[4 + 1] ANNULATION REACTIONS OF (TRIALKYLSILYL)KETENES: SYNTHESIS OF SUBSTITUTED INDANONES AND CYCLOPENTENONES

by

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To my wife Betsy,
and my family

[4 + 1] Annulation Reactions of (Trialkylsilyl)ketenes: Synthesis of Substituted Indanones and Cyclopentenones

by
Christopher Paul Davie

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requirements for the Degree of Doctor of Philosophy

ABSTRACT

(Trialkylsilyl)vinylketenes ("(TAS)vinylketenes") and (trialkylsilyl)arylketenes ("(TAS)-arylketenes") function as versatile four-carbon building blocks for the synthesis of carbocyclic and heterocyclic compounds. A new [4 + 1] annulation strategy for the synthesis of substituted 2-indanones, based on the reaction of TAS-arylketenes with trimethylsilyl diazomethane, has been developed. In addition, a new class of carbenoid reagents for our previously reported [4 + 1] cyclopentenone annulation has been identified. Studies have shown that the reaction of α-benzotriazolyl organolithium compounds (prepared via metallation of readily available *N*-substituted benzotriazole derivatives) with (TAS)vinylketenes generates dienolate intermediates which cyclize to form cyclopentenones. Most cases of the annulation proceed with a high level of diastereoselectivity, and deliver highly substituted and functionalized 2-silylcyclopentenones in good yield. Furthermore, the vinylsilane moiety incorporated in the [4 + 1] annulation products provides a useful handle for further synthetic transformations. Preliminary studies focused on elaboration of the cyclopentenone products have laid the groundwork for future applications of this [4 + 1] annulation methodology.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

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Part I

Introduction and Background:
Vinylketenes and (Trialkylsilyl)ketenes

Chapter 1

Vinylketenes: Versatile Four-Carbon Annulation Units

The development of annulation strategies for the synthesis of carbocyclic and heterocyclic compounds is one of the main objectives of research in the Danheiser laboratory. Toward this end, our group has had a longstanding interest in the use of vinylketenes and (silyl)vinylketenes as four-carbon annulation units. My research has focused on the use of (trialkylsilyl)*vinyl*ketenes ("TAS-*vinyl*ketenes") and (trialkylsilyl)*aryl*ketenes ("TAS-*aryl*ketenes") in [4 + 1] annulation reactions that deliver substituted cyclopentenones and 2-indanones, respectively. These [4 + 1] strategies will be discussed in detail in Parts II and III of this thesis. As an introduction, this chapter will highlight previous work by our group demonstrating the versatility of vinylketenes as synthetic building blocks, as well as work by our group and others in the area of (silyl)vinylketene-based annulations.

Scheme 1 presents three vinylketene-based annulations that have been extensively studied in our laboratory. Each of these strategies begins with the in situ trapping of a transient vinylketene intermediate in a [2 + 2] cycloaddition with an alkene or an alkyne. The resulting cycloadducts then undergo further reaction to deliver the illustrated six- and eight-membered carbocyles.

In the [4 + 2] cyclohexenol annulation (pathway a), the vinylketene is generated in situ by the dehydrohalogenation of an α,β-unsaturated acid chloride and trapped in a [2 + 2] cycloaddition with an electron-rich olefin. Hydride reduction of the resulting 2-vinylcyclobutanone followed by alkoxy-accelerated [1,3] sigmatropic rearrangement delivers the 3-cyclohexenol product.[1]

Pathway b illustrates a [4 + 4] annulation strategy for the synthesis of 2,6-cyclooctadienones.[2] In this case, the vinylketene can be generated via dehydrohalogenation of an α,β-unsaturated acid chloride or thermal electrocyclic ring opening of a cyclobutenone. The 2,3-divinylcyclobutanone derivative obtained by trapping the vinylketene in a [2 + 2]

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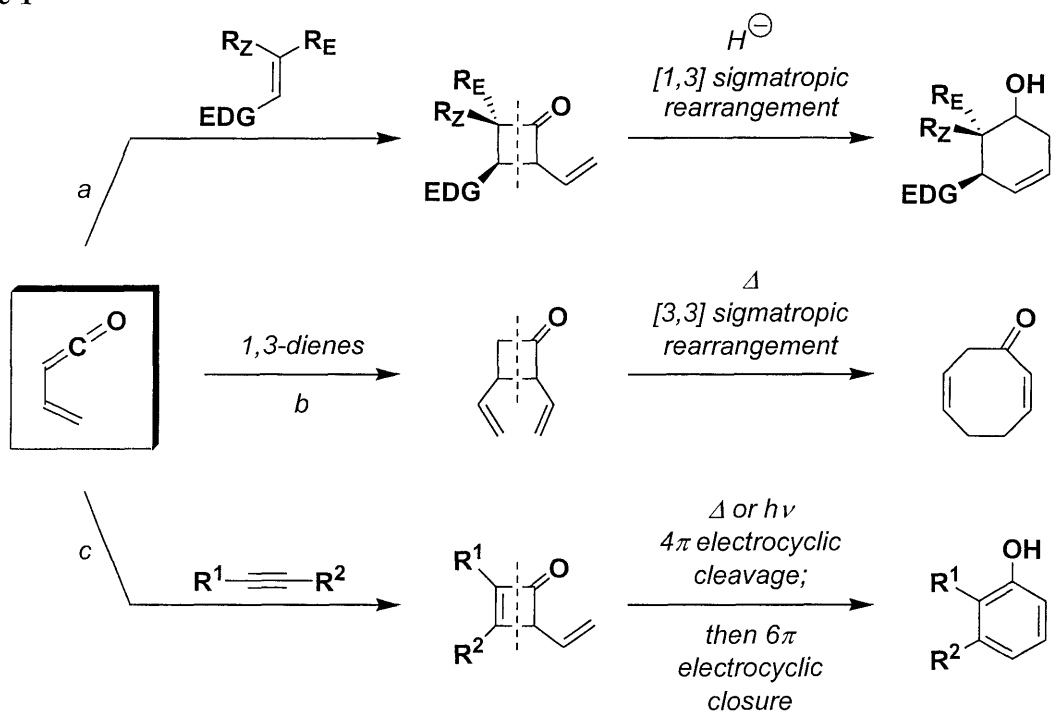
[1] Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943.
[2] Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

cycloaddition with a conjugated 1,3-diene can then undergo a [3,3] sigmatropic rearrangement to furnish the eight-membered carbocycle.

Scheme 1



Finally, pathway c summarizes a benzannulation strategy for the regiocontrolled synthesis of highly substituted phenol derivatives. The requisite vinylketene for this sequence is generated via electrocyclic opening of a cyclobutenone[3] or photochemical Wolff rearrangement of an α′-diazo-α,β-unsaturated ketone,[4] and then trapped in a regiospecific [2 + 2] cycloaddition with a substituted alkyne. Upon continued irradiation or thermolysis, the resulting vinyl-substituted cyclobutenone undergoes 4π electrocyclic ring opening to generate a dienylketene. Subsequent 6π electrocyclic ring closure followed by tautomerization furnishes the aromatic product. The utility of this strategy has been demonstrated by our group[5] and others[6] through its

[3] (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672. (b) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917.

[4] Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

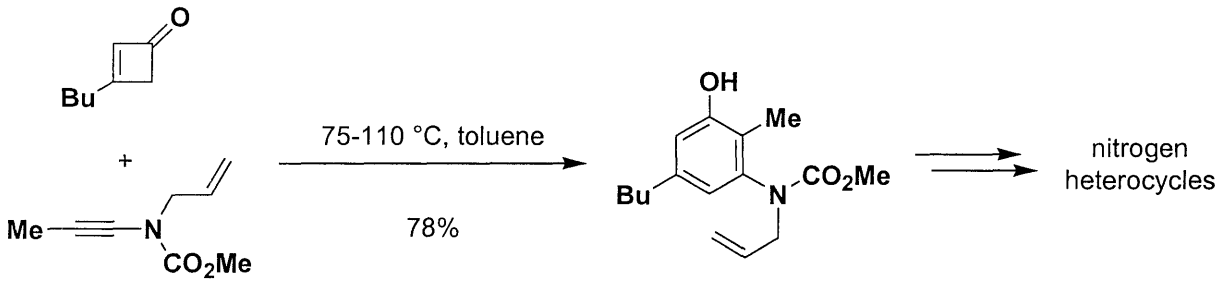
[5] For a recent example in which the Danheiser benzannulation is employed in the total synthesis of (–)-ascochlorin, see: Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407.

[6] For a recent example in which this strategy was employed in the total syntheses of (–)-cylindrocyclophanes A and F, see: Smith, A. B., III; Adams, C. M.; Kozmin, S. S.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

application to the total synthesis of a number of natural products possessing densely substituted aromatic rings.

Further development of these vinylketene-based annulations is an active area of research in our group. In particular, work towards extending the benzannulation strategy to encompass the use of ynamides as highly functionalized alkyne components (Scheme 2) was pioneered by former group member Dr. Aimee Crombie, and is currently being studied by Xiao-Yin Mak and Tammy Lam. This new variant of the benzannulation is especially exciting because the aromatic products are poised for elaboration into more complex nitrogen heterocycles.

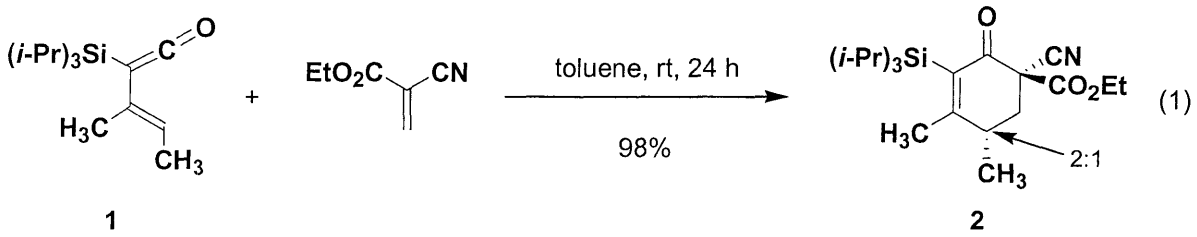
Scheme 2



Annulation Strategies Based on (Silyl)vinylketenes

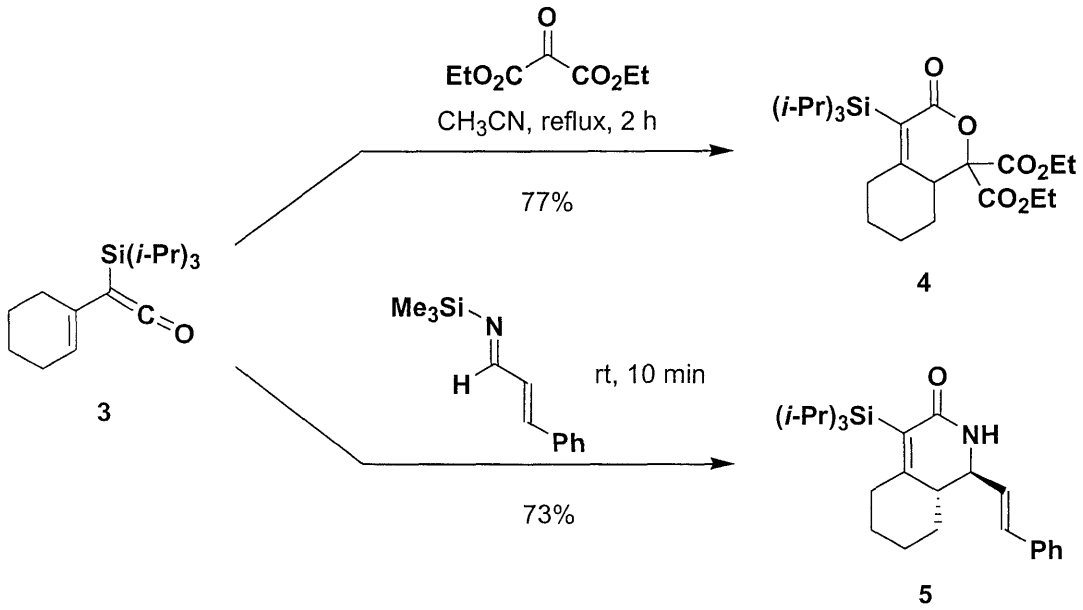
All of the annulation strategies highlighted in the previous section involve vinylketenes functioning as electron-deficient 2π components for [2 + 2] cycloadditions, a type of reactivity that is characteristic of ketenes. (Silyl)vinylketenes, on the other hand, exhibit a complementary pattern of reactivity. Silyl substituents suppress the natural tendency of ketenes to dimerize and participate in [2 + 2] cycloadditions, allowing them to express their underlying reactivity as electron-rich dienes and electrophilic carbonyl compounds. The factors that contribute to the stability and unique reactivity of silylketenes will be discussed in Chapter 2. This section will describe a number of synthetically useful annulation strategies that make use of (silyl)vinylketenes as four-carbon building blocks.

Research in our group has demonstrated that (silyl)vinylketenes can function as electron-rich dienes in a variety of [4 + 2] cycloadditions.[7] Equation 1 illustrates a representative Diels–



Alder cycloaddition between TAS-vinylketene **1** and ethyl cyanoacrylate to deliver enone **2** as a single regioisomer in excellent yield. This strategy has also been extended to carbonyl and imino dienophiles in hetero-Diels–Alder cycloadditions (Scheme 3) leading to α,β-unsaturated δ-valerolactones (e.g., **4**) and α,β-unsaturated δ-valerolactams (e.g., **5**).

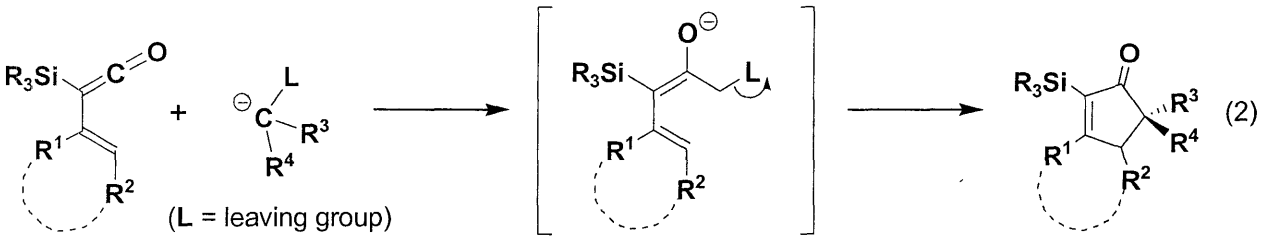
Scheme 3



In addition to serving as dienes for [4 + 2] cycloadditions, (silyl)vinylketenes can also function as electrophilic carbonyl compounds which undergo nucleophilic addition. Equation 2 illustrates a [4 + 1] annulation strategy for the synthesis of substituted cyclopentenones

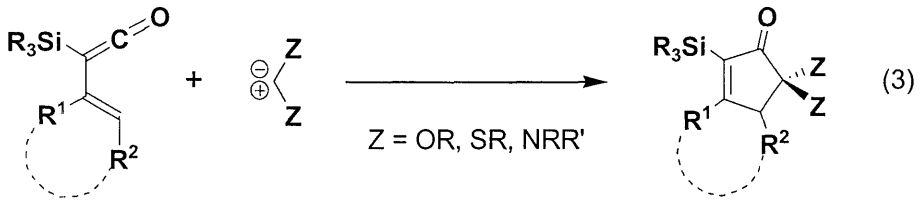
[7] (a) Danheiser, R. L.; Sard, H. *J. Org. Chem.* **1980**, *45*, 4810. (b) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 8380. (c) Bennett, D. M.; Okamoto, I.; Danheiser, R. L. *Org. Lett.* **1999**, *1*, 641.

developed in our laboratory[8] in which a "carbenoid reagent" (a nucleophilic species bearing a leaving group) adds to a TAS-vinylketene to generate a dienolate intermediate. Departure of the leaving group and cyclization deliver the desired cyclopentenone (eq 2).[9] Carbenoid reagents



(2)

successfully employed in this reaction include diazo compounds such as diazomethane and TMS-diazomethane, as well as sulfur ylides. Subsequent to our work, Rigby and co-workers reported the extension of our strategy to include reactions of nucleophilic carbenes as illustrated in eq 3.[10]



(3)

The research presented in Parts II and III of this thesis was conducted with the goal of extending the scope of the [4 + 1] annulation illustrated in eq 2 along two major fronts. Part II will discuss efforts to extend this strategy to include TAS-*aryl*ketenes (i.e., systems in which the vinyl group is embedded within the framework of an aromatic ring). This work has led to the development of a [4 + 1] annulation strategy for the synthesis of substituted indanones. Part III will discuss advances in the [4 + 1] annulation with respect to the one-carbon component ("carbenoid reagent") that have allowed access to a wide array of highly substituted and functionalized cyclopentenones. As background to this work, the next chapter will focus on the

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[8] Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690.

[9] Cyclization and displacement of the leaving group ("L") may be concerted, or alternatively, ionization of the leaving group may precede cyclization. This issue and other considerations related to the mechanism of the [4 + 1] annulation will be discussed in detail in Parts II and III of this thesis.

[10] Rigby, J. H.; Wang, Z. *Org. Lett.* **2003**, *5*, 263.

synthesis and properties of silylketenes, with a particular emphasis on (silyl)*aryl*ketenes and (silyl)*vinyl*ketenes.

Chapter 2

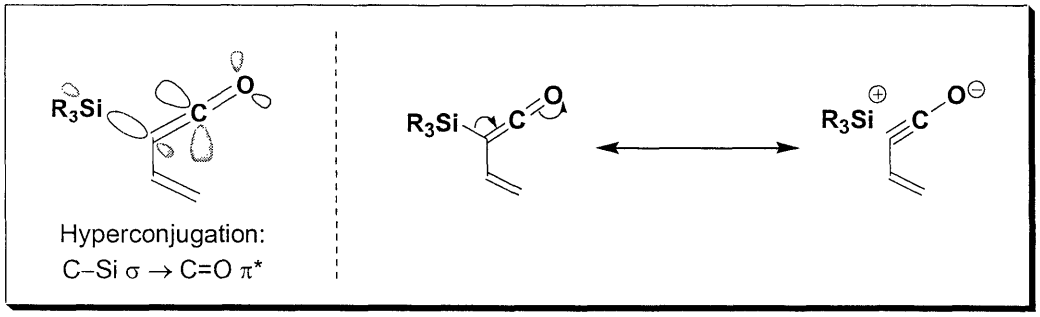
Synthesis and Properties of Silylketenes

Silylketenes are remarkably stable in comparison to their non-silyl counterparts, and have proven to be of great utility in organic synthesis.[11,12] Chapter 1 provided a summary of [4 + 1] and [4 + 2] annulation strategies employing (silyl)vinylketenes as four-carbon annulation units. This chapter will cover the origin of silylketene stability, representative physical properties, and synthetic approaches to this novel class of compounds.

Stability and Properties of Silylketenes

The exceptional stability of silylketenes relative to conventional ketene derivatives has been attributed to a hyperconjugative interaction between the C–Si σ bond and the co-planar C=O π* orbital (Scheme 4), as well as inductive σ donation by the C–Si bond due to the electropositive silyl group. As a result of these interactions, the electrophilicity of the carbonyl group is reduced and the ketene is less reactive towards both nucleophilic addition and [2 + 2] cycloaddition.

Scheme 4



[11] The stability, synthesis, and chemistry of silylketenes have been extensively reviewed. See: (a) Pons, J.-M.; Kocienski, P. J. In *Science of Synthesis: Houben Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Thieme: Stuttgart, Germany, 2001; Vol. 4, pp 657-668. (b) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995. (c) Schaumann, E.; Scheiblich, S. In *Methoden der organischen Chemie (Houben Weyl)*; Kropf, E., Schaumann, E., Eds.; Thieme: Stuttgart, Germany, 1993; Vol. E15, pp 2818-2881. (d) Loebach, J. L.; Danheiser, R. L. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A. Ed.; Wiley: New York, 1995; p 5266. (e) Pommier, A.; Kocienski, P.; Pons, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2105.

[12] For a review on the use of silylketenes in the synthesis of heterocycles, see: Shioiri, T.; Takaoka, K.; Aoyama, T. *J. Heterocyclic. Chem.* **1999**, *36*, 1555.

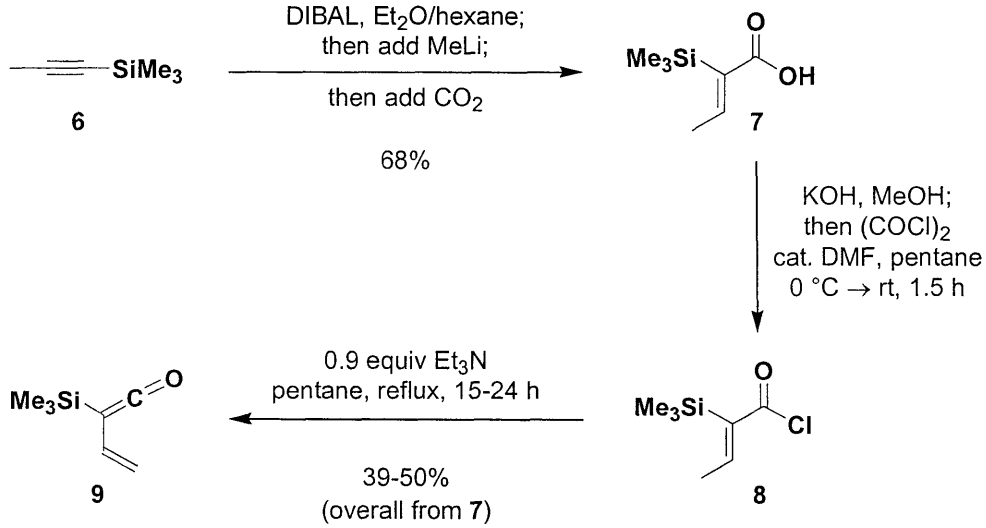
It is well known that many ketenes are not isolable, but rather must be generated and trapped in situ with a reactive ketenophile or nucleophile. In striking contrast to this, silylketenes can be isolated and purified by conventional methods such as silica gel chromatography (with no prior deactivation of the silica gel) and distillation at elevated temperature. Furthermore, silylketenes can generally be stored for prolonged periods of time with minimal decomposition. For example, (trimethylsilyl)ketene is routinely purified by distillation at 81-82 °C and can be stored at room temperature for several years without decomposition.

Synthesis of Silylketenes

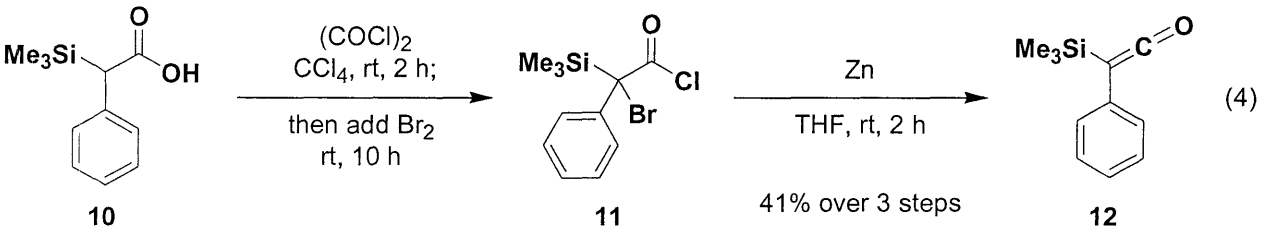
Numerous methods for the synthesis of substituted silylketenes have been reported, and these have been extensively covered in several reviews.[11] This section will discuss synthetic approaches towards (trialkylsilyl)*aryl*ketenes and (trialkylsilyl)*vinyl*ketenes which serve as the crucial four-carbon components in the [4 + 1] annulation strategies discussed in the subsequent parts of this thesis.

Our group reported the first synthesis of (trimethylsilyl)vinylketene in 1980.[7a] As outlined in Scheme 5, this ketene was prepared from 1-(trimethylsilyl)propyne (**6**) via a three-step sequence involving the dehydrohalogenation of α-silyl-α,β-unsaturated acid chloride **8** as the key step. While this route provides access to (trimethylsilyl)vinylketene, the regiochemical

Scheme 5



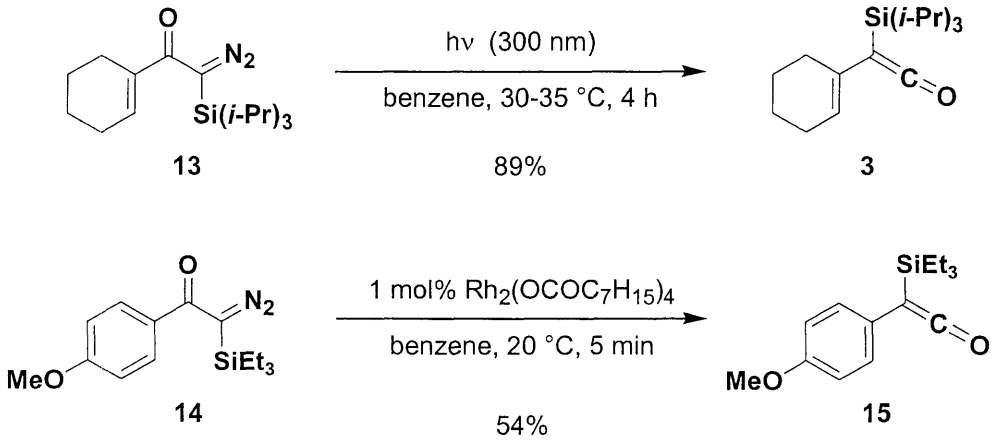
ambiguity associated with dehydrohalogenation of more highly substituted acid chlorides greatly limits the scope of this strategy. Brady has reported a related dehalogenation strategy for the synthesis of phenyl(trimethylsilyl)ketene (**12**, eq 4),[13] but there have been no reports of other (silyl)arylketenes prepared by this method.



10 **11** **12** (4)

A more general method for the synthesis of (silyl)vinylketenes and (silyl)arylketenes involves the Wolff rearrangement[14] of α′-silyl-α′-diazo-α,β-unsaturated ketones and α-silyl-α-diazo aryl ketones, respectively (Scheme 6). Both photochemical[15] and rhodium-catalyzed[16] variants of the Wolff rearrangement have been used for the synthesis of (TAS)vinyl- and (TAS)arylketenes. The Cu(OTf)-catalyzed Wolff rearrangement has been used to prepare a

Scheme 6. Representative photochemical[7b] and rhodium-catalyzed[16] Wolff rearrangements.



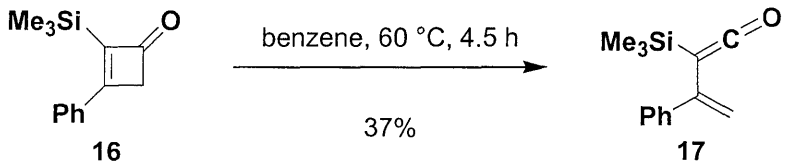
13 **3**

14 **15**

[13] Brady, W. T.; Cheng, T. C. *J. Organomet. Chem.* **1977**, *137*, 287.
[14] For a recent review of the Wolff rearrangement, see: Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.
[15] Reference 7b and (a) Maas, G.; Brückmann, R. *J. Org. Chem.* **1985**, *50*, 2801. (b) Brückmann, R.; Schneider, K.; Maas, G. *Tetrahedron* **1989**, *45*, 5517.
[16] Marsden, S. P.; Pang, W.-K. *J. Chem. Soc., Chem. Commun.* **1999**, 1199.

number of silylketenes, however 2-thiophenyl(triisopropylsilyl)ketene is the only unsaturated silylketene derivative that has been accessed by this approach.[15b]

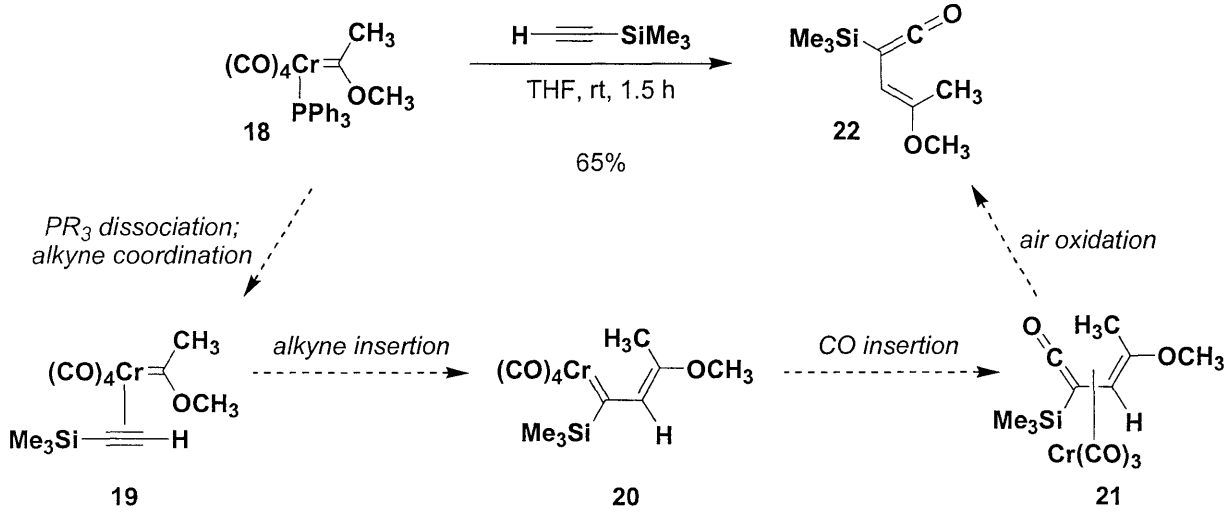
Two additional methods have also proven useful for the synthesis of (TAS)vinylketenes: the electrocyclic ring opening of 2-silylcyclobutenones (eq 5)[7b] and the reaction of chromium carbene complexes with alkynylsilanes.[17,18,19] Scheme 7 illustrates a representative example of



(5)

the synthesis of a uniquely substituted (TAS)vinylketene prepared by the latter method.[18] This transformation likely proceeds via a mechanism resembling the early steps of the Dötz benzannulation (which involves the reaction of an alkenyl- or aryl-substituted chromium carbene complex with an alkyne).[20]

Scheme 7



[17] For preliminary reports on the isolation of TAS-vinylketenes from reactions of chromium carbene complexes with alkynes, see: (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 954. (b) Dötz, K. H.; Fügen-Köster, B. *Chem. Ber.* **1980**, *113*, 1449.

[18] Xu, Y.-C.; Wulff, W. D. *J. Org. Chem.* **1987**, *52*, 3263.

[19] For an "interrupted" Dötz benzannulation strategy in which (TAS)vinylketene intermediates can be isolated, see: Moser, W. H.; Sun, L.; Huffman, J. C. *Org. Lett.* **2001**, *3*, 3389.

[20] For recent reviews of the Dötz benzannulation, see: (a) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187. (b) Dötz, K. H.; Stendel, J., Jr. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 250-296.

In conclusion, the exceptional stability and distinct reactivity of silylketenes (in comparison with other ketenes) has captured the attention of chemists in both theoretical and synthetic arenas. A number of methods for the preparation of these compounds have been reported in the literature, several of which were discussed above. Our group has had a particular interest in exploiting aryl- and vinyl-substituted silylketenes as versatile building blocks for the synthesis of five- and six-membered cyclic compounds, and has already reported on the successful execution of several such strategies.[7,8] The remaining sections of this thesis will detail further work in this area, particularly the development of new [4 + 1] annulation strategies for the synthesis of cyclopentanoid compounds.

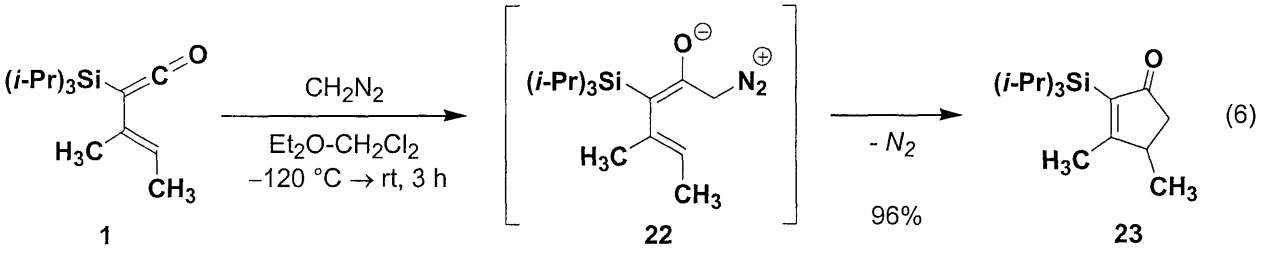
Part II

Synthesis of 2-Indanones via [4 + 1] Annulation Reactions of (Trialkylsilyl)arylketenes

Chapter 1

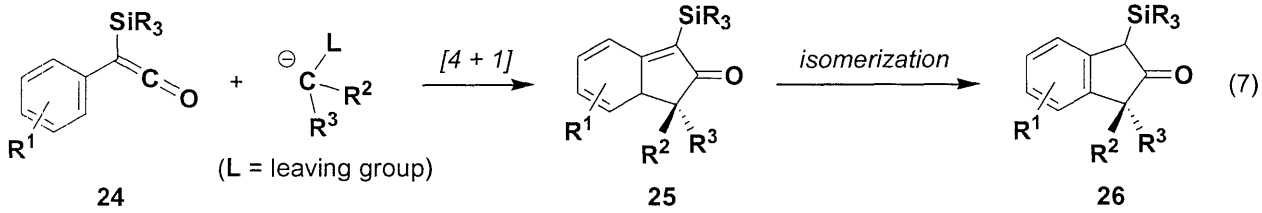
Introduction and Background

Part I of this thesis discussed our previously reported [4 + 1] annulation strategy for the synthesis of substituted cyclopentenones which is based on the reaction of (TAS)vinylketenes with a variety of carbenoid reagents.[8] A specific example involving the use of diazomethane as the one-carbon component is shown below (eq 6). This section of my thesis discusses a [4 + 1]



(6)

annulation strategy for the synthesis of 2-indanones that involves expanding our previous strategy to encompass the use of (TAS)arylketenes, systems in which the vinyl group is embedded within the framework of an aromatic ring, as the four-carbon component (eq 7). We anticipated that the reaction of a (TAS)arylketene with an appropriate carbenoid reagent would initially produce a hydrindenone intermediate of type **25** which would then undergo rapid isomerization to deliver the aromatic indanone product **26**.

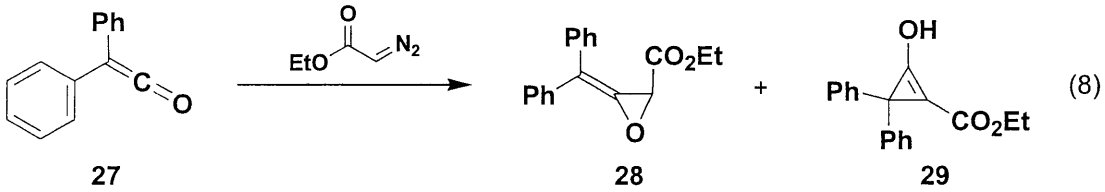


(7)

Reactions of Diarylketenes with Diazo Compounds

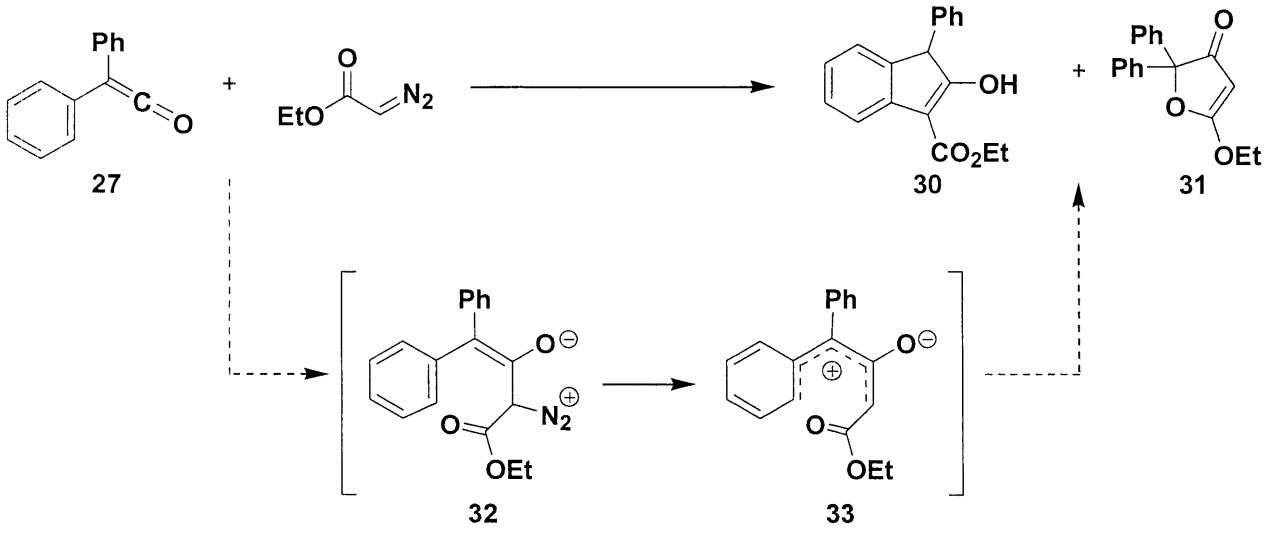
There have been several scattered reports in which indanone derivatives were previously observed in the reaction of diazo compounds with diarylketenes. In 1921, Staudinger reported

that the reaction of diphenylketene (**27**) with ethyl diazoacetate furnished allene oxide **28** and its constitutional isomer **29** (eq 8).[21] Thirty five years later, experiments by Kende demonstrated



that the structures of these products had been incorrectly assigned, and revised structures **30** and **31** (Scheme 9) were suggested.[22] The proposed mechanism involves nucleophilic addition of the diazo compound to the ketene to generate enolate **32**, followed by ionization to deliver "complex zwitterion" **33**. Kende notes that intermediate **33** can cyclize to deliver 2-indanone derivative **30** or furanone **31**.

