this sequence allows the preparation of all possible theoretical combinations of the sets of different building blocks. This figure is easily determined by multiplying together the number of building blocks that are used in each step.

Another pooling strategy entails the treatment of resin beads with equimolar mixtures of reactants in each synthesis step. Since the product distribution is dependent on the relative kinetics of the competing reactions, it is important that the reaction rates of all reagents in the mixture are comparable in order to ensure equimolar representation of each library component.\textsuperscript{12,13}

A critical issue when using the split synthesis procedure involves evaluation of the library, including correct structural elucidation of the molecules having the greatest biological activity. Houghten developed one of the most popular strategies for "deconvoluting" a soluble library after cleavage from the solid support.\textsuperscript{14,15} The process begins with the preparation of pools of compounds with a separate defined building block at one position and all combinations of other building blocks at the other sites. The optimal functional group at the selected position is determined by screening for the most active pool. In order to analyze the next position, new groups of compounds are then synthesized, each with the optimal building block at the original position. This iterative synthesis and screening process is continued until all positions are identified. A drawback of the deconvolution strategy stems from the fact that the biological activity observed for any pool of compounds depends on both the activity and abundance of the active molecules in each pool. As a result, the group which exhibits the greatest biological activity may not contain the most potent compounds. Several modifications have been reported to address this problem, including an affinity selection process, positional scanning deconvolution,\textsuperscript{16} and orthogonal library methods.\textsuperscript{17}

Library components can also be analyzed while still attached to resin beads. Because the split synthesis procedure affords a single compound structure per resin bead, Lam and co-workers recognized that by using appropriate detection methods such as those
commonly used in immunological research, it was possible to detect and isolate individual peptide beads that interact specifically with a protein target. Fluorescent-labeled soluble receptors have been employed for this purpose due to the sensitivity of fluorescence detection. The receptor binds to beads which contain molecules with high affinity for that receptor, and the labeled beads are subsequently selected for structure determination. This one-compound-one-bead strategy relies on the availability of extremely sensitive analytical techniques for the structure determination of the minute quantities of compound present on a single resin bead. Such techniques are readily available to screen peptide and oligonucleotide libraries, and some mass spectroscopic methods may be sufficiently sensitive to allow application for low molecular weight, small organic molecule combinatorial libraries.

Another method for the structural determination of support bound compounds involves the use of encoding strategies. By attaching readable tags to the resin bead concurrently with each reaction step, the chemistry performed on the bead is recorded, including the sequence and identity of each building block. DNA encoding strategies are popular due to the minute quantities of oligonucleotides required (the sequence can be amplified by the polymerase chain reaction) and the ease of analysis by DNA sequencing methods. Peptides have also been used for library coding. The applications of these coding systems are somewhat limited by the necessity of orthogonal protecting group strategies to differentiate the tags from the molecules of interest. In addition, the tags must withstand the reaction conditions imposed by the library synthesis, yet nucleic acid chemistry is often incompatible with the conditions of organic chemical reactions.

The encoding strategy reported by Still and co-workers is more applicable to organic molecule combinatorial libraries due to the stability of the tagging molecules to a wide range of reaction conditions. Still developed haloaromatic tags which can be detected at <0.1 pmol using electron-capture gas chromatography. A binary code is utilized to record the building block and reaction step in the synthetic sequence. Multiple tags are
utilized for each subunit, with the presence or absence of a tag corresponding to a 1 or a 0, respectively, in a binary sequence. A subsequent report details the use of a carbene insertion reaction for support attachment which obviates the need for a differential protection scheme.\textsuperscript{25} One of the latest innovations in the area of encoded combinatorial libraries involves the independent report by two groups of recording coupling reactions with radiofrequency transmitting chip.\textsuperscript{26,27}

\textbf{Small Organic Molecule Combinatorial Libraries}

While most of the methodology which has been developed for combinatorial library synthesis stems from the goal of improving peptide and oligonucleotide library synthesis, the utility of these types of molecules as bioavailable therapeutic agents is often limited by poor oral activities and rapid in vivo clearance. Small organic molecules, on the other hand, often possess much more favorable pharmacokinetic properties (e.g., bioavailability and resistance to protease degradation), and allow greater structural diversity. As a result, the preparation of combinatorial libraries of small organic molecules has become a very active area of research.\textsuperscript{1b,1d,1e,1i,1k,1l,1m}

Libraries of small, nonoligomeric molecules have been prepared to accelerate the drug discovery process, both for the identification of lead compounds and the optimization of previously identified drug candidates. Seminal work by Bunin and Ellman on the solid-phase synthesis of 1,4-benzodiazepine derivatives clearly displayed the efficacy and simplicity of the combinatorial synthesis of small organic molecule libraries.\textsuperscript{28} 1,4-Benzodiazepines display a diverse range of biological activity, including anxiolytic, anticonvulsant, and antihypnotic properties, opioid receptor ligands, and HIV Tat antagonists and reverse transcriptase inhibitors. The tranquilizer Valium is a well-known example (Figure 9).
Bunin and Ellman assembled a library from three simple components, aminobenzophenones, amino acids, and alkylation agents (Scheme 20). 9-Fluorenylmethoxycarbonyl (Fmoc) protected amine-derivatized pins were employed as the solid support. The aminobenzophenones were anchored to the pins using an acid cleavable linker, [4-(hydroxymethyl)phenoxy]acetic acid, through either a hydroxy or carboxylic acid functionality (Scheme 21). Alkylation of the 2-aminobenzophenone derivatives 174 and 175 with allyl 4-bromomethylphenoxyacetate (176) provides protected acids 177 and 179. Removal of the allyl groups is readily accomplished and the resulting carboxylic acids (178 and 180) are coupled with the amine-derivatized polyethylene pins (not shown).

Scheme 20
The synthesis proceeds with removal of the Fmoc protecting group with piperidine followed by coupling of the resulting unprotected 2-aminobenzophenone to an N-Fmoc-amino acid fluoride (Scheme 22). The acid fluoride is required due to difficulties in effecting amide bond formation with standard amino acid activation methods. The Fmoc protecting group in 181 was removed, and treatment of the free amine 182 with dilute acetic acid provided cyclized product 183. Alkylation of the anilide 183 provides the fully functionalized 1,4-benzodiazepine derivative 184. The most appropriate base for this final transformation is lithiated 5-(phenylmethyl)-2-oxazolidinone, because it is basic enough to completely deprotonate the N-H proton of 183, but not basic enough to deprotonate amide, carbamate, or ester functionalities. Addition of alkylating agent in the presence of N,N-dimethylformamide to deprotonated amide 183 resulted in high yields of benzodiazepine 184 with no observed overalkylation. The products were cleaved from solid support with
concomitant removal of acid-labile protecting groups by exposure to a trifluoroacetic acid/water/dimethyl sulfide mixture.

Scheme 22

Using this straightforward synthetic sequence, Bunin and Ellman created 192 benzodiazepines from 2 aminobenzophenones, 12 amino acids, and 8 alkylating agents. Rigorous analytical evaluation of the combinatorial library was performed after cleavage from the pins. The chemical structures of 28 of the 1,4-benzodiazepine derivatives were confirmed by reverse-phase HPLC and mass spectral analysis. Yields were determined for 20 compounds by the addition of a known volume of an internal standard stock solution and analyzing the mixtures by HPLC. Of the compounds studied in this fashion, the average amount of 1,4-benzodiazepine per pin was 86 nmol out of a 100 nmol theoretical yield, with 67 nmol being the lowest yield. Finally, no racemization was detected by chiral HPLC analysis of several derivatives prepared from D- and L-alanine.
This 1,4-benzodiazepine library was evaluated for binding to the cholecystokinin (CCK) receptor by employing a simultaneous competitive radioligand binding assay. These data provided valuable insight into structure-activity relationships of the functionality incorporated into the compounds of the library. Finally, the assay results were validated by synthesizing and purifying a number of the benzodiazepines on a large scale and then performing the assays relative to a known inhibitor. The relative IC₅₀ values of these samples directly paralleled the relative binding affinities that were observed in assaying the benzodiazepine library.

This relatively simple synthetic scheme for the preparation of 1,4-benzodiazepine derivatives is a fitting example of the immense level of diversity which can be achieved with combinatorial chemistry. Expanding to the >40 commercially available protected amino acids and the >50 alkylation agents would allow the preparation of thousands of compounds. Ellman also addressed the major limitation of his strategy, the lack of an abundant supply of appropriately functionalized 2-aminobenzophenones, by developing a general method for the solid-phase preparation of 2-aminoaryl ketone derivatives based on the Stille coupling reaction. Using this added diversity element, Bunin and co-workers created a library of 11,200 discrete 1,4-benzodiazepines from 20 acid chlorides, 35 amino acids, and 16 alkylation agents.

A multitude of combinatorial libraries have been prepared since the early work of Ellman and others, and heterocyclic compounds are extremely popular targets. Because of this intense interest, an abundance of examples have been generated concerning the compatibility of certain reaction types with solid-phase synthesis conditions. In addition to the amide bond formation originally introduced by Merrifield and thoroughly optimized through the years, many standard organic reactions have been adapted to solid-phase chemistry. These include oxidation, reduction, nucleophilic substitution and addition, carbene insertion, Diels-Alder cycloaddition, and metal-catalyzed cross-coupling reactions. Many researchers have undertaken methodology studies for the express
purpose of examining the generality of a particular reaction applied to solid-phase. Spurred by this intense interest, we were encouraged to apply our thio-substituted ketene cycloaddition methodology to the field of solid-phase combinatorial chemistry.

**General Strategy for the Solid-Phase Synthesis of Thio-Substituted Phenols**

Hexasubstituted aromatic rings are common features incorporated into the structures of a variety of biologically active natural products. Our ultimate synthetic goal is the synthesis of a library of highly substituted aromatic compounds by a convergent annulation approach as shown in Scheme 23.

**Scheme 23**

![Scheme 23](image)

\( R^6 = \text{H, alkyl, aryl, vinyl} \)

By employing solid-phase synthetic methods, the immediate precursors to our target molecules are the support-bound thio-substituted phenols 185. A library of these compounds would be derived from the aromatic annulation reaction\(^{32}\) of the support-bound \(\alpha\)-thiocyclobutenones 186, which would be prepared in turn from the rhodium-catalyzed \([2 + 2]\) cycloaddition reaction of \(\alpha\)-diazo thiol esters 187 with alkynes (Scheme 24). As previously discussed, the reactivity of alkynes with the thio-substituted ketene intermediates is not as general as that of alkenes, but this potential limitation may be alleviated to some degree by the nature of solid-phase chemical reactions. A large excess of reagents is commonly added to drive reactions to completion due to ease of removal by filtration, and site isolation of the molecules attached to the resin may minimize side reactions such as ketene dimerization. The diversity of our library strategy is quite promising, as a variety of heterosubstituted acetylenes are available for the aromatic

92
annulation step. It should also be possible to convert the hydroxyl groups of the product thio-substituted phenols into triflates, thus generating partners for a variety of transition metal-mediated coupling reactions to afford an even wider range of aromatic compounds (see Scheme 23).

Scheme 24

Model Studies on the Solid-Phase Linker Synthesis

In considering the options for anchoring the substrates for our library synthesis to solid support, we realized an inherent advantage of our thio-substituted ketene methodology in the realm of solid-phase chemistry. Compounds are typically anchored to polymer supports through a variety of linkers. The earliest forms of resin were partially cross-linked polystyrene beads, in which the styrene is cross-linked with 1-2% divinylbenzene to impart mechanical strength and insolubility while permitting sufficient flexibility. The first resin to find use for peptide synthesis, Merrifield resin, is derivatized with a chloromethyl group to which amino acids are coupled by nucleophilic displacement of the chlorine atom. The resulting ester bond is stable to peptide synthesis conditions and is cleaved under vigorous acidic conditions (HF) to give carboxylic acid products.

The acid lability of the original Merrifield benzyl linker has been increased by substitution of the benzyl position with aromatic rings or other electron-donating groups.¹\textsuperscript{a} A variety of base stable, acid-labile linker groups have been appended to Merrifield resin and are now commercially available (Figure 10). The Wang resin offers a benzyl alcohol as the point of attachment, and cleavage with strong protic acid (1-95% TFA) gives carboxylic acids. A preferred route to primary amides involves the use of Rink resin,
which also requires strong protic acid for cleavage. The trityl linker is extremely acid-sensitive but has been used to immobilize a wide range of nucleophiles. Other linkers designed for the release of carboxylic acids and hydroxyl groups have been reported.

**Figure 10**

Our thio-substituted ketene chemistry allows the versatility of not having to rely on a specialized linker. Because cleavage of the carbon-sulfur bond in \( \alpha \)-thiocyclobutanones is a key step in our methodology (see Chapter 3), attachment of our starting materials to solid support through the sulfur atom will provide the opportunity to effect sulfide reduction and cleavage from the resin in a single synthetic operation. As a result, the linker can be comprised of a very stable functional unit that will provide greater versatility than typical acid- or base-sensitive linker groups.

We chose Merrifield resin (1% cross-linked) as the solid support for our studies due to its availability, relatively low cost, and well-known properties. Merrifield and other polystyrene-based resins are commonly used for small molecule libraries but are somewhat limited by poor swelling properties in protic solvents. Tentagel and PEG-PS resins, which consist of polystyrene-polyethylene glycol copolymers, are swelled in organic and aqueous solvents and are thought to be more representative of ether and tetrahydrofuran reaction solvent media.\(^{33}\) Because the polyethylene glycol chains are not cross-linked, and the attached compounds are located far from the hydrophobic polystyrene chains; the reaction
sites are considered to be more accessible, and faster reaction rates are generally observed. These characteristics, coupled with good aqueous solvation properties, have made PEG-PS resins popular for support-bound assays. Limitations relative to polystyrene resins include higher cost and reduced loading levels and mechanical stability. The investigation of soluble polymer supports has been pursued by Janda and co-workers.⁵

A retrosynthetic analysis to the key support-bound α-diazo thiol ester 187 is shown in Scheme 25. Due to its stability, we employed a benzyl ether linkage to anchor the substrates to the resin. We chose the sulfur substituent, which serves as the linker, so that the steric and electronic properties of α-diazo thiol ester 187 would closely mimic those of the solution-phase α-diazo thiol ester 79 (see Chapter 2). Because of these considerations, the use of electron-donating or -withdrawing substituents on the phenyl ring was avoided in favor of the 4-(hydroxymethyl)thiophenol linker 188. The thio alcohol cannot be directly coupled to the resin due to the greater nucleophilicity of the aromatic thiol; however, an aromatic thiol equivalent such as the thioanisole derivative 189 provides a convenient alternative.

Scheme 25

Young and co-workers reported the mild, selective, and high-yielding conversion of methyl aryl sulfides to arylthiols.⁶ Prior to this work, the potential of the methyl thioether as a protecting group for arylthiols had not been exploited due to difficulties
encountered in the deprotection step. This method involves sulfoxide formation followed by trifluoroacetic anhydride-mediated Pummerer rearrangement, and the resulting hemithioacetal acetates (194) are readily hydrolyzed to provide the desired arylthiols (195-198) (Scheme 26). The three step sequence requires no purification of intermediates.

**Scheme 26**

\[
\begin{align*}
\text{X} & \quad \text{SMe} \\ 192 & \quad \xrightarrow{m-CPBA, \text{CHCl}_3, 0 \degree C} \quad \text{X} & \quad \text{SO} \\ & \quad \text{Ca(OH)}_2, 25 \degree C \\ & \quad \xrightarrow{1) \text{NEt}_3, \text{MeOH} \quad \text{or} \quad 2N \text{NaOH}} \quad \text{X} & \quad \text{SH} \\ & \quad \xrightarrow{2) \text{NH}_4\text{Cl}} \quad \text{X} & \quad \text{O} \quad \text{CF}_3 \\ & \quad \text{194} \\
\end{align*}
\]

Thiols (X) | Yield (%)  
---|---
195 X = p-CO_2Me | 97  
196 X = p-CHO | 100  
197 X = p-CH_2OH | 86  
198 X = p-C(\text{O})\text{CH(CH}_3)_2 | 98

In some cases stronger hydrolysis conditions, aqueous sodium hydroxide rather than triethylamine, were required. For example, in the deblocking of 4-(hydroxymethyl)thioanisole (192 X = p-CH_2OH), the hydroxyl group is trifluoracetylated in the Pummerer step. Standard triethylamine treatment provides mainly polymers, probably due to intermolecular reaction of the liberated thiolate anion with the benzylic trifluoroacetate. The stronger basic conditions presumably cleave both groups simultaneously, and afford the thiol 197 in good yield after acidification.