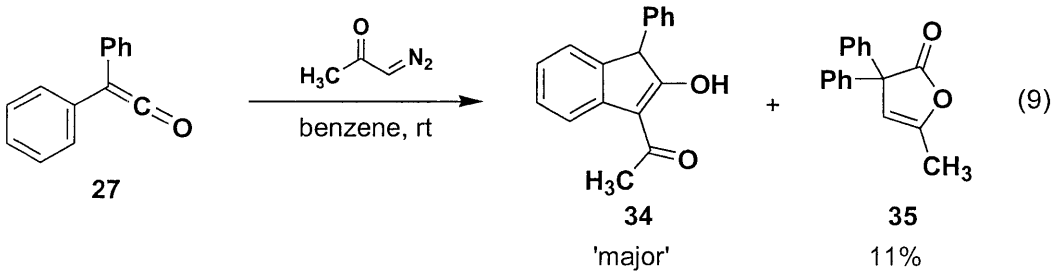
Scheme 9



In 1971, Yates and coworkers reported the synthesis of furanone **35** (eq 9) via the reaction of diphenylketene with diazoacetone.[23] While the desired product **35** was obtained, 2-indanone derivative **34** was isolated as the major product of this reaction. A related indanone byproduct was isolated from the reaction of diphenylketene with 2-diazoacetophenone. The

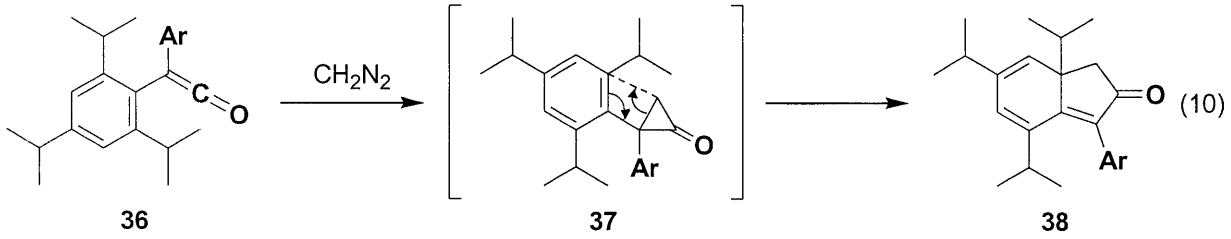
[21] Staudinger, H.; Reber, T. *Helv. Chim. Acta.* **1921**, *4*, 3.
[22] Kende, A. S.; *Chem. Ind. (London)* **1956**, 1053.
[23] Yates, P.; Abrams, G. D.; Betts, M. J.; Goldstein, S. *Can. J. Chem.* **1971**, *49*, 2850.

formation of indanones in these reactions is consistent with the results obtained by Kende, as discussed above.



(9)

During the course of their studies on the reversibility of ketene hydration, Rappoport and Frey reported that the reaction of ditipylketene (tipyl = 2,4,6-triisopropylphenyl) with diazomethane furnishes hydrindenone **38** (eq 10).[24] The authors suggest that aryl-substituted cyclopropanone **37** is formed initially, and a [1,3] sigmatropic rearrangement of this intermediate delivers the observed product.



(10)

Ar = 2,4,6-triisopropylphenyl

Finally, Doutheau and Léost have examined the reaction of several arylketenes with TMS-diazomethane (TMSDM) (Scheme 10).[25] Reactions of phosphonate-substituted ketene **39a** and sulfonylketene **39b** with TMSDM result in the formation of styrenes **41a** and **41b**, presumed to arise via loss of CO from initially formed cyclopropanes **40a** and **40b**. In contrast to these results, treatment of diphenylketene with TMSDM furnishes α-silylindanone **42** which undergoes protodesilylation to afford indanone **43** upon exposure to silica gel. Indanone formation is proposed to proceed via an aryl-substituted cyclopropanone intermediate analogous to **40**.

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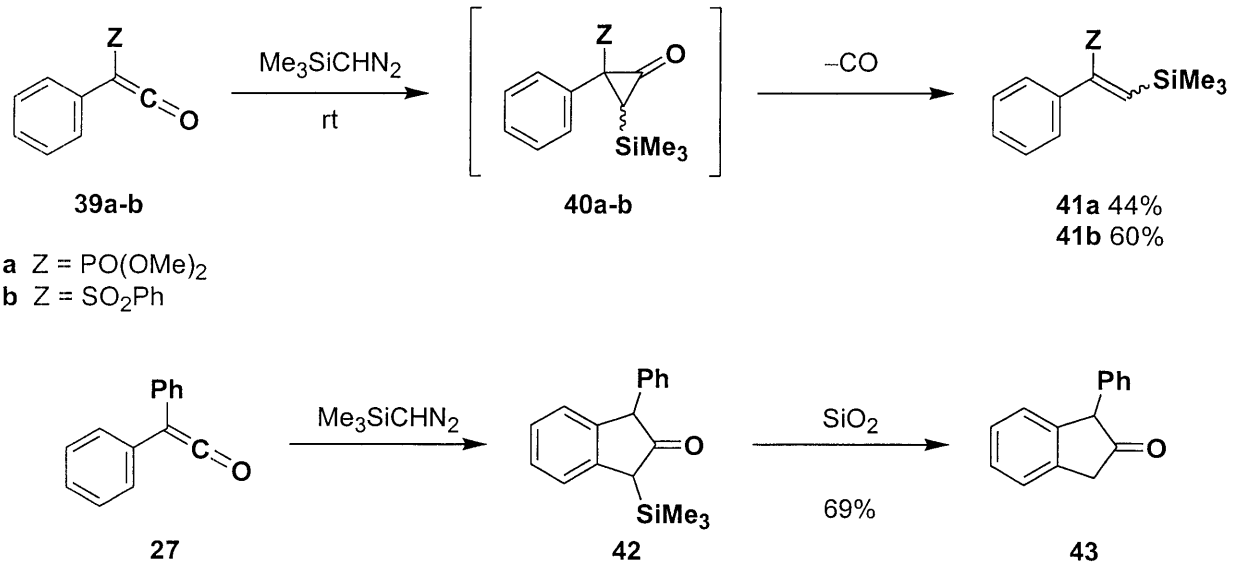
[24] Frey, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 1161.
[25] Léost, F.; Doutheau, A. *Tetrahedron Lett.* **1999**, *40*, 847.

Scheme 10



The results described in this section provide precedent for the formation of 2-indanone products in the reaction of an arylketene with certain diazo compounds; however, no systematic study has been reported. Furthermore, there have been no reports on the synthesis of indanones from aryl(*silyl*)ketenes, although the reactions of simple silylketenes with diazo compounds have been thoroughly investigated and will be presented in detail below.

Reactions of Silylketenes with Diazo Compounds

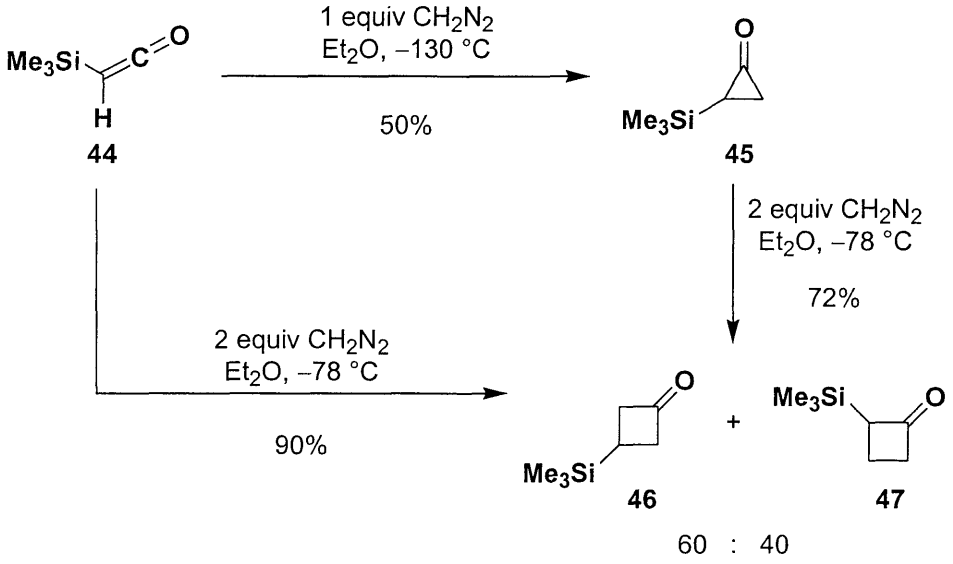
In the reactions of diarylketenes with diazo compounds discussed above, cyclopropanone intermediates were proposed by several of the authors, and it is plausible that cyclopropanones might be intermediates in all of these reactions. With regard to *silyl*ketenes, the formation of cyclopropanones and cyclobutanones upon reaction with diazo compounds has been well documented.

In 1976, Zaitseva and coworkers reported that slow addition of 1 equiv of diazomethane to trimethylsilylketene (**44**) in Et_2O at –130 °C delivers cyclopropanone **45** in modest yield (Scheme 11).[26] Upon exposure to additional diazomethane, this product undergoes ring expansion to furnish a 60:40 mixture of 3-silylcyclobutanone **46** and isomeric cyclobutanone **47**.

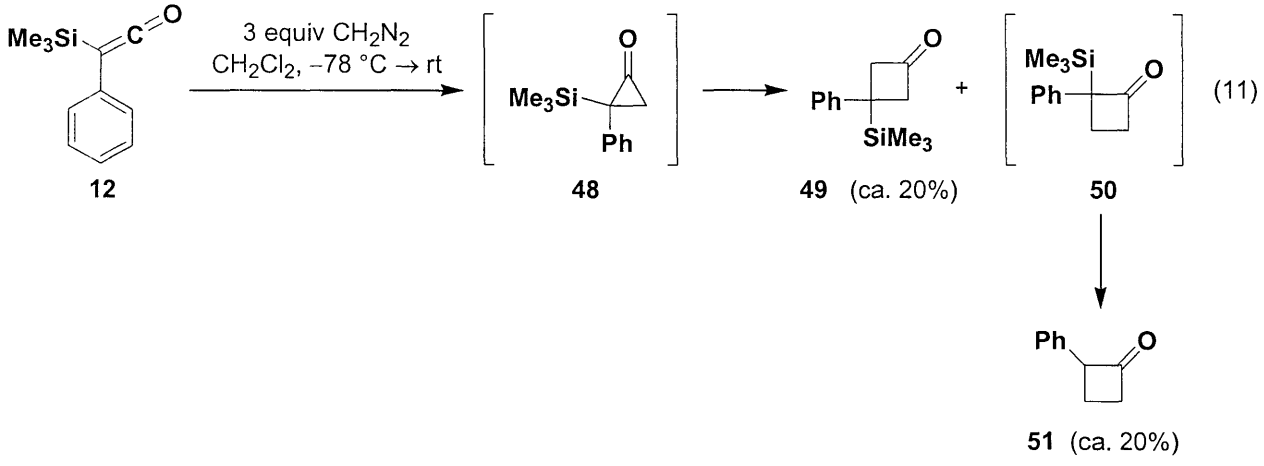
[26] (a) Zaitseva, G. S.; Bogdanova, G. S.; Baukov, Yu. I.; Lutsenko, I. F. *J. Organomet. Chem.* **1976**, *121*, C21. (b) Zaitseva, G. S.; Bogdanova, G. S.; Baukov, Yu. I.; Lutsenko, I. F. *J. Gen. Chem. USSR (Engl. Transl.)* **1978**, *48*, 111.

Reaction of trimethylsilylketene with 2 equiv of diazomethane in Et_2O at –78 °C produces a 60:40 mixture of isomeric cyclobutanones **46** and **47** directly.

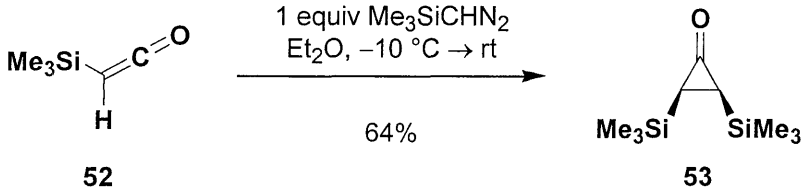
Scheme 11



In a related study, Brady and coworkers found that the reaction of phenyl(trimethylsilyl)ketene (**12**) with an excess of diazomethane furnishes a mixture of cyclobutanones **49** and **51** in approximately equal amounts (eq 11).[13] The authors suggest that cyclobutanone **50** undergoes facile C to O silyl migration to yield a silyl enol ether which is hydrolyzed by atmospheric moisture to deliver the observed product **51**. The four-membered ring products are presumed to have formed via ring expansion of an initially formed cyclopropanone intermediate **48**.



Zaitseva has also studied the reactions of silylketenes with silyldiazomethane derivatives including TMSDM.[27] In these cases (e.g., eq 12), the reactions furnish *cis*-substituted bis(silyl)cyclopropanones such as **53** in good to excellent yields.



52 **53** (12)

The reactions highlighted in this section provide precedent for our proposed [4 + 1] annulation and also serve as background for the mechanistic discussion that will be presented in subsequent portions of this thesis. Chapter 2 will detail the preparation of the requisite (TAS)arylketenes, and Chapter 3 will present the results of our study on the indanone annulation including an analysis of possible mechanistic pathways.

[27] (a) Fedorenko, E. N.; Zaitseva, G. S.; Baukov, Yu. I.; Lutsenko, I. F. *J. Gen. Chem. USSR (Engl. Transl.)* **1986**, *56*, 2150. (b) Zaitseva, G. S.; Kisin, A. N.; Fedorenko, E. N.; Nosova, V. M.; Livantsova, L. I.; Baukov, Yu. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1987**, *57*, 1836. (c) Zaitseva, G. S.; Lutsenko, I. F.; Kisin, A. V.; Baukov, Yu. I.; Lorberth, J. *J. Organomet. Chem.* **1988**, *345*, 253.

Chapter 2

Synthesis of (TAS)arylketenes

The (TAS)arylketenes required for our study were prepared from the corresponding α-diazo aryl ketones via a sequence involving silylation and subsequent photochemical Wolff rearrangement. The diazo ketone precursors were prepared either by addition of diazomethane to the corresponding acid chlorides, or from the corresponding methyl ketones via a diazo transfer protocol. Substrate preparation according to this strategy will be discussed below.[28]

Synthesis of α-Diazo Aryl Ketones

A number of synthetically useful methods for the preparation of α-diazo ketones have been reported.[29] The majority of the α-diazo aryl ketones used in our study were prepared from the corresponding methyl ketones by employing a detrifluoroacetylative diazo group transfer process developed in our laboratory.[30] As summarized in eq 13, this strategy involves initial trifluoroacetylation of the methyl ketone by trapping the kinetically generated lithium enolate with 2,2,2-trifluoroethyl trifluoroacetate (TFETFA). Treatment of the crude β-diketone with 1.5 equiv of methanesulfonyl azide (MsN_3)[31] and 1.5 equiv of Et_3N in acetonitrile containing 1 equiv of water at rt for 3 h furnishes desired diazo ketone **56** in excellent yield.[32]

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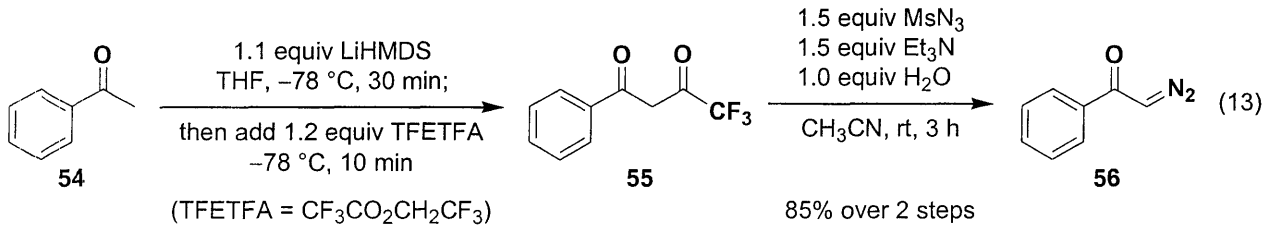
[28] The results presented in Chapters 2 and 3 (Part II) were obtained during a collaborative project with former group members Audra Dalton and Dr. Yongjun Zhang. All experiments conducted exclusively by one of these coworkers will be mentioned in the text or indicated by a footnote in the appropriate table.

[29] For reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. Synthesis of α-Diazo Carbonyl Compounds. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*; Wiley & Sons: New York, 1998; Chapter 1, pp 1-60. (b) Regitz, M.; Maas, G. Diazo Compounds: Properties and Synthesis; Academic Press: Orlando, 1986.

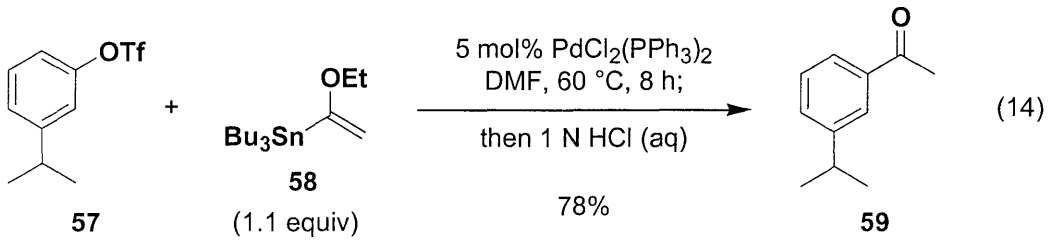
[30] (a) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959. (b) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, p 197.

[31] MsN_3 was prepared by the reaction of methanesulfonyl chloride with 1.5 equiv of NaN_3 in acetone at rt for 2h according to the procedure described in reference 30a.

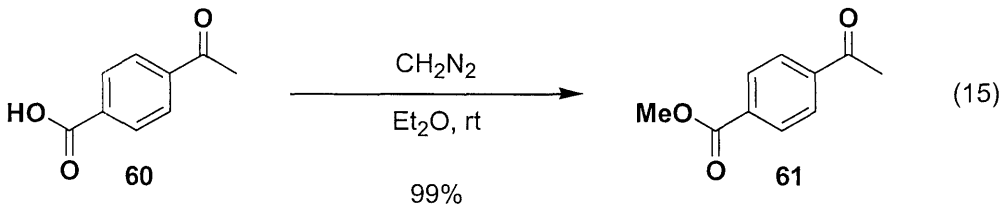
[32] Diazo ketone **56** has been prepared by this method in 95% yield; see reference 30a.



All but two of the substituted acetophenone derivatives required for the preparation of the diazo ketones by the above method are commercially available. The *m*-isopropyl derivative **59** was prepared via a Stille coupling of aryl triflate **57**[33] and commercially available stannane **58**.



Hydrolysis of the initially formed enol ether was achieved simply by exposure of the crude product to 1 N aq HCl during workup, delivering methyl ketone **59** in good yield. Ketone **61** was prepared in nearly quantitative yield by treatment of carboxylic acid **60** with diazomethane (eq 15), according to the previously reported procedure.[34]



α-Diazo aryl ketones **56** and **64-67** were all prepared by the diazo transfer process discussed above, and the results are summarized in Table 1. With these substrates in hand, we then turned our attention toward preparation of the necessary α-silyl-α-diazo ketones.

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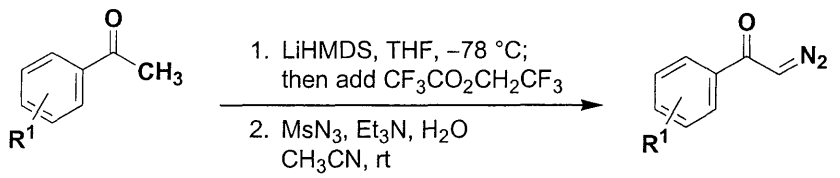
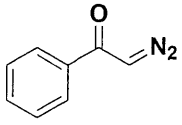
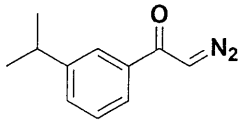
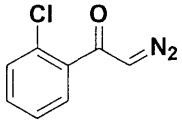
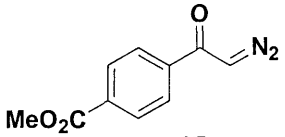
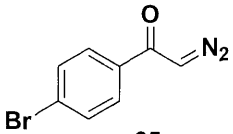
[33] 3-(Isopropyl)phenyl trifluoromethanesulfonate (**57**) was prepared in 88-94% yield by the reaction of 3-(isopropyl)phenol with 1.25 equiv of Tf_2O and 1.40 equiv of DMAP in CH_2Cl_2 (–20 °C → rt) according to the published procedure: Kane, J. L.; Shea, K. M.; Crombie, A. L.; Danheiser, R. L. *Org. Lett.* **2001**, *3*, 1081.

[34] Smissman, E. E.; Li, J. P.; Israili, Z. H. *J. Org. Chem.* **1968**, *33*, 4231.

Table 1. Preparation of α-Diazo Aryl Ketones **56** and **64-67**



entry	aryl ketone	product	yield[a]	entry	aryl ketone	product	yield[a]
1	**54**	 **56**	85%	4	**59**	 **66**	89%
2	**62**	 **64**	84%[b]	5	**61**	 **67**	57%
3	**63**	 **65**	80%[c]				

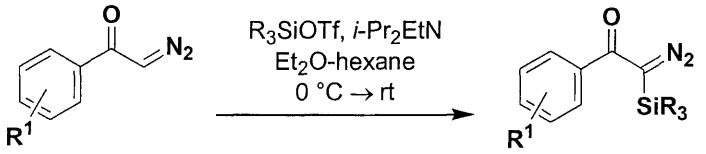
(a) Isolated yields of products purified by column chromatography. (b) Reaction performed by Dr. Yongjun Zhang. (c) Reaction performed by Audra Dalton.

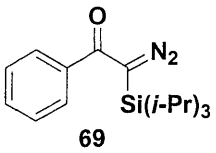
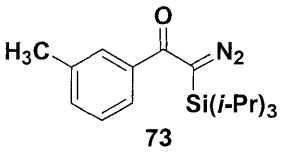
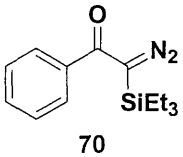
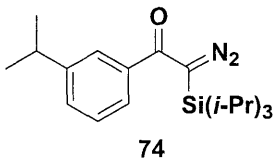
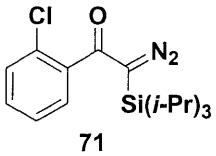
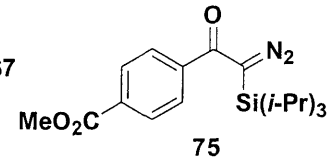
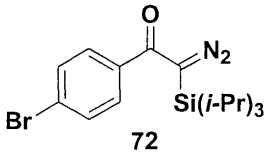
Silylation of α-Diazo Aryl Ketones

Maas has reported that α-diazo ketones can be silylated by treatment with the appropriate silyl triflate (R_3SiOTf) and *i*-Pr_2EtN in Et_2O (0 °C → rt).[15a, 35] One complication associated with this method is that the ammonium triflate byproduct (*i*-$Pr_2EtNH^+OTf^-$), which is soluble in Et_2O, can promote the reverse reaction (i.e., protodesilylation of the silyl diazo ketone product). Previous work in our group has demonstrated that using a 1:1 mixture of Et_2O-hexane as the reaction solvent greatly decreases the solubility of the ammonium triflate, thereby shifting the equilibrium toward the desired silylated product and resulting in higher yields.[7b] Synthesis of the α-silyl-α-diazo aryl ketones needed for our study was achieved by employing this modification of the Maas procedure, as summarized in Table 2.

[35] Brückmann, R.; Maas, G. *Chem. Ber.* **1987**, *120*, 635.

Table 2. Synthesis of α-Diazo-α-Silyl Aryl Ketones **69-75**



entry	diazo ketone	product	yield[a]	entry	diazo ketone	product	yield[a]
1	**56**	 **69**	79%	5	**68**[d]	 **73**	76%[c]
2	**56**	 **70**	63%	6	**66**	 **74**	75%
3	**64**	 **71**	82%[b]	7	**67**	 **75**	72%
4	**65**	 **72**	72-75%				

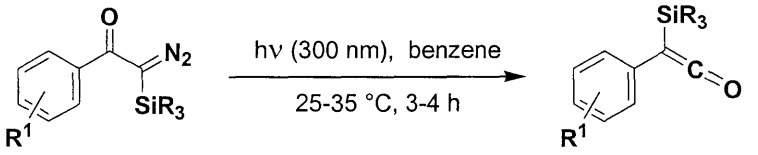
(a) Isolated yields of products purified by column chromatography. (b) Reaction performed by Dr. Yongjun Zhang. (c) Reaction performed by Audra Dalton. (d) Diazo ketone **68** was prepared by Audra Dalton in 92% yield by reaction of 3-methylbenzoyl chloride with diazomethane as reported by Tsuno, Y.; Ibata, J.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* **1959,** *32,* 960.

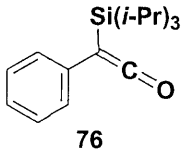
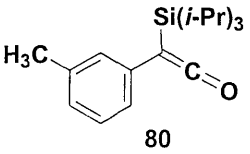
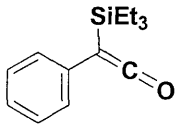
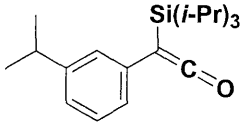
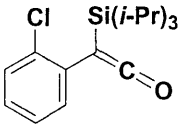
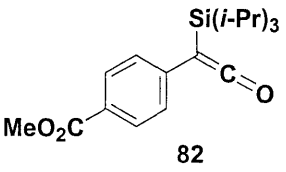
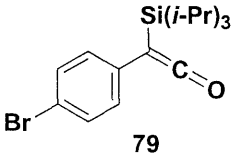
Photochemical Wolff Rearrangement of α-Silyl-α-Diazo Aryl Ketones

Wolff rearrangements of α-silyl-α-diazo aryl ketones **69-75** were conducted photochemically by irradiation with 300 nm light for 3-4 h at 25-35 °C in a Rayonet RPR-100 photochemical reactor. The desired (TAS)arylketenes were obtained in modest to excellent yield as indicated in Table 3. Interestingly, we were unable to isolate carbomethoxy-substituted aryl ketene **82** in greater than 90% purity, even after multiple purifications (e.g., chromatography on silica gel, basic alumina, or Florisil). It is postulated that the inductively withdrawing CO_2Me group at the *para* position of the aromatic ring renders the ketene carbonyl significantly more

electrophilic than (TAS)arylketenes **76-81**, and therefore much more susceptible to nucleophilic attack (e.g., by adventitious water to generate the corresponding carboxylic acid). The presence of an electron-withdrawing group on ketene **82** also gave rise to interesting results during our [4 + 1] annulation studies. Our investigation of the indanone annulation with all of the (TAS)arylketenes discussed above will be presented in detail in the next chapter.

Table 3. Synthesis of (TAS)arylketenes **76-82** via Photochemical Wolff Rearrangement



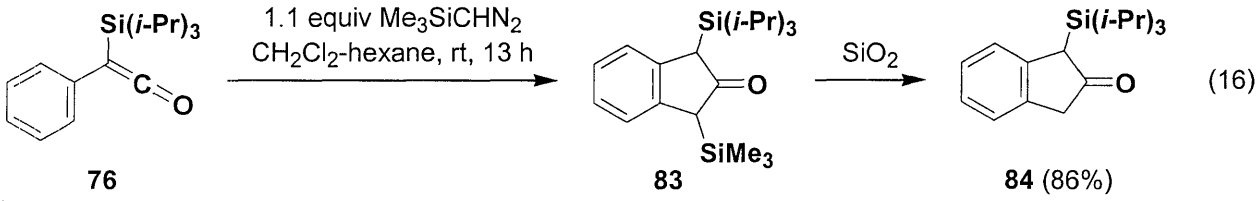
entry	diazo ketone	product	yield[a]	entry	diazo ketone	product	yield[a]
1	**69**	 **76**	89%[b]	5	**73**	 **80**	79%[d]
2	**70**	 **77**	52%[c]	6	**74**	 **81**	64%
3	**71**	 **78**	76%[b]	7	**75**	 **82**	62%[e]
4	**72**	 **79**	76%				

(a) Isolated yields of products purified by column chromatography. (b) Reaction performed by Dr. Yongjun Zhang. (c) Maas has reported the synthesis of ketene **77** in 49% yield by the same route; see reference 15b. (d) Reaction performed by Audra Dalton. (e) Approximately 90% pure by ^{1}H NMR analysis.

Chapter 3

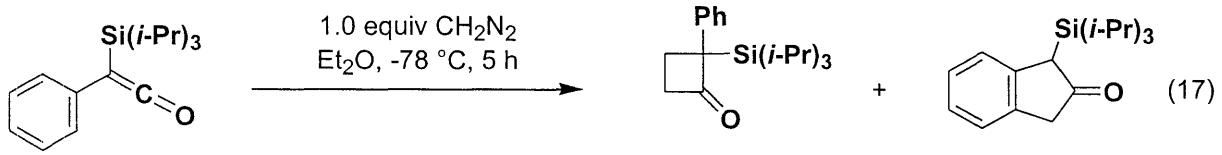
[4 + 1] Indanone Annulation

The feasibility of the [4 + 1] indanone annulation was first demonstrated by former group member Audra Dalton (eq 16). Treatment of phenyl(triisopropylsilyl)ketene (**76**) with a slight excess of trimethylsilyldiazomethane (TMSDM) in a mixture of CH_2Cl_2 and hexane at room temperature produced 1,3-bis(silyl)indanone **83** in nearly quantitative yield. Partial loss of the trimethylsilyl group was observed during the course of purification, and to avoid this complication the crude product was converted to mono(silyl)indanone **84** by brief stirring at room temperature in the presence of silica gel. In this fashion the desired indanone was obtained in 86% yield.



76 **83** **84** (86%) (16)

Dr. Yongjun Zhang investigated the use of diazomethane as the carbenoid reagent in this annulation. A preliminary experiment (eq 17) demonstrated that treatment of (TAS)arylketene **76** with an equimolar amount of diazomethane at –78 °C results in the formation of the desired indanone **84**, however, cyclobutanone **85** is also formed in comparable yield. We believe that



76 **85** (29%) **84** (22%) (17)

the four-membered product **85** is formed via ring expansion of an initially formed cyclopropanone intermediate (a transformation that consumes 2 equiv of diazomethane relative

to ketene **76**).[36] It thus appeared that the less reactive and sterically bulkier TMSDM would be a more suitable carbenoid reagent for the [4 + 1] indanone annulation. The remainder of this chapter will discuss the scope of this annulation with respect to substitution on the aromatic ring of the ketene as well as possible mechanistic pathways to account for this interesting transformation.

Scope of the [4 + 1] Indanone Annulation

Chapter 2 outlined the synthesis of a number of substituted (TAS)arylketenes, and these were used to investigate the scope of the [4 + 1] indanone annulation. As highlighted in Table 4, the [4 + 1] annulation proceeds smoothly with ketenes bearing substituents at the *ortho*, *meta*, or *para* positions of the aromatic ring. In the case of carbomethoxy-substituted ketene **82**, successful annulation requires the addition of 0.5 equiv of *i*-Pr_2EtN to the reaction mixture (vide infra).

The structural assignments for all of the indanones shown in Table 4 were based on analysis of IR, and ^1H and ^{13}C NMR data. The spectral and melting point data obtained for 2-indanone (**86**, entry 2) are consistent with data previously reported for this compound.[37] 1-Silyl-indan-2-ones **84** and **87-93** all exhibit a characteristic IR stretch between 1717-1731 cm^{-1} attributable to the ketone carbonyl, and a diagnostic ^{13}C NMR resonance between 214.0-217.6 ppm for the carbonyl carbon (for 2-indanone (**86**), the carbonyl carbon appears at 215.2 ppm in the ^{13}C spectrum, and the carbonyl stretch in the IR is at 1752 cm^{-1}). In addition to the expected ^1H NMR resonances for the aromatic protons, indanones **84** and **87-93** all exhibit a distinctive pair of coupled doublets at δ 3.41-3.84 with large (ca. 23 Hz) geminal coupling constants, assigned as the diastereotopic C-3 (α') protons.

The optimal conditions for cleavage of the trimethylsilyl group from the initially formed 1,3-bis(silyl)indanones (e.g., indanone **83**, eq 16) vary from case to case, as indicated in Table 4. In the case of the bromo-substituted indanone (entry 4), the TMS group is conveniently cleaved

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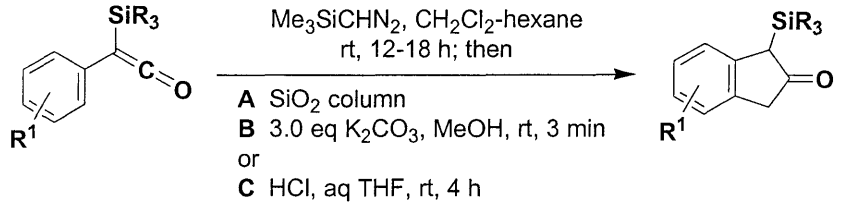
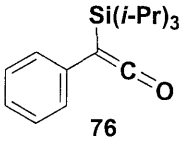
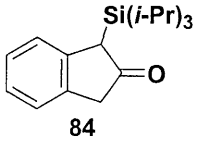
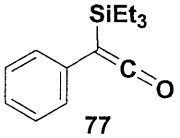
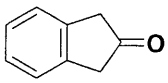
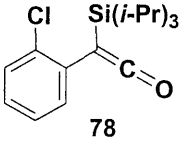
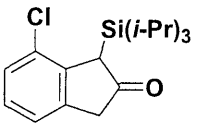
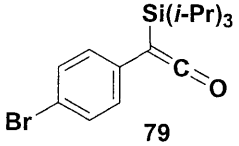
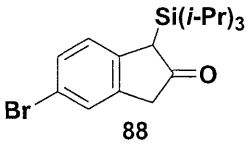
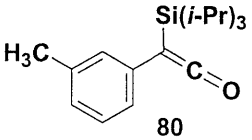
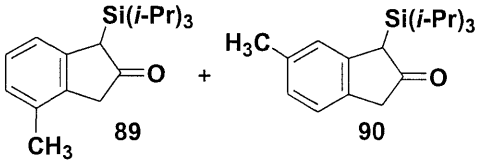
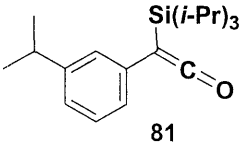
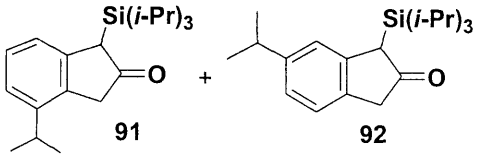
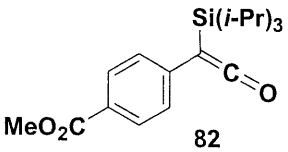
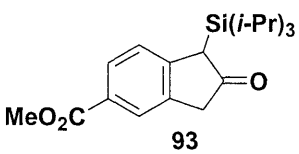
[36] The formation of a cyclobutanone product is consistent with the result obtained by Brady and Cheng in their examination of the reaction of diazomethane with trimethylsilyl(phenyl)ketene. See eq 11 (p 26) and reference 13.

[37] (a) Spectral data for 2-indanone (**86**): Lambert, J. B.; Wharry, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5857. (b) Literature melting point for 2-indanone (**86**): Levin, N.; Graham, B. E.; Kolloff, H. G. *J. Org. Chem.* **1944**, *9*, 380.