Before embarking on the solid-phase reaction sequence, we attempted to optimize the series of reactions leading to the α-diazo thiol ester on a model compound. In the event, benzyl ether 199 was synthesized using standard protection conditions on alcohol
191 (eq 49).* This model compound is particularly appropriate because it represents the monomeric equivalent of our designed solid-phase linker. Conversion to the thiol (208) proceeds smoothly in near quantitative yield, and the product was carried on without purification (see Scheme 29). In our hands, the sodium hydroxide hydrolysis procedure was more effective than the triethylamine method. The use of a very large excess of base (ca. 70 equiv) facilitated the hydrolysis step in early model studies with the free alcohol. Finally, we employed 10% HCl solution rather than saturated aqueous NH₄Cl to acidify the thiolate anion.

\[
\begin{align*}
\text{191} & \quad \overset{1.1 \text{ equiv NaH, THF} \atop 25 ^\circ \text{C, 10 min};}{\rightarrow} \quad \text{BnO} \\
& \quad \overset{1.3 \text{ equiv BnBr, cat. Nal} \atop \text{THF, 25 ^\circ C, 1 h}}{\rightarrow} \quad \text{199}
\end{align*}
\]

In our solution-phase methodology we employ a two step sequence to synthesize α-diazo thiol esters from thiols: acetylation followed by diazo transfer (see Chapter 2). A more straightforward route was desired for the solid-phase application based on possible difficulties with the diazo transfer step. A direct diazoacetylation reaction should proceed in high yield and afford the desired support-bound α-diazo thiol esters in one step from the thiol.

A few examples of the diazoacetylation reaction of heteroatoms are known. Blankley and co-workers reported the reaction of glyoxylic acid chloride p-toluenesulfonylhydrazone (201) with crotyl alcohol followed by treatment with triethylamine to provide crotyl diazoacetate (203) (Scheme 27).35 The reaction mechanism involves formation of glyoxylic ester 202 followed by cleavage of the hydrazone in a Bamford-Stevens reaction36 to give the diazo alkene 203. A serious drawback of this

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*Prepared in quantitative yield by the sodium borohydride reduction of commercially available 4-(methylthio)benzaldehyde.
method is the laborious procedure for the synthesis of the acid chloride, which requires many filtration and recrystallization steps.

Scheme 27

Badet and co-workers modified this process for the preparation of diazoacetamides of amino acids by forming the amide bond directly from the coupling reaction of amino acids with glyoxylic acid tosylhydrazone. Utilizing standard peptide synthesis methods, they prepared hydrazones 204 in moderate yields (Scheme 28). Treatment with triethylamine afforded the desired diazoacetamides (205).

Scheme 28

A subsequent report by Badet and co-workers detailed the preparation and utility of succinimidyl diazoacetate (206) for the diazoacetylation of amines and other nucleophiles in a single step. This compound is synthesized from the reaction of N-hydroxysuccinimide with glyoxylic acid tosylhydrazone in the presence of dicyclohexylcarbodiimide. The formation of succinimidyl diazoacetate (206), isolated as a white crystalline solid, occurs spontaneously, and no trace of succinimidyl glyoxylate tosylhydrazone was detected (eq 50).
Reagent 206 was employed for the diazoacetylation of a variety of amines, amino acids, and alcohols. Encouragingly, thiophenol was also included in the study, and \( S \)-phenyl 2-diazoethanethioate (79) was prepared in good yield (eq 51).

\[ \text{PhSH} \xrightarrow{\text{NaH, THF, 25 \text{ C}}} \text{PhS} \equiv \text{N}_2 \]

\( \alpha \)-Diazo thiol ester 79 has been prepared in 86% yield by a similar sequence in which the corresponding acid chloride, diazoacetyl chloride, serves as the diazoacetylation agent, but this compound reportedly decomposes slowly upon storage and relies on the use of phosgene for its preparation.\(^{39}\)

Succinimidyl diazoacetate is ideally suited for application to the synthesis of the solid-phase \( \alpha \)-diazo thiol ester. Glyoxylic acid tosylhydrazone (200) was prepared according to the procedure of Blankley and co-workers in 70% yield (see Scheme 27);\(^{35}\) however, we were unable to reproduce the results of Badet and co-workers for the synthesis of succinimidyl diazoacetate. In our hands, separation of the product from dicyclohexylurea required two chromatography operations and large amounts of solvent. Despite experimentation with variables such as solvent, concentration, and addition of catalytic 4-(dimethylamino)pyridine, the product 206 was isolated in low yields of 27-31%.

The series of reactions leading to the \( \alpha \)-diazo thiol ester was conducted on the model compound 199 as a test of its efficiency (Scheme 29). The first run was performed
with no purification of intermediates, leading to a 44% overall yield from the sulfide. In a second experiment, purification of the thiol before the diazoacylation reaction gave the product in 45% overall yield from the sulfide. The yield of the thiol was 90%, so the final step was calculated to proceed in 50% yield. Due to the low-yielding preparation of succinimidyl diazoacetate and its modest success in diazoacylation of model thiol 208, a new diazoacylation protocol was desired.

Scheme 29

We turned our attention back to the original results of Badet and co-workers (see Scheme 28) and wondered if we could synthesize α-diazo thiol esters in a similar fashion. Direct coupling of glyoxylic acid tosylhydrazone (206) to thiols would provide thiol ester tosylhydrazones, and triethylamine induced decomposition of these intermediates should give the desired α-diazo thiol esters. We investigated the phenyl dichlorophosphate coupling of carboxylic acids with thiols reported by Liu and Sabesan.40 These rear-neutral reaction conditions were applied to a very wide range of substrates, making the reaction quite general (eq 52).

* The author would like to thank Melanie Bartow for helpful discussions of this chemistry.
Thiophenol was chosen as a model substrate to test the application of this methodology to acid 200. The experimental procedure consisted of the sequential addition of pyridine, thiophenol, and phenyl dichlorophosphate to a solution of the acid in DME at 0 °C. The reaction was complete in 1-2 h; aqueous workup gave a crude product which was consistent with hydrazone 210 by $^1$H NMR analysis, with no trace of unreacted glyoxylic acid tosylhydrazone (Scheme 30). To our surprise, attempted purification of 210 by column chromatography on silica gel yielded the $\alpha$-diazoc thiol ester 79 as the product! In retrospect, this transformation is evident by TLC analysis, as baseline material is connected by a light streak to a spot with $R_f \sim 0.3$ (10% ethyl acetate-hexane). This method of hydrazone cleavage is inefficient, however, because large volumes of solvent are required to elute the column. In addition, this process is not amenable to solid-phase chemistry.

Scheme 30

Base-induced cleavage of the hydrazone was effected by treatment of the crude coupling reaction mixture with triethylamine at 25 °C for 1 h, followed by purification by silica gel chromatography. While the $\alpha$-diazoc thiol ester 79 was produced, an inseparable byproduct was also formed in all cases, regardless of hydrazone decomposition conditions. This byproduct is not distinguishable by TLC analysis and is characterized by two singlets at 2.38 and 2.42 ppm (ca. 1:2 area ratio) and some aromatic peaks in the $^1$H NMR spectrum. The $^{13}$C NMR spectrum of the product mixture also shows two extra peaks.
upfield and ca. 12 extra aromatic carbon signals. The isolated yields of the product mixture are >100% based on the α-diazo thiol ester, but without confirmation of the byproduct structure, it is difficult to assess the efficiency of this reaction. In the first run, in which the hydrazone was decomposed by silica gel chromatography (see above), a very small amount of the byproduct was produced, and the yield of α-diazo thiol ester was 88%. Increased byproduct formation was observed in subsequent experiments. Changing the ratio of thiophenol to acid, from 1:1 to 2:1, had no effect on the course of the reaction. Experimentation with the hydrazone cleavage procedure, including basic workup of the crude reaction mixture (10% NaOH solution) and triethylamine treatment before workup, likewise displayed no advantages over the standard workup conditions.

Solid-Phase Linker Synthesis

The problems notwithstanding, we embarked on solid-phase studies with the phenyl dichlorophosphate-mediated coupling and hydrazone cleavage as the method of choice for diazo thiol ester formation. We reasoned that if the hydrazone decomposition occurred in good yield, the byproduct would readily be separated from the support-bound diazo thiol ester by filtration.

Our solid-phase sequence began with the attachment of the linker to solid support. Treatment of Merrifield resin (1% DVB cross-linked, 100-200 mesh, 0.76 mmol Cl/g) with the alkoxide ion of 4-(methylthio)benzyl alcohol (191) provided support-bound masked thiol 189 (Scheme 31). The conditions for this solid-phase reaction, such as reaction time, temperature, and reagent stoichiometry, were adapted from experiments reported in the literature pertaining to the coupling of alcohols to Merrifield resin.41-43

A few technical notes are in order regarding our solid-phase synthetic procedures. The first involves the method of agitation of the reaction mixtures. Solid-phase reactions are typically shaken or placed on a rotating platform using equipment not commonly encountered in organic chemistry laboratories. While the use of stir bars is not
recommended, the mechanical stability of Merrifield resin is sufficient to withstand gentle stirring, and this is the manner in which our experiments were run. With respect to resin purification, filtration was effected with the use of plastic fritted funnels which were connected to a water aspirator. The resin beads were rinsed with several portions of a variety of solvents, usually starting with polar mixtures such as 1:1 methanol/water and proceeding to more nonpolar solvents. The final washes were always conducted in methylene chloride, in which optimal swelling of Merrifield resin occurs.

One disadvantage of our linker is that cleavage of a small portion of the intermediates from the resin for characterization after each step, a common practice in the field of solid-phase chemistry, is not feasible due to the harsh acidic conditions required. As a result, we must rely on methods for the analysis of support-bound compounds.1e,1k,1l Fortunately, a variety of techniques have been described for resin analysis, such as KBr pellet FT-IR44,45 and gel-phase 13C NMR spectroscopy.46 In addition, vastly improved resolution of solid-phase 1H NMR spectra has been achieved by using Magic Angle Spinning solid-state NMR to minimize the line broadening observed with conventional probes.47 Other methods which have been employed to monitor reactions include the use of traditional procedures for functional group titration, and elemental analyses for a variety of atoms.

We analyzed our support-bound compounds with KBr pellet FT-IR.* By comparing spectra of the functionalized beads with free Merrifield resin, the results of each solid-phase reaction can be assessed by observing the appearance and disappearance of characteristic functional group IR stretches. While quantitative data regarding the degree of completion of reactions is often not available with solid support IR spectroscopy, this technique does provide a straightforward and reliable means of monitoring solid-phase reactions without the need for specialized equipment.

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* See Experimental Section for information regarding pellet preparation. The author would like to thank Dan LeCloux for technical assistance.
FT-IR analysis of resin-bound sulfide 189 (Scheme 31) showed a diagnostic C-O stretch at 1087 cm\(^{-1}\), which compares favorably with the corresponding peak in the IR spectrum of model sulfide 199 (see eq 49), which occurs at 1090 cm\(^{-1}\). In addition, the stretch at 1264 cm\(^{-1}\) in the IR spectrum of Merrifield resin, presumably resulting from H-C-Cl bending,\(^{44}\) is absent.

The remainder of the α-diazo thiol ester synthesis was conducted similarly to the model system (Scheme 31). One standard adjustment of the reaction conditions for the solid-phase sequence was to increase the reaction times. In the case of the sulfide oxidation, support-bound sulfide 189 was allowed to react with \(m\)-CPBA at 0 °C for 4 h. The addition of calcium hydroxide was omitted because the byproduct \(m\)-chlorobenzoic acid is easily removed by filtration. The product (211) showed diagnostic IR stretches at 1053 and 1085 cm\(^{-1}\), which correspond with C-O and S-O peaks at 1045 and 1080 cm\(^{-1}\) in the IR spectrum of model sulfoxide 207 (see Scheme 29).

The Pummerer reaction mixture was stirred gently at reflux for 3 h, followed by hydrolysis. The IR spectrum of the resulting compound (188) showed a weak S-H stretch at 2566 cm\(^{-1}\), and a C-O stretch at 1072 cm\(^{-1}\), while the sulfoxide peak had disappeared. Based on the FT-IR spectral evidence, we concluded that the solid-phase reaction sequence provided support-bound thiol 188 in good yield.
The diazoacetylamine reaction was run using a 1:1 ratio of thiol 188 to glyoxylic acid tosylhydrazone (200), and the reaction time was extended to 5 h (Scheme 32). After cleavage of the hydrazone with triethylamine, FT-IR analysis of the resulting resin (187) showed a strong stretch at 2104 cm\(^{-1}\) and the absence of an S-H stretching frequency. The analogous model compound, \(\alpha\)-diazo thiol ester 209, displays a C-N stretch at 2100 cm\(^{-1}\) and a carbonyl peak at 1630 cm\(^{-1}\). A carbonyl stretching frequency is not evident in the IR spectrum of 187, but this may be due to overlapping polystyrene stretches in this region at 1600 and 1583 cm\(^{-1}\).

With a sample of the support-bound \(\alpha\)-diazo thiol ester (187) in hand, a [2 + 2] cycloaddition reaction was attempted using cyclopentadiene as the ketenophile (Scheme 32). Technical difficulties frustrated efforts to mimic the solution-phase conditions; slow addition of 187 to the reaction flask via solid addition funnel led to clumping of the resin in the reflux condenser. As a result, the \(\alpha\)-diazo thiol ester was introduced in one portion, and the reaction mixture was stirred gently at reflux for 3 h. FT-IR analysis of the product (212) was promising but not conclusive. The diazo stretch has disappeared, and new peaks are present at 1733 and 1697 cm\(^{-1}\). As a comparison, the IR carbonyl stretch for \(\alpha\)-thiocyclobutanone 86 (see Chapter 2) occurs at 1775 cm\(^{-1}\). The appearance of two peaks

105
in the carbonyl region of the IR spectrum of 212 is evidence for the formation of more than one product. In light of the rapid rate of addition of the α-diazo thiol ester, one explanation involves the formation of the ketene dimer, even though it was hoped that the site isolation offered by reactions on solid supports would minimize intermolecular side reactions of the resin-bound ketene intermediates. The use of a larger excess of the ketenophile may alleviate this problem.

Scheme 32

The previous discussion summarizes the extent of our solid-phase synthetic efforts. The design and anchoring of the linker to Merrifield resin has been achieved, and the aromatic thiol deprotection methodology has been successfully adapted to a support-bound sulfide. The next phase of this project should focus initially on the promising thiol diazoacetylation reaction sequence. If the byproduct could be identified and its formation minimized, the hydrazone coupling and decomposition reactions could replace the diazo transfer reaction currently used for the synthesis of α-diazo thiol esters in the solution-phase methodology (see Chapter 2). Finally, it may be necessary to devise a means for the slow addition of the resin to the refluxing reaction mixture in the cycloaddition step, but the potential of the solid-phase application of our thio-substituted ketene cycloaddition methodology has certainly been affirmed by the encouraging results thus far obtained.
References


(32) See Chapter 3 in Part II of this thesis for a discussion of this chemistry.

PART II

A Synthetic Approach to the Taxol A-Ring
CHAPTER 1

Introduction and Background

Isolation and Biological Activity of Taxol

As a result of a National Cancer Institute program initiating widespread screening of plant materials for anticancer activity in the 1960s, samples of the bark of the Pacific Yew (Taxus brevifolia) were collected and sent to chemists Wani and Wall at the Research Triangle Institute in North Carolina for analysis. Initial screening of a crude extract of the bark showed cytotoxic activity against L-1210, P-388, and P-1534 murine leukemias, as well as inhibitory action against a variety of tumors. Shortly thereafter, X-ray crystallographic analysis finalized the structural characterization of the active component of the extract, the diterpene Taxol® (Figure 11).\textsuperscript{1,2} Interest in this promising anticancer agent was slow to develop, primarily because of the extremely low yield of isolation from the natural source. When the unique mode of action of Taxol was reported by Horwitz\textsuperscript{3} in 1979, however, renewed interest emerged for the study of the chemistry and biology of Taxol.

Figure 11

213: Taxol\textsuperscript{®}, $R^1 = \text{Ph}$, $R^2 = \text{OAc}$
214: Taxotere, $R^1 = \text{O-But}$, $R^2 = \text{OH}$
The biological activity of Taxol stems from its interaction with cellular components called microtubules. These structures are composed primarily of two protein subunits, α- and β-tubulin, and are involved in many aspects of cellular biology, including cellular signal transmission and cytoskeleton formation. Microtubules also play a central role in the process of cell division. Microtubules are not static structures, but rather exist in a precarious equilibrium with free tubulin inside the cell. Taxol inhibits the normal dynamic reorganization of the microtubule network by decreasing the concentration of tubulin and the induction time for polymerization. As a result, Taxol causes the generally irreversible formation of bundles of nonfunctional microtubules, often described as a log jam, in all phases of the cell cycle. This stabilizing interaction with microtubules is unique to Taxol, as other antimicrotubule agents like colchicine and the vinca alkaloids induce their disassembly. One vital process during cell division that is affected by this absence of free tubulin is the assembly of a normal mitotic spindle. Cancer cells may lack a checkpoint to detect this abnormality, thus leading to cell death upon continuation of the altered cell cycle. Otherwise, the cell division cycle is simply shut down. Taxol has also been implicated in the disruption of many cellular functions aside from cell division, such as locomotion, intracellular transport, and protein secretion.

Due to promising in vitro cytotoxicity, Taxol was subjected to widespread Phase I clinical trials in the early 1980s. Initially, acute hypersensitivity reactions were problematic, stemming from the use of Cremaphor, a castor oil known to cause antihistamine release. This vehicle of administration was necessary due to the low aqueous solubility of Taxol. Longer infusion times and prophylactic pretreatment with antihistamines diminished the hypersensitivity reactions remarkably, but other side effects remained. Neutropenia, the inability to produce a certain class of white blood cells, is the major dose-limiting toxic side effect. With the appropriate dosage worked out, in vivo antineoplastic activity was observed with a number of cancers, including leukemia, melanoma, lung, breast, and ovarian tumors.
Extremely promising results have surfaced in Phase II trials with Taxol. The most exciting antineoplastic activity of Taxol is observed with advanced ovarian epithelial neoplasms. Response rates of 30% were documented in patients with advanced disease, encouragingly, many of which had shown resistance to other therapies. At the present time, Taxol has been approved for use against metastatic ovarian and breast cancers and is being evaluated for other cancers. Clearly, this drug exhibits tremendous promise as a treatment for the scourge of cancer.

The Supply Problem and the Role of Total Synthesis

The issue of the relatively low supply of Taxol available from the Pacific Yew has been a major concern in the past. The isolation of one kilogram of the drug, under current protocols sufficient to treat only about 500 patients, requires 10,000 kilograms of bark from roughly 3,000 yew trees! This grossly inefficient and environmentally harmful process has fortunately been supplanted by a semisynthetic procedure in which a suitable side-chain equivalent, β-lactam 217, is coupled with a 7-protected baccatin III intermediate (216) (Scheme 33). The precursor to 216, 10-deacetyl baccatin III (215), is obtained in large quantities from needles and twigs of the European shrub Taxus baccata. Cell culture also holds promise for the commercial production of Taxol.
While the chemical synthesis of Taxol is not currently relied on for large scale preparation of the drug, there are several reasons to allocate time and resources to the development of a viable synthetic plan. Better accessibility of analogs would allow more detailed study of structure-activity relationships. For instance, Taxotere (214, see Figure 11) was prepared by French chemists\textsuperscript{10,11} and shows antitumor activity similar to Taxol, with the added advantage of increased water solubility. In addition, advances in the current state-of-the-art organic synthetic methodology will undoubtedly follow from efforts to meet the demands imposed by the daunting structure of Taxol.

**A Ring Subunits in the Total Synthesis of Taxol**

This complex, highly oxygenated diterpene poses a formidable challenge to the synthetic organic chemist. The central B-ring presents one obvious hurdle, as the geminal dimethyl groups increase the typically high transannular strain of eight-membered rings. Other areas for concern include a bridgehead olefin in the A-ring, a \textit{trans}-fused C-ring
containing an angular methyl group, and the need for judicious use of protecting groups due to the dense oxygenated functionalities.

To date, a vast array of synthetic strategies have been reported for the synthesis of the taxane skeleton, yet only four groups have managed to complete the total synthesis of Taxol. One of the prevalent strategies for the preparation of this molecule can be expressed as $A + C \rightarrow ABC$, where suitably functionalized $A$- and $C$-ring partners are coupled to create the eight-membered $B$-ring (Scheme 34). An attractive feature of this plan is its highly convergent nature which is imparted by disconnection of the molecule into two comparably sized intermediates. Numerous routes have appeared for the construction of the $A$-ring, and both Nicolaou and Danishefsky utilized this general strategy in their Taxol syntheses.

**Scheme 34**

Nicolaou's synthesis of 7-OTES baccatin III (216) is shown in Scheme 35. The $A$-ring system is derived from a Diels-Alder reaction. Despite the severe steric interactions in the transition state between diene 219 and 1-chloroacrylonitrile and in the product, adduct 220 was the sole product. Exposure of chloro nitrile 220 to basic conditions resulted in carbonyl generation at C-1 and acetate hydrolysis at C-10 (Taxol numbering) to provide a hydroxy ketone, which was subsequently protected as the silyl ether 221. Aryl hydrazone formation completed the synthesis of the Taxol $A$-ring synthon 222. To initiate $B$-ring synthesis, the vinyllithium reagent derived from 222 was added to an appropriate $C$-ring aldehyde to form the C(1)-C(2) bond. The carbon atom adjacent to the acetate functionality served as the C(10) precursor, and the $B$-ring was ultimately
formed, albeit in low yield, by McMurry coupling with the C(10) aldehyde in 223. Finally, the oxygen atom at C(13) was installed late in the synthesis by allylic oxidation of 224 to the ketone followed by selective reduction to provide 7-OTES baccatin III (216).

Scheme 35
Danishefsky has devised routes to the Taxol A-ring encompassing nucleophilic sites at C(1) or C(10) (Taxol numbering).\textsuperscript{23,24} The starting material in all cases was diketone 226, available in three steps from the annulation reaction between 2-methyl-3-pentanone and acryloyl chloride via the morpholine-derived enamine 225. Differential carbonyl protection provided ketone 227, in which manipulations could be carried out selectively at C-12 (Taxol numbering) (Scheme 36).

\textbf{Scheme 36}

Early model studies involved conversion to a C-11 (Taxol numbering) vinylthiium reagent via the hydrazone-derived vinyl iodide 228. These nucleophiles were added to various aldehydes to form a carbon-carbon bond corresponding to the C-10-C-11 bond of Taxol (Scheme 37).

\textbf{Scheme 37}

Compounds enabling bond formation to occur at the C-1 carbon were also prepared by Danishefsky. Ketone 233 was prepared from monoprocted diketone 227 in seven
steps (Scheme 38). Enol triflate formation and a palladium-mediated cross-coupling reaction generated diene 231. Selective dihydroxylation of the primary olefin and oxidative cleavage of the resulting diol afforded the aldehyde 232, which was reduced and protected to provide the desired ketone 233 after unmasking of the carbonyl group. This A-ring subunit is identical to that of Nicolaou (see Scheme 35). Trisylhydrazone formation led to generation of the corresponding vinylolithium reagent, which was added to aldehydes in good yield.

Scheme 38

During the course of the actual Taxol studies, the route involving initial C-10-C-11 bond formation using nucleophiles of type 228 (see Scheme 37) was abandoned due to difficulties in arriving at a viable precursor for closing the B-ring at C-1-C-2. As a result, Danishefsky concentrated efforts on establishing the C-1-C-2 bond first. The vinylolithium species derived from 233 (see Scheme 38) proved to be unsuitable due to difficulties with functional group manipulations on subsequent intermediates. After much experimentation, a solution was developed which employed A-ring synthon 238. This 1,3-cyclohexadienyl
iodide was also prepared from diketone 226. Conversion to the monohydrazone 235 followed by treatment with iodine gave rise to iodo dienone 237. This product presumably arose from iodination and ensuing dehydrohalogenation of the vinyl iodide intermediate 236. Compound 237 was readily converted to protected cyanohydrin 238 (Scheme 39).

Scheme 39

1,3-Cyclohexadienyliodide 238 was lithiated and subsequently treated with a C-ring aldehyde to afford, after decyanation, a single stereoisomer of alcohol 239 (Scheme 40). The B-ring was eventually closed using an intramolecular Heck type olefination reaction to construct the C-10-C-11 bond. The A-ring vinyl triflate was prepared for this purpose, and subsequent palladium-mediated cyclization of 240 proceeded in reasonable yield. The product diene 241 was transformed in several steps to compound 242, an intermediate in the Nicolaou synthesis. The latter stages of Danishefsky’s synthesis of Taxol, including installation of the C-13 oxygen atom and introduction of the side-chain, were conducted by following previously described protocols.
An Annulation-Based Approach to the Taxol A-Ring

Our interest in Taxol stems from the realization that a proposed key intermediate in the synthesis of an A-ring synthon could be prepared by applying a new variant of methodology previously developed in the Danheiser laboratories. As shown in the partial retrosynthetic analysis depicted in Scheme 41, our target molecule of interest is the cyclohexa-2,4-dienone 245. The fully functionalized synthon 243, resembling those of Nicolaou and Danishefsky but with the C-13 oxygen atom (Taxol numbering) already installed, may be formed by an asymmetric reduction of diketone 244, which in turn can be prepared from the cyclohexadienone 245. Alternatively, it may be possible to derive 243 directly from 245 via an enantioselective reduction of the double bond. The preparation of the key intermediate 245 will be discussed presently.
Scheme 41

\[
\begin{align*}
\text{243} & \xrightarrow{\text{RO}} \text{244} & \text{244} & \xrightarrow{\text{OCH}_2\text{OCH}_3} \text{245}
\end{align*}
\]
References

(2) Taxol is the registered trademark of the compound with the generic name paclitaxel. For reviews, see:
(3) Horwitz, S. B.; Fant, J.; Schiff, S. B. Nature 1979, 277, 665.
CHAPTER 2

Synthesis of Cyclohexa-2,4-dienones

Methods of Preparation of Cyclohexa-2,4-dienones

Cyclohexa-2,4-dienones\(^1\) (hereafter referred to as CHDs) are useful intermediates in organic synthesis and have appeared in a number of syntheses.\(^2\) To \(^7\) For example, Danishefsky prepared the core of the antitumor antibiotic calicheamicin by utilizing a CHD to which an enediyne was attached.\(^2\) In addition, as previously described, the same author prepared a CHD as part of a sequence to generate a Taxol A-ring synthon. CHDs undergo useful photochemical rearrangements and possess Diels-Alder reactivity, but synthetic methodology for their preparation is not well developed.

Most methods for CHD synthesis involve the elaboration of six-membered rings. One classical example is the alkylation of phenols with alkyl or allyl halides to give mixtures of the desired dienone and \(O\)-alkylation or \(-\)allylation product (eq 53). In the case of the reaction of 2,6-dimethylphenol with methyl iodide, the alkylated phenol predominates in a ratio of 1.7:1. Diels-Alder dimers of the dienone are also formed but may be decomposed to the monomer by distillation.\(^8\)

\[
\begin{align*}
\text{R}_{\text{OLi}} & \quad \text{R}^1X \\
& \quad \text{R}^1 = \text{alkyl, allyl} \\
\text{R} & \quad \text{R}^1 \\
& \quad + \\
\text{OR'} & \quad \text{R} \\
\end{align*}
\]

Phenols can also be oxidized with lead tetraacetate in the presence of acetic acid, a reaction termed the Wessely oxidation (eq 54 and 55).\(^4\) A drawback of this method is that
mixtures of 2,4- and 2,5-CHDs and quinone products are formed with o- and p-substituted phenols.

Equation 54

One of the more general strategies for the synthesis of CHDs is the halogenation and dehydrohalogenation of gem-disubstituted cyclohexanones or cyclohexenones (eq 56). Halogenating agents have included bromine, N-bromosuccinimide, sulfuryl chloride, and iodine; collidine and other hindered amine bases, potassium hydroxide, and calcium carbonate have all been employed to effect elimination of the intermediate halo ketones.

Equation 55

Equation 56

Because these strategies for the synthesis of CHDs rely on the elaboration of intact six-membered rings, they all suffer from the limitation of being linear in their design. A more convergent approach reported by Wulff and Tang is based on chromium carbene chemistry. These workers investigated the benzannulation reaction (Dötz reaction) of alkenyl-substituted chromium carbene complexes in which the final tautomerization step to
the phenol product is blocked. In his groundbreaking studies, Dötz studied only one case in which tautomerization was not possible, a 2,6-dimethyl complex. Upon reaction with diphenylacetylene, he found that cyclization occurred without the normal carbon monoxide insertion, resulting in the isolation of indene products.\(^{13}\) Tang and Wulff were therefore quite surprised to find that isobutenyl chromium carbene complex 246 reacted smoothly with a variety of acetylenes to afford good yields of CHDs (247) (eq 57). These workers have extended this methodology to include the synthesis of bicyclic CHDs by a tandem Diels-Alder cycloaddition/benzannulation reaction of propynyl chromium carbene complexes.\(^{14}\) Due to the nature of the chromium carbene complexes (246), this reaction is limited to the synthesis of 4-alkoxyCHDs.

\[
\begin{align*}
\text{(CO)}_2C\equiv C\text{Me} & \xrightarrow{R_L\equiv CR_S} \text{Me} \xrightarrow{\text{CH}_2\text{CN, 50 °C}} \text{Me} \\
\end{align*}
\]

\[
\begin{array}{ccc}
R_L & R_S & \% \text{Yield of 247} \\
\text{Ph} & \text{H} & 81 \\
\text{Me}_2\text{Si} & \text{H} & 73 \\
\text{n-But} & \text{H} & 80 \\
\text{Et} & \text{Et} & 42 \\
\text{Me} & \text{H} & 62 \\
\text{CH}_2\text{OAc} & \text{H} & 55 \\
\end{array}
\]

Annulation-Based Approach to Cyclohexa-2,4-dienones

Classical approaches to the preparation of highly substituted aromatic compounds have involved the elaboration of commercially available aromatic starting materials using nucleophilic and electrophilic substitution reactions or directed metallation reactions. These reactions often suffer from poor regiochemical control and may require protection of sensitive functional groups. Because of the linear nature of this approach, a more efficient and convergent annulation strategy is preferred. Many annulation methods minimize the possibilities for regiochemical ambiguity by allowing the construction of the ring with all of
the substituents in place, provided that the annihilation components react in a regioselective fashion. As a result of this flexibility, annihilation approaches often allow for substitution patterns which are difficult to construct by other routes. An aromatic annihilation involves the reaction of two acyclic units to generate a substituted aromatic ring in a single step.

In 1984 our research group first published the details of an aromatic annihilation strategy in which the aromatic product was derived from a two-carbon acetylenic component and a four-carbon vinylketene component.\textsuperscript{15,16} Our proposed strategy for the synthesis of CHDs makes use of a convergent annihilation route which is a variant of this aromatic annihilation reaction. The process involves a cascade of pericyclic reactions as outlined in Scheme 42.

Scheme 42

Experimentally, the aromatic annihilation is a simple, one-pot process. The reaction is carried out by heating (80-160 °C) a 0.4-2.0 M solution of a cyclobutenone derivative in deoxygenated benzene, chloroform, or toluene with an acetylene. Mechanistically, however, several steps are involved. The first step yields a vinylketene (250) from reversible opening of the cyclobutenone (248).\textsuperscript{17} This intermediate reacts with a ketenophilic acetylene (249) to form a vinylcyclobutenone (251). Cleavage of this
compound leads to a dienylketene (252) which readily undergoes an electrocyclic ring closure to the CHD (253). In the original studies, R⁴ or R⁵ was a hydrogen atom, resulting in tautomerization to the aromatic product. Subsequent investigations employing dichlorocyclobutenones for the annulation (R⁴, R⁵ = Cl) resulted in the isolation of chlorophenols, which are formed by homolysis of a carbon-chlorine bond in CHD 253 under the elevated reaction temperatures.¹⁵,¹⁸ In our route, these substituents would be alkyl groups, and therefore the isolated product is expected to be a CHD. Previous studies have also shown that these annulations can be effected photochemically,¹⁹ thus extending the scope of the original reaction to accommodate thermally sensitive functionalities.

Some precedent exists for the suggested vinylketene to CHD annulation reaction. Sutherland and coworkers²⁰ synthesized the doubly unsaturated acid chloride 255. Upon treatment with triethylamine, the bicyclic CHD 256 was formed in 44% yield, presumably via cyclization of an intermediate dienylketene (Scheme 43). Tricyclic compounds (258) were also produced in good yields (eq 58).

**Scheme 43**

An even closer correlation to our proposed CHD annulation reaction resides with the work of England and Krespan.²¹ During the systematic study of the thermal cycloaddition reactions of bis(trifluoromethyl)ketene (259) with acetylenes, they prepared
bis(trifluoromethyl) cyclobutene 260 in 80% yield. When the reaction was conducted in the presence of two equivalents of phenylacetylene, a product was obtained in 73% yield and assigned structure 261 (eq 59). A mechanism for the formation of this CHD was proposed and is identical to ours in every detail. Further studies into the scope of this reaction were apparently not undertaken.