Table 4. [4 + 1] Indanone Annulation



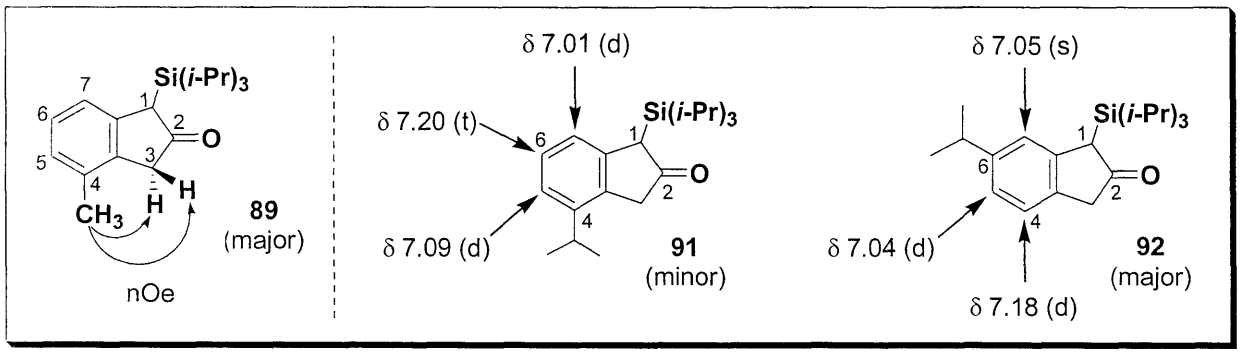
entry	ketene	product(s)	yield[a]
1	 **76**	 **84**	86%[b]
2	 **77**	 **86**	69%[c]
3	 **78**	 **87**	54%[d,i]
4	 **79**	 **88**	79%[e,j]
5	 **80**	 **89** + **90**	65%[b,i] (66:34)
6	 **81**	 **91** + **92**	91%[f] (46:54)
7	 **82**	 **93**	36%[g,h]

(a) Isolated yields of products purified by column chromatography. (b) Desilylation of the Me_3Si group was achieved by stirring the crude product in CH_2Cl_2 over silica gel at rt for 1 h. (c) Cleavage of both the Me_3Si and Et_3Si groups from the crude annulation product was accomplished by exposure to 1N HCl in THF at rt for 4 h. (d) Treatment of the annulation product with 3 equiv of K_2CO_3 in MeOH at rt for 3 min effected desilylation. (e) Cleavage of the Me_3Si group from the annulation product occurred during column chromatography on silica gel. (f) Exposure of the annulation product to 1N HCl (rt, 3.5 h) effected desilylation. (g) Overall yield for 2 steps from **75** (photochemical Wolff rearrangement and [4 + 1] annulation). (h) In this case the annulation was carried out in the presence of 0.5 equiv of *i*-Pr_2EtN. (i) Reaction performed by Dr. Yongjun Zhang. (j) Reaction performed by Audra Dalton.

during purification on silica gel, and for entries 1 and 5, simply stirring the crude product with silica gel in CH_2Cl_2 prior to chromatographic purification is sufficient. In other cases, exposure of the crude product to dilute acid (1 N HCl, THF) or methanolic K_2CO_3 (rt, several minutes) promoted clean desilylation. Interestingly, treatment of the crude product obtained from the annulation with phenyl(triethylsilyl)ketene (entry 2) with 1 N HCl in THF for 4 h at room temperature results in cleavage of both silyl groups to furnish 2-indanone (**86**).

In the case of annulations with arylketenes bearing *meta*-alkyl substituents (entries 5 and 6) a regiochemical ambiguity exists in the ring forming step – cyclization can occur to deliver an indanone substituted at C-4 (e.g., **89**) or C-6 (e.g., **90**). Surprisingly, annulations with 3-methyl and 3-isopropyl substituted (TAS)arylketenes both lead to the formation of a mixture of indanone regioisomers. In the case of methyl-substituted indanones **89** and **90**, the major isomer was assigned as 4-methyl indanone **89** based on the indicated nOe enhancements (Figure 1) observed in the NOESY spectrum of a mixture of **89** and **90**.[38] Enriched samples of isopropyl-substituted indanones **91** and **92** were obtained by preparative HPLC, and examination of the ^1H NMR splitting pattern for the aromatic protons allowed for unambiguous assignment of the major and minor regioisomers as indicated in Figure 1. In these cases, it appears that there is an intrinsic preference for cyclization adjacent to the alkyl substituent that is opposed by steric repulsion from this group.

Figure 1. Regiochemical Assignments for Indanones **89-92**

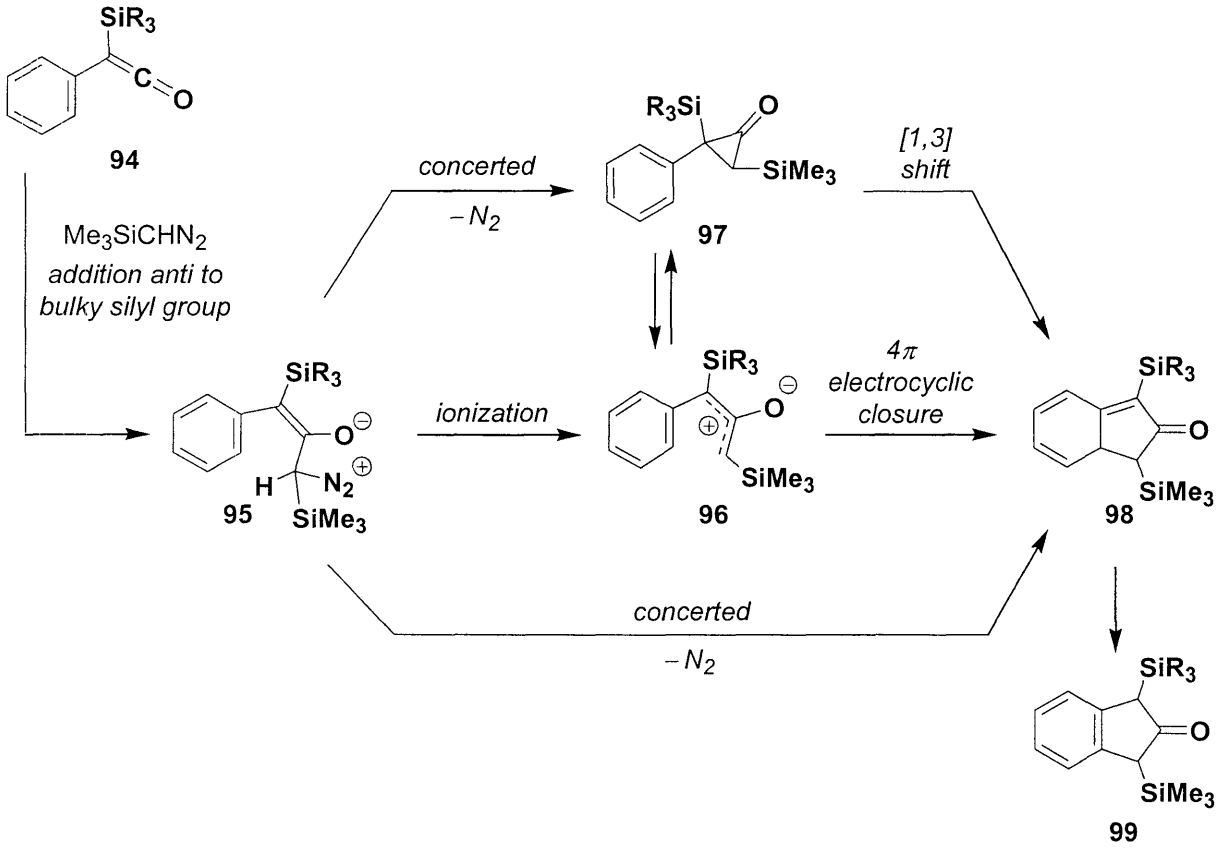


[38] The NOESY experiment on **89** and **90** was performed by Dr. Yongjun Zhang.

Mechanism of the [4 + 1] Annulation

Scheme 13 outlines several possible mechanistic pathways to account for the [4 + 1] annulation. Addition of TMSDM to (TAS)arylketene **94** is anticipated to occur *anti* to the bulky trialkylsilyl group to generate (*Z*)-enolate **95**. Ionization (loss of N_2) would produce oxidopentadienylic-type cation **96** which could then undergo 4π electrocyclic ring closure to generate the five-membered product **98**.[39] Alternatively, cyclization of enolate **95** could produce the hydrindenone intermediate **98** directly via a concerted process in which ring closure is concomitant with leaving group departure. Another possibility is that enolate **95** may cyclize to

Scheme 13. Possible Mechanistic Pathways for the [4 + 1] Annulation



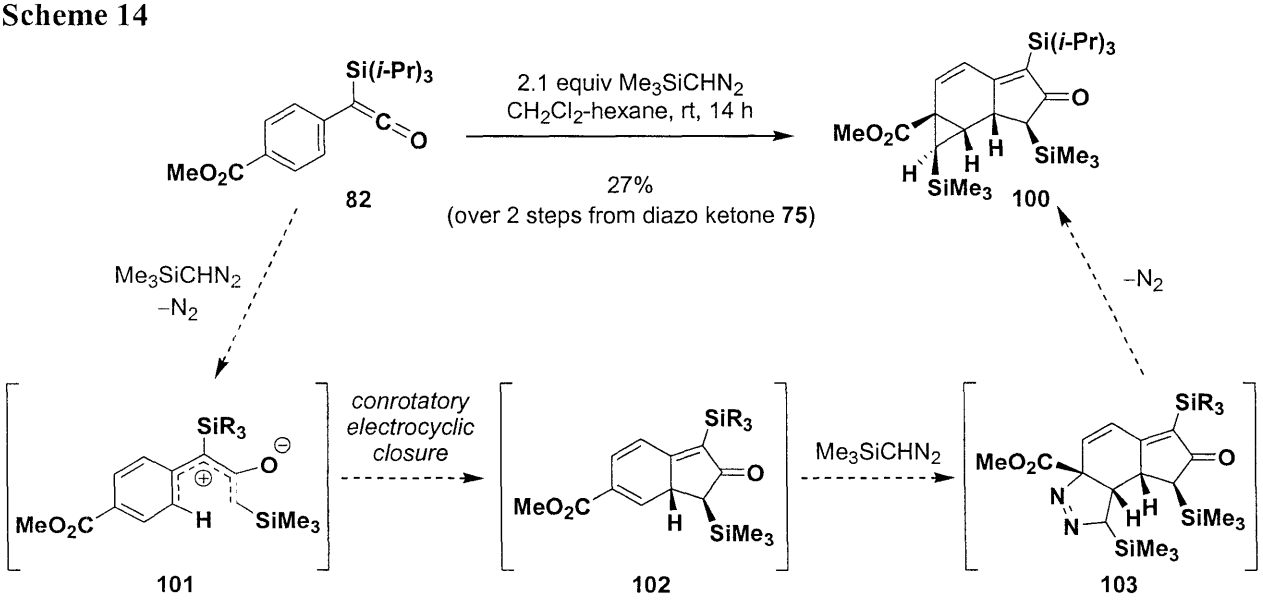
[39] Electrocyclic closure of a pentadienyl cation is involved in the mechanism of the Nazarov cyclization. For reviews, see: (a) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (b) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (c) Habermas, K. L.; Denmark, S. E.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1994; Vol. 45, pp 1-158. (d) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 751.

form the 2,3-bis(silyl)cyclopropanone **97**, which would likely be in equilibrium with oxyallyl cation **96** via 2π electrocyclic ring opening/closure. Five-membered ring formation could then proceed via electrocyclic closure of pentadienylic cation **96** as discussed above, or by a [1,3] sigmatropic rearrangement of arylcyclopropanone **97**. In all cases, initially formed intermediate **98** is expected to undergo rapid isomerization to furnish the aromatic product **99**.

The isolation of a cyclobutanone product (**85**, eq 17) in the reaction of (TAS)arylketene **76** with diazomethane as well as the previously discussed work of Zaitseva and Brady (Scheme 11 and eqs 11 and 12, pp 26-27) in which cyclopropanone and cyclobutanone products are produced in the reaction of silylketenes with TMSDM are consistent with the viability of a mechanism involving the intermediacy of a cyclopropanone of type **97**. Evidence consistent with a mechanism involving stereospecific electrocyclic closure of an intermediate of type **96** was obtained serendipitously during the course of investigating the [4 + 1] indanone annulation with carbomethoxy-substituted ketene **82**.

As noted earlier, successful annulation with carbomethoxy-substituted ketene **82** requires the addition of 0.5 equiv of *i*-Pr_2EtN (Table 4, entry 7). In preliminary annulation attempts with this ketene, only a trace amount of the desired indanone was observed and an interesting byproduct was isolated as the major product. Partial optimization of this undesired reaction (Scheme 14) allowed for isolation of a pure sample of this byproduct, later assigned as tricyclic enone **100** (vide infra). It appears that hydrindenone intermediate **102** is trapped in a 1,3-dipolar

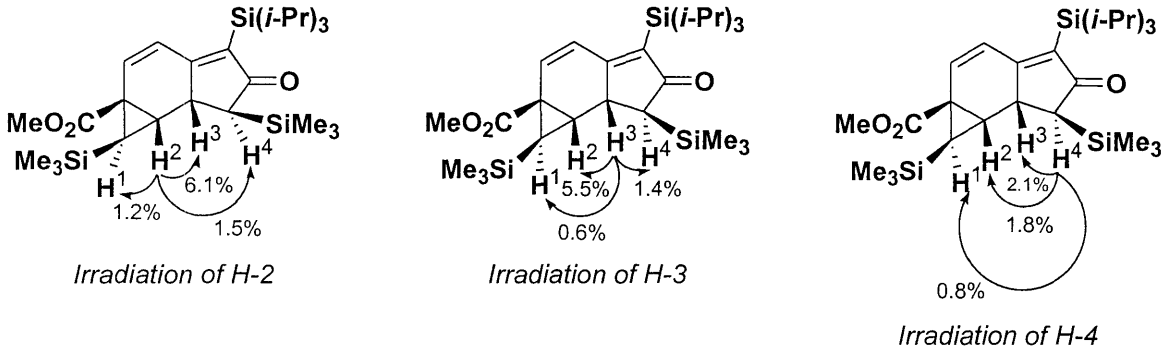
Scheme 14



cycloaddition with TMSDM,[40] a process which is competitive with isomerization to the indanone in this case due to the activating effect of the CO_2Me group. It is postulated that dipolar cycloaddition initially generates pyrazoline **103**,[41] and subsequent loss of dinitrogen[42] delivers observed product **100**.

The structure assignment for tricyclic enone **100** was based on IR, and ^1H and ^{13}C NMR data; satisfactory elemental analysis results and HRMS data lend further support to our assignment. The relative stereochemistry of compound **100** was determined by analysis of nOe data and ^1H NMR coupling constants. As illustrated in Figure 2, significant nOe enhancement

Figure 2. nOe Experiments on Tricyclic Enone **100**



was only observed between H-2 and H-3, indicating a *cis* relationship for these protons and a *trans* relationship between H-1 and H-2, and H-3 and H-4. Furthermore, the relatively small coupling constant (J = 4.3 Hz) observed between H-3 and H-4 is suggestive of a *trans* relationship between these two protons (Figure 3).

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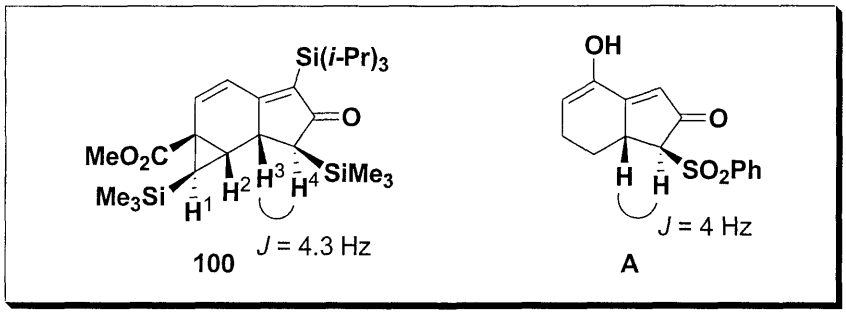
[40] For a review, see: Regitz, M.; Heydt, H. Diazoalkanes. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A. Ed.; Wiley: New York, 1984; Vol. 1, pp 393-558.

[41] Dipolar cycloaddition with intermediate **102** is anticipated to produce the illustrated regioisomer **103**. For a discussion, see reference 40.

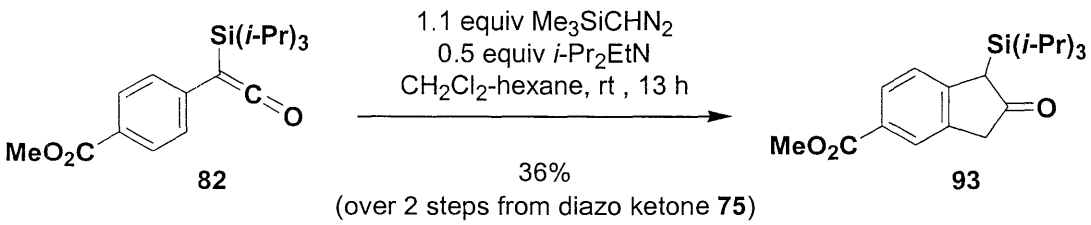
[42] Loss of N_2 from pyrazoline intermediates of type **103** is often observed at or below room temperature. For a discussion, see reference 40.

Figure 3. Comparison of Coupling Constants for **100** and Model Compound **A**[43]



With regard to the mechanism of the [4 + 1] annulation, it is noteworthy that the relative stereochemistry of hydrindenone intermediate **102** (preserved in isolated product **100**) is consistent with conrotatory 4π electrocyclic closure of pentadienylic cation **101**. Ionization of the initially formed dienolate intermediate (analogous to intermediate **95** in Scheme 13) is anticipated to result in the formation of the isomer of **101** shown in Scheme 14 in which the trimethylsilyl group is *cis* to the oxyanion to minimize nonbonded interactions.

A variety of conditions were examined in an attempt to promote formation of the desired indanone **93** and avoid formation of the tricyclic byproduct **100**. A combination of slow TMSDM addition and basic additives (to promote the isomerization of intermediate **102** to the indanone) were explored. Addition of 0.2 equivalents of 2,6-di-*t*-butyl-4-methylpyridine coupled with slow (syringe pump) addition of TMSDM results in the formation of a mixture of indanone **93** and tricyclic enone **100** in approximately a 2:1 ratio. Gratifyingly, addition of 0.5 equiv of *i*-Pr_2EtN to the reaction mixture was found to be even more effective - none of the undesired byproduct was observed, and slow addition of TMSDM was found to be unnecessary. In this fashion (eq 18), carbomethoxy-substituted indanone **93** was obtained in 36% yield over 2 steps (photochemical Wolff rearrangement and [4 + 1] annulation) from silyl diazo ketone **75**.



(18)

[43] Yechezkel, T.; Ghera, E.; Ostercamp, D.; Hassner, A. *J. Org. Chem.* **1995**, *60*, 5135.

In conclusion, a new [4 + 1] annulation for the synthesis of substituted 2-indanones based on the reaction of (TAS)arylketenes with TMSDM has been developed.[44] This strategy is well suited for arylketenes bearing a range of substituents at different positions on the aromatic ring. Furthermore, this operationally simple transformation proceeds through an interesting sequence of mechanistic steps. The next portion of this thesis (Part III) will detail our work on a related [4 + 1] annulation for the synthesis of highly substituted and functionalized cyclopentenones.

[44] The work presented in Part II (Chapters 2 and 3) of this thesis has appeared in the following publication: Dalton, A. M.; Zhang, Y,; Davie, C. P.; Danheiser, R. L. *Org. Lett.* **2002**, *4*, 2465.

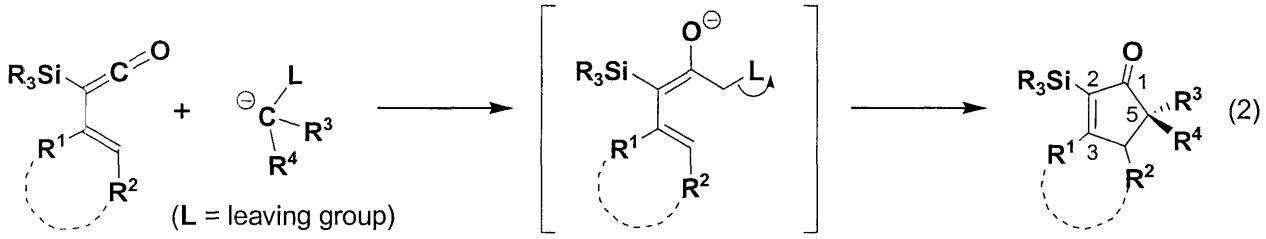
Part III

Synthesis of Cyclopentenones via [4 + 1] Annulation Reactions of (Trialkylsilyl)vinylketenes

Chapter 1

Introduction and Background

As discussed in Part I, previous work in our group has led to the development of a [4 + 1] annulation strategy for the synthesis of cyclopentenones that is based on the reaction of (TAS)vinylketenes with carbenoid reagents (eq 2, reproduced below). The research presented



(2)

in Part III of this thesis was conducted with the goal of extending the scope of our [4 + 1] annulation to include the synthesis of cyclopentenones bearing a much broader range of substitution at the C-5 position – an objective that has required the identification of a new class of carbenoid reagents for this transformation. As background, a discussion of the importance of cyclopentenones and previously reported approaches to this ring system, as well as an overview of general [4 + 1] strategies for the synthesis of five-membered carbocyles will be provided in this chapter.

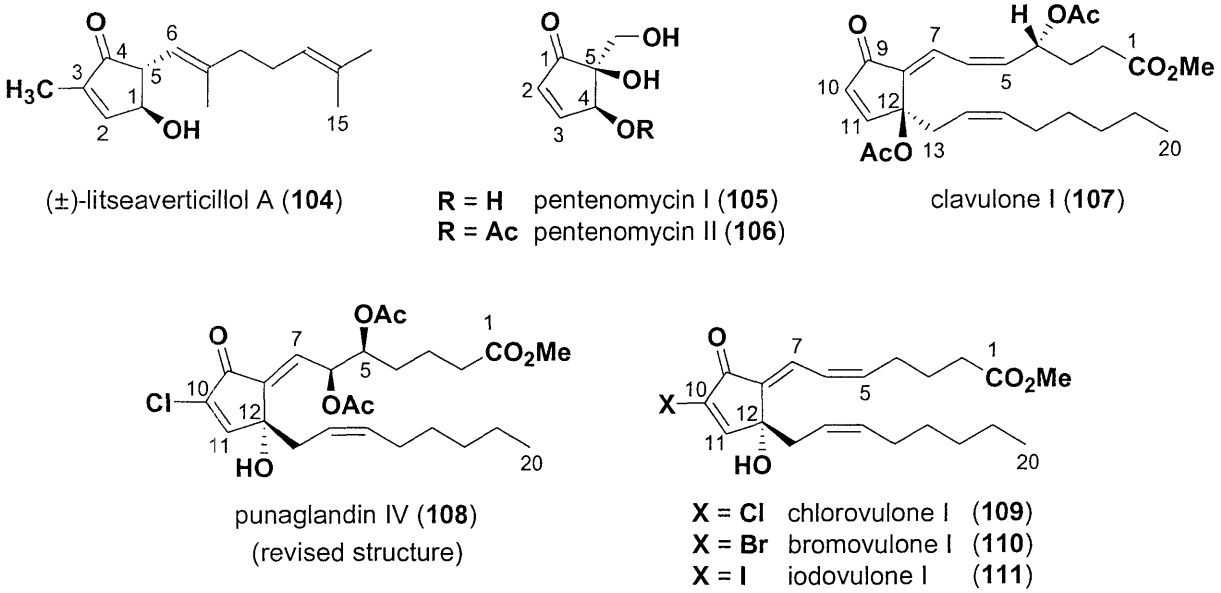
Importance of Cyclopentenones

Cyclopentenones serve as valuable synthetic building blocks and are also key structural motifs in a number of biologically active natural products, including those illustrated in Chart 1. Litseaverticillol A (**104**) is a representative member of a class of structurally related sesquiterpenes that were recently isolated (as racemic mixtures) and shown to exhibit anti-HIV activity.[45,46] Pentenomycins I (**105**) and II (**106**), isolated and characterized in the 1970's,[47]

[45] For the isolation and structure identification of litseaverticillols A-H, see: (a) Zhang, H.-J.; Tan, G. T.; Hoang, V. D.; Hung, N. V.; Cuong, N. M.; Soejarto, D. D.; Pezzuto, J. M.; Fong, H. H. S. *Tetrahedron Lett.* **2001**, *42*, 8587. (b) Zhang, H.-J.; Tan, G. T.; Hoang, V. D.; Hung, N. V.; Cuong, N. M.; Soejarto, D. D.; Pezzuto, J. M.; Fong, H. H. S. *Tetrahedron* **2003**, *59*, 141.

belong to the cyclopentanoid class of antibiotics. The cyclopentenone prostanoids (e.g., clavulone I (**107**),[48] punaglandin IV (**108**),[49] and halovulones **109-111**[50]) are another interesting group of natural products which exhibit properties including anti-inflammatory, anti-viral, and

Chart 1. Representative Cyclopentenone Natural Products



[46] (a) For total syntheses of litseaverticillols A, C, D, F, and G, see: Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 5465. (b) For total syntheses of litseaverticillols B and E, see: Vassilikogiannakis, G.; Margaros, I.; Montagnon, T. *Org. Lett.* **2004**, *6*, 2039.

[47] For preliminary reports on the isolation, structure identification and biological activities of pentenomycins I (**105**) and II (**106**), see: (a) Umino, K.; Furumai, T.; Matsuzawa, N.; Awataguchi, Y.; Ito, Y.; Okuda, T. *J. Antibiot.* **1973**, *26*, 506. (b) Umino, K.; Takeda, N.; Ito, Y.; Okuda, T. *Chem. Pharm. Bull.* **1974**, *22*, 1233.

[48] (a) Structure assignment: Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1982**, *23*, 5171. (b) Assignment of absolute stereochemistry: Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 1549.

[49] (a) For isolation and initial structural assignment of punaglandin IV (**108**), see: Baker, B. J.; Okuda, R. K.; Yu, P. T. K.; Scheuer, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 2976. (b) For a structural revision confirmed by total synthesis, see: Suzuki, M.; Morita, Y.; Yanagisawa, A.; Baker, B. J.; Scheuer, P. J.; Noyori, R. *J. Org. Chem.* **1988**, *53*, 286 and references cited therein.

[50] (a) Structure assignment for chlorovulone I (**109**): Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. *Tetrahedron Lett.* **1985**, *26*, 5787. (b) Assignment of absolute stereochemistry for chlorovulone I (**109**): Nagaoka, H.; Iguchi, K.; Miyakoshi, T.; Yamada, N.; Yamada, Y. *Tetrahedron Lett.* **1986**, *27*, 223. (c) Structure and absolute stereochemical assignments for bromovulone I (**110**) and iodovulone I (**111**): Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 981.

anti-tumor activity. Interest in this latter class of natural products has surged in recent years due to increasing information about their biological activities and potential therapeutic applications.[51]

In addition to their biological activity, the cyclopentenone natural products shown in Chart 1 also exhibit a variety of interesting structural features which have captured the attention of synthetic chemists. The clavulones, halovulones, and some punaglandins (e.g., punaglandin IV) contain a cross-conjugated dienone moiety which is believed to contribute to their biological activity.[52] The pentenomycins **105** and **106**, as well as the illustrated cyclopentenone prostaglandins **107-111** all contain an oxygenated quaternary center, posing a non-trivial challenge in the context of total synthesis. Moreover, the punaglandins and halovulones (e.g., **108-111**) possess a halogen substituent at C-10, a unique structural feature that has been shown (in some cases) to result in increased bioactivity relative to structurally similar compounds lacking this substitution.[53] Finally, all of the natural products illustrated in Chart 1 are oxygenated on the five-membered ring; however, synthetic prostaglandin analogues possessing C-12 amino substituents have also been shown to exhibit high levels of cytotoxic activity.[54]

Synthetic Approaches to Cyclopentenones

Due to the synthetic and biological importance of cyclopentenones, a number of strategies for the construction of this ring system have been developed.[55,56] As usual, ring-forming methods can be classified as involving either *cyclization* or *annulation* strategies. Scheme 15 illustrates some of the cyclization strategies that have been reported: the intramolecular aldol[57] and Wittig[58] reactions, ring-closing metathesis,[59] intramolecular rhodium-

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[51] For reviews on the structure, synthesis, and biological activity of cyclopentenone prostaglandins, see: (a) Roberts, S. M.; Santoro, M. G.; Sickle, E. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1735. (b) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185. (c) Noyori, R.; Suzuki, M. *Science* **1993**, *259*, 44.

[52] For a recent study that provides an example of the effect of the cross-conjugated dienone moiety (and C-10 halogen substitution) on the bioactivity of punaglandins, see: Verbitski, S. M.; Mullally, J. E.; Fitzpatrick, F. A.; Ireland, C. M. *J. Med. Chem.* **2004**, *47*, 2062.

[53] For examples illustrating the effect of C-10 halogen substitution on the biological activity of cyclopentenone prostaglandins, see references 51a and 52.

[54] Roulland, E.; Monneret, C.; Florent, J.-C.; Bennejean, C.; Renard, P.; Léonce, S. *J. Org. Chem.* **2002**, *67*, 4399.

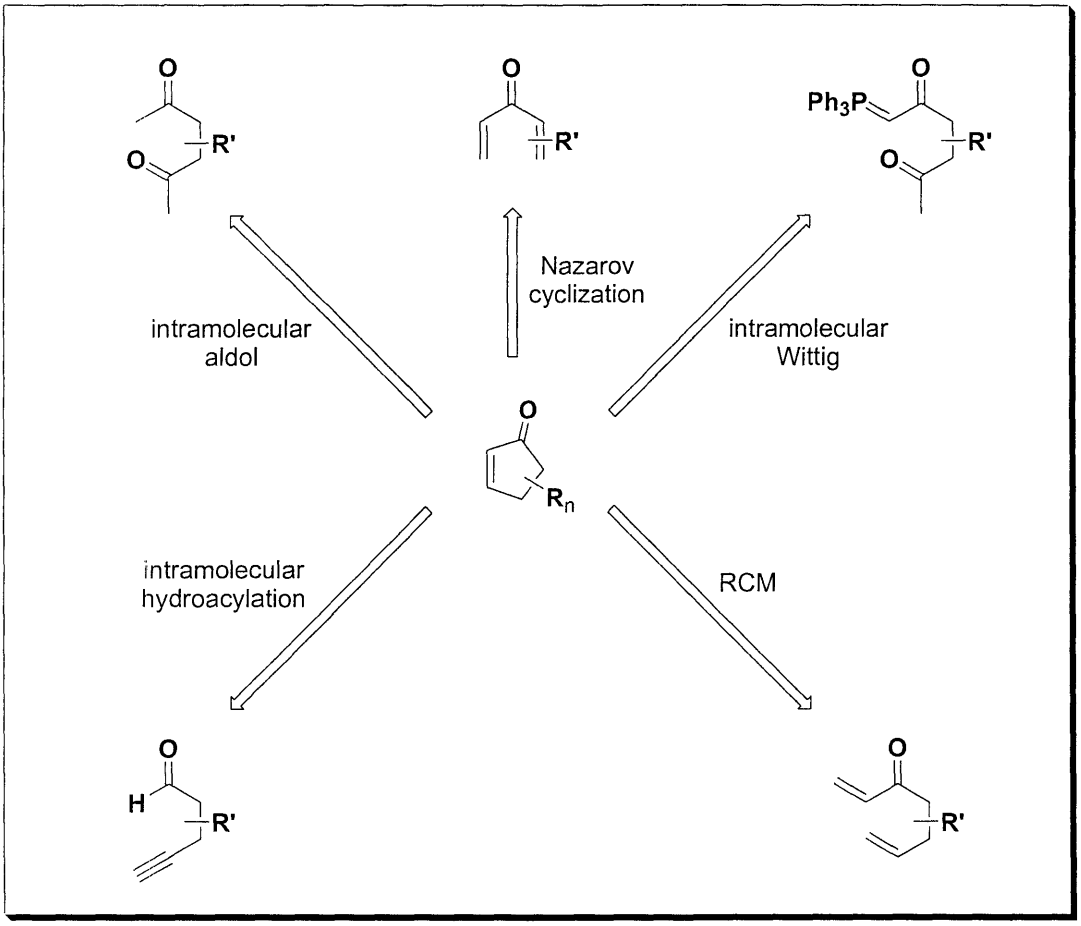
[55] For a review of transition metal-mediated routes to cyclopentenones, see: Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873.

[56] A number of methods for the synthesis of polycyclic cyclopentenones are described in the following review of cyclopentaannellation reactions: Ramaiah, M. *Synthesis,* **1984**, 529.

[57] For a discussion of the synthesis of cyclopentenones via the intramolecular aldol reaction, see reference 56 (pp 555-560).

catalyzed hydroacylation,[60] and the Nazarov cyclization.[39a-d] The latter strategy has proven to be one of the more powerful methods for cyclopentenone construction, and is mechanistically related to both the [4 + 1] indanone annulation discussed in Part II of this thesis, as well as the [4 + 1] cyclopentenone annulation that will be presented in the next chapter (Chapter 2).

Scheme 15. Representative Cyclization Strategies for the Synthesis of Cyclopentenones



In its simplest form, the Nazarov reaction involves the cyclization of a divinyl ketone to deliver a cyclopentenone product. This transformation can be catalyzed by Lewis or protic acids,

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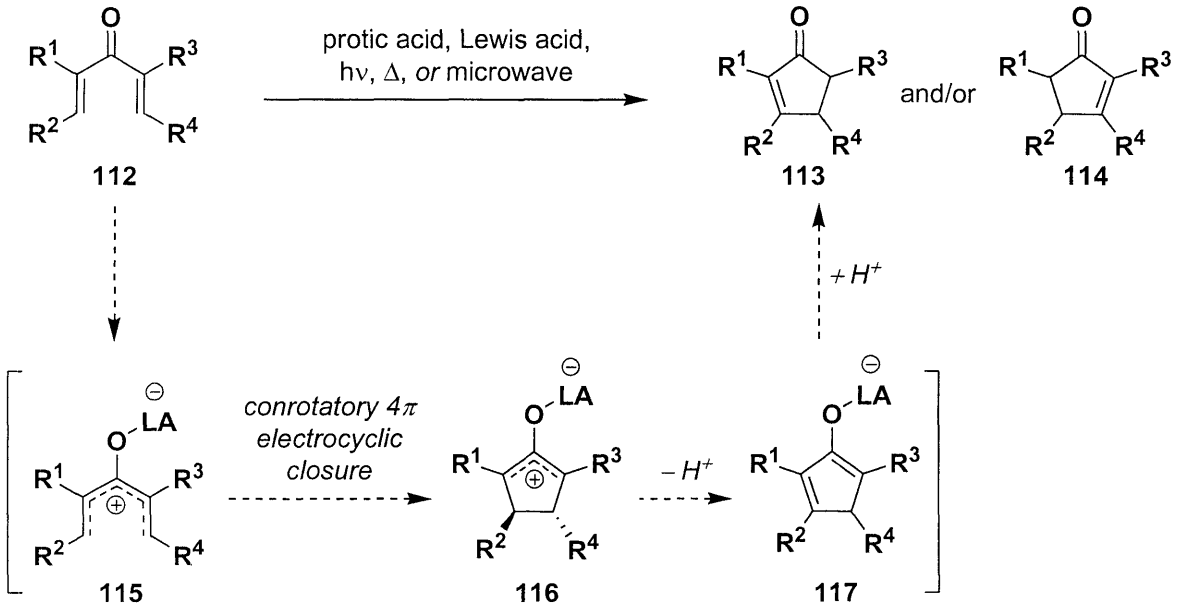
[58] For a recent example in which an intramolecular Wittig reaction was employed in the formal total synthesis of clavulone II, see: Kuhn, C.; Skaltsounis, L.; Monneret, C.; Florent, J.-C. *Eur. J. Org. Chem.* **2003**, 2585.

[59] (a) Chaterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) For a recent review on metathesis, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003.

[60] (a) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492. (b) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296.

or can be conducted thermally, photochemically, or by exposure to microwave irradiation.[61] A generalized mechanism for the Lewis-acid-catalyzed Nazarov cyclization is shown in Scheme

Scheme 16. Mechanism of the Nazarov cyclization



16. Coordination of the Lewis acid to the carbonyl group generates an oxidopentadienylic cation **115** which then undergoes conrotatory 4π electrocyclic closure to deliver allyl cation **116**. Proton loss, followed by protonation of the resulting enolate **117** produces cyclopentenone **113** and/or **114**, depending on the nature of the substituents (R^1 to R^4). The regiochemical ambiguity in the deprotonation of the allylic cation (**116** → **117**) can be problematic, but several strategies to control the regiochemical course of the reaction have been reported.[62]

Recently there has been a renewed interest in the Nazarov reaction, particularly focused on the development of new Lewis-acid catalyst systems[63] and catalytic asymmetric variants,[64] as

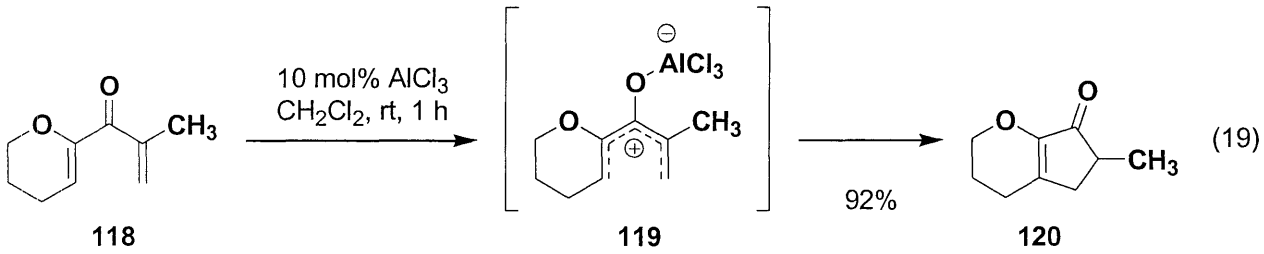
[61] For a recent report on successful thermal and microwave promoted Nazarov cyclizations, see: Douelle, F.; Tal, L.; Greaney, M. F. *Chem. Commun.* **2005**, 660.

[62] For example, Denmark has developed a silicon-directed Nazarov cyclization; see reference 39b (pp 13-17).

[63] (a) Janka, M.; He, W.; Frontier, A. J.; Flaschenriem, C.; Eisenberg, R. *Tetrahedron* **2005**, *61*, 6193. (b) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931. (c) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927.

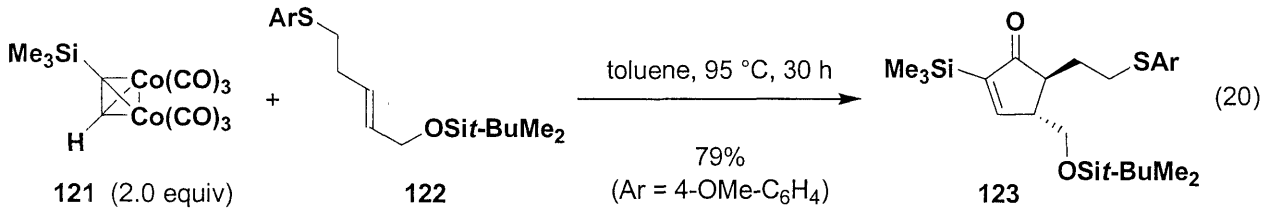
[64] (a) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004,** *126,* 9544. (b) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075.

well as the use of "polarized" Nazarov substrates.[65] Furthermore, the mechanism and scope of the retro-Nazarov reaction has also been the subject of research reported during the past several years.[66] A specific example of a recently reported Lewis-acid-catalyzed Nazarov cyclization is shown in eq 19; in this case, the presence of an α-alkoxy substituent on the divinyl ketone substrate leads to the formation of cyclopentenone **120** as the exclusive regioisomer.[63b]



(19)

In addition to the cyclization strategies discussed above, a number of *annulation strategies* for the synthesis of cyclopentenones have been developed. Among these, the Pauson–Khand reaction[67] - a transition metal-mediated coupling of an alkyne, an alkene and carbon monoxide - is one of the most popular and powerful methods. The initial version of this reaction involved the use of $Co_2(CO)_8$, although research spanning the past three decades has led to a large number of advances in this methodology, including the development of variations based on other transition metal catalysts. Equation 20 presents a representative example of this reaction used in the course of a formal total synthesis of the cyclopentenone prostaglandin PGA_2.[68] The successful application of the Pauson–Khand reaction in the total syntheses of a large variety of structurally complex molecules serves as a testament to its utility.

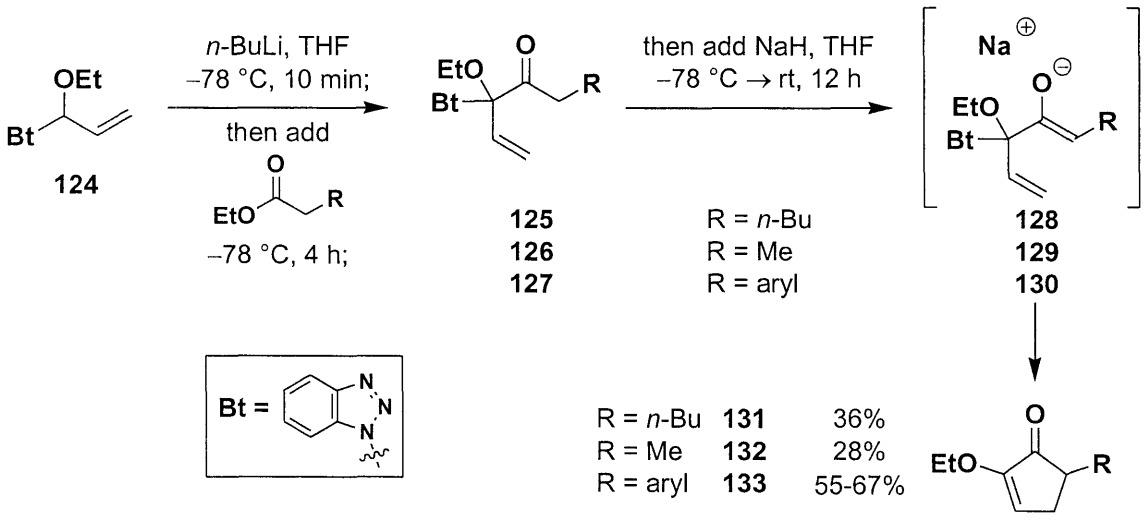


(20)

[65] He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278.
[66] See Harmata, M.; Lee, D. R.; Barnes, C. L. *Org. Lett.* **2005**, *7*, 1881 and references cited therein.
[67] For reviews, see: (a) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 3022. (b) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32. (c) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (d) Schore, N. E. *Org. React.* **1991**, *40*, 1.
[68] Krafft, M. E.; Wright, C. *Tetrahedron Lett.* **1992**, *33*, 151.

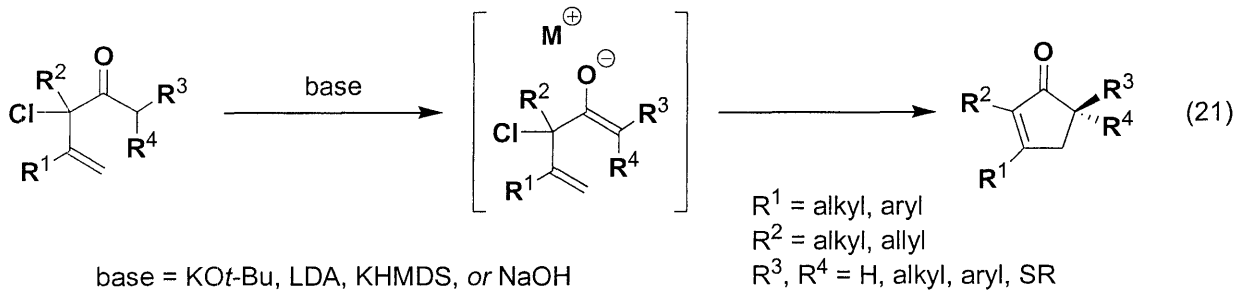
Katritzky and coworkers have reported a [3 + 2] annulation strategy for the synthesis of cyclopentenones (Scheme 17) employing substituted benzotriazole **124** as the three-carbon component.[69] Although this method appears to have limited utility, it is discussed here due to its mechanistic relevance to the chemistry investigated in our laboratory. Treatment of benzotriazole **124** with *n*-BuLi generates an α-benzotriazolyl organolithium compound which can then be acylated with a variety of esters to furnish the illustrated β,γ-unsaturated enones **125-127**. Treatment of the ketone (generated in situ) with NaH at –78 °C provides the corresponding enolate, and warming the reaction mixture to room temperature results in loss of the benzotriazole group and cyclization to furnish the illustrated cyclopentenones. The authors propose that the cyclization step (e.g., **128** → **131**) proceeds via an intramolecular S_N2' mechanism, however, we believe that these reactions more likely involve the cyclization of an oxidopentadienylic cation (a mechanistic pathway related to the Nazarov cyclization discussed above). As indicated, this reaction has only been applied to a limited number of esters and yields are poor in the case of aliphatic derivatives.

Scheme 17



[69] Katritzky, A. R.; Zhang, G.; Jiang, J. *J. Org. Chem.* **1995**, *60*, 7605.

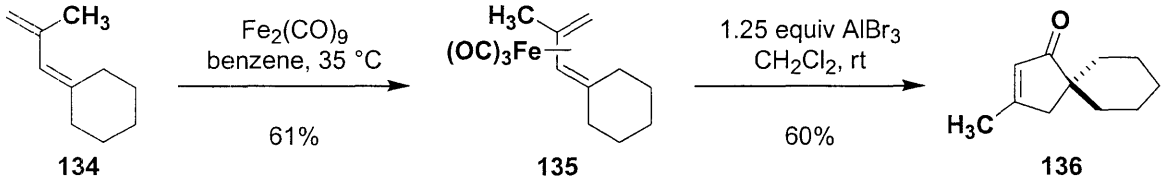
The [3 + 2] annulation discussed above is reminiscent of the base-induced cyclization of α-chloro-β,γ-unsaturated ketones reported several years earlier by Mathew (eq 21).[70] An



(21)

intermolecular S_N2' mechanism was also proposed in this case, but Mathew did note the possibility of an alternative mechanism involving the [1,3] sigmatropic rearrangement of a vinylcyclopropanone intermediate.[70c]

Several [4 + 1] annulation strategies for the synthesis of cyclopentenones have also been developed. Equation 22 provides a representative example of a strategy in which Lewis acid-promoted decomplexation of iron tricarbonyl 1,3-diene complexes (e.g., **135**) leads to the formation of substituted cyclopentenones.[71] This transformation has been successfully executed



(22)

with several substrates, but one limitation is that the 1,3-diene employed must be unsubstituted at C-4. Another annulation strategy based on the use of carbon monoxide as the one-carbon component was recently reported by Larock and Gagnier (eq 23).[72] In this strategy, a dienyl bromide, iodide, or triflate is employed as the substrate for a palladium-catalyzed carbonylative cyclization.

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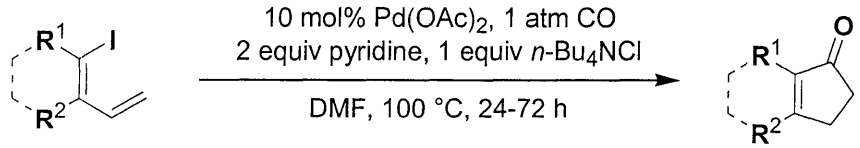
[70] (a) Mathew, J. *J. Org. Chem.* **1991**, *56*, 713. (b) Mathew, J. *J. Org. Chem.* **1990**, *55*, 3880. (c) Mathew, J. *J. Org. Chem.* **1990**, *55*, 5294.

[71] (a) Franck-Neumann, M.; Michelotti, E. L.; Simler, R.; Vernier, J.-M. *Tetrahedron Lett.* **1992**, *33*, 7361. (b) Franck-Neumann, M.; Vernier, J.-M. *Tetrahedron Lett.* **1992**, *33*, 7365.

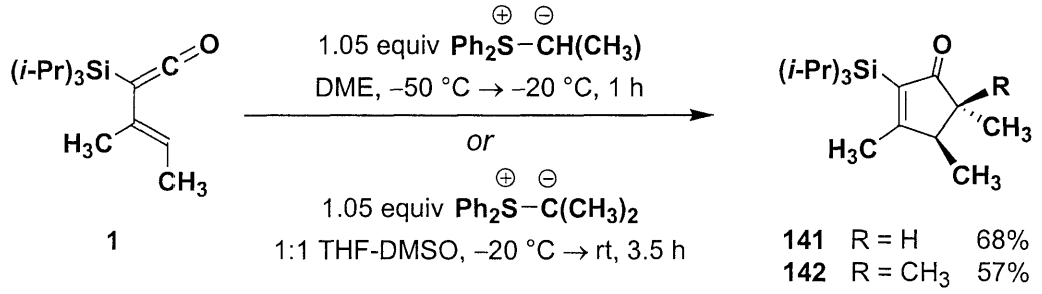
[72] Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804.



(23)

137 $R^1 = R^2 = n$-Pr **139** 70%
138 $R^1, R^2 = (CH_2)_4$ **140** 86%

As discussed previously (Part I, pp 13-14), our group has developed a [4 + 1] annulation strategy for the construction of cyclopentenones that involves the reaction of (TAS)vinylketenes with carbenoid reagents.[8] This annulation proceeds smoothly with diazomethane (eq 6, Part II, p 22) and TMS-diazomethane, however, attempts to use higher diazoalkanes and substituted TMS-diazomethanes proved unsuccessful. As illustrated in eq 24, sulfur ylides (generated in situ by treatment of the corresponding sulfonium salt with *n*-BuLi or *t*-BuLi) also function as competent carbenoid reagents, furnishing highly substituted cyclopentenones such as **141** and **142**.



(24)

141 R = H 68%
142 R = CH_3 57%

Furthermore, this process is highly stereoselective, resulting in the exclusive formation of *trans*-substituted cyclopentenones (e.g., **141**) in cases where the formation of *cis* and *trans* diastereomers is possible. Subsequent to this work, Rigby and coworkers reported the extension of our strategy to include reactions of heteroatom-substituted nucleophilic carbenes (eq 3, Part I, p 14).[10]

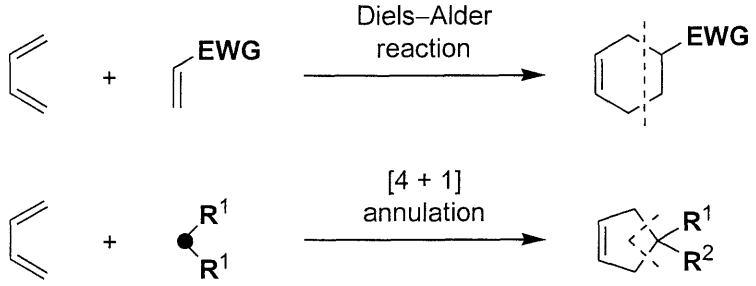
[4 + 1] Annulation Strategies

Annulation strategies represent an attractive and highly convergent approach to the synthesis of five-membered carbocycles; however, only a few general [4 + 1] routes to cyclopentanoid products have been developed. Several [4 + 1] annulation strategies for the synthesis of the cyclopentenone ring system were discussed above. Recent examples of [4 + 1]

strategies for the synthesis of other five-membered carbocycles include the 'cycloaddition' of electron-poor dienes and electron-rich carbenes reported by Spino,[73] and Murakami's strategy for the synthesis of 2-alkylidene-3-cyclopentenone derivatives based on the rhodium- and platinum-catalyzed coupling of vinylallenes and carbon monoxide.[74] Our interest in the development of a versatile [4 + 1] annulation approach to cyclopentenones stems from a broader, longstanding interest in the discovery of [4 + 1] routes for the construction of various five-membered carbocycles.

Research conducted early on in our group's history resulted in the development of a [4 + 1] annulation strategy for the synthesis of cyclopentenols based on oxyanion-accelerated vinylcyclopropane rearrangements.[75] The goal of this research was the development of a method, analogous to the Diels–Alder reaction, in which a one-carbon unit could be added to a 1,3-diene to afford a cyclopentene (rather than a cyclohexene) derivative (Scheme 18). The

Scheme 18



second generation version of this strategy, based on *carbanion*-accelerated vinylcyclopropane rearrangements, extended this methodology to encompass the synthesis of a broad range of substituted cyclopentenes (Scheme 19).[76] In the latter route, a 1,3-diene serves as the four carbon component and a carbene (:CHBr or :CBr_2) functions as the one-carbon component. The initially formed cyclopropane **144** is converted to sulfone **145** in two steps. Treatment of sulfone **145** with *n*-BuLi at –78 °C generates the organolithium intermediate **146**, which, upon warming, undergoes an anion-accelerated [1,3] sigmatropic rearrangement to furnish cyclopentene **147**.

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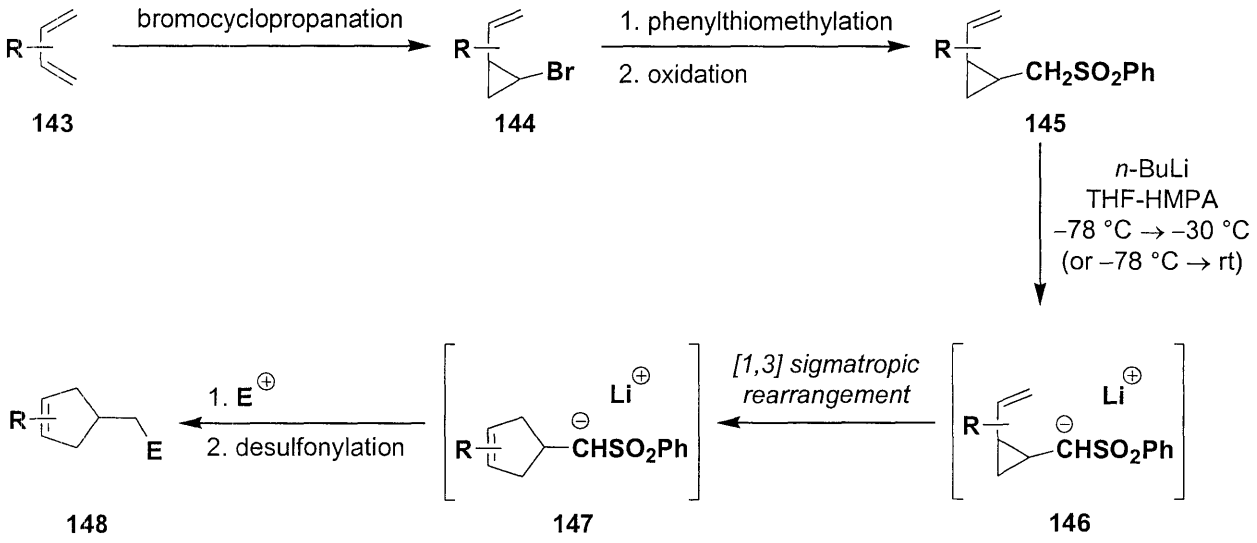
[73] Spino, C.; Rezaei, H.; Dupont-Gaudet, K.; Bélanger, F. *J. Am. Chem. Soc.* **2004**, *126*, 9926.
[74] (a) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 2950. (b) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4130.
[75] (a) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M., Jr. *J. Org. Chem.* **1980**, *45*, 1340. (b) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443.
[76] Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579.

The organolithium intermediate can then be trapped with a variety of electrophiles to furnish five-membered carbocycles of type **148**.

Scheme 19. General Strategy for [4 + 1] Cyclopentene Annulation



In the (TAS)vinylketene-based [4 + 1] route to substituted cyclopentenones described in this thesis, the 1,3-diene is embedded within the framework of a (silyl)vinylketene, and a carbenoid reagent rather than a true carbene is employed as the reactive one-carbon component. The further development of our (TAS)vinylketene annulation described in the remaining chapters of this thesis fits into the subsection of our research program aimed at the development of [4 + 1] annulation strategies for synthesizing various five-membered carbocyclic compounds.

Goals of Our Studies

As stated at the beginning of this chapter, the goal of the research presented in Part III of this thesis was to extend the scope of our [4 + 1] cyclopentenone annulation (eq 2, p 43) to include the synthesis of cyclopentenones bearing a much broader range of substitution at the C-5 position. Specifically, we sought to develop a new class of carbenoid reagents for this transformation that are easier to prepare and handle than the previously employed diazo compounds and sulfur ylides, and for which a larger variety of substituted precursors are readily

available. In general non-stabilized sulfur ylides[77] such as dimethylsulfonium methylide exhibit limited thermal stability (half-lives on the order of minutes at 10 °C), and in many cases the sulfonium salt precursors are hygroscopic and difficult to handle. In our previous work, methyl-, ethyl-, and isopropyl-substituted sulfur ylides were successfully employed;[8] however, exploratory studies with more substituted sulfur ylides (such as the ylides derived from allyl sulfonium salts) revealed that the limited thermal stability of these species compromises their ability to participate in (TAS)ketene-based annulations. These and other difficulties we encountered prompted us to search for a new class of carbenoid reagents for our [4 + 1] annulation.

Due to the ubiquity of heteroatom-substituted cyclopentenones in the structure of a large number of bioactive natural products (e.g., those illustrated in Chart 1), we were particularly interested in discovering a class of carbenoids that would allow us to install heteroatom substituents at the C-5 position. Furthermore, we anticipated that heteroatom-substituted carbenoid reagents might create new possibilities for asymmetric induction, perhaps through the incorporation of chiral auxiliaries. The results of our efforts to extend the scope of the [4 + 1] cyclopentenone annulation will be presented in the remaining chapters.

[77] For reviews on sulfur ylides, see: (a) Clark, J. S. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Clark, J. S., Ed.; Oxford University Press: Oxford, 2002; pp 40-57. (b) Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic Press: New York, 1975.

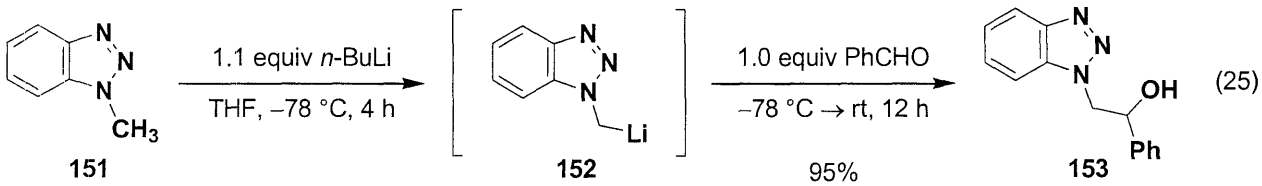
Chapter 2

[4 + 1] Annulations with α-Benzotriazolyl Organolithium Compounds

As discussed in Chapter 1, the aim of this investigation was to identify a new class of readily accessible and easily-handled carbenoid reagents for our [4 + 1] annulation that would allow access to cyclopentenones with a broad array of substitution, particularly heteroatom substitution, at the C-5 position. Of the carbenoid reagents screened, α-benzotriazolyl organolithium compounds (derived via lithiation of substituted 1-alkylbenzotriazoles, vide infra) have proven to best meet our requirements. This chapter begins with a discussion of our rationale for choosing to examine α-benzotriazolyl organolithium compounds as possible carbenoid reagents and then presents the results of our study on the [4 + 1] cyclopentenone annulation using these compounds.

Synthetic Utility of Benzotriazole Derivatives

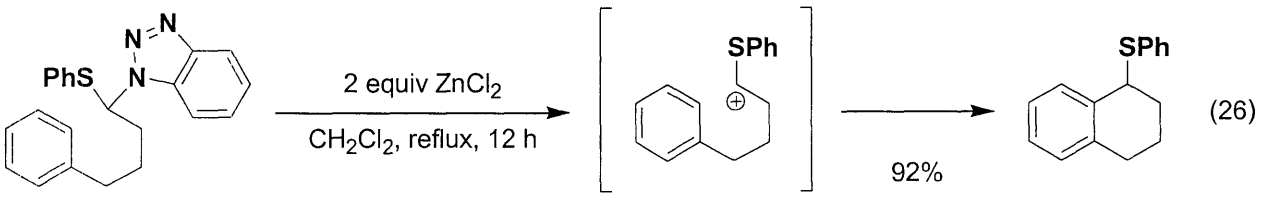
Benzotriazole has proven to be a versatile synthetic auxiliary in a variety of applications.[78] In the context of our [4 + 1] annulation, *N*-substituted benzotriazole derivatives garnered our attention for several reasons. First, it is well known that the benzotriazole group can activate an α-C-H bond towards deprotonation. The resulting metallated benzotriazoles (e.g., α-benzotriazolyl organolithium compound **152**) are competent nucleophiles in reactions with a variety of electrophiles such as alkyl halides and carbonyl compounds (eq 25). Second,



151 **152** **153** (25)

[78] For reviews, see: (a) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409. (b) Katritzky, A. R.; Rogovoy, B. V. *Chem. Eur. J.* **2003**, *9*, 4586. (c) Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555.

benzotriazole can serve as a leaving group under the appropriate conditions, most often upon treatment with a Lewis acid. For example, treatment of benzotriazole **154** (eq 26) with an excess of $ZnCl_2$ in refluxing CH_2Cl_2 results in ionization of the benzotriazole group and subsequent cyclization to furnish the tetralin **156** in excellent yield.[79] Benzotriazole has a pK_a of 8.2[78a] (11.9 in DMSO),[80] and its leaving group ability has been compared to that of the cyano and phenylsulfonyl groups. While benzotriazole may appear to be a 'bulky' leaving group, it has a molecular weight of 118 g/mol, less than that of traditional leaving groups such as iodide (MW = 127) and toluenesulfonate (TsO^-, MW = 171). In addition, a wide range of substituted 1-alkylbenzotriazole derivatives are either commercially available or easily prepared in 1-2 steps from inexpensive starting materials.



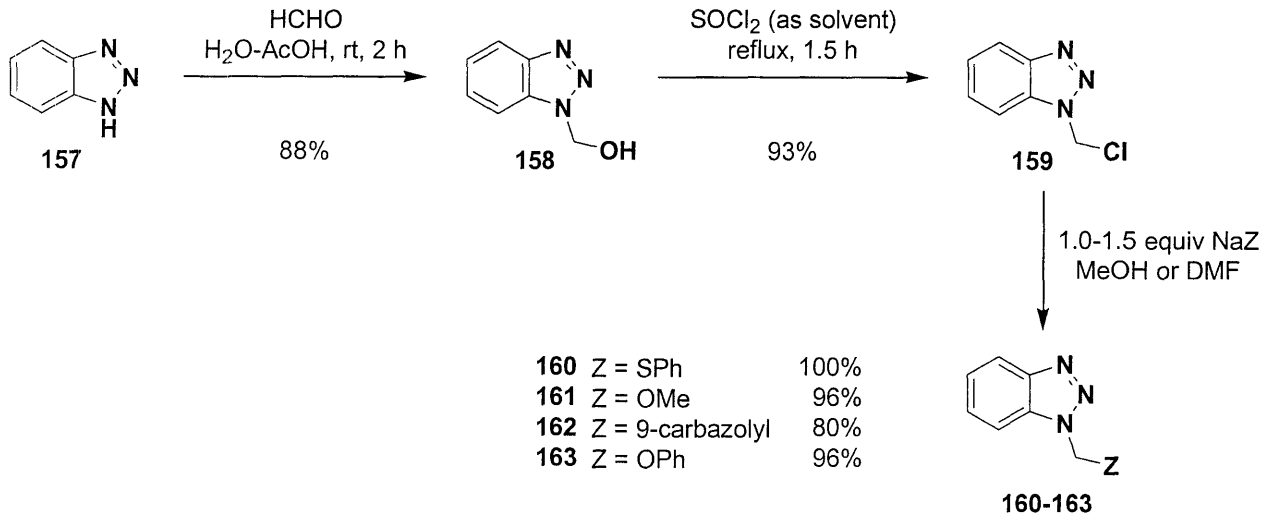
154 **155** **156** (26)

Scheme 20 illustrates a representative synthetic approach to several hetero-substituted 1-alkylbenzotriazole derivatives (**158-163**) beginning with benzotriazole (**157**), a very inexpensive starting material ($0.09/g; $10.35/mol).[81] Burckhalter has reported the preparation of chloromethyl derivative **159** in excellent yield via a two-step procedure involving the reaction of benzotriazole with formaldehyde in H_2O-AcOH, and treatment of the resulting hemiaminal **158** with thionyl chloride.[82,83] A variety of other derivatives can then be prepared in excellent yield by simple nucleophilic displacement reactions. A large number of hetero-substituted 1-alkylbenzotriazoles, including **160**,[84] **161**,[85] **162**,[86] and **163**,[87] have been previously prepared in this fashion.[88] Conveniently, benzotriazole derivatives **158-162** are also commercially available.

---

[79] Katritzky, A. R.; Yang, Z.; Lam, J. N.; Cundy, D. J. *Heterocycles* **1993**, *36*, 1367.
[80] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
[81] Price based on the purchase of a 1000 g bottle (99% purity) from Alfa Aesar.
[82] Burckhalter, J. H.; Stephens, V. C.; Hall, L. A. R. *J. Am. Chem. Soc.* **1952**, *74*, 3868.
[83] Katritzy has reported a related two-step, one pot sequence for the synthesis of **159** in 91% overall yield from benzotriazole (**157**), see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Org. Chem.* **1989**, *54*, 6022.
[84] Katritzky, A. R.; Rachwal, S.; Caster, K. C.; Mahni, F.; Law, K. W.; Rubio, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 781.

Scheme 20. Synthesis of Several 1-Alkylbenzotriazole Derivatives



Feasibility of the [4 + 1] Annulation with α-Benzotriazolyl Organolithium Compounds

In order for the proposed [4 + 1] cyclopentenone annulation to be successful, α-benzotriazolyl organolithium compounds must be suitable nucleophiles for addition to (TAS)vinylketenes. To investigate this question, we examined the reaction of α-benzotriazolyl organolithium **164**, prepared by treatment of benzotriazole derivative **160** with *n*-BuLi at –78 °C, with the known (TAS)vinylketene **1**[7b] (Scheme 21). Gratifyingly, nucleophilic addition proceeded smoothly at –78 °C, and quenching of the resulting dienolate intermediate furnished enone **166** as a mixture of diastereomers in nearly quantitative yield.

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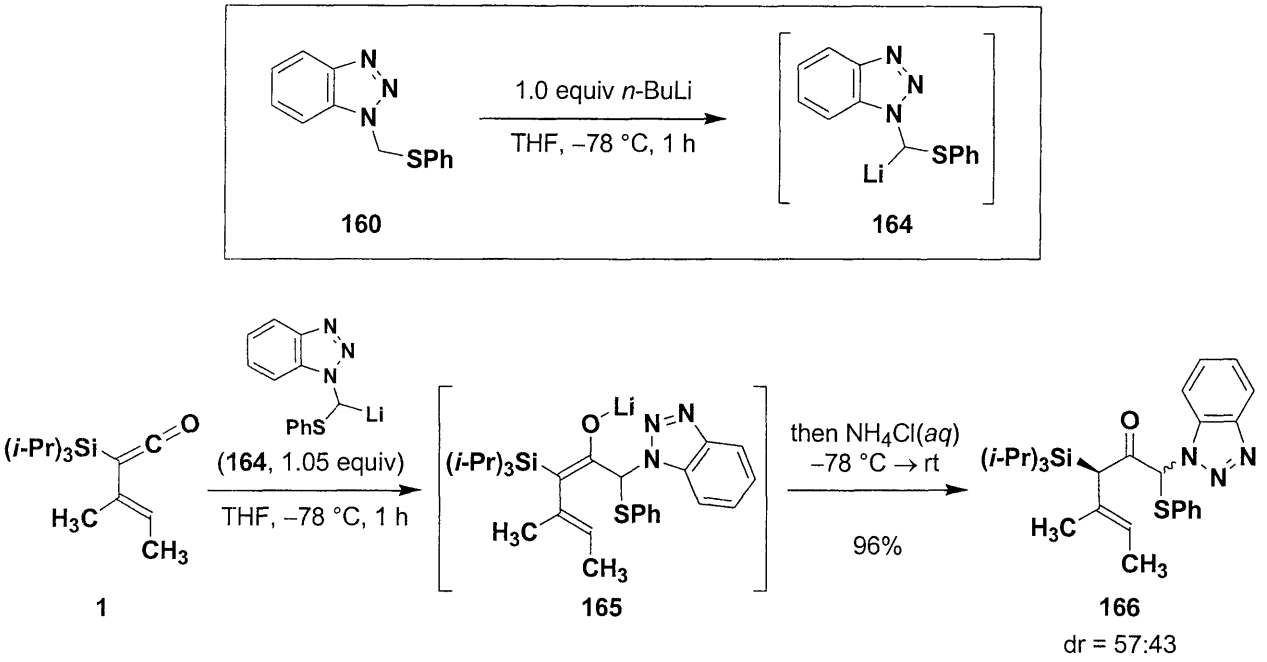
[85] For an experimental procedure, see: Katritzky, A. R.; Yang, Z.; Cundy, D. J. *Synth. Commun.* **1993**, *23*, 3061. For spectral data, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Org. Chem.* **1989**, *54*, 6022.

[86] Katritzky, A. R.; Yang, Z.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 2143.

[87] Katritzky, A. R.; Serdyuk, L.; Xie, L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1059.

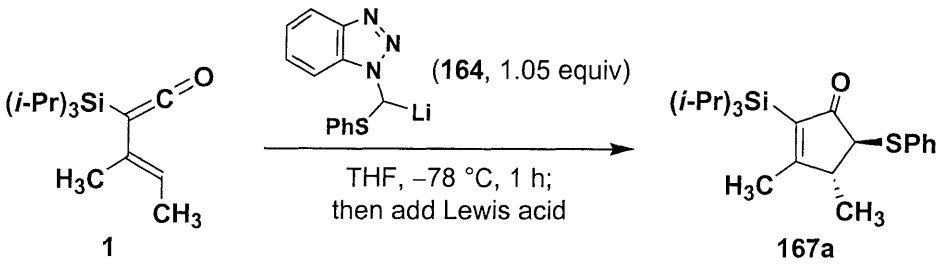
[88] Benzotriazole **161** and other hetero-substituted 1-alkylbenzotriazole derivatives related to **160** and **163** can also be prepared via the condensation of benzotriazole (**157**) with the corresponing aldehyde and thiol or alcohol. See reference 78a, pp 420-431.

Scheme 21



Having demonstrated that the α-benzotriazolyl organolithium compound **164** undergoes smooth nucleophilic addition to ketene **1**, we then turned our attention towards developing conditions to promote the cyclization of dienolate intermediate **165**. We rationalized that treatment of dienolate **165** with a Lewis acid might promote ionization of the benzotriazole group and cyclization to deliver the desired cyclopentenone, and we were pleased to find that a variety of Lewis acids were successful in this regard (Scheme 22). The use of 1 equiv of $ZnBr_2$ results in the formation of only a trace amount of cyclized product, however, addition of 2 or 3 equiv of $ZnBr_2$ to the dienolate solution at –78 °C followed by warming of the reaction mixture to room temperature delivers the desired cyclopentenone **167a** with 98:2 selectivity for the *trans* isomer. When 3 equiv of $AlCl_3$ or $BF_3{\cdot}OEt_2$ are employed, the desired product is obtained in very good yield, but the diastereoselectivity is not as high. TLC experiments indicated that $SnCl_4$, $Cu(OTf)_2$, and $TiCl_4$ also promote the desired reaction, although in these cases the yield was estimated to be in the range of 40-60%. Finally, when the reaction is performed without the addition of a Lewis acid, some of the desired product is observed upon warming the reaction to room temperature and then heating at reflux (65 °C) for several hours; however, TLC analysis

Scheme 22

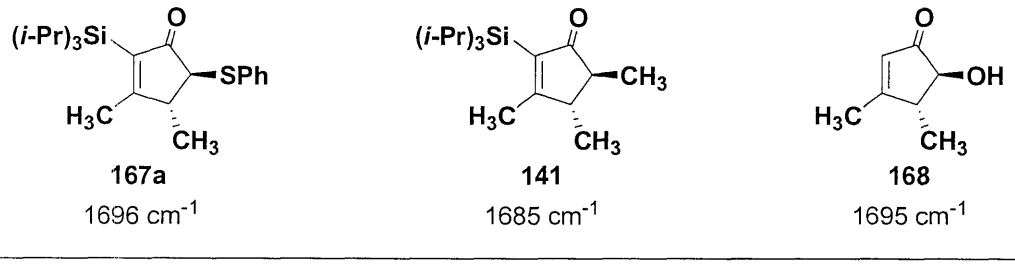


Lewis acid	Time and temperature	Yield	*trans* : *cis*
1.0 equiv $ZnBr_2$	–78 °C → rt, 20 h	trace	--
2.0 equiv $ZnBr_2$	–78 °C → rt, 18 h	57%	98:2
3.0 equiv $ZnBr_2$	–78 °C → rt, 17 h	74%	98:2
3.0 equiv $AlCl_3$	–78 °C → rt, 25 h	80%	90:10
3.0 equiv $BF_3 \cdot OEt_2$	–78 °C → rt, 1 h; then reflux 2.5 h	88%	88:12

indicates that the yield is poor (<20%). Based on these results, we concluded that the optimal reaction conditions for this case of the [4 + 1] annulation involve the addition of 3 equiv of $ZnBr_2$ to the dienolate solution at –78 °C and then warming of the reaction mixture to room temperature.

The structural assignment for cyclopentenone **167a** is based on an analysis of IR and ^1H and ^{13}C NMR data. Cyclopentenone **167a** exhibits a characteristic carbonyl stretch in the IR spectrum at 1696 cm^{-1}, which is consistent with data reported for a number of related cyclopentenones including **141**[8] and **168**[89] (Figure 4). ^{13}C NMR data for **167a** is also in good

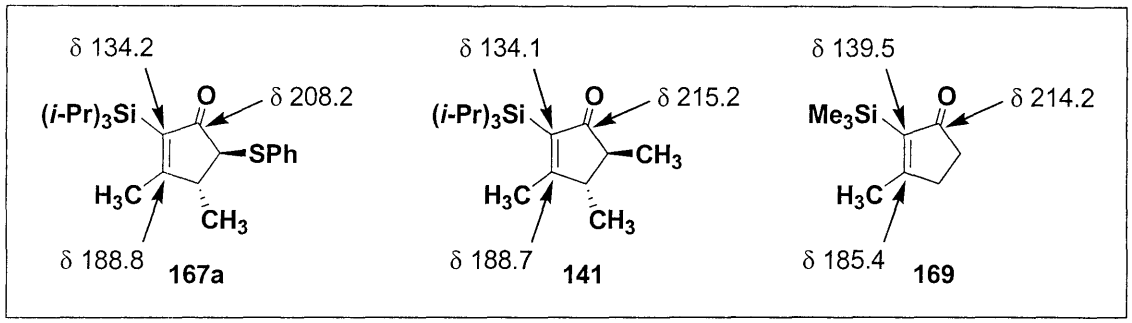
Figure 4. Carbonyl Stretching Frequencies for **167a** and Model Compounds **141** and **168**



[89] Preparation and spectral data for cyclopentenone **168**: Gowda, G.; McMurry, T. B. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 274.