![Reaction equation and structures](image)

**Retrosynthetic Analysis of a Taxol A-Ring Synthon**

CHD 262, the key intermediate in our proposed synthesis of a Taxol A-ring synthon, was anticipated to be the product of the annulation reaction of cyclobutene 263 with terminal silyloxyacetylene 264 (Scheme 44). Intermediate 263 may be synthesized by the addition of the lithium species derived from tin reagent 266 to cyclobutene 265, followed by hydrolysis. Finally, starting cyclobutene 265 should be available from the [2 + 2] cycloaddition reaction of dimethylketene (267) with 1-methoxypropyne (268). If successful, our proposed five step route to the Taxol A-ring would rank among the shortest and most efficient syntheses reported thus far. In addition, beyond the specific case of the Taxol A-ring, this methodology could be used to construct a series of CHDs with varying substitution patterns in a highly convergent manner.
Scheme 44

References


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CHAPTER 3

Studies Directed Towards the Synthesis of a Taxol A-Ring Synthon

Preparation of Cyclobutenones

Perhaps the most widely used method for the generation of alkyl- and arylketenes is the dehydrohalogenation of acid chlorides with tertiary amines.\(^1\) The reaction is often conducted in the presence of a ketenophile, whereby the in situ generated ketene is trapped, leading to the expected [2 + 2] cycloaddition products. A drawback of this method is the tendency of the amine hydrochloride byproduct to promote undesirable side reactions such as dimerization and polymerization\(^2\), however, the rate of cycloaddition is competitive when activated \(\pi\) bonds are used as ketenophiles. Ketenes generated in this fashion have been reacted with alkoxyacetylenes to form cyclobutenones.\(^3, 4\) Wasserman reported the formation of a cyclobutenone similar to our target (265, see Scheme 44 in Chapter 2) by generation of dimethylketene in the presence of ethoxyacetylene to afford 269 (eq 60). The experimental procedure called for the slow (45 min) addition of a solution of triethylamine in diethyl ether to a solution of isobutyryl chloride and the acetylene in diethyl ether. Presumably this protocol suppressed the buildup of free ketene, thereby limiting self-condensation byproduct formation.

\[ \text{NEt}_3, \text{EtO} \xrightarrow{\text{Et}_2\text{O, 0 to 25 ℃}} \text{66\%} \]

\[
\begin{array}{c}
\text{O} \\
\text{Cl} \\
\text{Et} \\
\text{O} \\
\end{array} \xrightarrow{\text{O}}
\]

\[
\begin{array}{c}
\text{O} \\
\text{Et} \\
\text{O} \\
\text{Et} \\
\end{array}
\]

(60)
It should be noted that the regiochemistry of the ketene cycloaddition is predicted by molecular orbital theory. The carbon atom of the acetylenic portion containing the highest HOMO coefficient reacts with the central carbon atom of the ketene, which possesses the highest LUMO coefficient. This theoretical analysis translates experimentally into cyclobutenones with a C-3 alkoxy substituent (as in 269) when alkoxyalkynes are employed.

Other methods have been reported for the generation of dimethylketene and its use in [2 + 2] cycloaddition reactions: pyrolysis of isobutyric anhydride, thermal cracking of the dimer (tetramethyleyclobutanedione), thermal decomposition of dimethylmalonic anhydride and dimethylketene acylal, and zinc-mediated dehalogenation of α-halo acid halides. After experimentation with a variety of these procedures, it was determined that the dehydrohalogenation protocol was far superior for our application, and we chose to utilize this method for the synthesis of our initial target cyclobutenone 265. Slow addition (approximately 30 min) of a solution of triethylamine in methylene chloride to a solution of 1-methoxypropyne (268) and isobutyryl chloride in methylene chloride at 0 °C, followed by reaction at room temperature for 17-24 h led to the desired cyclobutenone 265 in yields of 72-75% (eq 61). The expected regiochemistry was confirmed by analysis of the 13C NMR spectrum; an olefinic peak far downfield at 184.8 ppm can only be accounted for by the vinylogous ester structure in 265.

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, \text{CH}_2\text{Cl}_2, 0^\circ; \quad 268 \\
1.5 \text{ equiv} \\
\text{CH}_2\text{Cl}_2, 0^\circ; \\
1.1 \text{ equiv NEt}_3, \text{CH}_2\text{Cl}_2 \\
0^\circ, 30 \text{ min;} \\
20^\circ, 17-24 \text{ h} \\
72-75\% \\
\end{align*}
\]

(61)

With 265 in hand, the preparation of the Taxol A-Ring cyclobutenone 253 required the use of the tin reagent 266. This compound, which had previously been
developed in our laboratories, is a versatile hydroxymethyl anion equivalent and is synthesized in two steps in 74% yield as shown in Scheme 45.

Scheme 45

When treated with n-butyllithium, transmetallation occurs to yield an α-alkoxy alkyllithium species which reacts with cyclobutenones in the same manner as standard alkyllithium reagents. Addition of a THF solution of cyclobutenone 265 to an excess of this lithium reagent at -78 °C afforded an intermediate tertiary alcohol after 3 h at -78 °C. Mild acidic hydrolysis (5% HCl) resulted in the loss of methanol to provide the desired annulation partner 263 in 78-93% yield (eq 62). It was crucial for the reaction to be conducted and quenched at -78 °C; otherwise, products resulting from n-butyllithium addition to the cyclobutenone were observed. Use of less than 2 equiv of the lithium reagent was insufficient to consume all of the starting material (265). As with 265, cyclobutenone 263 is purified by column chromatography on silica gel and is stable upon storage at 0 °C as a solution in methylene chloride.

Preparation of Silyloxyacetylenes

Early studies on the aromatic annulation reaction demonstrated the excellent ketenophilicity of alkoxy acetylene derivatives. This fact was illustrated by the remarkably
concise total synthesis of the *Penicillium* metabolite mycophenolic acid (274), which utilized the annulation of cyclobutene 271 with acetylene 272 as the key step (Scheme 46).\(^{15}\)

**Scheme 46**

![Diagram of the reaction](image)

63: mycophenolic acid

Subsequent attempts to incorporate methoxyacetylenes in annulations leading to certain highly functionalized resorcinol natural products were hindered by the harsh conditions required for the cleavage of methyl aryl ethers. Most other alkoxyacetylenes are unsuitable due to a facile thermal retro-ene fragmentation of alkynyl ethers bearing beta C-H bonds (eq 63). Consequently, trialkysilyloxyalkynes were viewed as a potential solution to this dilemma due to the mild conditions which can be employed for the deprotection of silyl ether derivatives.

![Equation 63](image)

A majority of the methods for preparation of these compounds involve the *O*-silylation of lithium alkynoates, themselves generated by a variety of protocols. For example, Stang and Roberts found that by treating alkynyl tosylates 275 with two
equivalents of methyllithium followed by \( \text{i}-\text{butyldimethylsilyl chloride} \), silyloxyalkynes 277 were produced (eq 64).\(^{16}\)

\[
\begin{align*}
\text{R} & \equiv \text{OTs} \quad 2 \text{ equiv LiMe, THF or DME} \quad \text{at } -20 \degree \text{C} \\
\text{276} & \quad \text{R} \equiv \text{OLi} \quad \text{BuMe}_2\text{SiCl} \quad \text{278} \quad \text{R} \equiv \text{OSiBuMe}_2 \quad \text{277}
\end{align*}
\]

(64)

Kowalski and coworkers reported similar results. A variety of silyloxyalkynes 278 were isolated by trapping ynolate anions generated by an ester homologation reaction (eq 65).\(^{17}\) Products containing small trialkylsilyl groups such as trimethylsilyl underwent a facile rearrangement to silylketenes upon warming of the reaction mixture, a process suggested by Barton to occur by a salt-promoted isomerization rather than a purely thermal rearrangement.\(^{18}\)

\[
\begin{align*}
\text{RCO}_2\text{Et} & \quad \text{LITMP, CH}_2\text{Br}_2 \quad \text{n-BuLi, -78 to } 25 \degree \text{C} \\
\text{276} & \quad \text{R} \equiv \text{OLi} \quad \text{R}_3\text{SiCl} \quad \text{278} \quad \text{R} \equiv \text{OSiR}_3
\end{align*}
\]

(65)

More recently, Julia has reported a new procedure for the generation of ynolates. Addition of lithium \( \text{i}-\text{butyl peroxide} \) to phenylacetylide followed by trapping with triisopropylsilyl chloride afforded the siloxyacetylene 279 (eq 66).

\[
\begin{align*}
\text{Ph} & \equiv \quad 1) \text{LiHMDS} \\
\text{276} & \quad \text{Ph} \equiv \text{OLi} \quad \text{Pr}_3\text{SiCl, -70 } \degree \text{C} \quad 60\% \\
\text{Ph} & \equiv \text{OSi(Pr}_3\text{)}
\end{align*}
\]

(66)

The Kowalski reaction has been successfully applied in our lab for the synthesis of several silyloxyacetylenes which were employed in aromatic annulation studies. Due to the poor product recovery in the preparation of substrates in which \( R \) is a lower alkyl group (\( R = \text{i}-\text{Pr}, \text{Et}, \text{Me} \) in eq 65), however, it became clear that a new route was required.

This limitation of the known methods led us to examine the application of the base-promoted dehydrohalogenation of (Z)-2-halovinyl ethers, a well established route to
alkoxyacetylenes,\textsuperscript{19} for the synthesis of trialkylsilyloxyalkynes (Scheme 47).\textsuperscript{20} Various (Z)-2-bromovinyl silyl ether substrates (such as \textbf{281}) generated the necessary lithium trialkylsilyloxyacetylidides upon exposure to two equivalents of lithium diisopropylamide in tetrahydrofuran at 0 °C. Addition of ethanol and careful workup and isolation provided the parent silyloxyethyne derivatives. Encouraging results were also enjoyed when trimethylsilyl chloride and methyl iodide were employed as electrophiles. Since the (Z)-2-bromovinyl silyl ethers (such as \textbf{281}) are readily prepared in two steps using the method of Pirrung and Hwu,\textsuperscript{21} this sequence provided convenient access to alkynes not easily obtainable by other methods and thus expanded the scope and usefulness of the aromatic annulation reaction.\textsuperscript{20} Analogous to previous studies on the synthesis of silyloxyalkynes, however, this chemistry was only successful with the use of relatively bulky trialkylsilyl groups such as triisopropyl, \textit{t}-butyldimethyl, and di-\textit{t}-butylmethyl. Following this protocol, trialkylsilyloxyacetylenes \textbf{282} and \textbf{264} were prepared for annulation studies.*

Scheme 47

* The parent acetylene \textbf{264} was much more difficult to isolate and purify than \textbf{282}. 

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Cyclohexa-2,4-dienone (CHD) Annulation

Initial experiments were aimed at gauging the temperature at which our 4,4-dimethylcyclobutenones underwent ring opening to establish an equilibrium with the corresponding vinylketene species. The vehicles used to probe this question were nucleophilic trapping experiments with primary amines, which are known to add to the central carbon atom of ketenes to afford amides in good yields. Using two equivalents of \( t \)-butylamine, good conversion of 263 to the amide 283 was observed by thin layer chromatography over 16 h at a temperature range of 110-118 °C (eq 67). Similar results were found using \( n \)-hexylamine. Amide formation also proceeded smoothly at higher temperatures (up to 150 °C was studied).

\[
\begin{align*}
\text{CH}_3\text{OCH}_2\text{O} & \quad \text{R} \quad \text{O} \\
\text{263} & \quad \text{CH}_2\text{OCH}_2\text{OCH}_3 \\
\text{CH}_3\text{OCH}_2\text{O} & \quad \text{R} \\
\text{283} & \quad \text{CH}_2\text{OCH}_2\text{OCH}_3 \\
\end{align*}
\]

(67)

Thermal stability studies of the Taxol A-ring cyclobutene were also informative. Heating a solution of 263 in toluene at 95 °C for 17 h resulted in no appreciable decomposition by TLC analysis, but raising the temperature to 125 °C had a drastic effect. The formation of many new compounds was observed by TLC at the expense of a significant amount of the cyclobutene. Complete disappearance of the starting material was effected by heating at 155 °C for 27 h. These observations are consistent with the amine trapping experiments and indicate that reversible ring opening of cyclobutene 263 occurs between 95 and 125 °C. Furthermore, as the temperature is raised, the equilibrium concentration of vinylketene increases; and in the absence of a ketenophile, vinylketene reaction byproducts are formed. These results indicated that the success of the CHD annulation reaction hinged on the ability to maintain a favorable balance between the rate of the desired \([2 + 2]\) cycloaddition reaction of the vinylketene intermediate, and its decomposition by other pathways. The rate of amine trapping was sufficiently rapid as to
avoid noticeable decomposition of the cyclobutenone, but the initial cycloaddition reaction of the annulation sequence was not anticipated to be as rapid. Proper selection of variables such as temperature and reagent stoichiometry would be crucial.

Annulation results are summarized in Table 8. For the initial runs, methoxypropyne (268) was used due to its relative ease of preparation (eq 68). All annulation reactions were conducted in a resealable Pyrex tube at concentrations of ~0.2 M in cyclobutenone, with toluene as the solvent. It was quickly discovered that a very large excess of the acetylene was required in order to bring about the desired transformation. Byproduct formation from decomposition of both starting materials precluded the isolation of a clean sample of the product. Conducting the reaction at a lower temperature for a longer duration (run 5) afforded a much cleaner crude reaction mixture, seemingly without compromising CHD yield.

Table 8. CHD Annulation Results

<table>
<thead>
<tr>
<th>Run</th>
<th>Acetylene</th>
<th>R</th>
<th>equiv</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>2</td>
<td></td>
<td>155</td>
<td>24</td>
<td>decomposition products</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>5</td>
<td></td>
<td>150</td>
<td>42</td>
<td>CHD and decomposition products</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>10</td>
<td></td>
<td>150</td>
<td>42</td>
<td>&lt;44% CHD and decomposition products</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>10</td>
<td></td>
<td>170</td>
<td>18</td>
<td>slightly more comp. products than run 3</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>10</td>
<td></td>
<td>110</td>
<td>69</td>
<td>much less comp. products than previous runs</td>
</tr>
<tr>
<td>6</td>
<td>SiBuPh₂</td>
<td>10</td>
<td></td>
<td>150</td>
<td>42</td>
<td>&lt;33% and decomposition products</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>10</td>
<td></td>
<td>170</td>
<td>62</td>
<td>&lt;38% and decomposition products</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>10</td>
<td></td>
<td>130</td>
<td>72</td>
<td>&lt;41% and less decomposition products</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>10</td>
<td></td>
<td>110</td>
<td>70</td>
<td>29%, cleanest run</td>
</tr>
</tbody>
</table>
Silyloxyacetylene 282 was chosen as a model substrate for the Taxol A-ring acetylene 264 for the first silyloxyacetylene annulation runs due to its greater ease of preparation and isolation. These reactions exhibited analogous behavior to those of 1-methoxypropyne. Alkyne 282 is more thermally stable, therefore the crude reaction mixtures were cleaner and product purification was more successful. The best runs again took place at lower temperatures (Table 8). At 110 °C (run 9), the most favorable balance of reaction conditions was obtained. CHD formation occurred to the extent that complete consumption of cyclobutenone was observed, and it was accompanied by minimal decomposition, thus facilitating product purification. At higher temperatures, it is possible that more CHD was formed, but the greater amount of byproducts prevented complete product purification. Even so, CHD 284 (R = CH₃, R' = t-BuPh₂Si) was obtained in a low yield of 29% (10 mg) with the best conditions of run 9 (eq 68).

At this point, a simple assessment of the annulation results revealed its severe shortcomings. The primary obstacle was the fact that the practicality of the reaction was compromised by the large amount of acetylene required, only a fraction of which could be recovered. Based on the mode of preparation of 282 (see Scheme 47) and an annulation product yield of 30%, two grams of the silyloxyacetylene would be needed for one run to afford 100 mg of purified CHD. This factor translated into a required ten grams of tribromoethanol to begin the sequence to prepare 282! Matters would only get worse with Taxol A-ring acetylene 264, which was more difficult to prepare. It should be noted that photochemical amine trapping and annulation studies, carried out by irradiation of reaction mixtures at 300 nm on a Rayonet apparatus, suggested no advantages over thermal runs.
In fact, conditions corresponding to run 2 in Table 8 resulted in the formation of unidentified products with no apparent acetylene incorporation.

Having made these observations, it was clear that the current course of action was not ideal. We considered annulation partners other than trialkylsilyloxyalkynes, and it seemed that a logical course of action would be simply to vary the protecting group used in the first step of the silyloxyacetylene preparative sequence (see Scheme 47). Would the same sequence of reactions work on substrates other than silyl ethers? The work of Pirring and Hwu supplied a precedent, as they reported the facile formation of (Z)-chlorovinyl tetrahydropyranyl ether from THP-protected trichloroethanol under identical reaction conditions. Two requirements were essential for any new protecting group. First, beta-C-H bonds are not tolerated due to the previously described thermal instability of such acetylenes (see eq 63), and further, the protecting group must be subject to selective removal in the presence of the methoxy methyl ether. The use of other protecting groups offered other attractive features as well. For instance, the likely decrease in steric bulk should facilitate the annulation, and the accompanying reduction in molecular weight of the protecting group reduces the amount needed for the key reaction.