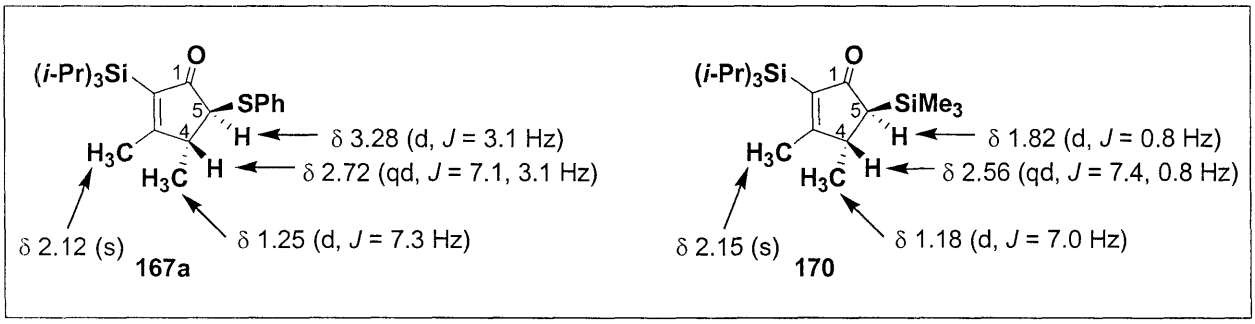
agreement with data for previously reported α-silylcyclopentenones: the resonance for the carbonyl carbon occurs at 208.2 ppm, and the α- and β-carbon resonances appear at 134.2 and 188.8 ppm, respectively (Figure 5). Finally, the ^{1}H NMR spectrum of **167a** is very similar to

Figure 5. Partial ^{13}C NMR Data for **167a** and Model Compounds **141**[8] and **169**[90]



that of the model trimethylsilyl-substituted cyclopentenone **170**[8] shown in Figure 6, with one major difference: in **167a**, the proton at C-5 exhibits a significant downfield shift relative to the corresponding proton in model compound **170** (3.28 vs. 1.82 ppm) due to the presence of an electron-withdrawing thiophenyl substituent at C-5 (compared with an electron-donating $SiMe_3$ group in the model).

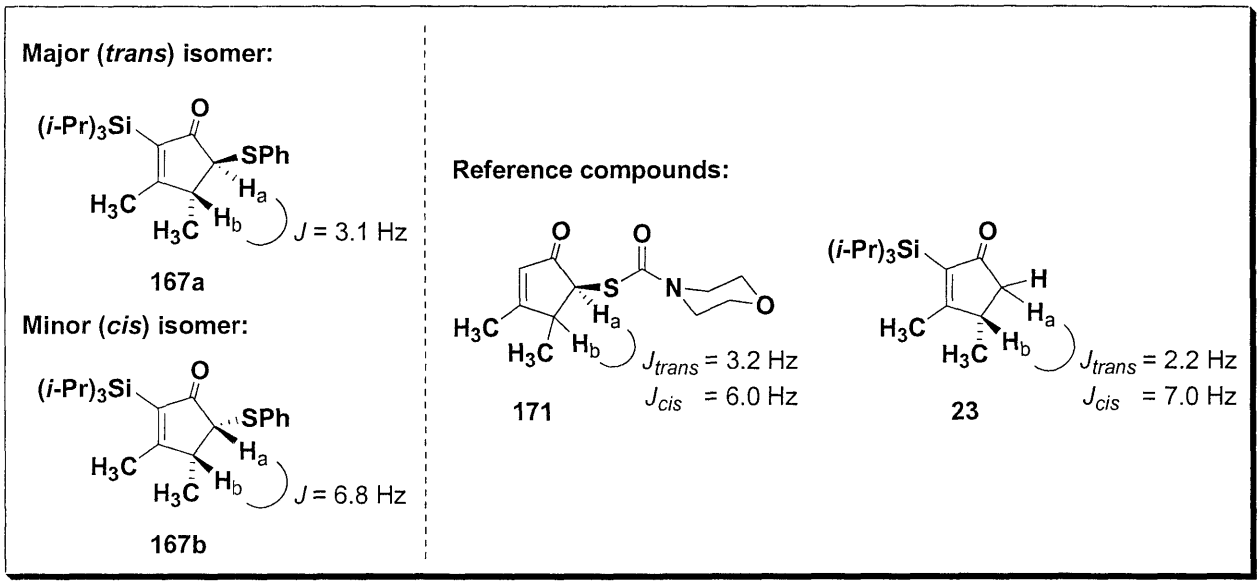
Figure 6. Partial ^{1}H NMR Data for **167a** and Model Compound **170**



[90] Takahashi, T.; Xi, Z.; Nishihara, Y.; Huo, S.; Kasai, K.; Aoyagi, K.; Denisov, V.; Negishi, E.-i. *Tetrahedron* **1997**, *53*, 9123.

The relative stereochemistry of cyclopentenone **167** was assigned based on an analysis of ^{1}H NMR coupling constants (Figure 7). The major isomer **167a**, for which a coupling constant of 3.1 Hz is observed between H_a and H_b, was assigned as the *trans* diastereomer by comparison with related compounds (e.g., **171**[91] and **23**[8]). For the minor (*cis*) isomer **167b**, a coupling constant of 6.8 Hz is observed between H_a and H_b, also consistent with the data for the illustrated reference compounds. Furthermore, models indicate that the dihedral angle between the C-4 and C-5 protons is approximately 120° for the *trans* isomer and 0° for the *cis* isomer; Karplus curve analysis suggests that J_{ab} should be larger for the *cis* isomer, consistent with our observations.

Figure 7



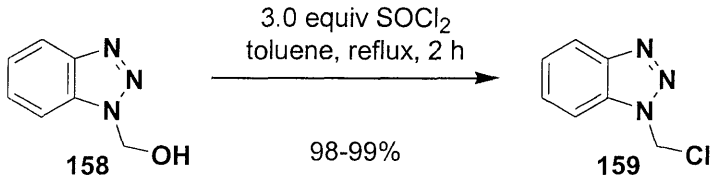
After the development of reaction conditions for our prototypical annulation, we were interested in examining the scope of this reaction, particularly with respect to the carbenoid reagents. Our synthetic approach to the required benzotriazole derivatives is discussed below.

Preparation and Metallation of 1-Alkylbenzotriazole Derivatives

A variety of substituted 1-alkylbenzotriazole derivatives were synthesized in order to probe the scope of our [4 + 1] annulation. Benzotriazoles **160-163** were prepared from

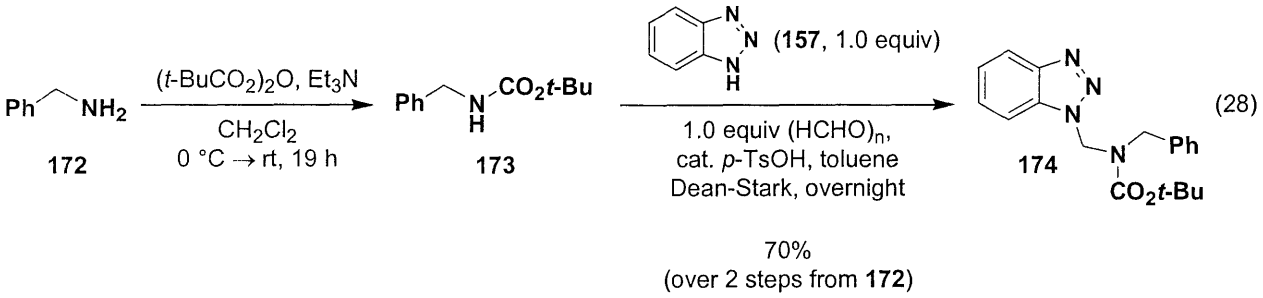
[91] Hartke, K.; Timpe, C. *Liebigs Ann. Chem.* **1994**, 183.

chloromethyl derivative **159** as discussed above (Scheme 20). We found it most convenient to prepare chloride **159**[92] from the commercially available derivative **158** by treatment with excess thionyl chloride in refluxing toluene (eq 27), a modification of the previously reported procedure

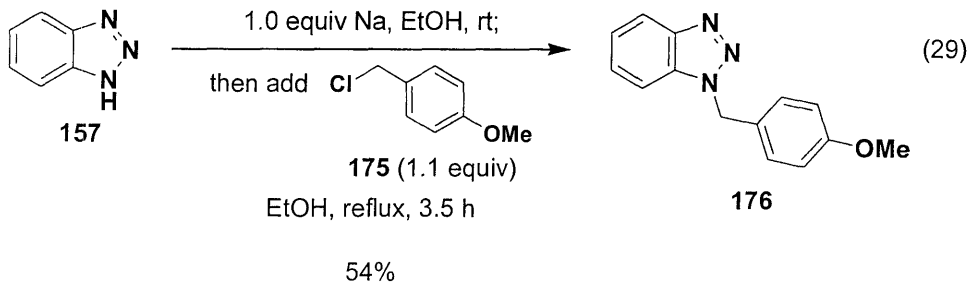


shown in Scheme 20. Excess thionyl chloride is readily removed from the crude reaction mixture by distillation, and evaporation of the remaining solvent *in vacuo* delivers benzotriazole **159** in nearly quantitative yield and >96% purity. We have performed this reaction on a scale which produces 7.6 g of **159** as an air-stable, crystalline solid that can be stored at room temperature for months with no special precautions.

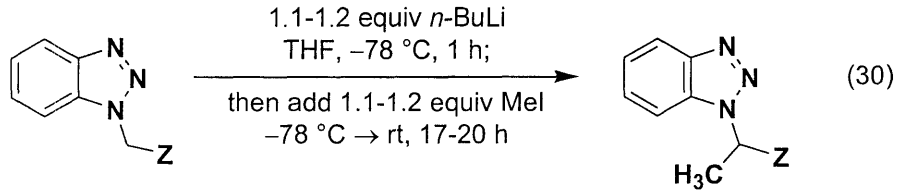
As shown in eq 28, the known benzotriazole **174** was prepared in 70% overall yield as previously described by Katritzky[93] via protection of benzylamine as its BOC derivative and reaction of the crude carbamate **173** with benzotriazole and paraformaldehyde in the presence of catalytic *p*-TsOH. In addition to heteroatom-substituted 1-alkylbenzotriazoles, *p*-methoxybenzyl derivative **176** was prepared according to a literature procedure by reaction of the sodium salt of benzotriazole with the corresponding benzyl chloride **175** (eq 29).[94]



[92] Benzotriazole **159** is commercially available, although it is approximately three times more expensive than **158**.
[93] Katritzky, A. R.; Luo, Z.; Fang, Y.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 2858.
[94] For an experimental procedure, see: Kang, Y. H.; Kim, K. *J. Heterocycl. Chem.* **1997**, *34*, 1741. For spectral data, see: Katritzky, A. R.; Lan, X.; Lam, J. N. *Chem. Ber.* **1991**, *124*, 1819.



Several tertiary 1-alkylbenzotrizole derivatives were also prepared, since successful [4 + 1] annulations with the corresponding α-benzotriazolyl organolithium compounds would provide access to cyclopentenones bearing a quaternary center at C-5 (vide infra). Thiophenoxy derivative **160** and phenoxy derivative **161** were readily lithiated by treatment with *n*-BuLi at –78 °C, and trapping of the resulting organolithium intermediates with methyl iodide furnished **177**[95] and **178**[96] in good yield (eq 30). As outlined in Scheme 23, benzotriazoles **124** and **182** were prepared in excellent yield simply by reaction of benzotriazole (**157**) with 3,3-diethoxy-1-propene (**179**) and 1,1,-diethoxy-2-butyne (**181**), respectively, in refluxing toluene. In each case a small amount of the 2-alkylbenzotriazole regioisomer was formed, but pure samples of the desired products were obtained by column chromatography on silica gel. Katritzky and



coworkers have reported the synthesis of benzotriazole **124** via the reaction of benzotriazole and acetal **179** in refluxing hexanes;[97] however, we observed no reaction under these conditions. Fortunately, employing toluene as the solvent resulted in clean formation of **124** and **180** (Scheme 23).

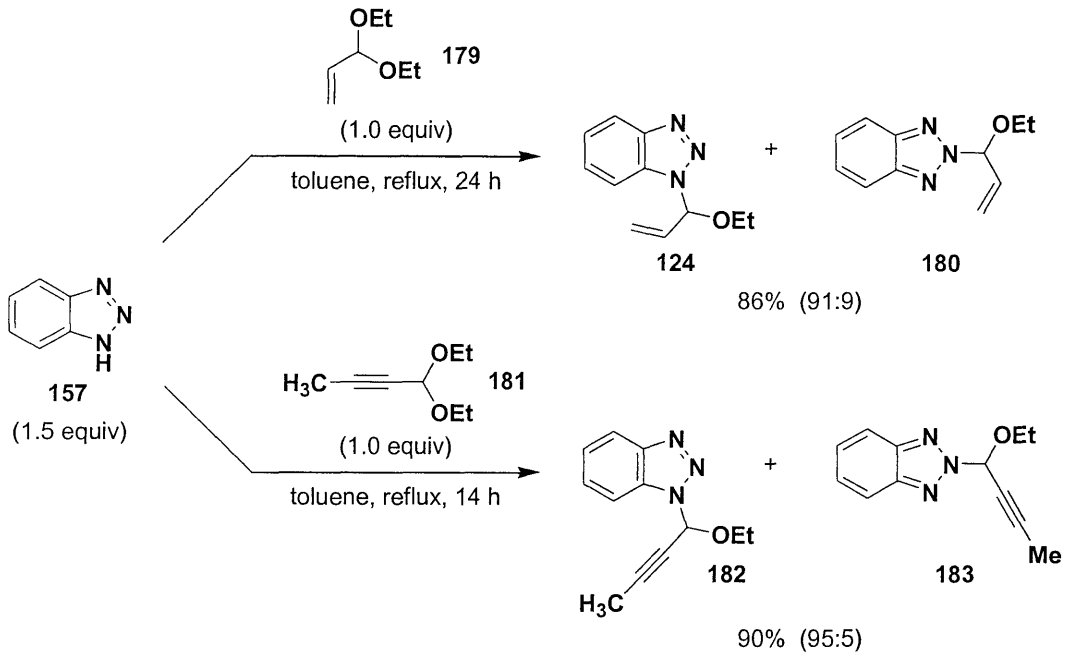
---

[95] Benzotriazole **177** has been prepared by this method in 49% yield, see reference 84. We were able to obtain **177** in 64% yield (eq 30) by making minor modifications to the previously reported procedure (see Experimental Section).

[96] Benzotriazole **178** has been previously prepared by this method, but was used in a subsequent step without purification (no yield was reported); see reference 87.

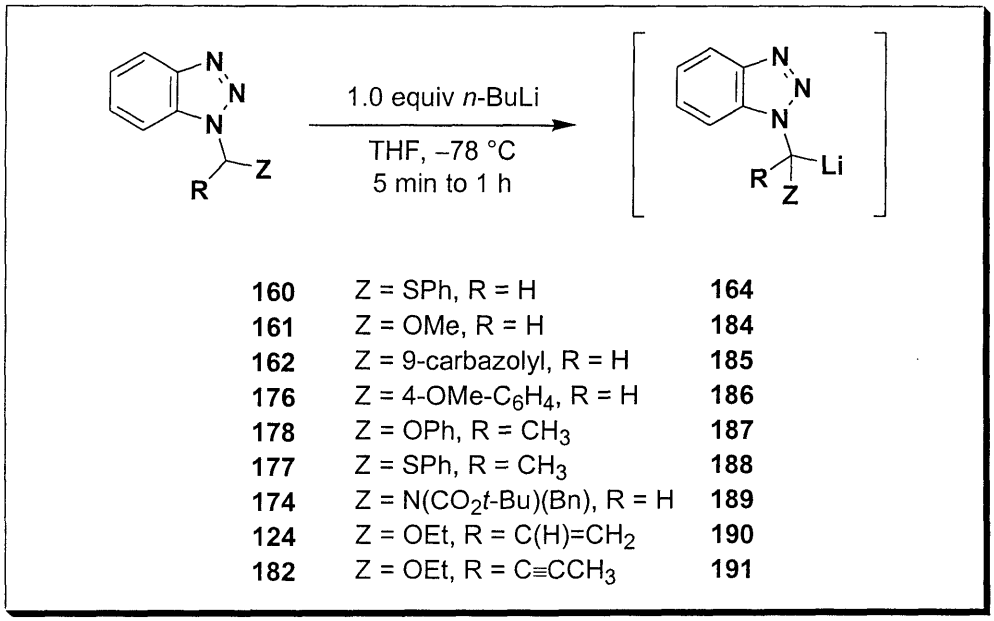
[97] Katritzky, A. R.; Feng, D.; Lang, H. *J. Org. Chem.* **1997**, *62*, 4131.

Scheme 23



With a variety of 1-alkyl benzotriazole derivatives in hand, we then examined metallation conditions for generation of the requisite α-benzotriazolyl organolithium compounds. The best results were obtained when the benzotriazole derivatives had been rigorously dried. Solid benzotriazole derivatives **160-162**, **174** and **176** were ground into a fine powder and dried overnight in a vacuum dessicator (ca. 0.2 mmHg) over P_2O_5 before use. The remaining compounds were dried by azeotropic removal of water with toluene immediately before use (see Experimental Section). Standard conditions for metallation of substituted 1-alkylbenzotriazoles involve treatment with *n*-BuLi at –78 °C in THF,[78] and these were the conditions we employed for the in situ generation of the α-benzotriazolyl organolithium compounds shown in Scheme 24. In most cases the reaction mixture was stirred at –78 °C for 1 h before addition of the (TAS)vinylketene. In the case of benzotriazole **178**, partial decomposition was observed when metallation was allowed to proceed for longer than 5 minutes. As a precaution, **187** and all other tertiary α-benzotriazolyl organolithium compounds (**188**, **190**, and **191**) were trapped by (TAS)vinylketene addition within 5 minutes of the completion of *n*-BuLi addition. Finally, metallation of benzotriazole **174** was allowed to proceed for 30 minutes at –78 °C, as previously reported by Katritzky.[93]

Scheme 24. Preparation of α-Benzotriazolyl Organolithium Compounds

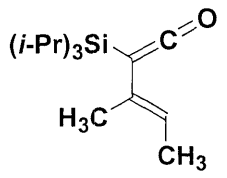


160	Z = SPh, R = H	**164**
161	Z = OMe, R = H	**184**
162	Z = 9-carbazolyl, R = H	**185**
176	Z = 4-OMe-C_6H_4, R = H	**186**
178	Z = OPh, R = CH_3	**187**
177	Z = SPh, R = CH_3	**188**
174	Z = N(CO_2t-Bu)(Bn), R = H	**189**
124	Z = OEt, R = C(H)=CH_2	**190**
182	Z = OEt, R = C≡CCH_3	**191**

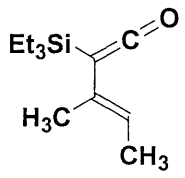
Scope of the [4 + 1] Annulation

The (TAS)vinylketenes used in this study (Chart 2) are known compounds and were prepared as previously reported via the photochemical Wolff rearrangement of the corresponding α′-silyl-α′-diazo-α,β-unsaturated ketones[7b] (for a representative example, see Scheme 6, p 18).

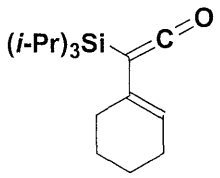
Chart 2. (TAS)vinylketenes used in [4 + 1] Annulations



1



192

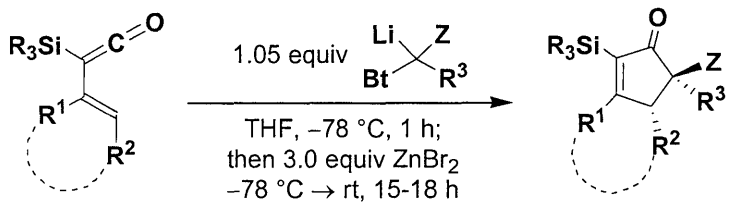


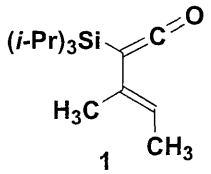
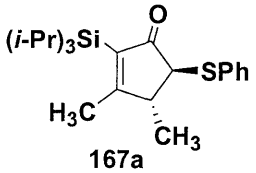
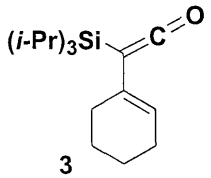
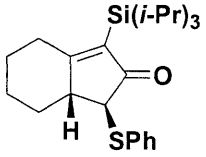
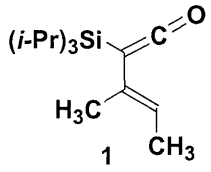
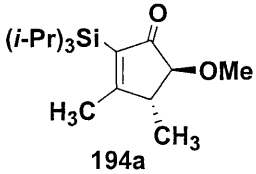
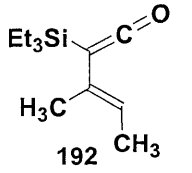
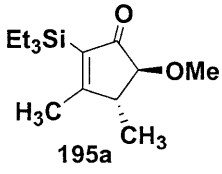
3

Tables 5-7 delineate the scope of the [4 + 1] annulation. Under the conditions described above for the reaction of **1** with the thiophenyl benzotriazole **164** (Scheme 22), the desired annulation can be achieved with a variety of carbenoid reagents bearing a single heteroatom

substituent (Tables 5 and 6). We next examined the aryl-substituted benzotriazole reagent **186**, and found that the annulation can be achieved in this case as well, albeit in poor yield. However, in this case it was necessary to heat the reaction mixture before any appreciable amount of cyclopentenone was observed. The latter result suggests that the heteroatom substituent (Z) plays a crucial role in facilitating the departure of the benzotriazole group and cyclization to form the cyclopentenone product. For this reason, we did not examine the use of less activated benzotriazoles (e.g., 1-ethylbenzotriazole) in our [4 + 1] annulation.

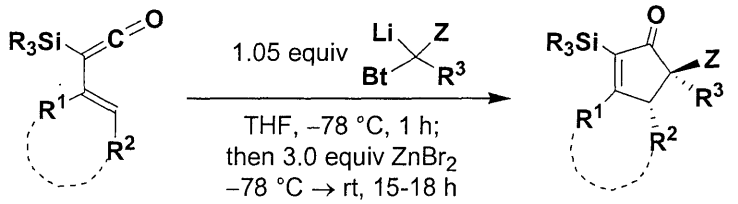
Table 5. Lewis Acid-Promoted [4 + 1] Cyclopentenone Annulations[a]

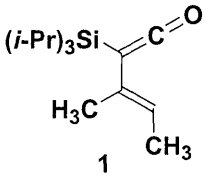
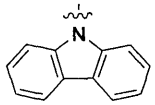
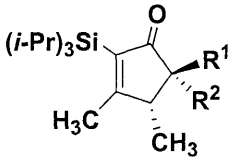
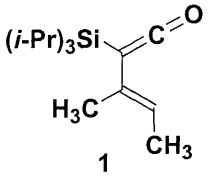
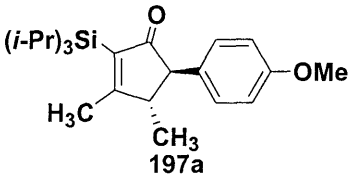
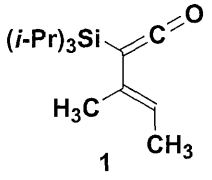
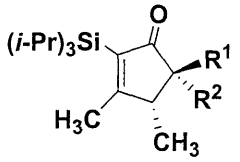
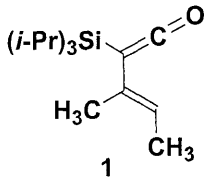
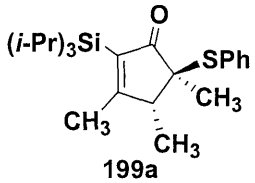


entry	ketene	carbenoid reagent	product	yield (%)[b] (*trans*:*cis*)[c]
1	 1	**164**	 **167a**	69-74 (98:2)
2	 3	**164**	 **193a**	75 (98:2)
3	 1	**184**	 **194a**	68-82 (≥99:1)
4	 **192**	**184**	 **195a**	67-70 (≥99:1)

(a) For cases where dr ≥97:3 only the major diastereomer is shown. (b) Isolated yields of products purified by column chromatography. (c) Ratios determined by ^{1}H NMR analysis.

Table 6. Lewis Acid-Promoted [4 + 1] Cyclopentenone Annulations[a]



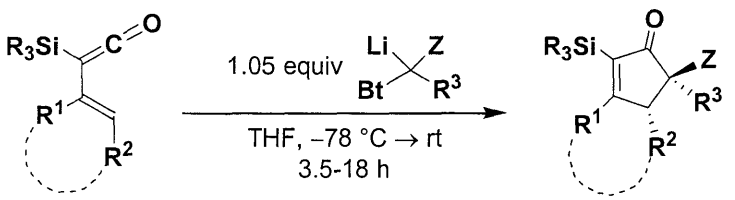
entry	ketene	carbenoid reagent	product	yield (%)[b] (*trans*:*cis*)[c]
1	 **1**	**185** Cb = 	 **196a** R^1 = Cb, R^2 = H **196b** R^1 = H, R^2 = Cb	85 (74:26)
2	 **1**	**186**	 **197a**	34[d] (≥99:1)
3	 **1**	**187**	 **198a** R^1 = OPh, R^2 = CH_3 **198b** R^1 = CH_3, R^2 = OPh	65 (77:23)
4	 **1**	**188**	 **199a**	64 (97:3)

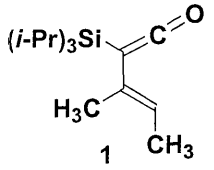
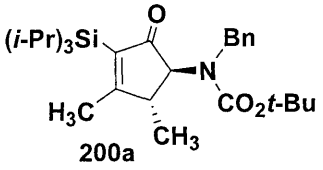
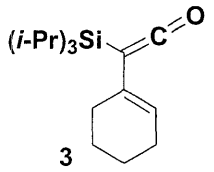
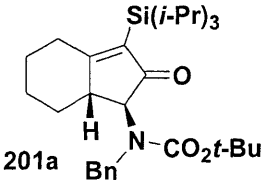
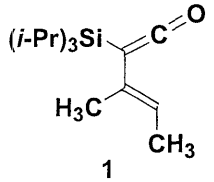
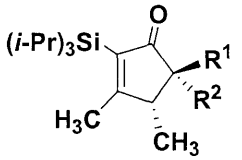
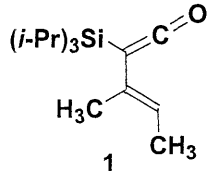
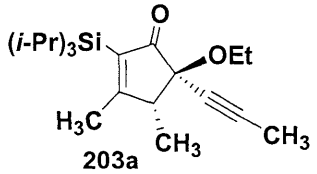
(a) For cases where dr ≥98:2 only the major diastereomer is shown. (b) Isolated yields of products purified by column chromatography. (c) Ratios determined by ^{1}H NMR analysis. (d) Reaction mixture allowed to warm to rt over 10 h, and then heated at reflux for an additional 4 h.

Interestingly, the annulations presented in Table 7, which involve carbenoid reagents bearing strong electron-donor substituents such as amine derivatives (entries 1, 2) and the combination of an alkoxy and vinyl or alkynyl group (entries 3, 4), did not require the addition of a Lewis acid to promote cyclization. In these cases, the desired cyclopentenone begins to appear

at low temperature during the organolithium addition step (as evidenced by TLC), and formation of the five-membered ring product is completed simply by warming the reaction mixture to room temperature. These results, as well as the observation of the role of the Z group discussed above, suggest that the cyclization step of the annulation is facilitated by substituents on the carbenoid reagent that can stabilize a transition state in which the α-carbon has δ+ character (see discussion of mechanism below).

Table 7. [4 + 1] Cyclopentenone Annulations[a]



entry	ketene	carbenoid reagent	product	yield (%)[b] (*trans*:*cis*)[c]
1		**189**	 **200a**	73 (≥96:4)
2		**189**	 **201a**	67 (≥99:1)
3		**190**	 **202a** R^1 = OEt, R^2 = –CH=CH_2 **202b** R^1 = –CH=CH_2, R^2 = OEt	70 (76:24)
4		**191**	 **203a**	54 (97:3)

(a) For cases where dr ≥96:4 only the major diastereomer is shown. (b) Isolated yields of products purified by column chromatography. (c) Ratios determined by ^{1}H NMR analysis.

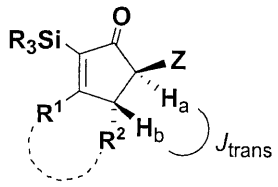
It is also noteworthy that each of these reactions was observed to proceed with a preference for the formation of the cyclopentenone with the C-5 heteroatom substituent *trans* to the substituent at C-4; this preference is particularly high with small R groups such as H or an alkyne. Possible explanations for the high level of diastereoselectivity in this [4 + 1] annulation will be presented below, following a discussion of the methods employed to assign the relative stereochemistry of the cyclopentenone products.

Structural and Stereochemical Assignments for Cyclopentenone Products

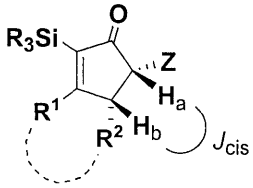
The structural assignments for all of the cyclopentenones prepared by [4 + 1] annulations with α-benzotriazolyl organolithium reagents were made based on analysis of IR and ^{1}H and ^{13}C NMR data, and are consistent with the structural assignment of cyclopentenone **167a** described above (Figures 4-6). For cyclopentenones bearing a single substituent at C-5, relative stereochemical assignments were based on an analysis of ^{1}H NMR coupling constants as described above for cyclopentenone **167a**. Table 8 provides a comparison of the relevant coupling constants which were used for stereochemical assignments. For the amino-substituted

Table 8. ^{1}H NMR Coupling Constant Comparison

Major (*trans*) isomer:



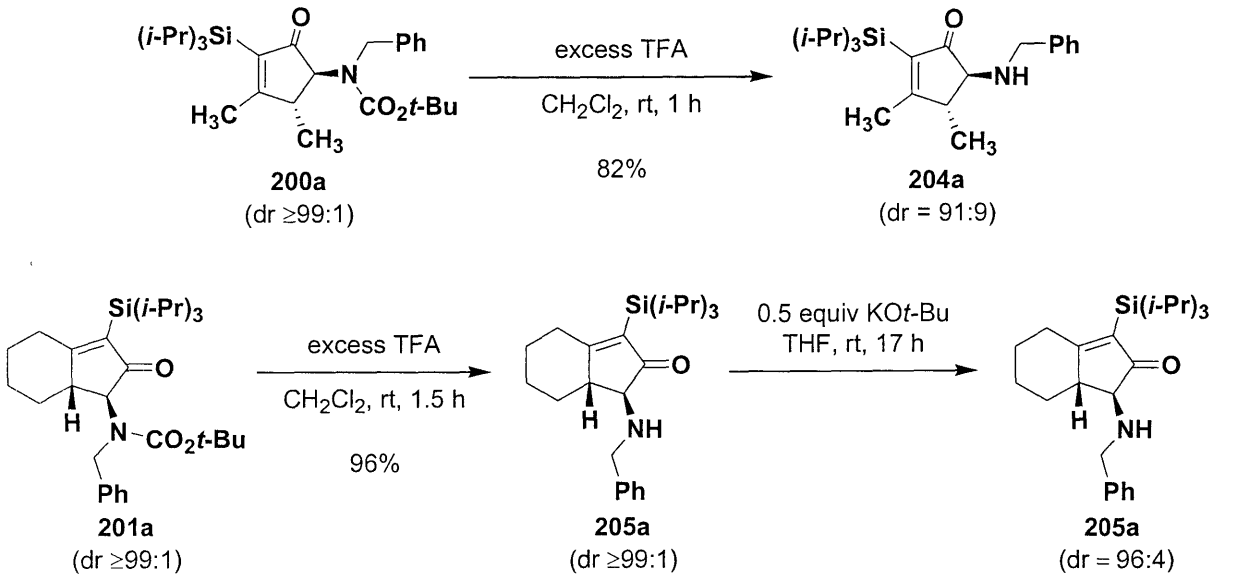
Minor (*cis*) isomer:



entry	cyclopentenone	R_3Si	R^1, R^2	Z	J_{trans}	J_{cis}
1	**167**	$(i\text{-Pr})_3Si$	$R^1 = R^2 = CH_3$	SPh	3.1 Hz	6.8 Hz
2	**193**	$(i\text{-Pr})_3Si$	$R^1, R^2 = (CH_2)_4$	SPh	3.3 Hz	7.2 Hz
3	**194**	$(i\text{-Pr})_3Si$	$R^1 = R^2 = CH_3$	OMe	3.4 Hz	6.7 Hz
4	**195**	Et_3Si	$R^1 = R^2 = CH_3$	OMe	3.3 Hz	6.7 Hz
5	**196**	$(i\text{-Pr})_3Si$	$R^1 = R^2 = CH_3$	9-carbazolyl	4.9 Hz	7.5 Hz
6	**197**	$(i\text{-Pr})_3Si$	$R^1 = R^2 = CH_3$	4-OMe-C_6H_4	3.2 Hz	--
7	**200**	$(i\text{-Pr})_3Si$	$R^1 = R^2 = CH_3$	N(CO_2t-Bu)(Bn)	4.5 Hz	--
8	**201**	$(i\text{-Pr})_3Si$	$R^1, R^2 = (CH_2)_4$	N(CO_2t-Bu)(Bn)	4.3 Hz	--
9	**204**	$(i\text{-Pr})_3Si$	$R^1 = R^2 = CH_3$	NH(Bn)	3.2 Hz	6.4 Hz
10	**205**	$(i\text{-Pr})_3Si$	$R^1, R^2 = (CH_2)_4$	NH(Bn)	3.1 Hz	6.9 Hz

cyclopentenones **200** and **201** (entries 7 and 8), only one diastereomer was observed by ^{1}H NMR, and the observed coupling constants (J_{ab} = 4.3-4.5 Hz) were between the expected values for *cis* and *trans* isomers. To determine the relative stereochemistry in these cases we relied on an analysis of the coupling constants of the corresponding secondary amines **204** and **205** (Table 8, entries 9 and 10), prepared by cleavage of the BOC group under standard conditions (Scheme 25). The acidic conditions for BOC cleavage resulted in equilibration of cyclopentenone **204** to deliver the corresponding secondary amine as a 91:9 mixture of diastereomers; however, negligible equilibration was observed in the analogous reaction of bicyclic cyclopentenone **201**.[98] Comparison of the coupling constants observed for the secondary amine derivatives **204** and **205** with the values for the reference compounds illustrated in Figure 7 (p 61) indicates that the major isomer in each case has a *trans* relationship between the C-5 amino substituent and the C-4 alkyl group. Given that deprotection of **201** (obtained from the annulation in ≥99:1 diastereoselectivity) produces **205** with ≥99:1 selectivity for the *trans* isomer, and that an equilibration experiment (Scheme 25) demonstrated that the thermodynamic ratio of *trans*:*cis* isomers for this compound is 96:4, the major product of the [4 + 1] annulation must also have the

Scheme 25

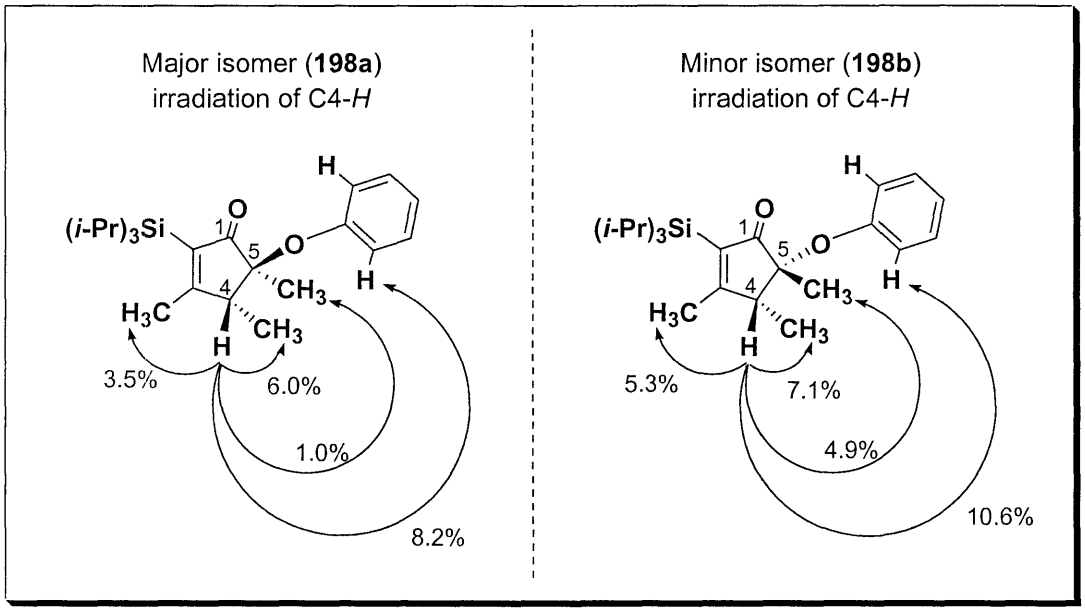


[98] Although secondary amine **205** was obtained as a ca. 99:1 mixture of isomers, it was still possible to determine J_{ab} for the minor isomer **205b**.

same (*trans*) relative stereochemistry. Finally, comparison of J_{ab} for **200a** (4.5 Hz) with J_{ab} for **201a** (4.3 Hz) allows **200a** to be assigned as the *trans* diastereomer.

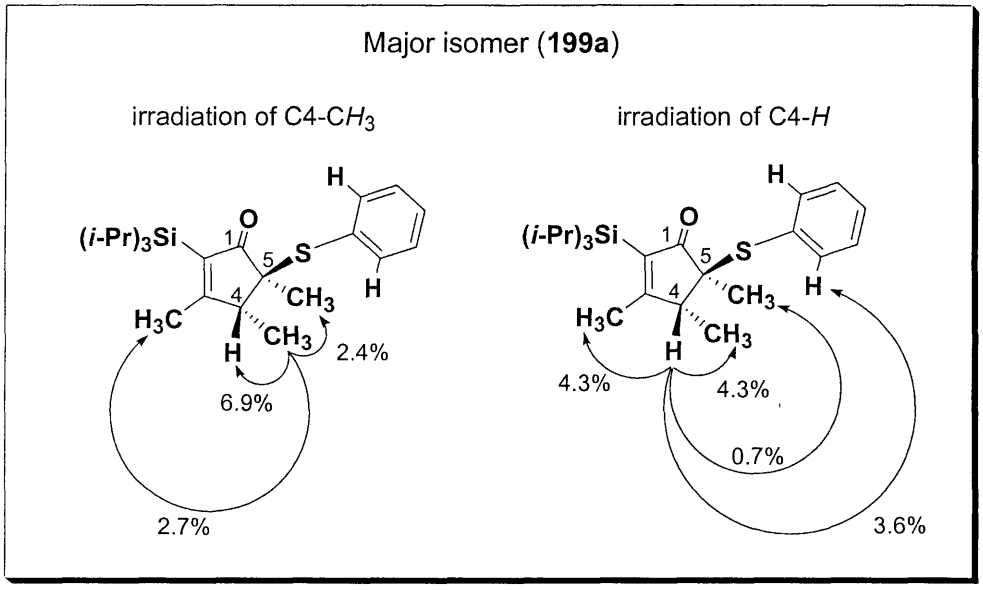
Relative stereochemical assignments for annulation products in which C-5 is a quaternary center were made on the basis of nOe experiments, as summarized in Figures 8-10. Irradiation of the C-4 proton in phenoxy-substituted cyclopentenone **198b** (the minor isomer) gave rise to a significant (4.9%) nOe enhancement of the C-5 methyl group (Figure 8). A much smaller nOe (1.0%) was obtained by irradiating the analogous proton in the major isomer **198a**, indicating a *trans* relationship between the C-4 methyl group and the C-5 phenoxy group in **198a** and a *cis* relationship between these two substituents in minor isomer **198b**. Thiophenyl derivative **199**

Figure 8. nOe Experiments on Cyclopentenone **198**



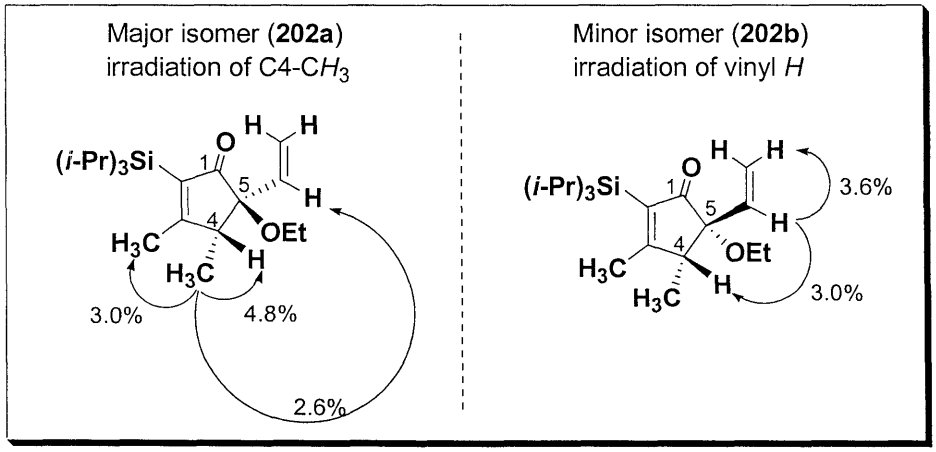
was obtained from the annulation as a 97:3 mixture of isomers, and the major isomer **199a** was assigned as the illustrated *trans* diastereomer (Figure 9) based on the much smaller nOe enhancement observed between the C-4 proton and the C-5 methyl group (0.7%) compared with the 2.4% enhancement of the C-5 methyl group observed upon irradiation of the C-4 methyl group. Finally, in the case of vinyl-substituted cyclopentenones **202a** and **202b**, a pure sample of the major isomer and an enriched sample of the minor isomer were obtained by preparative TLC,

Figure 9. nOe Experiments on Cyclopentenone **199a**



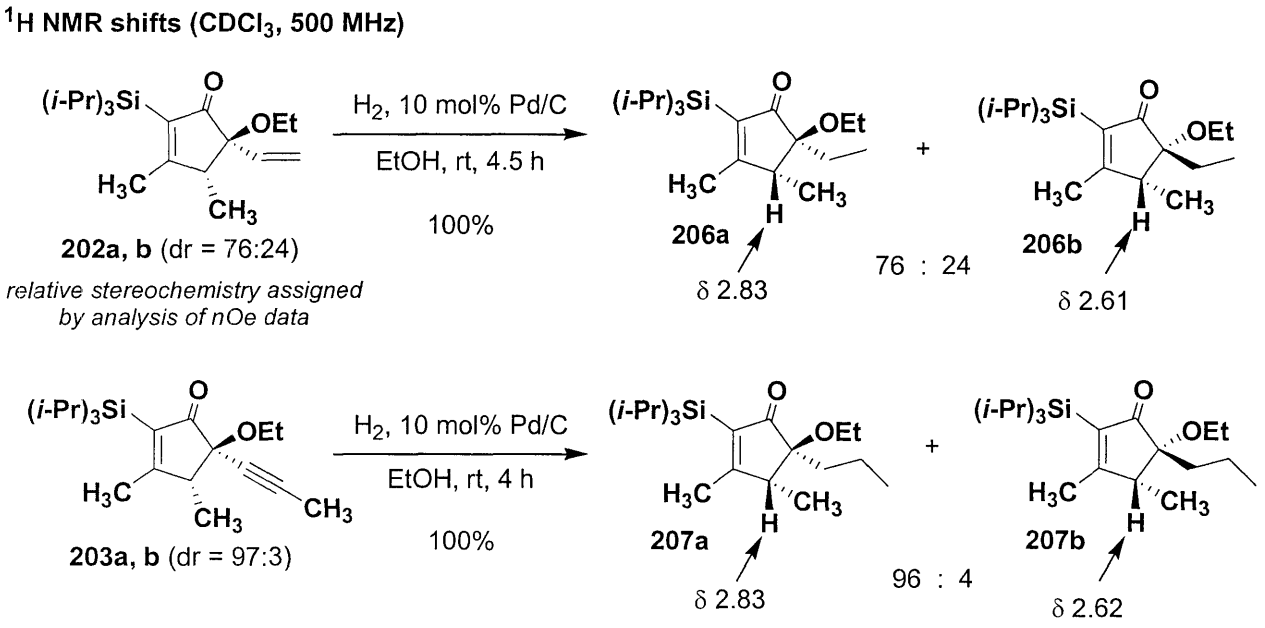
and nOe experiments were performed on both samples (Figure 9). Irradiation of the indicated vinyl proton Irradiation of the indicated vinyl proton in minor isomer **202b** resulted in a 3.0% enhancement of the C-4 proton, but no enhancement of the C-4 methyl group was observed, indicating a *cis* relationship between the vinyl group and the C-4 H. This assignment was further supported by the observation of a 2.6% nOe enhancement of the C-5 vinyl group in *trans* isomer **202a** upon irradiation of the C-4 methyl group (the analogous nOe was not observed for the *cis* isomer).

Figure 10. nOe Experiments on Cyclopentenone **202**



The nOe results obtained for propynyl substituted cyclopentenone **203** were not helpful in assigning the relative stereochemistry of this compound. However, comparison of ^{1}H NMR chemical shift data of the hydrogenation products derived from **203** (**207a** and **207b**, Scheme 26) with the products obtained via hydrogenation of vinyl substituted cyclopentenone **202** demonstrate that the *trans* isomer **203a** is the major product of the [4 + 1] annulation. It should

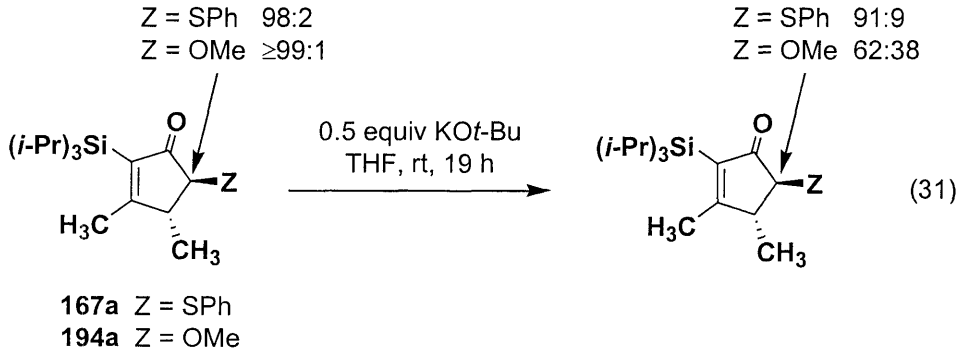
Scheme 26. Hydrogenation of 5-Vinyl and 5-Alkynyl Substituted Cyclopentenones



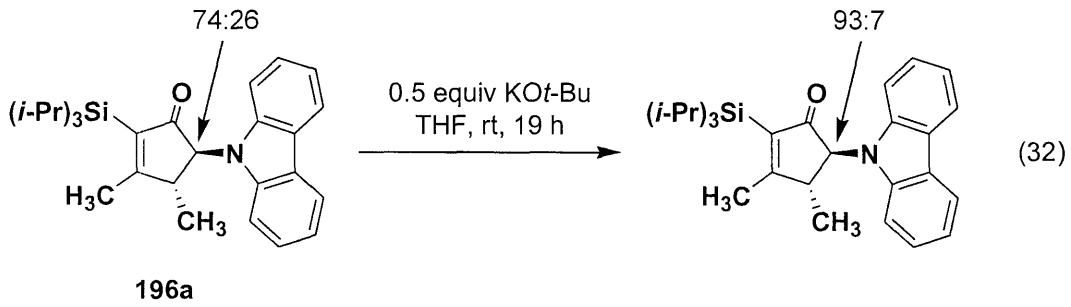
also be noted that in addition to aiding in stereochemical analysis, the experiments illustrated in Scheme 25 demonstrate that hydrogenation of 5-alkynyl substituted cyclopentenones such as **203** provides access to 5-*alkyl* substituted cyclopentenones with a much higher degree of diastereoselectivity than can be obtained directly in the [4 + 1] annulation (compare Table 6, entry 3 with Table 7, entry 3). In conclusion, the major isomer in all of the [4 + 1] annulation has a *trans* relationship between the C-5 heteroatom substituent and the C-4 methyl group. The next section provides a mechanistic rationale to account for this observation.

Mechanism and Stereochemistry of the [4 + 1] Annulation

A notable feature of these [4 + 1] annulations is the high level of stereoselectivity observed in most cases of the reaction. Control experiments established that the stereochemical outcome of the [4 + 1] annulation is not a consequence of thermodynamic control. For example, exposure of either cyclopentenone **167a** or **194a** to a catalytic amount of KO*t*-Bu in THF at room temperature produces mixtures of *trans* and *cis*-substituted cyclopentenones with ratios significantly different from those obtained in the annulation (eq 31). Equilibration of carbazole



substituted cyclopentenone **196**, obtained from the annulation as a 74:26 mixture of *trans*:*cis* isomers, under similar conditions results in significant enrichment of the thermodynamically more stable *trans* isomer (eq 32). It thus appears likely that the stereochemical course of the [4 + 1] annulation reflects a mechanism-based kinetic preference for the observed products.

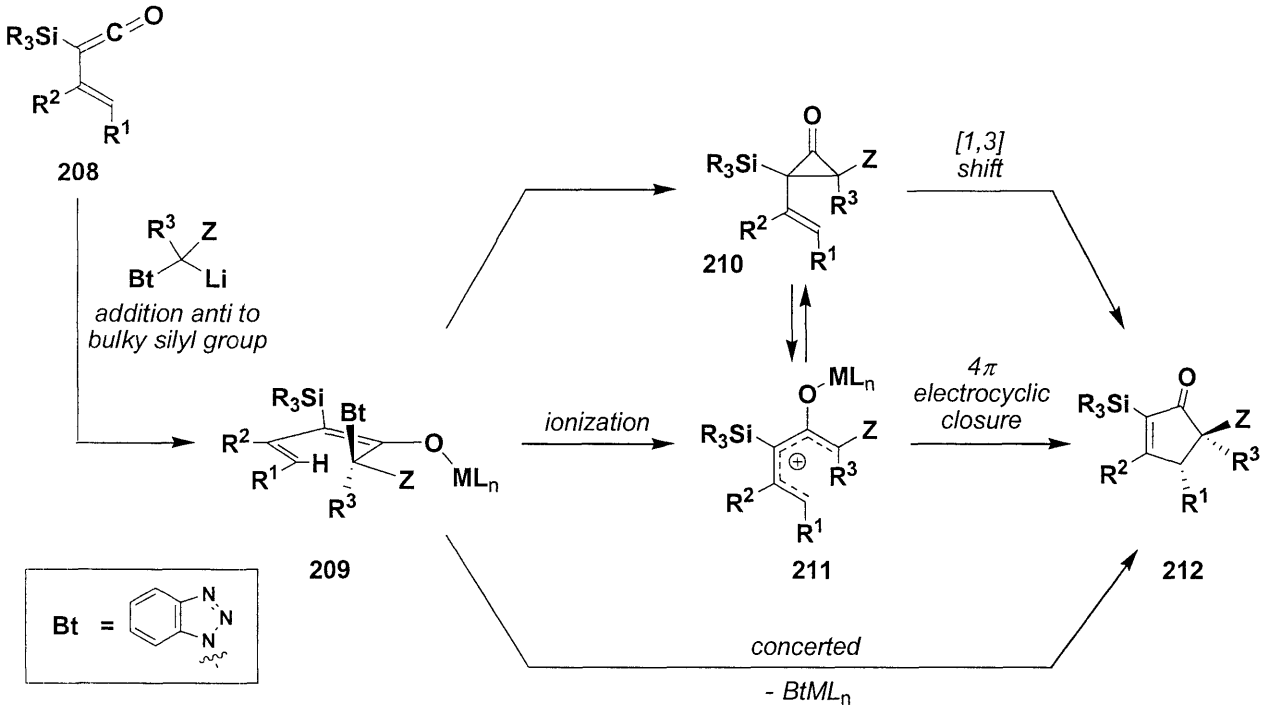


Scheme 27 outlines several alternative pathways to account for the mechanism of the [4 + 1] annulation. Addition of the carbenoid reagent to the vinylketene is predicted to be highly stereoselective due to the shielding effect of the bulky trialkylsilyl group and should result in the

formation of the (*Z*)-enolate **209**. Direct formation of the five-membered ring product could then occur via a concerted process in which ring closure is concomitant with leaving group departure. An alternative pathway involves ionization to produce oxidopentadienylic cation **211**,[99] which should then undergo rapid conrotatory 4π electrocyclic closure[100] to generate the cyclopentenone product. Finally, the involvement of cyclopropanone intermediates of type **210** cannot be excluded, particularly in view of the finding that simple silylketenes react with diazomethane and TMS-diazomethane to form mono- and bis(silyl)cyclopropanones (see Scheme 11, eqs 11 and 12 and the related discussion on pp 25-27).

The stereochemical course of the [4 + 1] annulations we investigated previously (e.g., eq 24, p 51)[8] is consistent with a mechanism involving stereospecific conrotatory electrocyclic closure of a 2-oxidopentadienylic cation. In those prior cases, we suggested that ionization of the dienolate intermediate occurs to generate a cation in which the single C-1 substituent is *cis* to

Scheme 27. Possible Mechanistic Pathways for the [4 + 1] Annulation

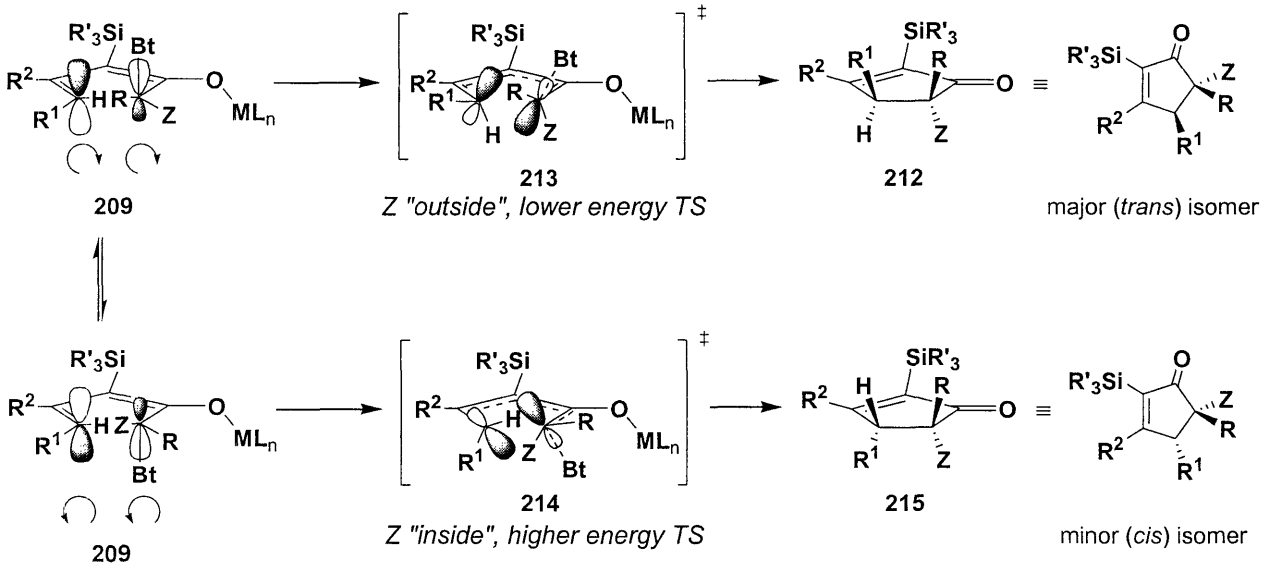


[99] Depending on reaction conditions, this intermediate may be a free zwitterionic species or could still be associated with the metal.

[100] Pentadienyl cation electrocyclic ring closures are involved in the mechanism of the Nazarov cyclization which was discussed in Chapter 1 (pp 46-48). For reviews, see references 39a-d.

the oxyanion to minimize nonbonded interactions. A similar mechanism can account for the reactions reported here, provided that one assumes that ionization leads to the isomer of intermediate **211** shown in Scheme 27 due to an associative interaction between the heteroatom Z and the metal (M = Zn or Li). Alternatively, if cyclization of **209** involves a concerted process, then the stereochemical outcome could reflect a preference for the mode of conrotation from **209** that rotates the leaving group anti to the incipient σ bond and which proceeds via the transition state in which the donor heteroatom occupies an "outside" position (Scheme 28) for reasons discussed in detail below.

Scheme 28. Concerted Cyclization Mechanism

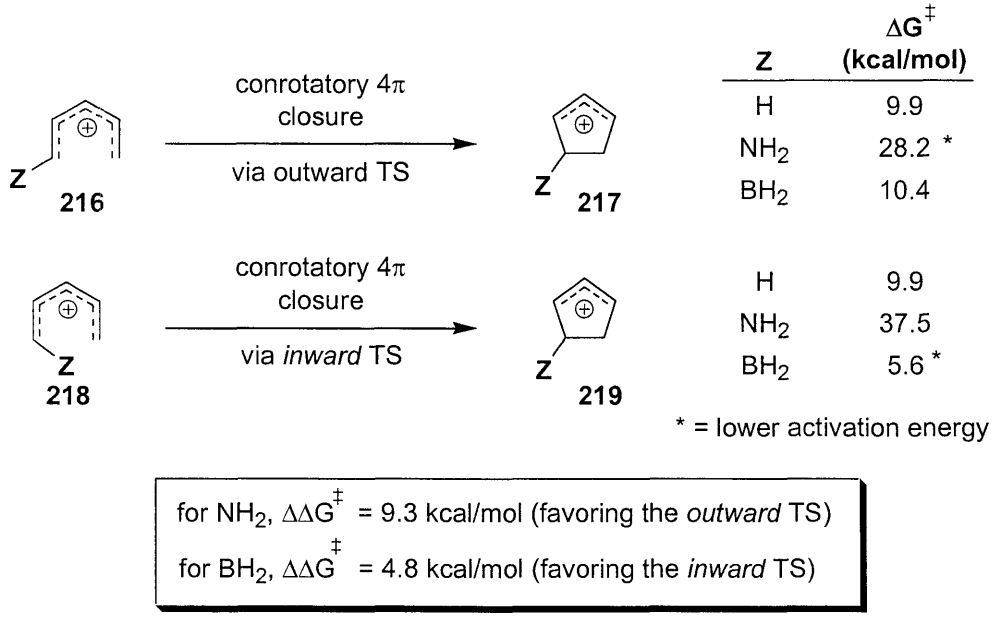


The effects of electron-donating and electron-withdrawing substituents on the stereochemical course of conrotatory 4π electrocyclic ring opening reactions of cyclobutenes were analyzed using computational methods by Houk and coworkers in the mid-1980's.[101] Subsequent theoretical studies by Houk indicated that this phenomenon ("torquoselectivity") is also relevant to the electrocyclization of pentadienylic cations.[102] In this context, the energetics for the cyclization of several pentadienylic cations bearing a substituent (Z) at one of the

[101] (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (b) For a review, see Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471.
[102] Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 6006.

terminal carbons were calculated (Figure 11). Electrocyclic closure can occur from the conformation in which the substituent Z occupies an outside position (e.g., **216**) or an inside position (e.g., **218**). In cases where Z is an electron-donating substituent such as an amino group, the activation barrier for cyclization from a pentadienylic cation with an outward positioning of the Z group (via an "outward" transition state) is significantly lower than the activation barrier for cyclization from the analogous pentadienylic cation in which the Z group has an inside position (e.g., **218**). The reverse is true in cases where the Z group is electron-withdrawing (Z = BH_2 in the model). The authors suggest that for cyclization via an inward transition state when Z is a donating group, the non-bonding electrons on the donor substituent can have a destabilizing interaction with the incipient σ bond. In the case of an electron withdrawing substituent, inward rotation allows for a stabilizing interaction between the incipient σ bond and a low lying orbital on the donor group.

Figure 11. Energetics for the Electrocyclic Closure of Pentadienylic Cations

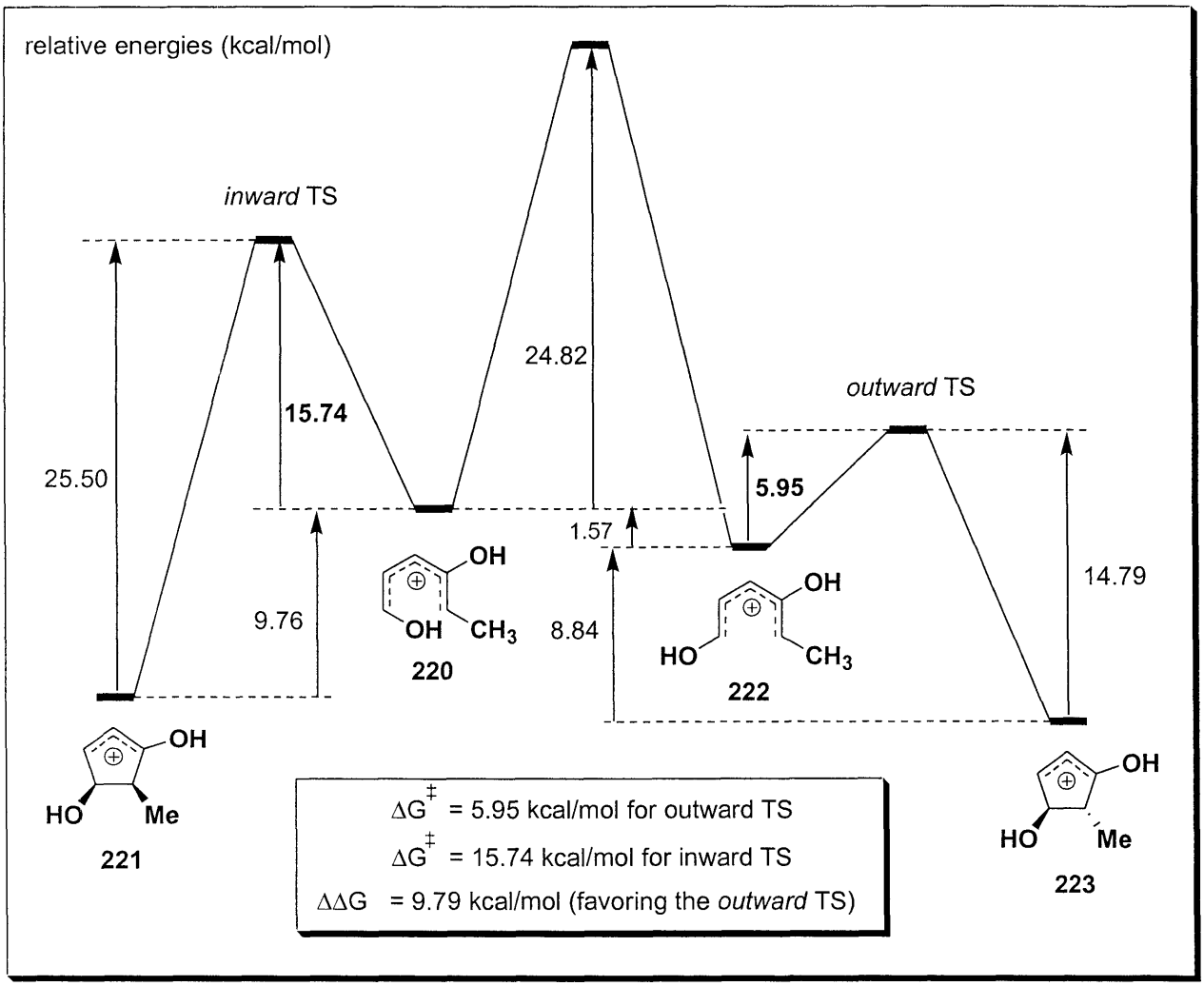


de Lera and coworkers have recently reported theoretical studies on the electrocyclic closure of hydroxypentadienylic cations,[103] systems which are very relevant to the mechanism of

[103] Faza, O. N.; López, C. S.; Álvarez, R.; de Lera, Á. R. *Chem. Eur. J.* **2004**, *10*, 4324.

our [4 + 1] annulation. A reaction profile for one of the systems included in their study is shown in Figure 12. In this case, the activation energy for cyclization via an outside transition state (**222** → **223**) is 9.79 kcal/mol lower than the barrier for cyclization via an inside transition state (**220** → **221**), consistent with the previous findings of Houk. These computational results provide support for our hypothesis that if our [4 + 1] annulation proceeds via a concerted pathway (Scheme 27), the activation barrier for cyclization of an intermediate of type **209** should be lower for the mode of conrotation in which the donor heteroatom occupies an "outside" position in the transition state (**209** → **213** → **212**).

Figure 12. Energy Diagram for Electrocyclic Closure of Pentadienylic Cations **220** and **222**



A concerted mechanism similar to the one shown in Scheme 28 could be considered in order to account for the stereochemical outcome of our previous [4 + 1] annulations with sulfur ylides (e.g., eq 24, p 51) and TMS-diazomethane.[8] In these cases, cyclopentenones in which the C-5 methyl or trimethylsilyl substituent is *trans* to the C-4 alkyl or aryl substituent are the exclusive products of the annulation. Torquoselectivity considerations indicate that outward rotation is favored for a methyl group, consistent with the *trans* stereochemistry observed in [4 + 1] annulations with diphenylsulfonium ethylide (e.g., **1** → **141**, eq 24, p 51). In contrast, silyl groups exhibit a preference for *inward* rotation,[104] although the magnitude of this effect is relatively small (for the ring opening of 3-trimethylsilyl cyclobutene, calculations indicate that inward rotation is favored by 1.3 kcal/mol).[104b] Therefore, if [4 + 1] annulations with TMS-diazomethane proceed via a concerted mechanism similar to that shown in Scheme 28, then the preference for outward rotation of the trimethylsilyl group (required for formation of the observed *trans* products) must arise from a preference for minimization of nonbonded interactions in the transition state that overwhelms the inward torquoselectivity of the silyl group.

It should also be noted that the previous [4 + 1] annulations with diazo compounds and sulfur ylides may proceed via a different mechanism than the [4 + 1] annulations with α-benzotriazolyl organolithium compounds described in this chapter. In the former cases, the desired reaction involves loss of N_2 or a neutral sulfide, both excellent leaving groups, and ionization to produce an oxidopentadienylic cation may well precede cyclization. With a poorer leaving group such as benzotriazole, the activation barrier for ionization should be higher, and participation of the dienolate (Scheme 28) may be required. Given these considerations, it is entirely possible that the selectivity for *trans* substituted cyclopentenones in annulations involving diazo compounds or sulfur ylides reflects a preference for the formation of the lower energy pentadienylic cation (in which the single C-1 substituent is *cis* to the oxyanion to minimize nonbonded interactions), whereas the *trans* selectivity observed in annulations with α-benzotriazolyl organolithium compounds arises from a preference for outward rotation of the heteroatom substituent in a concerted cyclization.

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[104] For experimental and computational studies on the torquoselectivity observed in the ring opening of silyl-substituted cyclobutenes, see: (a) Ikeda, H.; Kato, T.; Inagaki, S. *Chem. Lett.* **2001**, 270. (b) Lee, P. S.; Zhang, X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072. (c) Murakami, M.; Miyamoto, Y.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 189. (d) Murakami, M.; Hasegawa, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4874.

In conclusion, we have developed a new variant of our (TAS)vinylketene-based [4 + 1] annulation that employs α-benzotriazolyl organolithium compounds as versatile carbenoid reagents. A wide variety of hetero-substituted and highly functionalized cyclopentenones (including those in which C-5 is a quaternary center) can be prepared in good yield using this methodology, and most cases proceed with high levels of diastereoselectivity. Furthermore, the 1-alkylbenzotriazole derivatives that serve as precursors for the active carbenoid reagents are more readily available and/or easier to handle than the sulfur ylides and diazo compounds employed in our previously reported [4 + 1] annulation. Chapter 3 will discuss our efforts to further extend the utility of this methodology by examining synthetic transformations of these annulation products.

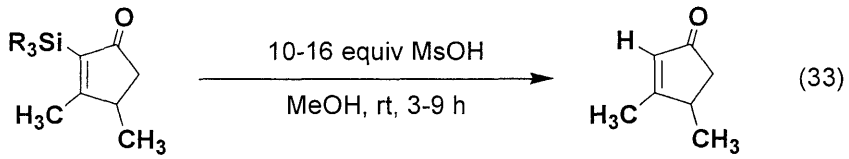
Chapter 3

Synthetic Transformations of Annulation Products

As discussed in Chapter 2, our [4 + 1] annulation based on the reaction of (TAS) vinylketenes with α-benzotriazolyl organolithium compounds provides a new route to highly substituted and functionalized cyclopentenones. We sought to further extend the utility of this strategy by examining methods for synthetic elaboration of the annulation products. In particular, the vinylsilane moiety incorporated in the [4 + 1] annulation products provides a useful handle for further synthetic transformations. The results of our studies in this area are discussed below.

Protodesilylation of 2-Silylcyclopentenones

Previous work in our group[8] demonstrated that treatment of 2-triisopropylsilyl and 2-triethylsilylcyclopentenones (e.g., **23** and **224**, eq 33) with an excess of methanesulfonic acid in methanol at room temperature for several hours delivers the corresponding protodesilylated



(33)

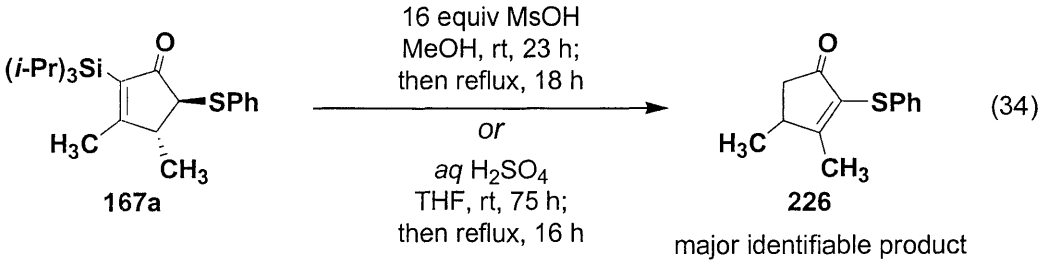
23 R = *i*-Pr 95% **225**
224 R = Et 89%

products in excellent yield. These conditions were discovered during extensive screening of a variety of acidic and fluoride-based reagents (e.g., TFA, HF•pyridine, HBF_4, and HCl in $CHCl_3$) to promote the desilylation of cyclopentenone **23**. No reaction was observed in any of these cases except under the conditions shown in eq 33.[105] Subsequent work by former group member

[105] For a discussion of all of the conditions examined, see pp 151-152 in Loebach, J. L. I. Total Synthesis of Dan Shen Diterpenoid Quinones. II. Synthesis and Chemistry of (Trialkylsilyl)vinylketenes. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1995.

Dawn Bennett demonstrated that the use of 5 equiv of TBAF (refluxing THF, 3 h) was effective for the desilylation of a related 2-(triisopropylsilyl)cyclopentenone.[106]

We first attempted to effect the protodesilylation of annulation product **167a** using an excess of methanesulfonic acid (eq 34), however the results were rather disappointing. Upon



(34)

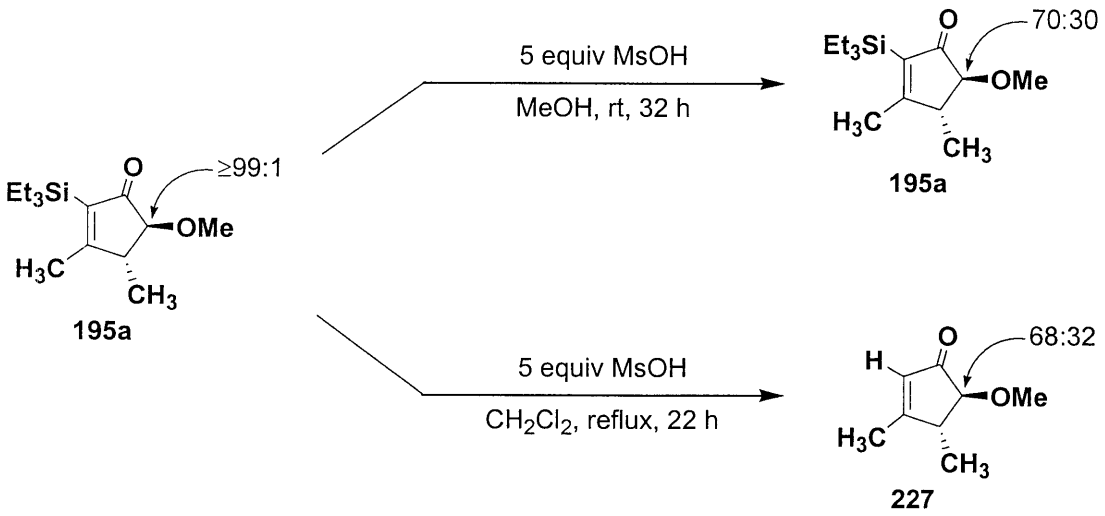
treatment of α-triisopropylsilylcyclopentenone **167a** with 16 equiv of methanesulfonic acid at room temperature for 23 h, TLC analysis indicated that ≤10% of the starting material had been consumed. Heating the reaction mixture at reflux in an attempt to promote the desired reaction proved effective, however, under these conditions protodesilylation was accompanied by isomerization to deliver cyclopentenone **226** as the major identifiable product. Treatment of **167a** with aqueous sulfuric acid in THF gave similar results. Finally, treatment of **167a** with 5 equiv of TBAF (THF, rt, 19 h) produced a complex mixture of unidentified products.