Three protecting groups which met the above criteria were investigated. Tribromoethanol protection proceeded smoothly in all cases under standard procedures, but vinyl bromide formation was problematic. Despite considerable experimentation with the standard conditions, the vinyl bromides (288) were formed in low yields (<40%) along with considerable TLC baseline material (Scheme 48). Perhaps heteroatom addition to the carbene intermediate (in each case, there is a heteroatom five atoms away from the carbene carbon) competes with 1,2-H migration in these transformations, leading to intermolecular side reactions or undesired rearrangements.
Scheme 48

\[
\begin{align*}
\text{CBr}_3\text{CH}_2\text{OH} \quad \text{see refs} & \quad \text{CBr}_3\text{CH}_2\text{OR} & 2.0 \text{ equiv n-BuLi} \\
& \text{Et}_2\text{O/pentane} & -78 \text{ to } 25 \degree \text{C} \\
& & \quad \text{Br}_2 \text{OR} \\
\end{align*}
\]

285 \(R = \text{CH}_2\text{SCH}_3\) (MTM)  
286 \(R = \text{CH}_2\text{O(\text{CH}_2)}_3\text{SiMe}_3\) (SEM)  
287 \(R = \text{CH}_2\text{OSi}\text{-BuMe}_2\)

Given the impractical, low-yielding nature of the CHD annulation reaction and the inability to remedy the situation through the development of a better ketenophilic partner, the Taxol A-ring project was abandoned. Why did the CHD annulation proceed in such poor yield? The cyclobutenone may be part of the problem. In previous aromatic annulation reactions of trialkylsilyloxyalkynes with cyclobutenones conducted in our laboratories, substituents at C-2 of the cyclobutenone resulted in a lower yield of product (eq 69 and 70). In addition, the silyloxyalkynes failed to react with the vinylketene generated from 2,4-dimethyl-3-ethoxycyclobutenone (291).20

A similar trend surfaced with the annulation reaction of 1-methoxypropyne with a series of cyclobutenones of varying substitution patterns.23 The yield of the phenol steadily decreases as substituents are added at C-2 and then C-4 (eq 71). These effects may be the result of steric interactions in the transition state of one or all of the steps in the pericyclic reaction sequence.
\[
\begin{align*}
\text{R}^2 & \quad \text{R}^3 & \quad \text{R}^4 & \quad \text{Rxn Temp and Time} & \quad \text{Yield (\%)} \\
\text{H} & \quad \text{Me} & \quad \text{H} & \quad 80 \degree \text{C, 21 h} & \quad 92 \\
\text{Me} & \quad \text{Me} & \quad \text{H} & \quad 120 \degree \text{C, 71 h} & \quad 61 \\
\text{Et} & \quad \text{Et} & \quad \text{Me} & \quad 160 \degree \text{C, 48 h} & \quad 33
\end{align*}
\]

Considering the fact that the Taxol A-ring cyclobutenone 263 possesses a methyl group at C-2 and is disubstituted at C-4, these precedents did not bode well for the success of our desired transformation. It does appear that in our CHD annulation, the lack of a driving force (formation of an aromatic product) has allowed steric interactions to overwhelm the desired reactivity. The end result is low product recovery, even with a large excess of the acetylenic annulation partner.
References


(5) See Chapter 1 in Part I of this thesis for a discussion.


(11) Several dialkylketenes, not including dimethylketene, have been prepared in this fashion, see: Baigrie, L. M.; Lenior, D.; Seikaly, H. R.; Tidwell, T. T. *J. Org. Chem.* 1985, 50, 2105.


PART III

Experimental Section
General Procedures

All reactions were performed in flame-dried glassware under a positive pressure of argon unless otherwise noted. Air and/or moisture sensitive reagents and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction mixtures were stirred magnetically unless otherwise noted. Reaction product solutions and chromatography fractions were concentrated using a Büchi rotary evaporator at approximately 20 mmHg unless otherwise indicated. Residual solvents were removed via a single stage vacuum pump at approximately 0.1 mmHg. Resins were rinsed, dried, and stored in plastic fritted funnels supplied by Bio-Rad. IR pellets for resin analysis were prepared by pressing a finely ground mixture of ca. 200 mg of KBr and 6-8 mg of resin.

Materials

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

Distilled under argon or vacuum from calcium hydride: acetonitrile, boron trifluoride etherate, dichloromethane, dichloroethane, diisopropylamine, 1,1,1,3,3,3-hexamethyldisilazane, pyridine, toluene, triethylamine.

Distilled under argon from sodium benzophenone ketyl or dianion: diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran.

Distilled under argon or vacuum: tributyltin hydride.

Other reagents were purified by the following methods: methyl iodide was passed through a short column of neutral alumina or distilled under argon immediately before prior to use. Acetyl chloride was distilled under argon from quinoline. \(N,N\)-dimethylformamide was sequentially dried in three portions over activated 3 Å molecular sieves.
\( \text{n-Butyllithium was titrated in tetrahydrofuran with menthol using 1,10-}
\text{phenanthroline as indicator by the method of Watson and Eastham.}^1 \)

4-Phenyl-1-butene and 2-methyl-4-phenyl-1-butene were prepared by
methylenation of the corresponding carbonyl compounds.

**Chromatography**

Analytical thin-layer chromatography was performed on Merck precoated glass-
backed silica gel 60 F-254 0.25 mm plates. Visualization was effected by one or more of
the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c)
immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by
heating to ca. 200 °C, (d) immersion of the plate in an ethanolic solution of 3% \( p \)-vanillin
containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, (e)
immersion of the plate in an aqueous solution of 1% potassium permanganate containing
7% potassium carbonate and 5% sodium hydroxide followed by heating to ca. 200 °C, or
(f) immersion of the plate in an ethanolic solution of 3% \( p \)-anisaldehyde containing 0.5%
concentrated sulfuric acid followed by heating to ca. 200 °C.

Column chromatography was performed using 230-400 mesh Merck or Baker silica
gel.

**Instrumentation.**

Melting points were determined with a Fisher-Johns melting point apparatus and are
uncorrected. Boiling points are uncorrected.

Infrared spectra (IR) were recorded using a Perkin-Elmer 1320 grating or a Bio-
Rad FTS-135 FT-IR spectrophotometer.

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$^1$H NMR spectra were recorded with a Varian XL-300 (300 MHz) and a Bruker AC-250 (250 MHz) spectrophotometer. Chemical shifts are expressed in parts per million (δ), relative to tetramethylsilane.

$^{13}$C NMR spectra were recorded on a Varian XL-300 (75 MHz) spectrophotometer. Chemical shifts are expressed in parts per million (δ), relative to tetramethylsilane (with the central peak of CDCl$_3$ at 77.0 ppm used as a standard).

Elemental analyses were performed by Robertson Microlit Laboratories, Inc., of Madison, New Jersey.
S-2,4,6-Trimethylphenyl ethanethioate (76).

A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and a rubber septum was charged with 2,4,6-trimethylbenzenethiol\(^2\) (1.81 g, 11.9 mmol), 35 mL of dichloromethane, and pyridine (1.15 mL, 1.12 g, 14.2 mmol) and cooled to 0 °C. Acetyl chloride (1.0 mL, 1.10 g, 14.1 mmol) was added slowly via syringe over ca. 8 min. The resulting mixture was stirred at 0 °C for 10 min, then at 25 °C for an additional 2 h. The cloudy white reaction mixture was then poured into 20 mL of water. The aqueous phase was separated and extracted with two 10-mL portions of dichloromethane. The organic phases were washed with 20 mL of brine, dried over MgSO\(_4\), filtered and concentrated to afford 2.38 g of a pale yellow oil. Purification by column chromatography on 48 g of silica gel (gradient elution with 0-2.5% ethyl acetate-hexane) provided 2.21 g (96%) of 76 as a white solid, mp 54.5-55.5 °C.

IR (CCl\(_4\)):

3020, 2960, 29 °0, 2910, 2840, 1700, 1600, 1460, 1435, 1370, 1350, 1120, 1060, 1030, 950, and 850 cm\(^{-1}\).

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

6.98 (s, 2 H), 2.41 (s, 3 H), 2.31 (s, 6 H), and 2.29 (s, 3 H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)):

193.8, 142.4, 139.9, 129.2, 123.9, 30.1, 21.5, and 21.1.

\(^2\)For preparation, see Part I, Chapter 2.
General Procedure for Diazo Transfer. S-Phenyl 2-diazoethanethioate (79).

A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, pressure-equalizing addition funnel fitted with a septum, and a rubber septum was charged with 1,1,1,3,3,3-hexamethyldisilazane (1.50 mL, 1.15 g, 7.11 mmol) and 18 mL of tetrahydrofuran and cooled to 0 °C while n-butyllithium solution (2.40 M in hexane, 2.90 mL, 6.96 mmol) was added rapidly dropwise. The resulting LiHMDS solution was stirred at 0 °C for 15 min, then cooled at -78 °C while a solution of 75 (0.89 mL, 1.0 g, 6.57 mmol) in 14 mL of THF was added dropwise from the addition funnel over 15 min. The enolate solution was stirred at -78 °C for 30 min, and then 2,2,2-trifluoroethyl trifluoroacetate (1.10 mL, 1.61 g, 8.21 mmol) was added rapidly in one portion. The reaction mixture was stirred at -78 °C for 10 min and then partitioned between 40 mL of 5% HCl solution and 50 mL of diethyl ether. The aqueous phase was separated and extracted with two 40-mL portions of diethyl ether. The organic phases were washed with 45 mL of brine and concentrated to afford 2.25 g of a yellow oil. The oil was dissolved immediately in 25 mL of acetonitrile and transferred via cannula to a 100-mL, three-necked, round-bottomed flask equipped as before. Water (0.118 mL, 0.118 g, 6.55 mmol) and triethylamine (1.40 mL, 1.02 g, 10.0 mmol) were added followed by a solution of methanesulfonyl azide (1.15 mL, 1.20 g, 9.89 mmol) in 28 mL of acetonitrile from the addition funnel over 20 min. The resulting yellow solution was stirred at 25 °C for 2.5 h and then concentrated to a volume of ca. 10 mL. The residue was diluted with 50 mL of diethyl ether and washed with three 40-mL portions of 10% NaOH solution and 40 mL of brine, dried over MgSO4, filtered and concentrated to afford 1.18 g of an orange oil. Purification by column chromatography on 70 g of silica gel (gradient elution with 5-10%
ethyl acetate-hexane) provided 0.885 g (76%) of α-diazo thiol ester 79 as a dark yellow oil.

IR (thin film): 3090, 3060, 2260, 2100, 1625, 1470, 1430, 1330, 1130, 1010, 845, 740, and 680 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 7.38-7.52 (m, 5 H), and 5.25 (s, 1 H).

¹³C NMR (75 MHz, CDCl₃): 184.1, 135.3, 129.8, 129.3, 127.3, and 54.2.
S-2,4,6-Trimethylphenyl 2-diazoethanethioate (57).

Reaction of thiol ester 76 (1.0 g, 5.15 mmol) with LiHMDS (5.46 mmol) and 2,2,2-trifluoroethyl trifluoroacetate (0.83 mL, 1.22 g, 6.20 mmol) in 26 mL of tetrahydrofuran according to the general procedure provided 1.88 g of a yellow oil which was then treated as a solution in 24 mL of acetonitrile with water (0.093 mL, 0.093 g, 5.16 mmol), triethylamine (1.10 mL, 0.799 g, 7.89 mmol), and a solution of methanesulfonyl azide (0.90 mL, 0.938 g, 7.74 mmol) in 20 mL of acetonitrile at 25 °C for 2.5 h to afford 1.2 g of a yellow solid. Purification by column chromatography on 60 g of silica gel (gradient elution with 2.5-5% ethyl acetate-hexane) provided 1.01 g (89%) of 57 as a light yellow solid, mp 91.5-93 °C.

IR (CCl₄): 3100, 3010, 2960, 2940, 2910, 2840, 2100, 1630, 1600, 1450, 1370, 1330, 1145, 1010, and 850 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 7.00 (s, 2 H), 5.18 (s, 1 H), 2.39 (s, 6 H), and 2.30 (s, 3 H).

¹³C NMR (75 MHz, CDCl₃): 184.4, 143.2, 140.5, 129.4, 123.6, 53.3, 21.8, and 21.1.
General Procedure for Cycloaddition. 2-(Phenylthio)spiro[3.5]nonan-1-one (82).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and a reflux condenser fitted with a rubber septum and a needle inlet was charged with rhodium(II) acetate (0.010 g, 0.023 mmol), 3.5 mL of dichloroethane, and methylene-cyclohexane (0.680 mL, 0.544 g, 5.66 mmol). The rubber septum was replaced with a glass stopper and the green reaction mixture was heated at reflux while a solution of α-diazo thiol ester 79 (0.202 g, 1.13 mmol) in 2.5 mL of dichloroethane was added slowly dropwise via syringe pump (through the reflux condenser) over ca. 2.25 h. An additional 1.5 mL of dichloroethane was used to rinse the syringe and was added to the reaction mixture over ca. 5 min. The reaction mixture was cooled to 25 °C and then concentrated to afford 0.279 g of a brown oil. Purification by column chromatography on 28 g of silica gel (gradient elution with 2.5-5% ethyl acetate-hexane) gave 0.219 g of 82 (78%)\(^3\) as a yellow oil.

IR (thin film):

3040, 2920, 2840, 1770, 1580, 1480, 1435, 1380, 1340, 1290, 1250, 1190, 1160, 1100, 1060, 1020, 920, 730, and 685 cm\(^{-1}\).

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

7.43-7.47 (m, 2 H), 7.19-7.31 (m, 3 H), 4.19 (m, 1 H), 2.89 (d, J = 18.2 Hz, 1 H), 2.81 (d of m, J = 17.8 Hz, 1 H), 1.54-1.83 (m, 7 H), and 1.24-1.43 (m, 3 H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)):

204.6, 135.4, 130.5, 129.0, 126.8, 69.2, 54.6, 38.3, 37.2, 32.2, 25.4, 24.2, and 23.1.

\(^3\)Yields for this reaction ranged from 73-78%.
2-(2,4,6-Trimethylphenylthio)spiro[3.5]nonan-1-one (83).

Reaction of α-diazothiol ester 57 (0.100 g, 0.454 mmol) with methylene-
cyclohexane (~87%, 0.310 mL, 0.216 g, 2.24 mmol) and catalytic rhodium(II) acetate
(0.004 g, 0.009 mmol) in 5 mL of dichloroethane for ca. 3 h according to the general
procedure provided 0.150 g of a green oil. Purification by column chromatography on 15
g of silica gel (gradient elution with 0-1% ethyl acetate-hexane) yielded 0.106 g (81%) of a
pale yellow solid.

IR (CCl₄): 3020, 2920, 2850, 1780, 1600, 1445, 1375, 1290,
1160, 1090, 1055, 1025, 920, and 850 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 6.92 (s, 2 H), 3.62 (s, 1 H), 2.83 (d, J = 17.3 Hz, 1
H), 2.66 (d, J = 17.0 Hz, 1 H), 2.53 (s, 6 H), 2.25
(s, 3 H), 1.54-1.89 (m, 9 H), and 1.31-1.44 (m, 3
H).

¹³C NMR (75 MHz, CDCl₃): 204.6, 142.9, 138.5, 129.4, 129.1, 70.8, 53.9,
37.9, 36.9, 32.0, 25.4, 24.3, 23.1, 22.1, and 20.9.

Elemental Analysis: Calcd for C₁₈H₂₄OS: C, 74.95; H, 8.39
Found: C, 74.67; H, 8.44
7-(Phenylthio)bicyclo[3.2.0]hept-2-en-6-one (86a,86b).4

A 100-mL, three-necked, round-bottomed flask equipped with a reflux condenser fitted with a pressure-equalizing addition funnel (fitted with a rubber septum and a needle inlet), glass stopper, and a rubber septum was charged with rhodium(II) acetate (0.086 g, 0.19 mmol), 35 mL of dichloromethane, and freshly cracked cyclopentadiene (3.90 mL, 3.20 g, 48.4 mmol). The green reaction mixture was heated at reflux while a solution of α-diazo thiol ester 79 (1.74 g, 9.76 mmol) in 25 mL of dichloromethane was added slowly dropwise from the addition funnel over ca. 2.5 h. (Note: The rate of addition may be difficult to control and should be closely monitored.) The reaction mixture was cooled to 25 °C and then concentrated to give a brown oil. Purification by column chromatography on 50 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) followed by a second purification of mixed fractions by column chromatography on 5 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) provided 2.02 g (96%)5 of 86a and 86b as a yellow solid, mp 77-85 °C, obtained as an approximately 11:1 mixture of diastereomers by 1H NMR analysis.

86a:

IR (thin film): 3050, 3040, 3010, 2840, 1775, 1580, 1475, 1435, 1345, 1290, 1270, 1140, 1085, 1045, 1020, 980, 740, and 690 cm⁻¹.

1H NMR (300 MHz, CDCl3): 7.39-7.43 (m, 2 H), 7.20-7.31 (m, 3 H), 5.93-5.97 (m, 1 H), 5.83-5.89 (m, 1 H), 4.77-4.81 (m, 1 H),

5Yields for this reaction on smaller scales, 0.85 and 0.28 mmol of 79, were 90 and 87%, respectively.
3.87-3.97 (m, 2 H), 2.73-2.82 (m, 1 H), and 2.44-2.56 (m, 1 H).

$^{13}$C NMR (75 MHz, CDCl$_3$):

209.1, 135.5, 135.5, 129.9, 129.3, 129.0, 126.6, 65.6, 59.9, 44.5, and 35.2.