Given the difficulties encountered above, we turned our attention towards developing conditions for the protodesilylation of triethylsilyl-substituted cyclopentenones which were anticipated to undergo the desired transformation under milder conditions (due to the fact that the triethylsilyl group is significantly less bulky than the triisopropylsilyl group), thereby avoiding the complication of cyclopentenone isomerization. As shown in Scheme 29, treatment of methoxy-substituted cyclopentenone **195a** with excess methanesulfonic acid at room temperature (conditions that proved effective for the related substrate shown in eq 33) resulted in equilibration of the starting material to produce a 70:30 mixture of *trans*:*cis* isomers and only a trace amount of the corresponding desilylated product. Conducting this reaction in refluxing CH_2Cl_2 resulted in efficient protodesilylation without double bond isomerization; however, in

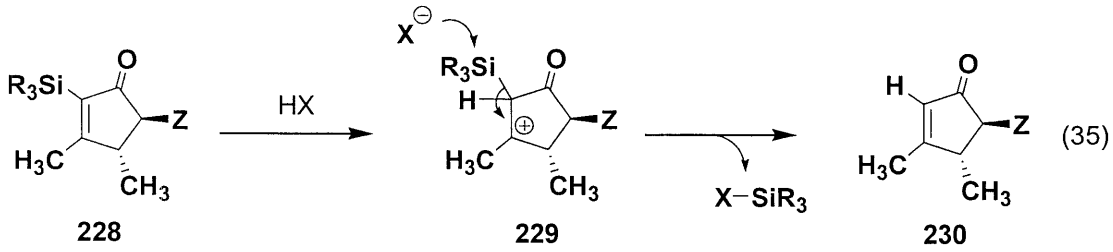
[106] See p 103 in Bennett, D. M. Synthesis and Chemistry of (Trialkylsilyl)vinylketenes. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1999.

this case, the desired cyclopentenone **227** was obtained as a 68:32 mixture of *trans*:*cis* diastereomers.

Scheme 29



To explain these results it is necessary to consider the mechanistic pathways for protodesilylation. Equation 35 outlines the most straightforward of these – protonation of cyclopentenone **228** delivers β-silyl cation **229**, and elimination of R_3SiX delivers the protodesilylated product **230**. However, this is an oversimplification, and under the acidic

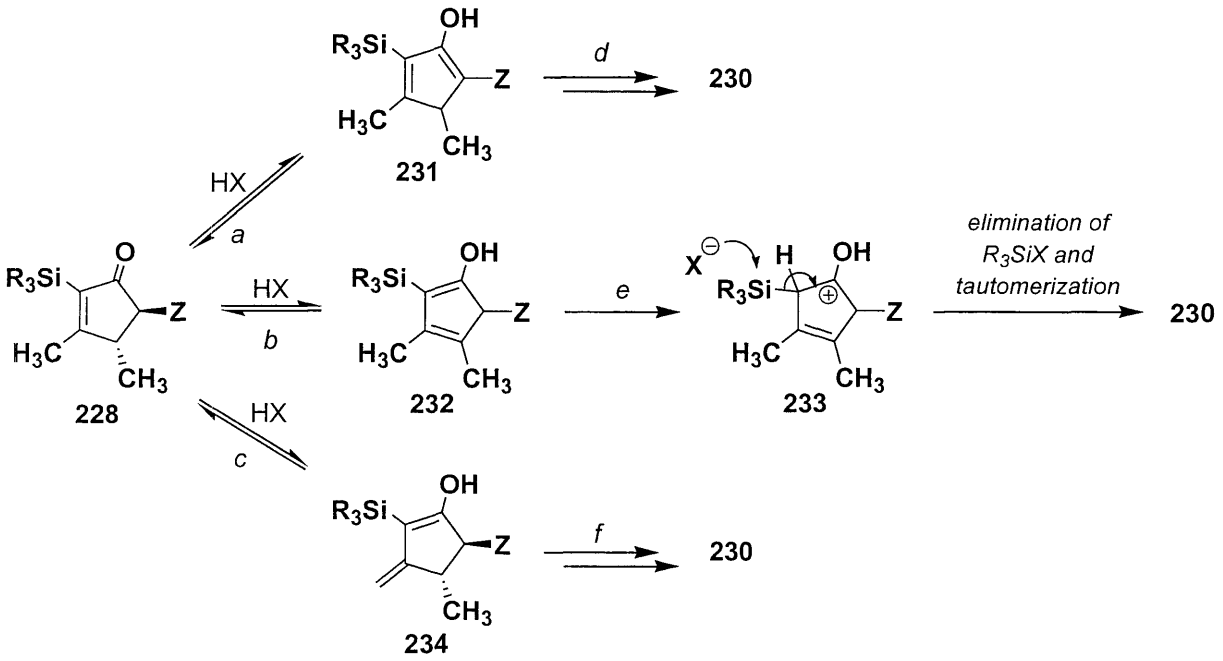


(35)

reaction conditions a number of equilibria (Scheme 30) must be considered. In particular, the three illustrated dienol tautomers (**231**, **232**, and **234**) can be formed under the acidic reaction conditions. If an equilibrium exists between **228** and **231** or **232**, this will result in *trans-cis* equilibration, and desilylation proceeding via a pathway involving a dienol intermediate of type **232** (pathway *e*) is anticipated to be the most favorable because the β-silyl cation generated (**233**) is greatly stabilized due to the presence of an α-oxygen substituent. The results shown in Scheme

29 suggest that *trans-cis* equilibration is more facile than protodesilylation, and that this equilibration likely proceeds via the intermediacy of an enol of type **231** or **232** (equilibria

Scheme 30



a or *b*). These complications prompted us to stop exploring the use of protic acids to effect the desilylation of our 2-silylcyclopentenone annulation products and to examine the use of electrophilic reagents which might have greater selectivity for reaction at the vinylsilane moiety rather than at the carbonyl group.

Halodesilylation of 2-silylcyclopentenones

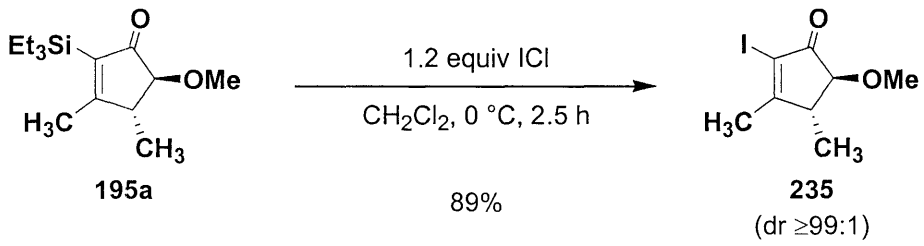
Negishi has reported that treatment of 2-trimethylsilyl enones with ICl generates the corresponding 2-iodo enones, often in very good yield.[107] Procedures for the bromodesilylation of 2-trimethylsilyl enones involving the use of electrophilic brominating reagents such as NBS have also been reported.[108] These transformations were of interest to us for a number of reasons. As discussed in Chapter 1, a variety of naturally occurring 2-halocyclopentenones such as

[107] Alimardanov, A.; Negishi, E.-i. *Tetrahedron Lett.* **1999**, *40*, 3839.
[108] Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi. T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

iodovulone I and bromovulone I (Chart 1, p 44) as well as other halogenated cyclopentenone prostanoids exhibit a range of interesting biological activity, and have significant potential as therapeutic agents.[51] Furthermore, a survey of the literature indicates that 2-halo enones are good substrates for a variety of transition metal-catalyzed cross-coupling reactions. Finally, we anticipated that halodesilylation followed by reductive dehalogenation of the resulting 2-halocyclopentenone might allow access to the products of protodesilylation (e.g., **227**) without the complication of isomerization and equilibration that were encountered during attempts to access these products directly.

Negishi and coworkers found that the optimal conditions for the iododesilylation of 2-trimethylsilyl enones involve the use of either 2 equiv of ICl or 1 equiv of ICl in combination with 1 equiv of $AlCl_3$ in CH_2Cl_2 at 0 °C. Iodine monochloride[109] is a source of electrophilic iodine, and is widely available either as a 1 M solution in CH_2Cl_2 or neat (as a low melting solid). Numerous synthetic applications of ICl have been reported, including the iodination of aromatic compounds, chloroiodination of alkenes and alkynes, and cleavage of carbon-metal bonds (e.g., cleavage of the C-Si bond in vinyl- or arylsilanes).

We first investigated the Negishi protocol (2 equiv of ICl) with triethylsilylcyclopentenone **195a**, and were pleased to find that the desired product was formed in very good yield and with no equilibration or double bond migration. Further optimization revealed that the use of 1.2 equiv of ICl gave very similar results (eq 36), furnishing the desired iodide **235** in excellent yield and in ≥99:1 dr. Attempts to effect the analogous transformation on

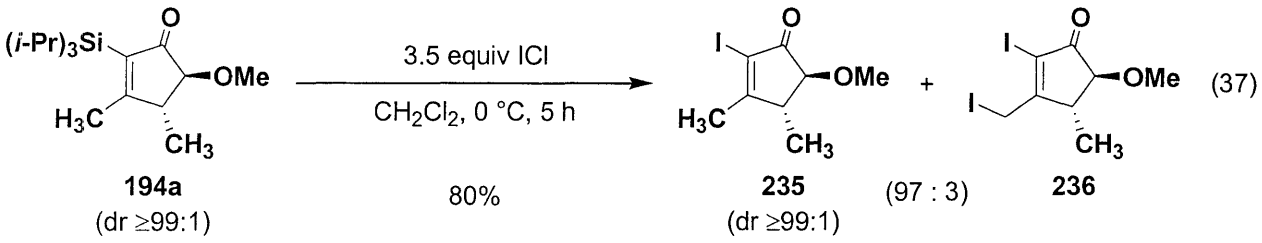


195a **235** (dr ≥99:1) (36)

the triisopropylsilyl-substituted annulation product **194a** proved more challenging. In all reactions using 2 equiv or less of ICl, a significant amount of unreacted starting material **194a** remained, even after 20 h at 0 °C. By TLC analysis, the reaction appears to have stopped

[109] For a review on the synthetic uses of iodine monochloride, see: McCleland, C. W. Iodine Monochloride. In *Synthetic Reagents*; Pizey, J. S., Ed.; Wiley: New York, 1983; Vol. 5, pp 85-164.

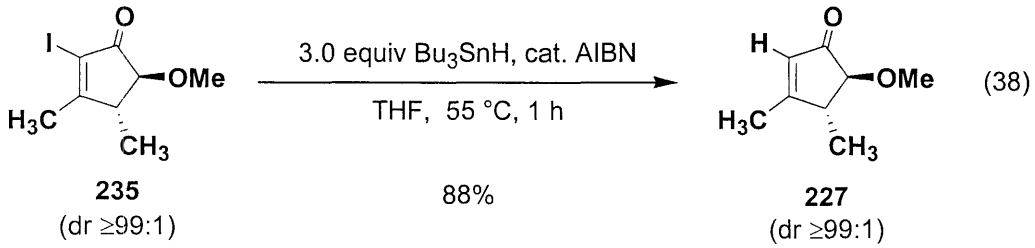
progressing after ca. 2 h at 0 °C, suggesting that the ICl was decomposing (possibly via disproportionation).[110] Fortunately, we found that this problem could be overcome by adding a



total of 3.5 equiv of ICl to the reaction mixture in three portions (eq 33). In this fashion, 2-iodocyclopentenone **235** was prepared in very good yield, although in this case, the product was contaminated with ca. 3% of an inseparable impurity assigned as bis-iodide **236**. This byproduct presumably forms via allylic iodination of the desired product with ICl, or perhaps with I_2 generated in situ via the disproportionation of ICl. Having demonstrated that annulation products such as **194a** and **195a** can be readily iododesilylated, we decided to examine the use of the resulting vinyl iodides in subsequent transformations.

Reduction and Cross-Coupling of 2-iodocyclopentenones

As noted above, we anticipated that reductive dehalogenation[111] of 2-iodocyclopentenones might allow us to access products such as **227** without the significant equilibration observed during protodesilylation of the corresponding 2-silylcyclopentenones under acidic conditions (Scheme 29). Tributyltin hydride-mediated dehalogenation was

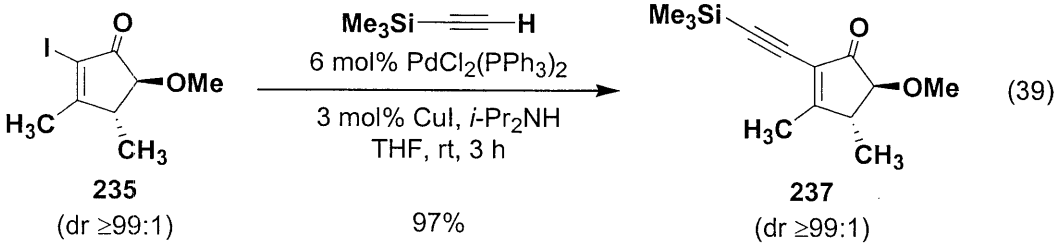


[110] Iodine monochloride can disproportionate into I_2 and Cl_2; for a discussion see reference 109, pp 87-88.

[111] For a review on the reduction of vinyl halides to alkenes, see: Hudlicky, M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 895-922.

examined with iodide **235**, and was found to give the best results (eq 38) when 3 equiv of Bu_3SnH were used and THF was employed as the reaction solvent. Interestingly, the use of benzene as solvent (a very common solvent for tributyltin hydride-mediated radical reactions) was found to result in the formation of several unidentified byproducts as evidenced by TLC. Furthermore, use of less than 3 equiv of Bu_3SnH in THF also gave rise to byproducts that are not observed when 3-5 equiv of Bu_3SnH are employed. The excess Bu_3SnH was readily separated from the desired product by column chromatography on silica gel. However, the removal of Bu_3SnI and other tributyltin-containing impurities posed a more significant challenge. The well-established protocols involving treatment of the crude product with aq KF (to convert Bu_3SnI to an insoluble Bu_3SnF polymer)[112] or with $NaBH_3CN$ in *t*-BuOH (to reduce Bu_3SnI to Bu_3SnH)[113] were examined, but neither of these methods allowed for isolation of cyclopentenone **227** in acceptable purity.[114] Gratifyingly, we found that the tributyltin-containing impurities that remained after column chromatography could be removed by dissolving this material in acetonitrile and washing with three portions of hexanes.[115] Subsequent concentration of the acetonitrile phase delivers the desired product **227** in excellent yield and >96% purity, and with complete diastereomeric integrity. Thus, the two-step process of iododesilylation followed by reductive deiodination (e.g., **195a** → **235** → **227**) constitutes a high yielding (78% over 2 steps in the case of **195a**) alternative to protodesilylation.

Cross-coupling reactions of 2-iodocyclopentenones such as **235** provide a highly attractive strategy for further elaboration of the cyclopentenone products obtained from our



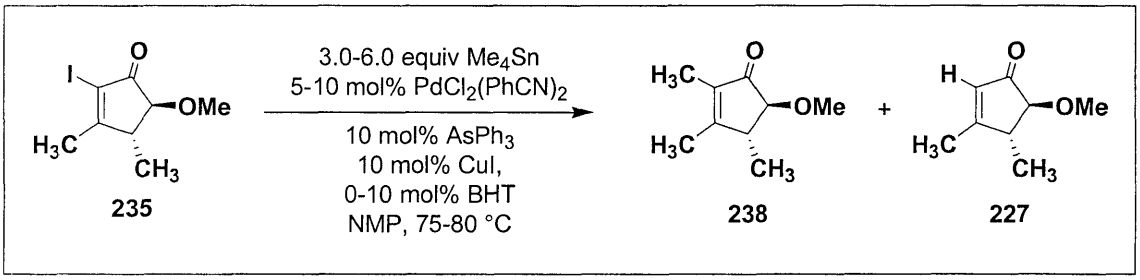
(39)

[112] (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.
[113] Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200.
[114] Reference 113 also provides a discussion of a number of other methods for removal of tributyltin-containing impurities.
[115] For a discussion of the removal of organotin impurities by this extraction procedure see: Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.

annulation, and should be particularly valuable for the synthesis of a wide variety of 2-substituted cyclopentenones. Sonogashira coupling of iodoenone **235** with TMS-acetylene proceeded uneventfully under standard conditions (eq 39) to deliver cyclopentenone **237** in excellent yield. We then decided to examine alternative cross-coupling methods that would allow direct access to 2-*alkyl*-substituted cyclopentenones.

Rossi and coworkers have reported conditions for the Stille cross-coupling[116] of 2-iodoenones, including 2-iodocyclopentenone, with tetramethylstannane.[117] We examined the Stille coupling of iodide **235** with tetramethylstannane using these conditions (Scheme 31). In a preliminary experiment (run 1), we obtained a mixture of desired product **238** and reduction

Scheme 31. Stille Coupling Reactions of **228** with Me_4Sn



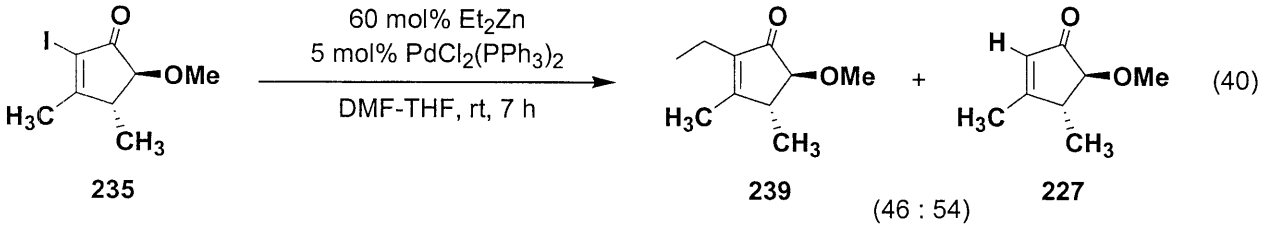
Run	Amount of 235	Conditions	Results
1	0.039 g	no BHT added; 6.0 equiv Me_4Sn (in 2 portions); 25 h (ran in a flask with cold finger condenser)	approx. 40 : 40 : 20 mixture of **238** : **227** : unreacted **235**
2	0.025 g	10 mol% BHT added; 3.0 equiv Me_4Sn; 2.5 h (reaction run in a sealed tube)	mostly **238** by ^1H NMR analysis (no evidence of **227** or unreacted **235**)
3	0.075 g	10 mol% BHT added; 3.0 equiv Me_4Sn; 4.5 h; then added an additional 3.0 equiv of Me_4Sn and more catalyst (Pd^{II}, CuI) and ligand ($AsPh_3$), and heated for 15 h (reaction run in a sealed tube).	approx. 40 : 40 : 20 mixture of **238** : **227** : unreacted **235**

product **227** in approximately equal amounts, along with ca. 20% unreacted starting material (based on ^1H NMR analysis of the crude reaction product). Although it is not uncommon to observe reduction byproducts such as **227** in Stille reactions,[118] the formation of such a product

[116] For a review, see Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.
[117] Bellina, F.; Carpita, A., Ciucci, D.; De Santis, M.; Rossi, R. *Tetrahedron* **1993**, *49*, 4677.
[118] For a discussion on the observation of reduction byproducts in the Stille reaction see reference 116, p 49.

with Me_4Sn (which lacks a β-H) as a coupling partner is intriguing. We rationalized that cyclopentenone **227** likely forms via a radical pathway, and decided to investigate the use of BHT as a radical inhibitor; we also chose to run the reaction in a sealed tube to avoid losing Me_4Sn (bp = 75 °C) during the course of the reaction. A small scale run (run 2) employing these modifications gave a very promising result – the desired product was formed cleanly, and there was no evidence of reduction product **227** or unreacted iodide **235** based on ^{1}H NMR analysis of the crude reaction mixture. Disappointingly, conducting this reaction under identical conditions on a slightly larger scale (run 3) gave results very similar to those obtained in our preliminary experiment (run 1). In all three runs the solvent (NMP) was thoroughly deoxygenated by bubbling argon through it for at least 10 minutes immediately before use, so it is unlikely that adventitious oxygen is responsible for the discrepancy between runs 2 and 3. Frustrated and perplexed by these results, we decide to investigate the application of an alternative method, Negishi cross-coupling, to access the desired 2-alkyl cyclopentenone.

Negishi and coworkers have reported an optimized set of conditions for the palladium-catalyzed cross-coupling of cyclic α-iodoenones,[119] and our initial results employing these



235 **239** (46 : 54) **227** (40)

conditions for the coupling of iodide **235** with diethylzinc are shown in eq 40. The desired product was formed; however, as in our Stille coupling attempts discussed above, a significant amount of reduction product **227** was observed by ^{1}H NMR analysis of the crude product. Vinyl halide reduction is not as perplexing in this case since, in the ultimate step of the catalytic cycle, β-hydride elimination could be competitive with reductive elimination. Nonetheless, the results of this reaction were quite disappointing. Although a number of modifications to these conditions could be explored, because of time constraints we could not examine such transformations further at this time.

[119] Negishi, E.-i.; Tan, Z.; Liou, S.-Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197.

In summary, we have demonstrated that triisopropylsilyl-substituted cyclopentenone **167a** and related triethylsilyl-substituted cyclopentenone **195a** can be readily converted to 2-iodocyclopentenone **235** in excellent yield. With respect to other [4 + 1] annulation products such as those bearing an alkenyl (**202**) or an alkynyl substituent (**203**), further studies are necessary to determine the reactivity of the vinylsilane moiety relative to other functional groups that are present in these molecules. Furthermore, vinyl iodide **235** undergoes tributyltin hydride-promoted dehalogenation and participates in transition metal-catalyzed cross-coupling reactions. Although competitive dehalogenation of the iodocyclopentenone substrate was observed in our preliminary Stille and Negishi cross-coupling studies, the desired products were formed in ca. 40% yield. These initial studies have laid the groundwork for future applications of our [4 + 1] annulation methodology.

Chapter 4

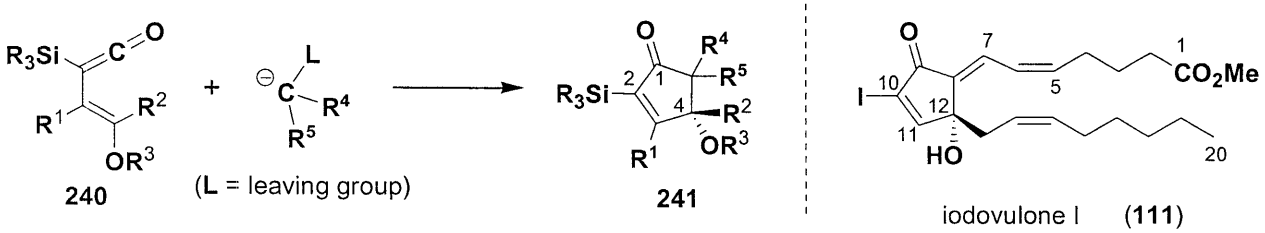
Preliminary Results and Future Studies

The previous chapters of this thesis have detailed the results of our studies aimed at the development of (TAS)vinylketene-based annulation strategies for the synthesis of 2-indanones and cyclopentenones. This chapter, the final section of this thesis, will present preliminary results we have obtained during our efforts to further increase the scope and generality of our [4 + 1] cyclopentenone annulation.

[4 + 1] Cylopentenone Annulation with Oxygenated (TAS)vinylketenes

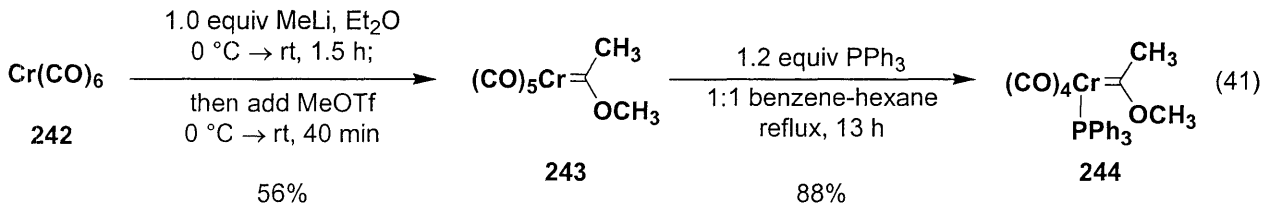
As discussed in Part I (p 19 and Scheme 7), (TAS)vinylketenes can be prepared via the reaction of chromium carbene complexes with alkynylsilanes. This method captured our attention because it provides access to *oxygenated* TAS(vinylketenes) of type **240** (Scheme 32). Successful [4 + 1] annulations with such ketenes would deliver cyclopentenones bearing an oxygenated quaternary center at C-4, a structural motif found in many bioactive cyclopentenone prostanoids (see Chart 1 and the related discussion on pp 43-45) including iodovulone I (**111**).

Scheme 32

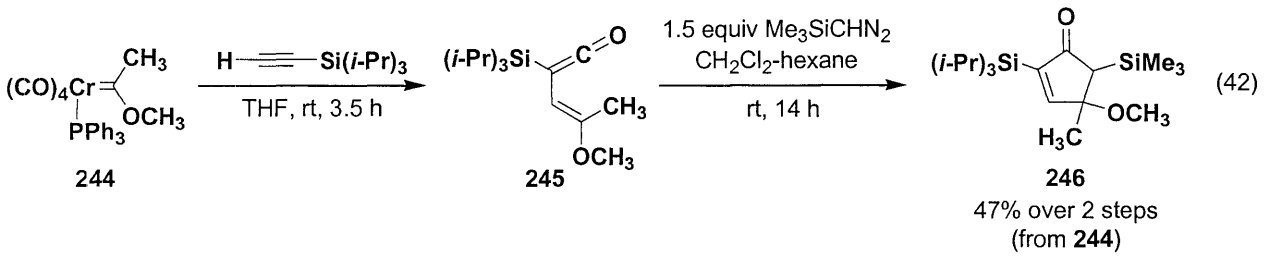


To test the feasibility of using (TAS)vinylketenes of type **240** in our [4 + 1] cyclopentenone annulation, we prepared **245** via the reaction of chromium carbene complex **244** with (triisopropylsilyl)acetylene (eq 42). The requisite chromium carbene complex **244** was prepared in two steps from $Cr(CO)_6$ according to the previously reported procedures outlined in

eq 41.[120,121] Unfortunately, purification of (TAS)vinylketene **245** proved to be problematic, and



we could only isolate this ketene in ca. 90% purity after column chromatography on silica gel. Nonetheless, we used this material in a model [4 + 1] annulation and obtained promising results. Treatment of (TAS)vinylketene **245** with TMS-diazomethane in CH_2Cl_2-hexane at room temperature furnished the desired cyclopentenone **246** as a single diastereomer[122] in 47% yield over two steps from chromium carbene complex **244**. It should be noted that the first step (**244** → **245**) in this sequence is responsible for the low overall yield, as the [4 + 1] annulation delivers cyclopentenone **246** in 88% yield based on the amount of *impure* ketene used.



While further studies are needed to examine the generality of the above [4 + 1] annulation with respect to the use of carbenoid reagents other than TMS-diazomethane and the use of oxygenated (TAS)vinylketenes that are more functionalized than **245**, these initial results are encouraging. Although only a limited number of (TAS)vinylketenes have been prepared from chromium carbene complexes, a variety of chromium carbene complexes of type **243** are known and are readily available by treatment of $Cr(CO)_6$ with an organolithium compound (MeLi in eq 41) and trapping of the resulting intermediate with a suitable electrophile (MeOTf in

[120] For the preparation of **243** as shown in eq 41, see: Zora, M.; Li, Y.; Herndon, J. W. *Organometallics* **1999**, *18*, 4429. For an alternative procedure for the synthesis of **243**, see: Hegedus, L. S.; McGuire, M. A.; Schultze, L. M. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 216.

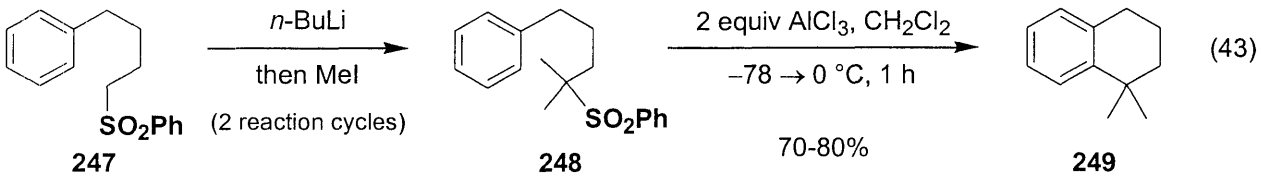
[121] For the preparation of **244** from **243**, see reference 18.

[122] The relative stereochemistry of cyclopentenone **246** has not yet been assigned.

eq 41). Therefore, it is conceivable that this route could provide access to an array of highly substituted (TAS)vinylketenes to employ in the synthesis of natural product targets.

Lithiated Sulfones – A New Class of Carbenoid Reagents for the [4 + 1] Annulation

Chapter 2 described our results using α-benzotriazolyl organolithium compounds as carbenoid reagents in our [4 + 1] cyclopentenone annulation. We have also conducted preliminary experiments to examine the possibility of employing metallated sulfones as a new class of carbenoid reagents.[123] It is well known that the sulfone group can activate an α-C-H bond towards deprotonation by stabilizing the resulting carbanion (for example, $CH_3(SO_2)Ph$ has a pK_a of 29 in DMSO). In addition, the sulfone group can also function as a leaving group. Trost has reported the use of sulfones as "1,1-dipole synthons" in reaction strategies which demonstrate both types of sulfone reactivity.[124] Treatment of sulfone **247** (eq 43) with *n*-BuLi generates an α-sulfonyl organolithium compounds which can be trapped with methyl iodide; repeating this sequence delivers tertiary sulfone **248**. Treatment of compound **248** with an excess of $AlCl_3$ promotes ionization of the sulfone group and subsequent cyclization (a Friedel–Crafts alkylation) delivers tetrahydronapthalene derivative **249** in good yield. As illustrated in

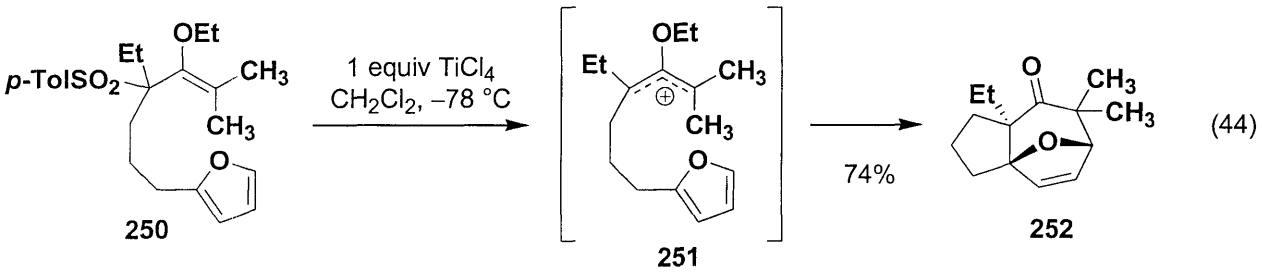


(43)

eq 44, Harmata has also employed the Lewis acid-promoted ionization of sulfone groups to generate transient allylic cations (e.g., **251**) which are trapped with a tethered 1,3-diene in intramolecular [4 + 3] cycloadditions.[125] Given the ability to convert sulfones into nucleophilic species by metallation and the ability of sulfones to function as leaving groups, we decided to

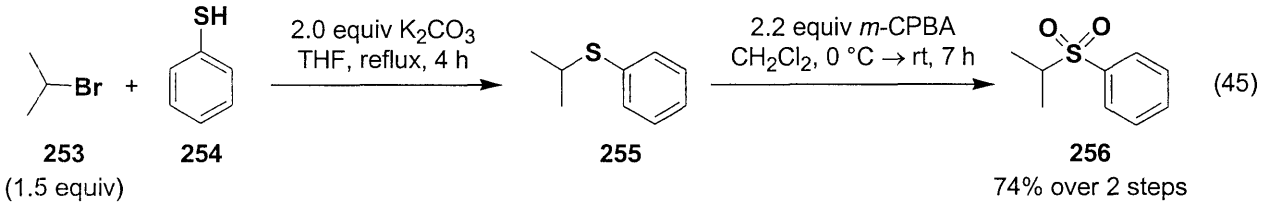
[123] For reviews on the use of sulfones in organic synthesis, see: (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Baldwin, J. E., Magnus, P. D.; Eds.; Tetrahedron Organic Chemistry Series, Vol. 10; Permagon Press Ltd: Oxford, 1993. (b) *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C., Eds.; The Chemistry of Functional Groups; Wiley: New York, 1988.
[124] Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 7260.
[125] For a review, see: Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595.

investigate the use of metallated sulfones as a potentially new class of carbenoid reagents for our [4 + 1] annulation.



(44)

In addition to the reactivity described above, we were also attracted to sulfones because a variety of derivatives are readily available. For our preliminary studies, we prepared phenyl isopropyl sulfone (**255**) in 74% yield over 2 steps according to a literature procedure[126] that involves the reaction of thiophenol and 2-bromopropane to furnish sulfide **255**, and oxidation of the crude reaction product with *m*-CPBA (eq 45). A number of sulfones can be prepared by this strategy, and some (such as methyl phenyl sulfone) are commercially available.



253 (1.5 equiv) **254** **255** **256** 74% over 2 steps

(45)

We first examined nucleophilic addition of the organolithium compound derived from sulfone **256** to (TAS)vinylketene **1** (Scheme 33). Sulfone **256** was lithiated by treatment with an equimolar amount of *n*-BuLi in THF at –78 °C for 45 min, and then trapped by the addition of ketene **1**. Quenching of the initially formed dienolate intermediate **257** furnished enone **258** in good yield. Given the successful use of Lewis acids to promote the ionization of the sulfone group in a variety of reactions (e.g., those shown in eqs 43 and 44), we hypothesized that treatment of dienolate **257** with a Lewis acid under the appropriate conditions might facilitate loss of the sulfone group and cyclization to deliver the desired cyclopentenone annulation product.

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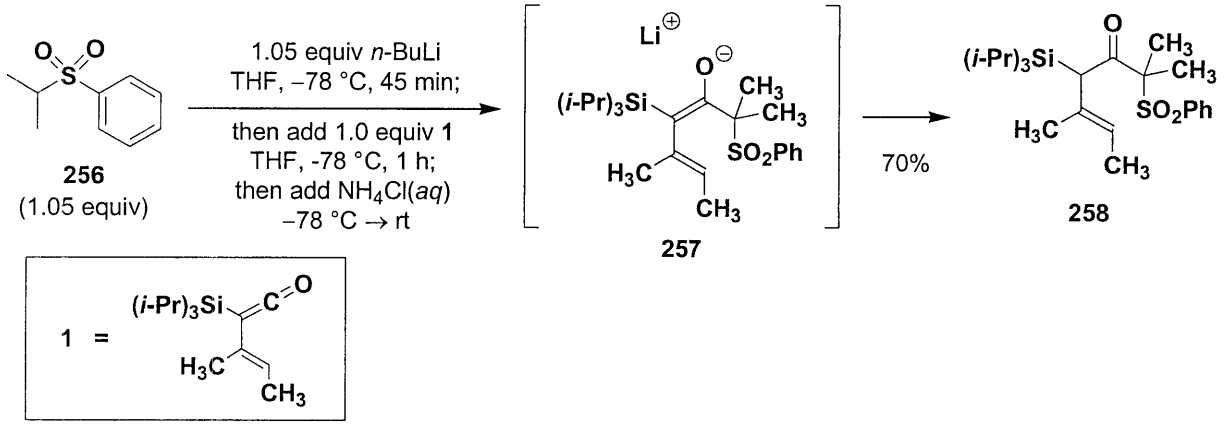
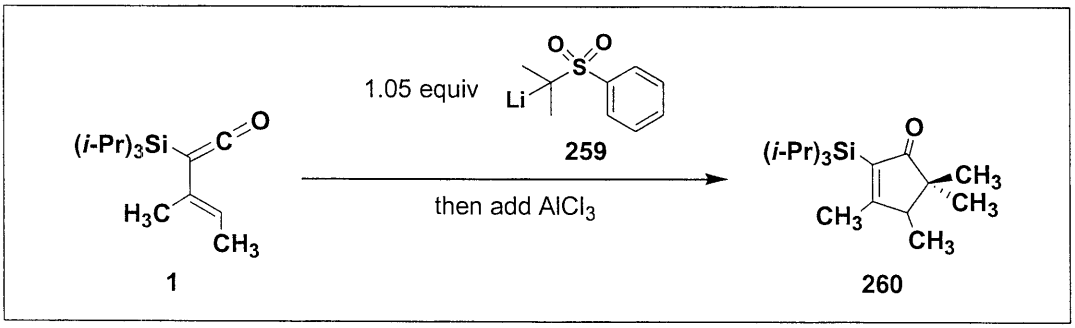
[126] Lamothe, M.; Anderson, M. B.; Fuchs, P. L. *Synth, Commun.* **1991**, *21*, 1675.