Elemental Analysis:

Calcd for C$_{13}$H$_{12}$O$_{5}$: C, 72.19; H, 5.59

Found: C, 71.95; H, 5.59
7-endo-(2,4,6-Trimethylphenylthio)bicyclo[3.2.0]hept-2-en-6-one (87a, 87b).

Reaction of α-diazo thiol ester 57 (0.123 mg, 0.558 mmol) with freshly cracked cyclopentadiene (0.46 mL, 0.377 g, 5.71 mmol) and catalytic rhodium(II) acetate (0.005 g, 0.011 mmol) in 4 mL of dichloromethane for ca. 3 h according to the general procedure provided 0.180 g of a green oil. Purification by column chromatography on 18 g of silica gel (gradient elution with 0-0.5% ethyl acetate-hexane) produced 0.133 g (92%) of 87a and 87b as a white solid, mp 77-88 °C, obtained as an approximately 98:2 mixture of diastereomers by ¹H NMR analysis.

87a:

IR (CCl₄):

3040, 3010, 2940, 2910, 2840, 1775, 1595, 1460, 1435, 1370, 1340, 1270, 1235, 1140, 1010, 980, and 850 cm⁻¹.

¹H NMR (300 MHz, CDCl₃):

6.92 (s, 2 H), 5.96-5.98 (m, 2 H), 4.23 (dd, J = 8.8, 2.3 Hz, 1 H), 3.84 (appar t, J = 7.3 Hz, 1 H), 3.75 (appar t, J = 7.9 Hz, 1 H), 2.75 (d, J = 17.6 Hz, 1 H), 2.42-2.51 (m, 1 H), 2.53 (s, 6 H), and 2.25 (s, 3 H).

¹³C NMR (75 MHz, CDCl₃):

209.7, 142.7, 138.5, 135.4, 130.1, 129.8, 129.0, 67.9, 59.4, 45.2, 35.1, 22.2, and 21.0.
2-(Phenylthio)-1,2,2a,7a-Tetrahydro-7H-cyclobut[a]inden-1-one (91).

Reaction of α-diazo thiol ester 79 (0.298 g, 1.67 mmol) with indene (1.0 mL, 0.996 g, 8.57 mmol) and catalytic rhodium(II) acetate (0.015 g, 0.034 mmol) in 11 mL of dichloroethane for ca. 2.5 h according to the general procedure provided a brown oil. Purification by column chromatography on 45 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) served to remove most of the excess indene and provided 0.316 g of product as a white-yellow solid. Recrystallization of the product from ethyl acetate-hexane (two crops) afforded 0.214 g (48%) of 91 as white-yellow crystals.

\[
\text{IR (CCl}_4): \quad 3060, 3020, 2950, 2910, 2840, 1770, 1670, 1470, 1450, 1430, 1250, 1220, 1170, 1130, 1080, 1030, 1020, 760 \text{ (br), and 680 cm}^{-1}.\]

\[
\text{H NMR (300 MHz, CDCl}_3): \quad 7.20-7.42 \text{ (m, 9 H), 4.98 (dd, J = 9.0, 3.8 Hz, 1 H), 4.41 (appar t, J = 8.3 Hz, 1 H), 4.08-4.15 \text{ (m, 1 H)}, 3.36 \text{ (d, J = 16.5 Hz, 1 H), and 3.12 (dd, J = 16.6, 9.8 Hz, 1 H).}\]

\[
\text{C NMR (75 MHz, CDCl}_3): \quad 208.7, 143.8, 139.0, 135.7, 130.0, 129.0, 128.3, 127.6, 126.7, 126.6, 125.5, 65.6, 60.3, 43.5, \text{ and 34.4.}\]

\[
^6\text{Yields for this reaction ranged from 40-51%.}\]
2-(2,4,6-Trimethylphenylthio)-1,2,2a,7a-Tetrahydro-7H-cyclobuta[a]inden-1-one (92).

Reaction of α-diazo thiol ester 57 (0.302 g, 1.37 mmol) with indene (0.80 mL, 0.797 g, 6.86 mmol) and catalytic rhodium(II) acetate (0.012 g, 0.027 mmol) in 10 mL of dichloroethane for ca. 2.75 h according to the general procedure provided 1.1 g of crude product as an oil. Purification by column chromatography on 22 g of silica gel (gradient elution with 5-20% ethyl acetate-hexane) served to remove the excess indene and gave 0.335 g of a white-yellow solid. Recrystallization from ethyl acetate-hexane (four crops) afforded 0.244 g (58%) of 92 as fluffy white crystals, mp 165.5-167.5 °C.

**IR (CCl₄):**

3050, 3010, 2940, 2900, 2840, 1750, 1550, 1450, 1430, 1370, 1265, 1215, 1020, 980, and 850 cm⁻¹.

**¹H NMR (300 MHz, CDCl₃):**

7.58-7.61 (m, 1 H), 7.24-7.30 (m, 3 H), 6.93 (s, 2 H), 4.34 (dd, 9.4, 3.0 Hz, 1 H), 4.29 (apparr, J = 9.4 Hz, 1 H), 3.90-3.96 (m, 1 H), 3.34 (d, J = 16.5 Hz, 1 H), 3.08 (dd, J = 16.7, 9.7 Hz, 1 H), 2.55 (s, 6 H), and 2.25 (s, 3 H).

**¹³C NMR (75 MHz, CDCl₃):**

209.2, 143.8, 142.6, 139.4, 138.5, 130.6, 129.0, 128.1, 127.8, 126.6, 125.4, 67.9, 59.6, 43.8, 34.4, 22.3, and 21.0.
3-(2-Phenylethyl)-2-(2,4,6-trimethylphenylthio)cyclobutanone (59a, 59b).\(^7\)

Reaction of \(\alpha\)-diazothiol ester 57 (0.200 g, 0.908 mmol) with 4-phenyl-1-butene (1.20 g, 9.08 mmol) and catalytic rhodium(II) acetate (0.008 g, 0.018 mmol) in 7 mL of dichloroethane for ca. 3 h according to the general procedure provided 1.4 g of crude product as a brown-green oil. Removal of excess alkene by column chromatography on 10 g of silica gel (gradient elution with 0-2% ethyl acetate-hexane) afforded 0.250 g of a brown oil. Purification by column chromatography on 50 g of silica gel (gradient elution with 1-5% ethyl acetate-hexane) yielded 0.183 g (62%) of 59a and 59b as an approximately 5:1 ratio by \(^1\)H NMR analysis.

59a:

**IR (thin film):**

3080, 3060, 3020, 2920, 2840, 1775, 1595, 1490, 1445, 1370, 1170, 1070, 1050, 1025, 845, 740, and 690 cm\(^{-1}\).

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

7.19-7.30 (m, 3 H), 7.11 (d, \(J = 7.2 \) Hz, 2 H), 6.91 (s, 2 H), 4.09 (d of t, \(J = 9.4, 2.7 \) Hz, 1 H, 59b), 3.77 (d of t, \(J = 6.7, 2.9 \) Hz, 1 H), 3.12 (ddd, \(J = 17.5, 9.1, 2.7 \) Hz, 1 H), 2.51-2.66 (m, 3 H), 2.48 (s, 6 H), 2.25 (s, 3 H), 2.14-2.25 (m, 1 H), 1.91-2.07 (m, 1 H), and 1.73-1.88 (m, 1 H).

**\(^13\)C NMR (75 MHz, CDCl\(_3\)):**

204.0, 143.2, 141.1, 138.9, 129.1, 128.5, 128.3, 127.9, 126.1, 64.9, 49.6, 37.1, 34.3, 33.1, 22.1, and 21.0.

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\(^7\)This experiment was run by Thomas Lee.
3-Methyl-3-(2-phenylethyl)-2-(2,4,6-trimethylphenylthio)cyclobutanone (90a, 90b).

Reaction of α-diazo thiol ester 57 (0.075 g, 0.340 mmol) with 2-methyl-4-phenyl-1-butene (0.254 g, 1.74 mmol) and catalytic rhodium(II) acetate (0.003 g, 0.007 mmol) in 2.5 mL of dichloroethane for ca. 3 h according to the general procedure gave 0.389 g of a green oil. Purification by column chromatography on 30 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) yielded 0.068 g (59%) of 90a and 90b as a yellow oil, obtained as an approximately 1.3:1 mixture of isomers by 1H NMR analysis.

90a + 90b:

IR (thin film): 3050, 3020, 2940, 2920, 2840, 1780, 1600, 1500, 1450, 1375, 1115, 1070, 1020, 900, 850, 730, and 695 cm⁻¹.

1H NMR (300 MHz, CDCl₃): 7.17-7.33 (m, 8 H, a + b), 7.14 (d, J = 6.6 Hz, 2 H, a), 6.92 (s, 4 H, a + b), 3.80 (appar t, J = 2.4 Hz, 1 H, a), 3.73 (appar t, J = 2.1 Hz, 1 H, b), 2.93 (dd, J = 16.8, ~2 Hz, 1 H, b), 2.57-2.86 (m, 6 H, a + b), 2.53 (s, 12 H, a + b), 2.25 (s, 6 H, a + b), 2.15 (d of t, J = 12.4, 5.1 Hz, 1 H, b), 1.80-2.02 (m, 2 H, a; m, 1 H, b), 1.48 (s, 3 H, b), and 1.39 (s, 3 H, a).

13C NMR (75 MHz, CDCl₃): 204.3, 204.1, 142.9, 142.7, 141.8, 141.5, 138.7, 129.5, 129.2, 129.1, 128.5, 128.3, 128.2, 126.0, 71.9, 70.9, 55.5, 54.5, 43.7, 38.5, 36.0, 35.7, 32.1, 31.6, 26.0, 22.1, and 21.0.

8 The minor product in the 1H NMR spectrum reproduced here, taken of mixed compound fractions from the column, is actually the major product of the reaction.
trans-1,4-Diphenyl-3-(phenylthio)-azetidin-2-one (93).

Reaction of α-diazo thiol ester 79 (0.045 g, 0.253 mmol) with N-benzylideneaniline (0.160 g, 0.883 mmol) and catalytic rhodium(II) acetate (0.003 g, 0.007 mmol) in 2.25 mL of dichloromethane for ca. 3 h according to the general procedure provided the crude product as a light brown oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) yielded 0.071 g (85%) of trans-β-lactam 93 as an off-white solid, mp 116-177 °C. The stereochemistry of the product was determined by ¹H NMR analysis.

IR (CCl₄): 3060, 3030, 2920, 1760, 1590, 1495, 1450, 1430, 1370, 1130, and 1015 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 7.51 (d, J = 7.2 Hz, 2 H), 7.17-7.35 (m, 12 H), 7.00-7.04 (m, 1 H), 4.81 (d, J = 2.5 Hz, 1 H), and 4.26 (d, J = 2.5 Hz, 1 H).

¹³C NMR (75 MHz, CDCl₃): 163.3, 137.1, 136.2, 132.2, 132.1, 129.2, 129.0, 128.9, 128.0, 125.9, 124.3, 117.2, 62.9, and 61.4.
3-Methoxy-2-methyl-4-(phenylthio)cyclobuten-1-one (97).

Reaction of α-diazo thiol ester 79 (0.101 g, 0.567 mmol) with 1-methoxypropyne (0.166 mL, 0.139 g, 1.98 mmol) and catalytic rhodium(II) acetate (0.005 g, 0.011 mmol) in 5 mL of dichloromethane for ca. 3 h according to the general procedure gave 0.137 g of a brown oil. Purification by column chromatography on 15 g of silica gel (gradient elution with 20-30% ethyl acetate-hexane) yielded 0.090 g (72%) of cyclobutenone 97.

IR (thin film): 3020, 2990, 2940, 2910, 2850, 1760, 1620, 1580, 1450, 1435, 1380, 1340, 1210, 1170, 1110, 1060, 1020, 965, 740, and 690 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 7.47-7.50 (m, 2 H), 7.29-7.31 (m, 3 H), 4.59 (q, J = 1.8 Hz, 1 H), 4.14 (s, 3 H), and 1.54 (d, J = 1.7 Hz, 3 H).

¹³C NMR (75 MHz, CDCl₃): 184.2, 176.1, 134.1, 130.8, 128.7, 128.2, 120.8, 62.7, 59.7, and 6.6.

Elemental Analysis: 
Calcd for C₁₂H₁₂O₂S: C, 65.43; H, 5.49
Found: C, 65.22; H, 5.58
3-Methoxy-2-methyl-4-(2,4,6-trimethylphenylthio)cyclobuten-1-one (98).

Reaction of α-diazo thiol ester 57 (0.050 g, 0.227 mmol) with 1-methoxypropyne (0.066 mL, 0.055 g, 0.787 mmol) and catalytic rhodium(II) acetate (0.002 g, 0.005 mmol) in 1.9 mL of dichloromethane for ca. 3 h according to the general procedure provided crude product as a light brown oil. Purification by column chromatography on 6 g of silica gel (elution with 15% ethyl acetate-hexane) gave 0.042 g (71\%)\(^9\) of cyclobutenone 98 as a yellow oil.

\[
\text{IR (thin film):} \quad 3025, 2980, 2955, 2880, 1780, 1640, 1470, 1400, 1350, 1230, 1185, 1140, 990, \text{ and } 870 \text{ cm}^{-1}.
\]

\[
\text{\(^1\)H NMR (300 MHz, CDCl}_3\):} \quad 6.92 (s, 2 H), 4.30 (q, J = 2.1 Hz, 1 H), 4.12 (s, 3 H), 2.52 (s, 6 H), 2.24 (s, 3 H), \text{ and } 1.63 (d, J = 1.8 \text{ Hz}, 3 \text{ H}).
\]

\[
\text{\(^13\)C NMR (75 MHz, CDCl}_3):} \quad 184.5, 177.0, 143.9, 138.8, 129.0, 127.0, 119.6, 63.5, 59.6, 22.1, 21.0, \text{ and } 6.9.
\]

\(^9\)Yields for this reaction ranged from 71-92\%.
2-Methyl-3-phenyl-4-(2,4,6-trimethylphenylthio)cyclobuten-1-one (96).

Reaction of α-diazo thiol ester 57 (0.155 g, 0.704 mmol) with 3-phenyl-2-propyne (0.425 mL, 0.394 g, 3.40 mmol) and catalytic rhodium(II) acetate (0.007 g, 0.016 mmol) in 5 mL of dichloroethane for ca. 3 h according to the general procedure provided 0.535 g of crude product as a dark green oil. Purification by column chromatography on 53 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) afforded 0.109 g (50%) of 96 as an orange oil.

IR (thin film):

3040, 3020, 2940, 2920, 2840, 1760, 1610, 1570, 1490, 1450, 1370, 1350, 1310, 1290, 1200, 1175, 1060, 1010, 970, 850, 760, and 690 cm\(^{-1}\).

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

7.65-7.68 (m, 2 H), 7.47-7.50 (m, 3 H), 7.25 (s, 2 H), 4.84 (q, J = 2.0 Hz, 1 H), 2.46 (s, 6 H), 2.26 (s, 3 H), and 1.97 (d, J = 1.8 Hz, 3 H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)):

187.7, 165.9, 143.7, 143.0, 138.7, 131.3, 131.2, 129.4, 129.1, 129.0, 127.8, 64.7, 22.3, 21.0, and 9.5.
1,2,2a,7a-Tetrahydro-7H-cyclobuta[\textit{a}]inden-1-one (114).\textsuperscript{10}

Procedure A: Zinc Reduction

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with sulfide 91 (0.095 g, 0.357 mmol) and 4 mL of tetrahydrofuran. Activated zinc dust (0.466 g, 7.13 mmol) was added in one portion, followed by 4 mL of saturated aqueous ammonium chloride. The flask was fitted with a reflux condenser and heated at reflux with vigorous stirring for 25 h. The reaction mixture was cooled to 25 °C and filtered, washing the solids with diethyl ether. The combined filtrates were washed with two 10-mL portions of saturated aqueous NaHCO\textsubscript{3}. The combined aqueous phases were extracted with 10 mL of diethyl ether. The combined organic extracts were washed with 10 mL of brine, dried over MgSO\textsubscript{4}, filtered and concentrated (\textit{use of an ice bath during rotary evaporation is recommended to minimize product loss}) to afford 0.088 g of crude product. Purification by column chromatography on 9 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) afforded 0.047 g (84%) of 114 as an oil which solidified to a white solid upon storage at 0 °C. The product contained <5% remaining starting material as determined by $^1$H NMR analysis.

Procedure B: Tributyltin hydride Reduction

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with sulfide 91 (0.094 g, 0.353 mmol) and 2.5 mL of toluene. The flask was fitted with a reflux condenser and heated at reflux while a solution of tributyltin hydride (0.114 mL, 0.123 g, 0.424 mmol) and AIBN (0.006 g, 0.037 mmol) in

1.5 mL of toluene was added slowly dropwise (through the reflux condenser) over ca. 35 min. An additional 1 mL of toluene was used to rinse the syringe and was added to the reaction mixture. After 1 h at reflux, the reaction mixture was cooled to 25 °C and concentrated (use of an ice water bath during rotary evaporation is recommended to prevent product loss) to give 0.250 g of a yellow oil. Purification by column chromatography on 20 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) provided 0.050 g (89%) of 114 as a colorless oil which solidified to a white solid upon storage at 0 °C, mp 33.5-36 °C.

IR (thin film): 3060, 3010, 2940, 2900, 2840, 1775, 1475, 1450, 1430, 1390, 1270, 1220, 1090, 1070, 1050, 980, and 750 cm⁻¹.

¹H NMR¹¹ (300 MHz, CDCl₃): 7.21-7.31 (m, 4 H), 4.03-4.06 (m, 2 H), 3.55-3.65 (m, 1 H), 3.30 (d, J = 16.8 Hz, 1 H), 3.04-3.13 (m, 1 H), and 2.88 (d, J = 17.7 Hz, 1 H).

¹³C NMR (75 MHz, CDCl₃): 212.2, 144.5, 143.0, 127.4, 125.3, 125.0, 62.7, 55.6, 36.5, and 33.9.

¹¹The product of the tin hydride reduction produced the spectrum which is reproduced here.
2-Methyl-2-(phenylthio)spiro[3.5]nonan-1-one (131).

A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with lithium t-butoxide (0.043 g, 0.537 mmol) and 2 mL of tetrahydrofuran and cooled to 0 °C. A solution of α-thiocyclobutaneone 82 (0.110 g, 0.446 mmol) in 1 mL of tetrahydrofuran was added slowly dropwise via cannula over ca. 3 min, followed by a 0.5 mL tetrahydrofuran rinse. The yellow enolate solution was stirred at 0 °C for 30 min, and then methyl iodide (0.110 mL, 0.251 g, 1.77 mmol) was added rapidly dropwise. The ice bath was removed, and the reaction mixture (Note: the reaction flask was wrapped in foil to prevent light exposure) was stirred at 25 °C for 26 h. The resulting yellow, slightly cloudy reaction mixture was partitioned between 10 mL of diethyl ether and 10 mL of saturated aqueous NH₄Cl. The organic phase was separated and washed with 5 mL of water. The combined aqueous layers were extracted with 5 mL of diethyl ether. The combined organics were washed with 8 mL of brine, dried over MgSO₄, filtered and concentrated to provide 0.104 g of crude product. Purification by column chromatography on 13 g of silica gel (gradient elution with 0-2.5% ethyl acetate-hexane) gave 0.089 g (ca. 77%) of 131 as an oil, isolated along with a minor O-alkylation-type impurity in a ratio of 12:1.

IR (thin film): 3050, 2920, 2840, 1770, 1580, 1470, 1440, 1370, 1200, 1080, 1060, 1020, 740, and 690 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 7.49 (dd, J = 7.7, 2.1 Hz, 2 H), 7.28-7.33 (m, 3 H), 3.43 (d, J = 16.2 Hz, 1 H), 2.75 (d, J = 16.4 Hz, 1 H), 2.03-2.06 (m, 1 H), 1.23-1.76 (m, 9 H), and 1.23 (s, 3 H).
$^{13}$C NMR$^{12}$ (75 MHz, CDCl$_3$): 205.4, 136.1, 134.1, 128.8, 128.7, 128.6, 128.5, 71.2, 53.2, 38.8, 34.5, 33.6, 32.5, 25.6, 23.8, 23.3, and 15.5.

$^{12}$Two aromatic peaks are due to the byproduct.
7-Methyl-7-(phenylthio)bicyclo[3.2.0]hept-2-en-6-one (122a, 122b).

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with lithium t-butoxide (0.068 g, 0.849 mmol) and 2.5 mL of tetrahydrofuran and cooled to 0 °C. A solution of α-thiocyclobutanone 86 (0.153 g, 0.707 mmol) in 2 mL of tetrahydrofuran was added slowly dropwise via cannula over ca. 10 min, followed by a 0.5 mL tetrahydrofuran rinse. The enolate solution was stirred at 0 °C for 30 min, and methyl iodide (0.175 mL, 0.399 g, 2.81 mmol) was added rapidly dropwise. The ice bath was removed, and the orange reaction mixture was stirred at 25 °C for 23 h (Note: the reaction flask was wrapped in foil to prevent light exposure) and was then partitioned between 10 mL of diethyl ether and 10 mL of saturated aqueous NH₄Cl. The organic layer was separated and washed with 5 mL of water, and the combined aqueous phases were extracted with 5 mL of diethyl ether. The combined organic phases were washed with 10 mL of brine, dried over MgSO₄, filtered and concentrated to give 0.163 g of an orange oil. Purification by column chromatography on 16 g of silica gel (gradient elution with 2.5-5% ethyl acetate-hexane) afforded 0.142 g (87%) of 122a and 122b, obtained as an approximately 12:1 mixture of diastereomers by ¹H NMR analysis.

122a:

IR (thin film): 3050, 2950, 2910, 2850, 1770, 1580, 1470, 1435, 1370, 1340, 1260, 1235, 1165, 1060, 1035, 970, 915, 725, and 690 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 7.57-7.60 (m, 2 H), 7.28-7.32 (m, 3 H), 5.90-5.96 (m, 2 H), 3.96-4.03 (m, 1 H), 3.46-3.51 (m, 1 H), 2.74-2.82 (m, 1 H), 2.46-2.56 (m, 1 H), and 1.48 (s, 3 H).
$^{13}$C NMR (75 MHz, CDCl$_3$): 212.6, 135.0, 134.9, 131.6, 129.8, 128.7, 128.0, 70.7, 57.7, 51.9, 34.6, and 22.9.
7-*exo*-(Phenylmethyl)-7-(phenylthio)bicyclo[3.2.0]hept-2-en-6-one (124a).

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with lithium *t*-butoxide (0.070 mg, 0.874 mmol) and 2.5 mL of tetrahydrofuran and cooled to 0 °C. A solution of α-thiocyclobutanone 86 (0.157 g, 0.726 mmol) in 2 mL of tetrahydrofuran was added slowly dropwise via cannula over ca. 8 min, followed by a 0.50 mL tetrahydrofuran rinse. The deep orange enolate solution was stirred at 0 °C for 30 min, and benzyl bromide (0.345 mL, 0.496 g, 2.90 mmol) was added rapidly dropwise. The ice bath was removed, and the reaction mixture was stirred at 25 °C for 17 h (the flask was wrapped in foil to prevent light exposure). The crude orange reaction mixture was then partitioned between 10 mL of saturated aqueous NH₄Cl and 10 mL of diethyl ether. The organic layer was separated and washed with 10 mL of water, and the combined aqueous phases were extracted with 10 mL of diethyl ether. The combined organic phases were washed with 8 mL of brine, dried over MgSO₄, filtered and concentrated to give 0.402 g of an orange oil. Purification by column chromatography on 25 g of silica gel (gradient elution with 2.5-5% ethyl acetate-hexane) afforded 0.192 g (86%) of 124a as a single isomer based on ¹H NMR analysis, isolated along with a minor O-alkylation-type impurity in a ratio of ca. 11:1.

IR (thin film): 3060, 3030, 2960, 2920, 2860, 1775, 1600, 1580, 1490, 1480, 1450, 1440, 1350, 1290, 1265, 1240, 1160, 1070, 1050, 1030, 920, 750, and 700 cm⁻¹.
$^{1}\text{H NMR (300 MHz, CDCl}_3\text{)}$: 7.66 (dd, J = 8.2, 2.0 Hz, 2 H), 7.22-7.34 (m, 6 H), 7.10 (dd, J = 8.1, 2.0 Hz, 2 H), 5.88 (s, 2 H), 3.63 (dd, J = 8.2, 1.3 Hz, 1 H), 3.10 (d, J = 13.8 Hz, 1 H), 2.97 (d, J = 13.8 Hz, 1 H), 2.93 (ddd, J = 9.7, 8.0, 1.6 Hz, 1 H), 2.66 (ddd, J = 18.1, 3.1, 1.7 Hz, 1 H), and 2.29 (ddd, J = 18.1, 10.2, 2.1 Hz, 1 H).

$^{13}\text{C NMR (75 MHz, CDCl}_3\text{)}$: 212.8, 136.2, 135.1, 134.6, 131.8, 130.1, 129.4, 128.9, 128.5, 128.0, 127.0, 74.9, 59.3, 48.3, 41.5, and 34.6.
7-(Phenylmethyl)bicyclo[3.2.0]hept-2-en-6-one (125a, 125b).

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with sulfide 124a (0.159 g, 0.519 mmol) and 4.5 mL of toluene. The flask was fitted with a reflux condenser and heated at reflux while a solution of tributyltin hydride (0.167 mL, 0.181 g, 0.621 mmol) and AIBN (0.009 g, 0.055 mmol) in 1.5 mL of toluene was added slowly dropwise (through the reflux condenser) over ca. 35 min. An additional 1 mL of toluene was used to rinse the syringe and was added to the reaction mixture. After stirring for 20 min at reflux, the reaction mixture was cooled to 25 °C and concentrated to afford 0.344 g of a colorless oil. Purification by column chromatography on 35 g of silica gel followed by a second column on 10 g of silica gel (gradient elution with 2.5-5% ethyl acetate-hexane) provided 0.089 g (86%) of 125a and 125b, obtained as an approximately 7:1 mixture of isomers by 1H NMR analysis.

125a:

IR (thin film): 3080, 3060, 3020, 2940, 2910, 2840, 1770, 1600, 1500, 1450, 1440, 1345, 1270, 1240, 1145, 1070, 1030, 1000, and 695 cm⁻¹.

1H NMR (300 MHz, CDCl₃): 7.27-7.32 (m, 2 H), 7.17-7.24 (m, 3 H), 5.91-5.92 (m, 1 H), 5.74-5.79 (m, 1 H), 3.75-3.85 (m, 2 H), 3.59-3.66 (m, 1 H), 2.94 (dd, J = 14.7, 5.0 Hz, 1 H), 2.63-2.72 (m, 1 H), ~2.67 (dd, J = ~15, 5 Hz, 1 H), and 2.41 (dddd, J = 17.1, 6.8, 3.9, 2.0 Hz, 1 H).

13C NMR (75 MHz, CDCl₃): 214.3, 139.5, 135.1, 129.5, 128.5, 128.3, 126.1, 65.5, 59.4, 42.5, 34.1, and 30.6.
Lactone 135.

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with α-thiocyclobutanone 82 (0.060 g, 0.244 mmol) and 3 mL of methanol. Hydrogen peroxide (30%, 0.110 mL, 0.033 g, 0.970 mmol) was added; the reaction mixture was stirred at 25 °C for 23 h and then partitioned between 8 mL of dichloromethane and 8 mL of water. The aqueous phase was saturated with sodium chloride and washed with three 8-mL portions of dichloromethane. The combined organic layers were dried over MgSO₄, filtered and concentrated to provide 0.068 g of crude product. Purification by column chromatography on 30 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) afforded 0.046 g (72%) of lactone 135 as a colorless oil.

IR (thin film): 3020, 2900, 2820, 1760, 1560, 1460, 1420, 1390, 1330, 1310, 1280, 1230, 1200, 1170, 1130, 1070, 1045, 960, 930, 820, 720, and 670 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 7.53-7.56 (m, 2 H), 7.29-7.36 (m, 3 H), 5.49 (s, 1 H), 2.62 (d, J = 17.1 Hz, 1 H), 2.38 (d, J = 17.6 Hz, 1 H), and 1.34-1.70 (m, 10 H).

¹³C NMR (75 MHz, CDCl₃): 175.2, 132.9, 132.5, 129.2, 128.1, 96.6, 44.9, 40.0, 34.9, 31.6, 25.4, 22.7, and 22.7.
2-(Phenylsulfanyl)spiro[3.5]nonan-1-one (141).

Procedure A: $m$-CPBA Oxidation

A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter, and a rubber septum was charged with sulfide 82 (0.101 g, 0.410 mmol) and 5 mL of dichloromethane and cooled to 0 °C. A solution of $m$-chloroperbenzoic acid (85%, 0.083 g, 0.409 mmol) in 2 mL of dichloromethane was added slowly dropwise by syringe over ca. 8 min, followed by a 1 mL dichloromethane rinse. The reaction mixture was stirred at 0 °C for 70 min (became slightly cloudy) and was then partitioned between 40 mL of diethyl ether and 10 mL of 10% aqueous Na$_2$SO$_3$. The organic phase was separated and washed with two 10-mL portions of saturated aqueous NaHCO$_3$ and 10 mL of brine, dried over MgSO$_4$, filtered and concentrated to afford 0.110 g of a light brown oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 20-30% ethyl acetate-hexane) gave 0.095 g (88%) of 141 as a colorless oil, obtained as an approximately 1.5:1 mixture of diastereomers by $^1$H NMR analysis.

Procedure B: NaIO$_4$ Oxidation

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with sodium periodate (0.125 g, 0.584 mmol) and 1.25 mL of water and cooled to 0 °C. A solution of sulfide 82 (0.096 g, 0.390 mmol) in 0.75 mL of methanol was added dropwise via cannula, followed by a 0.5 mL methanol rinse. The resulting cloudy white reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for an additional 26 h. The reaction mixture was partitioned between 10 mL of
dichloromethane and 10 mL of water. The aqueous phase was separated and extracted with three 10-mL portions of dichloromethane. The combined organic phases were dried over MgSO₄, filtered and concentrated to afford 0.109 g of crude product as a yellow oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 20-30% ethyl acetate-hexane) yielded 0.078 g (76%) of 141 as an off-white solid, obtained as an approximately 1.5:1 mixture of diastereomers by ¹H NMR analysis.

IR (thin film): 3040, 2920, 2840, 2220, 1770, 1470, 1435, 1370, 1285, 1250, 1190, 1160, 1140, 1080, 1040, 1010, 990, 900, 725, and 680 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 7.72-7.75 (m, 2 H), 7.63-7.67 (m, 2 H), 7.50-7.57 (m, 6 H), 4.03 (appar t, J = 2.4 Hz, 1 H), 3.66 (dd, J = 4.5, 2.3 Hz, 1 H), 3.08 (dd, J = 17.1, 2.0 Hz, 1H), 2.97 (dd, J = 17.5, 1.1 Hz, 1H), 2.82 (ddd, J = -17.5, 3.0, 1.4 Hz, 1 H), 2.76 (dd, J = 17.2, 4.6 Hz, 1 H), 2.22-2.29 (m, 2 H), 2.05-2.12 (m, 1 H), and 1.26-2.29 (m, 17 H).

¹³C NMR (75 MHz, CDCl₃): 198.6, 197.3, 142.7, 141.6, 131.6, 131.3, 129.2, 129.1, 125.0, 124.7, 87.0, 84.5, 58.9, 55.9, 39.1, 38.1, 38.0, 37.1, 32.2, 25.3, 25.1, 23.8, 23.5, and 22.9.

Elemental Analysis: Calcd for C₁₅H₁₈O₂S: C, 68.67; H, 6.92
Found: C, 68.71; H, 7.01

Sulfoxide 141 (0.091 g, 0.35 mmol) was dissolved in 3 mL of toluene in a 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet. Acetic anhydride (0.164 mL, 0.177 g, 1.74 mmol) and p-toluenesulfonic acid (0.002 g, 0.001 mmol) were added, and the flask was fitted with a reflux condenser and heated at reflux for 1 h. The reaction mixture was cooled to 25 °C and concentrated to afford 0.113 g of crude product as an oil. Purification by column chromatography on 6 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) provided 0.094 g (89%) of 154 as a colorless oil.

IR (thin film): 3040, 3000, 2920, 2840, 1780, 1745, 1570, 1465, 1430, 1390, 1360, 1280, 1210, 1170, 1140, 1125, 1080, 1065, 1050, 1025, 970, 890, 870, 750, and 685 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 7.29-7.44 (m, 5 H), 3.27 (d, J = 16.5 Hz, 1 H), 2.71 (d, J = 16.5 Hz, 1 H), 2.13-2.21 (m, 2 H), 2.11 (s, 3 H), 1.67-1.84 (m, 3 H), 1.43-1.45 (m, 2 H), and 1.18-1.33 (m, 3 H).

¹³C NMR (75 MHz, CDCl₃): 193.9, 168.6, 135.1, 129.3, 129.2, 128.9, 128.9, 98.4, 49.8, 44.2, 32.6, 30.5, 25.3, 24.0, 23.5, 22.5, and 21.2.
2-(Phenylthio)-2'-carbethoxyspiro[4.5]decan-1-one (169a,169b).

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with cyclobutanone 82 (0.048 g, 0.195 mmol) and 0.750 mL of diethyl ether and cooled to 0 °C. Boron trifluoride etherate (0.048 mL, 0.055 g, 0.390 mmol) was added in one portion, followed by a solution of ethyl diazoacetate (0.041 mL, 0.044 g, 0.390 mmol) in 0.750 mL of diethyl ether, slowly dropwise via syringe over ca. 10 min (the solution was carefully added down the side-arm of the flask, so that it would be cooled before contact with the reaction mixture). A 0.50 mL diethyl ether rinse was then added over ca. 1 min, and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction mixture was diluted with 5 mL of diethyl ether and washed with one 3-mL portion each of saturated aqueous NaHCO₃, water, and brine. The organic phase was then dried over MgSO₄, filtered and concentrated to provide 0.062 g of a yellow oil. Purification by column chromatography on 6 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) afforded 0.043 g (66%) of diastereomeric products 169a and 169b as a ca. 1:1 mixture by ¹H NMR analysis.

IR (thin film):

3040, 2960, 2910, 2840, 1750, 1720, 1660, 1570, 1470, 1440, 1385, 1360, 1320, 1300, 1250, 1200, 1170, and 1110 cm⁻¹.
$^1$H NMR (300 MHz, CDCl$_3$): 7.44-7.49 (m, 4 H), 7.24-7.33 (m, 6 H), 4.16-4.27 (m, 4 H), 3.53 (dd, J = 9.6, 7.8 Hz, 1 H), 3.49 (s, 1 H), 3.48 (s, 1 H), 3.33 (appar t, J = 9.5 Hz, 1 H), 2.47 (two dd, J = 13.5, 10.0 Hz, 2 H), 2.11 (dd, J = 13.6, 8.0 Hz, 1 H), 2.06 (dd, J = 14.4, 9.5 Hz, 1 H), 1.70-1.85 (m, 2 H), 1.34-1.65 (m, 18 H), 1.29 (appar t, J = 7.7 Hz, 3 H), and 1.28 (appar t, J = 7.1 Hz, 3 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): 206.0, 202.5, 169.6, 168.8, 134.3, 133.4, 132.3, 131.9, 129.0, 128.8, 128.1, 127.5, 66.2, 62.2, 61.6, 61.5, 50.4, 50.3, 42.0, 41.3, 36.6, 36.4, 34.0, 33.0, 31.1, 25.6, 25.4, 22.2, 22.1, 14.2, and 14.1.
4-(Benzyloxy)methyl)thioanisole (199).

A 15-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and a rubber septum was charged with sodium hydride (60% dispersion in mineral oil, 0.143 g, 3.58 mmol). The mineral oil was removed by washing with three 1-mL portions of hexane followed by careful evacuation by pumping. 2 mL of tetrahydrofuran was added, and the reaction flask was immersed in a 25 °C water bath. A solution of 4-(methylthio)benzyl alcohol (191) (0.499 g, 3.24 mmol) in 1.5 mL of tetrahydrofuran was added slowly dropwise via cannula over 10 min, followed by a 0.50 mL tetrahydrofuran rinse. Vigorous hydrogen gas evolution was observed. The resulting alkoxide solution was stirred at 25 °C for 10 min, and a solution of benzyl bromide (0.500 mL, 0.719 g, 4.20 mmol) and catalytic sodium iodide (0.005 g, 0.033 mmol) in 1.5 mL of tetrahydrofuran was added dropwise via cannula over ca. 2 min, followed by a 0.50 mL tetrahydrofuran rinse. The cloudy reaction mixture (the reaction flask was wrapped in foil to minimize light exposure) was stirred at 25 °C for 1 h and then poured into 15 mL of water. The resulting mixture was extracted with four 10-mL portions of diethyl ether, and the combined organic phases were washed with 15 mL of brine, dried over MgSO4, filtered and concentrated to provide 1.0 g of a light yellow oil. Purification by column chromatography on 30 g of silica gel (gradient elution with 2.5-5% ethyl acetate-hexane) gave 0.735 g (93%) of protected alcohol 199.

IR (thin film): 3060, 3020, 2980, 2910, 2850, 1595, 1490, 1450, 1430, 1400, 1355, 1320, 1200, 1090, 1070, 1010, 960, 790, 730, and 690 cm⁻¹.

1H NMR (300 MHz, CDCl3): 7.36 (d, J = 4.4 Hz, 4 H), 7.23-7.31 (m, 5 H), 4.54 (s, 2 H), 4.51 (s, 2 H), and 2.48 (s, 3 H).
$^{13}$C NMR (75 MHz, CDCl$_3$): 138.2, 137.7, 135.2, 128.4, 127.8, 127.7, 126.7, 72.0, 71.7, and 16.0.
\[ \text{S-4-(Benzyloxymethyl)phenyl 2-diazoethanethioate (209).} \]

**Sulfide Oxidation:**

A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with sulfide 199 (0.134 g, 0.548 mmol) and 7.5 mL of dichloromethane and cooled to 0 °C. A solution of \( m \)-CPBA (85\%, 0.111 g, 0.547 mmol) in 2.5 mL of dichloromethane was added dropwise via cannula over ca. 6 min, followed by a 1 mL dichloromethane rinse. The reaction mixture was stirred at 0 °C for 50 min, and Ca(OH)\(_2\) (0.061 g, 0.823 mmol) was added in one portion. The cooling bath was removed, and stirring was continued at 25 °C for 20 min. The resulting cloudy reaction mixture was filtered through a pad of Celite\textsuperscript{®}, washing with several portions of dichloromethane. The filtrates were concentrated to give sulfoxide 207 as an off-white solid.

**IR (thin film):** 3050, 3020, 2980, 2900, 2840, 1700, 1590, 1550, 1485, 1445, 1390, 1350, 1285, 1240, 1200, 1080, 1040, 950, and 900 cm\(^{-1}\).

**Pummerer Rearrangement:**

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with crude sulfoxide 207, 4 mL of dichloromethane, and trifluoroacetic anhydride (0.386 mL, 0.574 g, 2.73 mmol). The flask was fitted with a reflux condenser and heated at reflux for 30 min. The reaction mixture was cooled to 25 °C and concentrated to give a light brown oil which was dissolved in 6 mL of methanol and transferred to a 15-mL, one-necked, round-bottomed flask containing 15 mL of 10%
NaOH solution (37.5 mmol). Heat was evolved, and the resulting cloudy reaction mixture was stirred vigorously for 20 min, then acidified by the addition of ca. 16 mL of 10% HCl solution. The reaction mixture was extracted with four 12-mL portions of dichloromethane, and the combined organic phases were dried over MgSO₄, filtered and concentrated to afford 0.225 g of a white solid. Due to the presence of residual m-chlorobenzoic acid, the crude thiol was purified by column chromatography on 10 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) to give 0.113 g (90% from 199) of thiol 208 as a pale yellow oil.

Diazooacetylation:

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with sodium hydride (60% dispersion in mineral oil, 0.022 mg, 0.55 mmol). The mineral oil was removed by washing with three 0.5 mL portions of hexane, followed by careful evacuation by pumping. 1.5 mL of tetrahydrofuran was added, followed by a solution of thiol 208 (0.113 g, 0.491 mmol) in 1 mL of tetrahydrofuran, dropwise via cannula, and a 0.50 mL tetrahydrofuran rinse. Hydrogen gas evolution was observed. The resulting light yellow thiolate solution was stirred at 25 °C for 20 min, then cooled to 0 °C as a solution of succinimidyl diazoacetate (206) (0.90 g, 4.91 mmol) in 1 mL of tetrahydrofuran was added dropwise via cannula, followed by a 0.50 mL tetrahydrofuran rinse. The reaction mixture rapidly changed colors from yellow to orange to brown to dark brown. The cooling bath was removed and stirring was continued at 25 °C for 30 min. The crude reaction mixture was filtered through a pad of Celite®, washing with several portions of diethyl ether. The dark orange filtrates were concentrated to afford 0.123 g of a viscous, dark brown-orange oil. Purification by column chromatography on 12 g of silica gel (gradient elution with 5-20% ethyl acetate-hexane) provided 0.073 g (50%) of α-diazo thiol ester 209 as a yellow oil.
IR (thin film): 3080, 3050, 3010, 2910, 2840, 2100, 1630, 1490, 1445, 1400, 1385, 1330, 1200, 1130, 1085, 1010, 850, 800, 730, and 690 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): 7.48 (d, J = 8.2 Hz, 2 H), 7.42 (d, J = 8.2 Hz, 4 H), 7.37 (d, J = 4.3 Hz, 2 H), 7.30-7.50 (m, 3 H), 5.24 (s, 1 H), and 4.58 (s, 4 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): 184.1, 142.6, 140.4, 137.9, 135.3, 128.4, 128.3, 127.7, 127.7, 126.3, 72.4, 71.3, and 54.2.
Support-Bound Sulfide 189.

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and a needle inlet was charged with sodium hydride (60% disperion in mineral oil, 0.076 g, 1.90 mmol). The mineral oil was removed by washing with three 2-mL portions ofhexane followed by careful evacuation by pumping. 1.5 mL of N,N-dimethylformamide was added. To the resulting sodium hydride suspension was added a solution of 4-(methyithio)benzyl alcohol (191) (0.234 g, 1.52 mmol) and catalytic 18-Crown-6 (0.006 g, 0.023 mmol) in 0.500 mL of N,N-dimethylformamide, dropwise via syringe over ca. 5 min. A 0.50 mL N,N-dimethylformamide rinse was also added. Hydrogen gas evolution was observed. The resulting yellow thiolate mixture was stirred at 25 °C for 1 h, then transferred dropwise via cannula over 1 min to a slurry of Merrifield resin (190, chloromethylated copolystyrene-1% divinylbenzene, 100-200 mesh) (1.00 g, 0.76 mmol Cl/g) in 5 mL of tetrahydrofuran prepared in a 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and a rubber septum. A 0.50 mL N,N-dimethylformamide rinse was also transferred. The flask was fitted with a reflux condenser and heated to ca. 85 °C\(^{13}\) with gentle stirring for 48 h. Due to loss by evaporation at this temperature, the solvents were replenished as needed. The reaction mixture was cooled to 25 °C and transferred to a 20-mL, plastic fritted funnel with the aid of dichloromethane. The resin was washed with 10-mL portions of the following solvents: N,N-dimethylformamide/water (1:1, 4 times), N,N-dimethylformamide (3 times), and dichloromethane (3 times). The resin was dried under vacuum to afford 1.09 g of 189 as light yellow beads.

\(^{13}\)A subsequent run at 55 °C also worked well.
IR (KBr): 1087 cm$^{-1}$. 
Support-Bound Sulfoxide 211.

A 50-mL, three-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel fitted with a septum, a glass stopper, and a rubber septum was charged with polymer-supported sulfide 189 (0.76 mmol S-H) and 10 mL of dichloromethane and cooled to 0 °C. The slurry was stirred gently as a solution of m-chloroperbenzoic acid (85%, 0.154 g, 0.759 mmol) in 5 mL of dichloromethane was added dropwise from the addition funnel over 30 min. The reaction mixture was stirred at 0 °C for 4 h, and then transferred to a 20-mL, plastic fritted funnel with the aid of dichloromethane. The resin was washed with 12 mL portions of the following solvents: methanol/water (1:1, 4 times), methanol (3 times), and dichloromethane (3 times). The resin was dried under vacuum to give support-bound sulfoxide 211.

IR (KBr): 1085 and 1053 cm⁻¹.
Support-Bound Thiol 188.

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with resin-bound sulfoxide 211 (<0.76 mmol), 8 mL of dichloromethane, and trifluoroacetic anhydride (0.540 mL, 0.803 g, 3.82 mmol). The flask was fitted with a reflux condenser and heated at reflux (oil bath ~43 °C) for 3 h, then cooled to 25 °C and transferred to a 20-mL, plastic fritted funnel with the aid of dichloromethane. The resin was washed with two 8-mL portions of dichloromethane and poured as a slurry in 15 mL of dichloromethane/methanol (1:1) into 20 mL of 10% NaOH solution (53 mmol) contained in a 100-mL, one-necked, round-bottomed flask. The resulting mixture was agitated by stirring on a rotary evaporator for 30 min, and then acidified with ca. 22 mL of 10% HCl solution. The crude reaction mixture was filtered through a 20-mL, plastic fritted funnel with the aid of methanol/dichloromethane (1:1). The resin was washed with 10-mL portions of the following solvents: methanol/water (1:1, 4 times), methanol (4 times), and dichloromethane (4 times). The support-bound thiol 188 was obtained after drying under vacuum.

IR (KBr): 2566 (weak) and 1072 cm⁻¹.
Support-Bound α-Diazo Thiol Ester 187.

A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with glyoxylic acid p-toluenesulfonylhydrazone (0.184 g, 0.760 mmol) and 6 mL of dichloromethane and cooled to 0 °C. Pyridine (0.184 mL, 0.180 g, 2.27 mmol), resin-bound thiol 188 (<0.76 mmol), and phenyl dichlorophosphate (0.170 mL, 0.240 g, 1.14 mmol) were added, the cooling bath was removed, and the resulting deep orange-red reaction mixture was stirred gently at 25 °C for 5 h. The reaction mixture was transferred to a 20-mL, plastic fritted funnel with the aid of dichloromethane, and the resin was washed with 15-mL portions of the following solvents: water (3 times), methanol/water (1:1, 3 times), methanol (4 times), and dichloromethane (4 times). The orange-red resin was transferred to a 25-mL, one-necked, round-bottomed flask as a slurry in 5 mL of dichloromethane. Triethylamine (0.212 mL, 0.154 g, 1.52 mmol) was added, and the reaction mixture was agitated by stirring on a rotary evaporator at 25 °C for 2 h. The dark reaction mixture was then transferred to a 20-mL, plastic fritted funnel, and the resin was washed with 15-mL portions of the following solvents: methanol/water (1:1, 2 times), methanol (2 times), and dichloromethane (3 times). After drying under vacuum, support-bound α-diazo thiol ester 187 was produced as deep orange beads.

IR (KBr): 2104 and 1067 cm⁻¹.
3-Methoxy-2,2,4-trimethylcyclobuten-1-one (265).\textsuperscript{14}

A 100-mL, one-necked, round-bottomed flask equipped with a rubber septum and needle inlet was charged with isobutyryl chloride (1.50 mL, 1.53 g, 14.3 mmol) and 30 mL of dichloromethane and cooled to 0 °C. 1-Methoxypropyne (268) (1.80 mL, 1.50 g, 21.5 mmol) was added, followed by a solution of triethylamine (2.20 mL, 1.60 g, 15.8 mmol) in 4 mL of dichloromethane, dropwise via syringe over ca. 30 min. The resulting light pink\textsuperscript{15} reaction mixture (a precipitate gradually formed) was stirred at 25 °C for 24 h and then poured into 15 mL of 5% HCl solution. The organic phase was separated and washed with 10 mL of water. The aqueous layers were extracted with three 10-mL portions of dichloromethane, and the combined organic phases were washed with 10 mL of 10% aqueous K$_2$CO$_3$ and 15 mL of brine, dried over MgSO$_4$, filtered and concentrated to give 1.78 g of a pink oil. Purification by column chromatography on 30 g of silica gel (gradient elution with 10-30% ethyl acetate-hexane) yielded 1.51 g (75%) of cyclobuteneone 265 as a yellow oil.

IR (thin film): 2980, 2920, 2860, 1750, 1620, 1460, 1390, 1350, 1280, 1200, 1160, 1040, 960, 920, and 730 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): 4.12 (s, 3 H), 1.69 (s, 3 H), and 1.22 (s, 6 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): 195.6, 184.8, 112.7, 59.2, 58.7, 19.9, and 6.8.


\textsuperscript{15}The reaction mixture appeared orange in other runs.
3-(Methoxymethoxymethyl)-2,4,4-trimethylocyclobuten-1-one (263).

A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and a rubber septum was charged with tin reagent 266 (0.975 g, 2.67 mmol) and 6 mL of tetrahydrofuran and cooled to -78 °C while n-butyllithium solution (2.49 M in hexane, 1.07 mL, 2.66 mmol) was added dropwise via syringe over 10 min. The resulting lithium reagent solution was stirred at -78 °C for 15 min, then a solution of cyclobutenone 265 (0.175 g, 1.25 mmol) in 3 mL of tetrahydrofuran was added via cannula over 10 min, followed by a 1 mL tetrahydrofuran rinse. The reaction mixture was stirred at -78 °C for 3 h, and was then quenched by the addition of 10 mL of 5% HCl solution. Stirring was continued at 0 °C for 10 min and at 25 °C for 10 min. The crude reaction mixture was diluted with 15 mL of diethyl ether, and the aqueous layer was separated and extracted with two 5-mL portions of diethyl ether. The organic phases were washed with 10-mL portions of saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated to give 1.16 g of a yellow oil. Purification by column chromatography on 35 g of silica gel (gradient elution with 5-20% ethyl acetate-hexane) provided 0.213 g (93%) of cyclobutenone 263 as a colorless oil.

IR (thin film): 2950, 2920, 2880, 1750, 1640, 1440, 1370, 1270, 1210, 1160, 1100, 1040, 990, and 920 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): 4.69 (s, 2 H), 4.51 (q, J = 1.6 Hz, 2 H), 3.42 (s, 3 H), 1.71 (t, J = 1.6 Hz, 3 H), and 1.23 (s, 6 H).

¹³C NMR (75 MHz, CDCl₃): 198.0, 176.3, 140.6, 96.3, 62.5, 61.4, 55.4, 20.6, and 8.0.

¹⁶Yields for this reaction ranged from 78-93%.