Scheme 33



Scheme 34 summarizes the preliminary experiments we have conducted in this area. Treatment of dienolate **257** (generated as shown in Scheme 33) with 3 equiv of $AlCl_3$ at –78 °C followed by warming of the reaction mixture to room temperature results in the formation of a trace amount of the desired cyclopentenone (run 1). Heating the resulting reaction mixture at reflux for several hours had minimal effect (we estimate that an additional 10% or less of the desired product was formed during the 6 h at reflux). In this fashion, cyclopentenone **260** was isolated in 22% yield, but was contaminated with ca. 25% of unknown impurities. Encouraged

Scheme 34



Run	Conditions	Results
1	1.05 equiv **259**, THF, -78 °C, 1.5 h; then add 3.0 equiv $AlCl_3$, -78 °C → rt, 21 h; then reflux 6 h	22% yield, ca. 75% purity
2	1.05 equiv **259**, Et_2O, -78 °C, 1 h; then add 3.0 equiv $AlCl_3$ (in CH_2Cl_2) -78 °C → rt, 22 h	44% yield, ca. 75% purity

by this preliminary result, we decided to conduct the reaction in Et_2O, considering that THF could be attenuating the Lewis acidity of $AlCl_3$. In this case (run 2), we added the Lewis acid as a solution in CH_2Cl_2, with the rationale that a more polar solvent system (Et_2O-CH_2Cl_2) might facilitate sulfone ionization. With these modifications, we observed a significant increase in the amount of product formed compared with run 1; however, as before, cyclopentenone **260** was only obtained in ca. 75% purity after purification by column chromatography on silica gel.

To date, the experiments summarized in Scheme 34 are the only [4 + 1] annulation reactions with metallated sulfones that we have studied. There is clearly significant room for improvement in both the initial nucleophilic addition step (70%, Scheme 33) as well as the conditions to promote ionization and cyclization of the initially formed dienolate intermediate **257**. With respect to the latter, there are a number of different Lewis acids and/or solvents that can be screened. Although optimization is needed, these preliminary results demonstrate that metallated sulfones of type **259** can, in fact, function as competent carbenoid reagents for our [4 + 1] annulation strategy, and may serve to complement the α-benzotriazolyl organolithium reagents discussed in Chapter 2. In particular, it is encouraging that metallated sulfones such as **259**, lacking an α-donating substituent (such as a heteroatom in the case of the α-benzotriazolyl organolithium reagents previously discussed), can be employed in the [4 + 1] annulation.

In summary, the results described in this Chapter have set the stage for further development of our [4 + 1] annulation strategy for the synthesis of substituted cyclopentenones. Although additional studies are required to delineate the scope and generality of using oxygenated (TAS)vinylketenes such as **245** in the [4 + 1] annulation and only preliminary results using metallated sulfones as carbenoid reagents have been obtained, the groundwork for future studies has been laid.

Part IV

Experimental Procedures

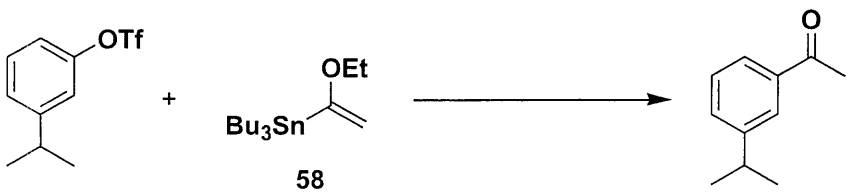
General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on EMD (Merck) precoated glass-backed silica gel 60 F-254 0.25 mm plates. Preparative-scale thin layer chromatography was performed on Analtech precoated glass-backed silica gel GF 2000 μm plates. Column chromatography and desilylations were performed on Silicycle silica gel 60 (230-400 mesh) or Sorbent Technologies silica gel 60 (230-450 mesh). Photochemical Wolff rearrangements were carried out in a Rayonet photochemical reactor Model RPR-100 containing sixteen 300-nm, low-pressure mercury vapor bulbs (Southern New England Ultraviolet Company).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane and diethyl ether were purified by pressure filtration through activated alumnia. Tetrahydrofuran was distilled under argon from sodium benzophenone ketyl or dianion or purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Dimethylformamide was EM Dri-Solv grade and used as received. Iodine monochloride (Aldrich, 1.0 M in CH_2Cl_2) was used as received. Acetonitrile, benzene, diisopropylamine, diisopropylethylamine, 1,1,1,3,3,3-hexamethyldisilazane, triethylamine, triethylsilyl trifluoromethanesulfonate, and triisopropylsilyl trifluoromethanesulfonate were distilled under argon from calcium hydride. Tributyl(1-ethoxyvinyl)tin, 2,2,2-trifluoroethyl trifluoroacetate, tributyltin hydride, and methyl iodide were distilled under argon. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). Palladium(II) chloride (bis)triphenylphosphine was recrystallized from boiling chloroform. *n*-BuLi was titrated according to the Watson-Eastham method using BHT in THF or toluene at 0 °C with 1,10-phenanthroline as an indicator.[127] 3-(Isopropyl)phenyl trifluoromethanesulfonate[33]

[127] (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165. (b) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209.

and methanesulfonyl azide[30a] were prepared according to procedures described previously. Benzotriazole derivatives **160**,[84] **161**,[85] **162**,[86] **174**,[93] **176**,[94] and **177**[84] were prepared according to previously reported procedures. Solid benzotriazole derivatives **160-162**, **174**, and **176** were dried overnight in a vacuum dessicator (ca. 0.2 mmHg) over P_2O_5 before use in [4 + 1] annulations. Other benzotriazole derivatives (**124**, **177**, **178**, and **182**) were dried by azeotropic removal of water with toluene immediately before use (vide infra). $ZnBr_2$ (Alfa Aesar, 99.9%) was ground into a fine powder (in a glove box) and dried under vacuum ($\leq$ 0.25 mmHg) at 200-240 °C for ca. 20 h before use.

Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Varian XL-300 (300 MHz), Varian Unity 300 (300 MHz), and Varian Inova 500 (500 MHz) spectrometers. ^{13}C NMR spectra were recorded on Varian XL-300 (75 MHz) and Varian Inova 500 (125 MHz) spectrometers. ^{1}H NMR chemical shifts and ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. Preparative HPLC purification was performed on a Waters 600E multisolvent delivery system with a Waters Prep Nova Pak HR™ column (silica 6 μ, 19 mm $\times$ 30 cm). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer. Low-resolution Mass Spectra (LRMS) were measured on a Hewlett Packard 5890 Series II Gas Chromatograph with Hewlett Packard 5971 series mass selective detection. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ.



57 58 59

1-(3′-Isopropylphenyl)ethanone (59).

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum was charged with 3-isopropylphenyl trifluoromethanesulfonate (2.008 g, 7.49 mmol) and tributyl(1-ethoxyvinyl)tin (2.78 mL, 2.97 g, 8.23 mmol) in 7.5 mL of DMF. Bis(triphenylphosphine)palladium(II) chloride (0.260 g, 0.370 mmol) was added and the resulting yellow suspension was stirred at room temperature for 30 min. The flask was then equipped with a reflux condenser, and the reaction mixture was heated at 60 °C for an additional 8 h. The reaction mixture was allowed to cool and then filtered through 10-15 g of silica gel in a short column with the aid of 175 mL of Et_2O to remove the majority of the residual palladium. This process was repeated two additional times. The filtrate was then washed with two 50-mL portions of 1 N aq HCl solution, five 50-mL portions of water, and two 50-mL portions of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 3.37 g of a dark brown oil. Column chromatography on 170 g of silica gel (elution with 5% EtOAc-hexanes) furnished 1.09 g of the desired ketone contaminated with trace organotin impurities. Further purification on 55 g of silica gel afforded 0.951 g (78%) of ketone **59** as a colorless oil with spectral characteristics consistent with those reported previously:[128] IR (film) 2962, 1684, 1600, 1435, 909, 899, 797, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (app t, J = 1.8 Hz, 1 H), 7.78 (app dt, J = 7.6, 1.5 Hz, 1 H), 7.45 (app dt, J = 7.7, 1.4 Hz, 1 H), 7.39 (app t, J = 7.6 Hz, 1 H), 2.98 (sept, J = 7.0 Hz, 1 H), 2.62 (s, 3 H), 1.29 (d, J = 7.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 149.6, 137.4, 131.6, 128.7, 126.4, 126.3, 34.3, 26.9, 24.1.

[128] Campbell, B. N.; Spaeth, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 5933.

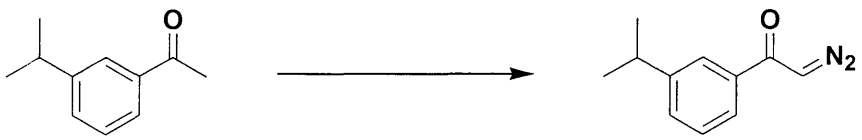
62 64

General Procedure for Diazo Transfer. 1-(2′-Chlorophenyl)-2-diazoethanone (64).

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with HMDS (3.54 mL, 2.71 g, 16.8 mmol) in 30 mL of THF and then cooled at 0 °C while *n*-BuLi (2.49 M in hexanes, 6.74 mL, 16.8 mmol) was added rapidly over 2 min. After 10 min, the solution was cooled at -78 °C while a solution of 2′-chloroacetophenone (**62**) (2.36 g, 15.3 mmol) in 15 mL of THF was added dropwise over 5 min. The reaction mixture was stirred at -78 °C for 30 min and then 2,2,2-trifluoroethyl trifluoroacetate (4.09 mL, 5.99 g, 30.5 mmol) was added in one portion. After 10 min, the reaction mixture was poured into a separatory funnel containing 40 mL of 5% aq HCl solution and 40 mL of Et_2O. The aqueous phase was extracted with two 30-mL portions of Et_2O, and the combined organic phases were washed with 40 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give a yellow-orange oil which was dissolved in 30 mL of CH_3CN and transferred to a 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and a 25-mL pressure-equalizing addition funnel. Water (0.275 mL, 0.275 g, 15.3 mmol) and Et_3N (3.19 mL, 2.32 g, 22.9 mmol) were added rapidly, and a solution of methanesulfonyl azide (2.77 g, 22.9 mmol) in 20 mL of CH_3CN was added dropwise over 10 min (the addition funnel was rinsed with another 2 mL of CH_3CN). The resulting solution was stirred at room temperature for 4 h, concentrated to a volume of ca. 5 mL, diluted with 40 mL of Et_2O and extracted with three 20-mL portions of 10% aq NaOH solution, three 25-mL portions of water, and 25 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford an orange oil. Column chromatography on 100 g of silica gel (gradient elution with 0-20% EtOAc-hexanes) provided 2.320 g (84%) of diazo ketone **64** as a yellow solid with spectral characteristics consistent with those reported previously:[129] mp 45-47 °C (lit.[130] mp 49-50 °C); IR (CH_2Cl_2) 2110, 1620, 1434, 1359 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.51-7.55 (m, 1 H), 7.29-

[129] Sorriso, S.; Foffani, A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1497.
[130] Hörmann, W. D.; Fahr, E. *Justus Liebigs Ann. Chem.* **1963**, *663*, 1.

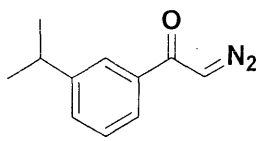
7.42 (m, 3 H), 5.78 (s, 1 H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 186.8, 137.5, 132.0, 131.2, 130.7, 129.5, 127.2, 58.0.



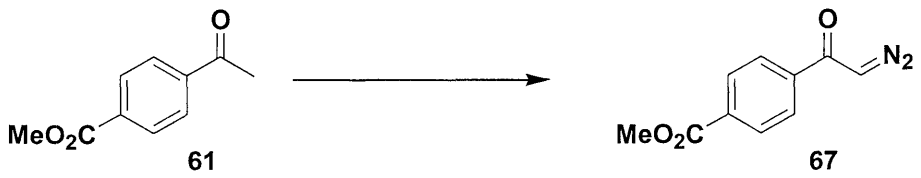
59 66

1-(3′-Isopropylphenyl)-2-diazoethanone (66).

Reaction of 1-(3′-isopropylphenyl)ethanone (0.939 g, 5.79 mmol) with LiHMDS [prepared *in situ* from HMDS (1.34 mL, 1.03 g, 6.37 mmol) and *n*-BuLi (2.51 M, 2.54 mL, 6.37 mmol)] and 2,2,2-trifluoroethyl trifluoroacetate (0.930 mL, 1.36 g, 6.95 mmol) in 30 mL of THF according to the general procedure provided a yellow oil which was diluted with 40 mL of CH_3CN, and treated with H_2O (0.104 mL, 0.104 g, 5.79 mmol), Et_3N (1.21 mL, 0.879 g, 8.68 mmol), and methanesulfonyl azide (1.05 g, 8.68 mmol) at room temperature for 3.5 h to yield 1.121 g of a yellow oil. This material was purified by column chromatography on 55 g of silica gel (elution with 15% EtOAc-hexanes) to provide 0.970 g (89%) of diazo ketone **66** as a yellow oil: IR (film): 2962, 2105, 1618, 1440, 1362 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (app t, J = 1.8 Hz, 1 H), 7.54 (app dt, J = 7.6, 1.7 Hz, 1 H), 7.42 (app dt, J = 7.7, 1.6 Hz, 1 H), 7.37 (app t, J = 7.7 Hz, 1 H), 5.92 (s, 1 H), 2.97 (sept, J = 6.9 Hz, 1 H), 1.28 (d, J = 6.9 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.8, 149.7, 136.9, 131.1, 128.8, 125.0, 124.4, 54.3, 34.3, 24.0.



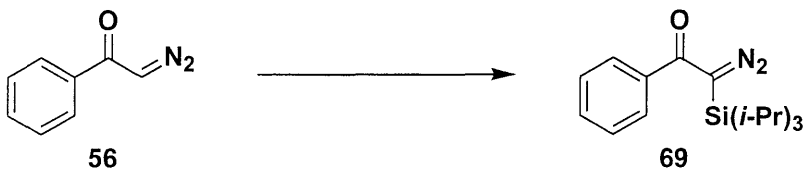
66



Methyl 4-(2′-diazoacetyl)benzoate (67).

Reaction of methyl 4-acetylbenzoate (0.154 g, 0.864 mmol) with LiHMDS [prepared *in situ* from HMDS (0.201 mL, 0.153 g, 0.951 mmol) and *n*-BuLi (2.49 M, 0.382 mL, 0.951 mmol)] and 2,2,2-trifluoroethyl trifluoroacetate (0.139 mL, 0.203 g, 1.04 mmol) in 5.4 mL of THF according to the general procedure provided 0.252 g of an off-white solid which was diluted with 7 mL of CH_3CN, and treated with H_2O (0.016 mL, 0.016 g, 0.86 mmol), Et_3N (0.181 mL, 0.131 g, 1.30 mmol), and methanesulfonyl azide (0.157 g, 1.30 mmol) at room temperature for 13.5 h to yield 0.140 g of a pale yellow solid. This material was deposited onto 2 g of silica gel and purified by column chromatography on 20 g of silica gel (elution with 7% *t*-BuOMe-benzene) to provide 0.100 g (57%) of diazo ketone **67** as a yellow solid with spectral characteristics consistent with those reported previously:[131] mp 104-106 °C (lit.[131] mp 98-101 °C); IR (CH_2Cl_2) 3054, 2987, 2111, 1723, 1624, 1422, 1358, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.9 Hz, 2 H), 7.82 (d, J = 8.9 Hz, 2 H), 5.98 (s, 1 H), 3.96 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.5, 160.0, 140.0, 134.0, 130.3, 126.7, 55.0, 52.4.

[131] Firestone, R. A.; Maciejewicz, N. S.; Christensen, B. G. *J. Org. Chem.* **1974**, *39*, 3384.

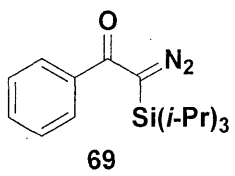


56 69

General Procedure for Silylation of Diazo Ketones. 2-Diazo-1-phenyl-2-(triisopropylsilyl)ethanone (69).

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with diazo ketone **56**[132] (0.209 g, 1.43 mmol) in 8 mL of a 1:1 solution of Et_2O-hexanes and then cooled at 0 °C using an ice-water bath while *i*-Pr_2EtN (0.250 mL, 0.185 g, 1.43 mmol) was added dropwise over 2 min. After 10 min, TIPSOTf (0.380 mL, 0.433 g, 1.43 mmol) was added dropwise over 3 min and the resulting solution was stirred for 12 h while the ice-water bath warmed to 25 °C. The reaction mixture was filtered through Celite with the aid of 10 mL of Et_2O and the filtrate was concentrated to give 0.579 g of an orange oil. Column chromatography on 30 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.340 g (79%) of diazo ketone **69** as a yellow oil: IR (CCl_4) 2946, 2867, 2065, 1622, 1578, 1464 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60-7.63 (m, 2 H), 7.49-7.51 (m, 1 H), 7.43-7.47 (m, 2 H), 1.45 (sept, J = 7.3 Hz, 3 H), 1.20 (d, J = 7.3 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 138.7, 131.5, 128.8, 127.2, 51.6, 18.7, 11.7.

[132] Diazo ketone **56** was prepared according to the previously reported procedure described in reference 30a. See pp 28-29 and eq 13 (p 29) for further details.

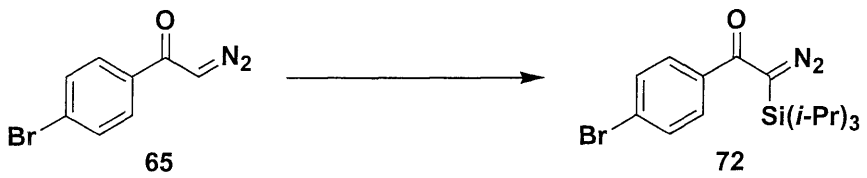


69

56 70

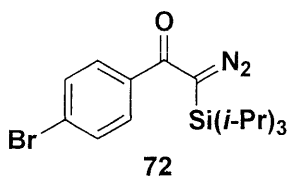
2-Diazo-1-phenyl-2-(triethylsilyl)ethanone (70).

Reaction of diazo ketone **56** (0.122 g, 0.835 mmol), *i*-Pr_2EtN (0.153 mL, 0.113 g, 0.876 mmol), and Et_3SiOTf (0.198 mL, 0.232 g, 0.876 mmol) in 4 mL of a 1:1 solution of Et_2O-hexanes at 0-25 °C for 3 h according to the general procedure gave 0.244 g of an orange oil. Column chromatography on 20 g of acetone-deactivated silica gel (gradient elution with 0-2.5% *t*-BuOMe-hexanes) provided 0.136 g (63%) of diazo ketone **70** as yellow oil with spectral characteristics consistent with those reported previously:[15a] IR (film) 2956, 2877, 2067, 1621, 1577, 1285 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61-7.63 (m, 2 H), 7.42-7.52 (m, 3 H), 1.03 (t, J = 7.9 Hz, 9 H), 0.84 (q, J = 7.9 Hz, 6 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 193.9, 138.8, 131.5, 128.7, 127.2, 52.3, 7.4, 3.2.



1-(4′-Bromophenyl)-2-diazo-2-(triisopropylsilyl)ethanone (72).

Reaction of diazo ketone **65** (0.400 g, 1.78 mmol), *i*-Pr_2EtN (0.310 mL, 0.230 g, 1.78 mmol), and TIPSOTf (0.480 mL, 0.547 g, 1.78 mmol) in 10 mL of a 1:1 solution of Et_2O-hexanes at 0-25 °C for 12 h according to the general procedure gave an orange oil which was immediately dissolved in CH_2Cl_2, deposited onto 1.2 g of silica gel, and purified by column chromatography on 30 g of silica gel (gradient elution with 0-2.5% *t*-BuOMe-hexanes) to provide 0.508 g (75%) of diazo ketone **72** as a yellow oil: IR (film) 2065, 1605, 1415, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 6.4 Hz, 2 H), 7.54 (d, J = 6.4 Hz, 2 H), 1.42 (sept, J = 7.6 Hz, 3 H), 1.15 (d, J = 7.6 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 137.4, 132.0, 128.3, 127.7, 51.8, 18.6, 11.7.

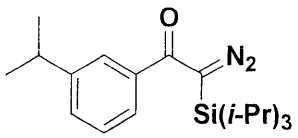


72

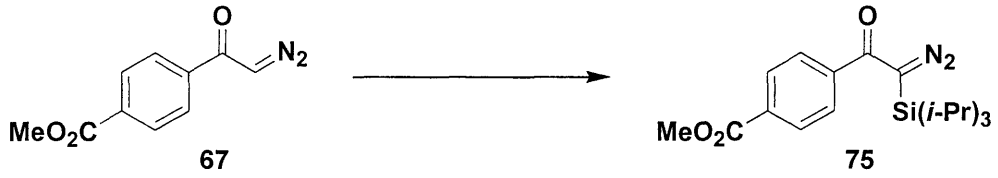
66 74

2-Diazo-1-(3′-isopropylphenyl)-2-(triisopropylsilyl)ethanone (74).

Reaction of diazo ketone **66** (0.884 g, 4.70 mmol), *i*-Pr_2EtN (0.820 mL, 0.608 g, 4.70 mmol), and TIPSOTf (1.26 mL, 1.44 g, 4.70 mmol) in 28 mL of a 1:1 solution of Et_2O-hexanes at 0-25 °C for 12 h according to the general procedure gave 1.664 g of a yellow-orange oil, which was purified by column chromatography on 100 g of silica gel (gradient elution with 3-10% *t*-BuOMe-hexanes) to provide 1.212 g (75%) of diazo ketone **74** as a yellow oil: IR (film) 2961, 2064, 1624, 1463, 1290 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1 H), 7.43-7.47 (m, 1 H), 7.35-7.38 (m, 2 H), 2.97 (sept, J = 6.7 Hz, 1 H), 1.46 (sept, J = 7.3 Hz, 3 H), 1.28 (d, J = 6.7 Hz, 6 H), 1.18 (d, J = 7.3 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 149.6, 138.7, 129.8, 128.6, 125.5, 124.7, 51.5, 34.3, 24.1, 18.7, 11.7.

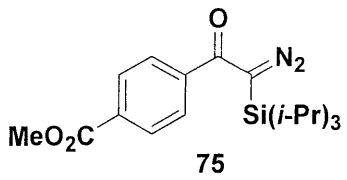


74



Methyl 4-(2′-diazo-2′-triisopropylsilylacetyl) benzoate (75).

Reaction of diazo ketone **67** (0.164 g, 0.803 mmol), *i*-Pr_2EtN (0.140 mL, 0.104 g, 0.803 mmol), and TIPSOTf (0.216 mL, 0.246 g, 0.803 mmol) in 5 mL of a 1:1 solution of Et_2O-hexanes at 0-25 °C for 13.5 h according to the general procedure gave 0.344 g of an orange oil. Column chromatography on 25 g of acetone-deactivated silica gel (elution with 8% *t*-BuOMe-benzene) provided 0.210 g (72%) of diazo ketone **75** as a yellow oil: IR (film) 2948, 2067, 1729, 1625 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.00 (d, J = 7.9 Hz, 2 H), 7.49 (d, J = 7.9 Hz, 2 H), 3.47 (s, 3 H), 1.37 (sept, J = 7.6 Hz, 3 H), 1.11 (d, J = 7.6 Hz, 18 H); ^{13}C NMR (125 MHz, C_6D_6) δ 192.7, 166.2, 142.8, 133.2, 130.5, 127.6, 52.2, 51.8, 19.0, 12.1.



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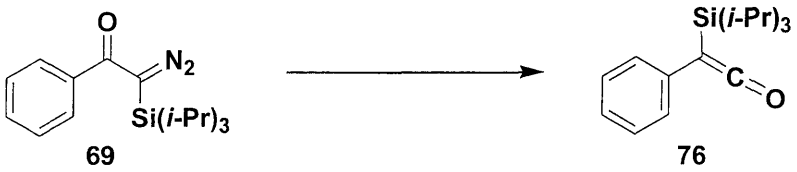
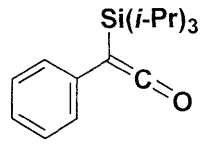


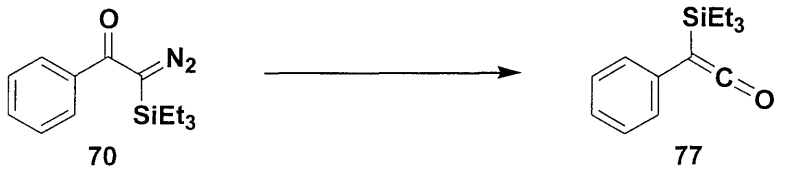
69 76

General Procedure for Photochemical Wolff Rearrangement. 2-Phenyl-2-(triisopropylsilyl)ketene (76).

A solution of diazo ketone **69** (1.210 g, 4.00 mmol) in 35 mL of benzene was distributed evenly between two 25-cm vycor tubes fitted with rubber septa. A second rubber septum (inverted) was secured with wire to each tube to ensure a good seal, and the reaction mixtures were degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mmHg) and then irradiated with 300 nm light for 3 h in a Rayonet reactor. The resulting solutions were combined and concentrated to afford 1.062 g of a yellow oil. Column chromatography on 80 g of silica gel (elution with hexanes) provided 0.980 g (89%) of ketene **76** as a viscous yellow oil: IR (film) 2945, 2887, 2081, 1595, 1495, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, J = 7.5 Hz, 2 H), 7.17 (d, J = 7.5 Hz, 2 H), 7.11 (t, J = 7.5 Hz, 1 H), 1.29 (sept, J = 7.5 Hz, 3 H), 1.11 (d, J = 7.6 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.2, 132.0, 129.4, 129.1, 125.2, 19.3, 18.8, 12.7.



76

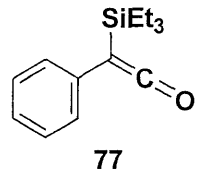


70 77

2-Phenyl-2-(triethylsilyl)ketene (77).

Reaction of diazo ketone **70** (0.785 g, 3.01 mmol) in 30 mL of benzene for 3.5 h according to the general procedure gave 0.771 g of an orange oil. Column chromatography on 80 g of silica gel (elution with hexanes) provided 0.365 g (52%) of ketene **77** as a pale yellow oil with spectral characteristics consistent with those reported previously:[133] IR (film) 3057, 2955, 2875, 2080, 1596, 1576, 1496, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.28 (m, 2 H), 7.08-7.14 (m, 3 H), 1.02 (t, J = 7.9 Hz, 9 H), 0.90 (q, J = 7.9 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.0, 132.1, 129.2, 128.3, 124.9, 20.4, 7.4, 4.2.

[133] Brückmann, R.; Schneider, K.; Maas, G. *Tetrahedron* **1989**, *45*, 5517.



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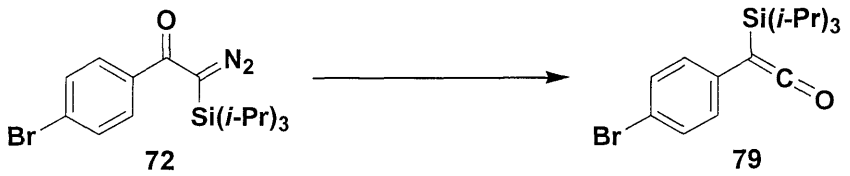
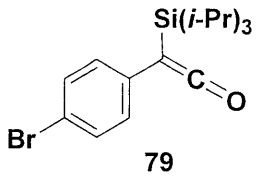


2-(4′-Bromophenyl)-2-(triisopropylsilyl)ketene (79).

Reaction of diazo ketone **72** (0.452 g, 1.19 mmol) in 14 mL of benzene for 3 h according to the general procedure gave 0.402 g of a yellow-orange oil. Column chromatography on 13 g of silica gel (elution with hexanes) provided 0.321 g (76%) of ketene **79** as a viscous yellow oil: IR (film) 2946, 2890, 2082, 1653, 1559, 1486, 1464 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, J = 6.6 Hz, 2 H), 7.08 (d, J = 6.6 Hz, 2 H), 1.33 (sept, J = 7.6 Hz, 3 H), 1.15 (d, J = 7.6 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.5, 132.1, 131.3, 130.8, 118.6, 19.0, 18.7, 12.6.



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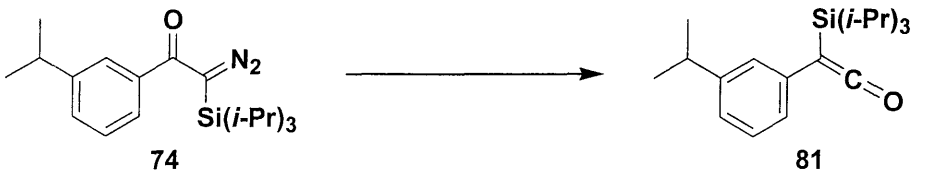
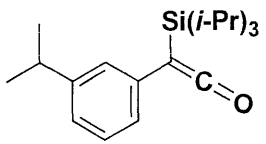


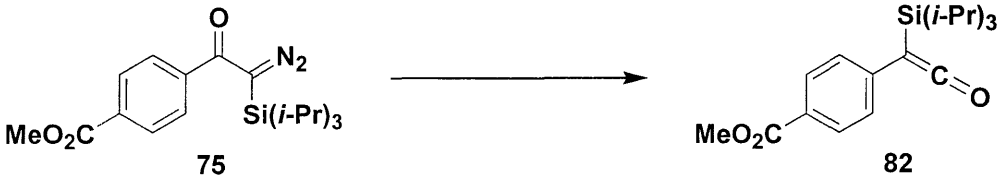
74 81

2-(3′-Isopropylphenyl)-2-(triisopropylsilyl)ketene (81).

Reaction of diazo ketone **74** (1.154 g, 3.35 mmol) in 34 mL of benzene for 3 h according to the general procedure gave 1.131 g of a yellow-orange oil. Column chromatography on 110 g of silica gel (elution with hexanes) provided 0.683 g (64%) of ketene **81** as a pale yellow oil: IR (film) 2960, 2081, 1599, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (app t, J = 7.6 Hz, 1 H), 7.05 (s, 1 H), 6.97-7.03 (m, 2 H), 2.87 (sept, J = 7.0 Hz, 1 H), 1.31 (sept, J = 7.6 Hz, 3 H), 1.25 (d, J = 7.0 Hz, 6 H), 1.14 (d, J = 7.6 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5, 149.7, 131.7, 129.0, 127.5, 126.7, 123.4, 34.3, 24.2, 19.3, 18.8, 12.7.

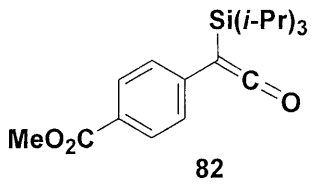


81

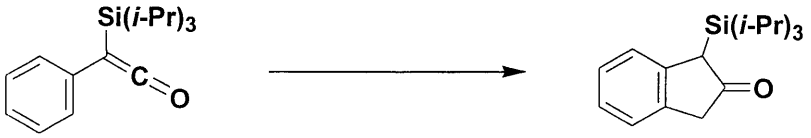


2-(4′-Carbomethoxyphenyl)-2-(triisopropylsilyl)ketene (82).

Reaction of diazo ketone **75** (1.107 g, 3.07 mmol) in 35 mL of benzene for 3.5 h according to the general procedure gave 1.046 g of an orange oil. Column chromatography on 75 g of silica gel (elution with 4% *t*-BuOMe-hexanes) provided 0.605 g (62%) of ketene **82** as a viscous yellow oil (ca. 90% purity by ^{1}H NMR analysis): IR (film) 2948, 2081, 1724, 1602, 1435, 1280 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 3.90 (s, 3 H), 1.33 (sept, J = 7.6 Hz, 3 H), 1.13 (d, J = 7.4 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 167.1, 138.9, 130.4, 128.2, 126.5, 52.2, 21.2, 18.7, 12.8; LRMS (EI): *m/z* 332 (M^+).



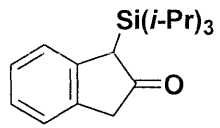
82



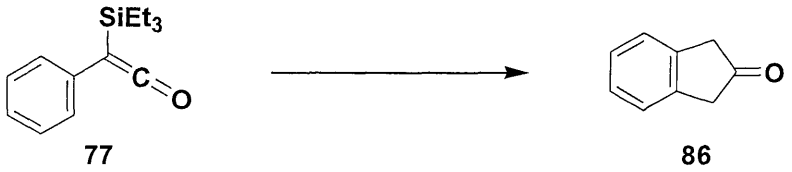
76 84

General Procedure for [4 + 1] Annulation. 1-(Triisopropylsilyl)indan-2-one (84).

A 10-mL, two-necked flask equipped with a rubber septum and argon inlet adapter was charged with a solution of ketene **76** (0.112 g, 0.409 mmol) in 0.4 mL of CH_2Cl_2. A solution of (trimethylsilyl)diazomethane (2.0 M in hexanes, 0.23 mL, 0.45 mmol) was added dropwise by syringe over 3 min. The reaction mixture was stirred at room temperature for 12.5 h and then concentrated to give a yellow oil. This material was dissolved in 10 mL of CH_2Cl_2, 0.6 g of silica gel was added, and the resulting mixture was stirred at 25 °C for 1 h and then concentrated. The resulting silica gel was deposited onto a column of 6 g of silica gel and eluted with 0-1% *t*-BuOMe-hexanes to provide 0.101 g (86%) of indanone **84** as an off-white solid: mp 81-82 °C; IR (CH_2Cl_2) 3054, 2987, 1726, 1422 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.26 (m, 1 H), 7.16-7.20 (m, 3 H), 3.76 (s, 1 H), 3.69 (d, J = 22.6 Hz, 1 H), 3.50 (d, J = 22.6 Hz, 1 H), 1.34 (sept, J = 7.4 Hz, 3 H), 1.10 (d, J = 7.6 Hz, 9 H), 1.00 (d, J = 7.6 Hz, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.0, 142.2, 136.7, 127.3, 125.9, 124.9, 123.9, 46.8, 45.3, 18.8, 18.6, 11.4; LRMS (EI): *m/z* 288 (M^+); Anal. Calcd for $C_{18}H_{28}OSi$: C, 74.94; H, 9.78. Found: C, 74.96; H, 9.87.



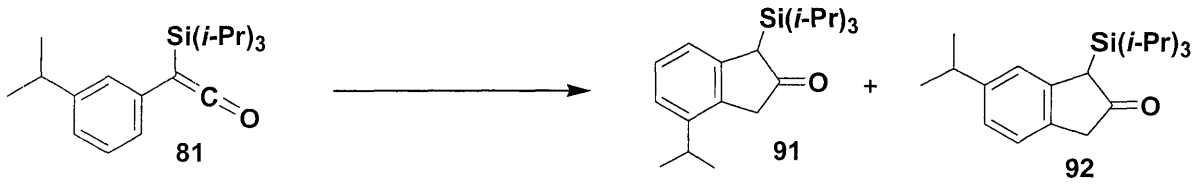
84



77 86

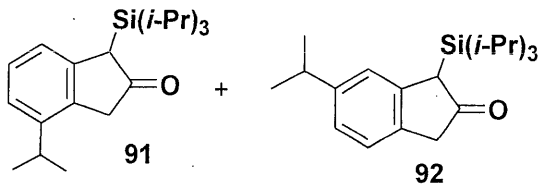
Indan-2-one (86).

Reaction of ketene **77** (0.257 g, 1.11 mmol) and (trimethylsilyl)diazomethane (2.0 M in hexanes, 0.60 mL, 1.2 mmol) in 1.1 mL of CH_2Cl_2 at 25 °C for 13 h according to the general procedure provided an orange oil, which was diluted with 4.4 mL of THF and 4.4 mL of 1N aq HCl solution and then stirred at room temperature for 4 h. The resulting mixture was diluted with 20 mL of Et_2O and washed with 20 mL of saturated NaCl solution. The aqueous layer was extracted with 20 mL of Et_2O, and the combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.312 g of a brown oil. This material was deposited onto 0.6 g of silica gel and purified by column chromatography on 6 g of silica gel (elution with 10% EtOAc-hexanes) to provide 0.101 g (69%) of 2-indanone (**86**) as a white solid with spectral characteristics consistent with those reported previously:[37a] mp 53-54 °C (lit.[37b] mp 56-57 °C); IR (CH_2Cl_2) 1752, 1483, 1392, 1306, 1184, 1143, 951; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.29-7.33 (m, 2 H), 7.24-7.29 (m, 2 H), 3.54 (s, 4 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 215.2, 138.6, 127.7, 125.4, 44.6; LRMS (EI): *m/z* 132 (M^+).



4-Isopropyl-1-(triisopropylsilyl)indan-2-one (91) and 6-isopropyl-1-(triisopropylsilyl)indan-2-one (92).

Reaction of ketene **81** (0.404 g, 1.28 mmol) and (trimethylsilyl)diazomethane (2.0 M in hexanes, 0.70 mL, 1.4 mmol) in 1.28 mL of CH_2Cl_2 at 25 °C for 12 h according to the general procedure provided 0.574 g of a yellow-orange oil to which was added 5 mL of THF and 5 mL of 1N aq HCl solution. The resulting mixture was stirred at room temperature for 3.5 h, diluted with 25 mL of Et_2O, and washed with 25 mL of saturated NaCl solution. The aqueous layer was extracted with 25 mL of Et_2O, and the combined organic phases were then washed with 25 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.441 g of a brown oil. Column chromatography on 20 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) provided 0.384 g (91%) of indanones **91** and **92** (46:54 mixture by ^1H NMR analysis) as a pale yellow oil. Samples of **91** and **92** were obtained by preparative HPLC (95:5 hexanes-EtOAc) as pale yellow oils: IR (film) 2961, 2867, 1727, 1649, 1590, 1563, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for **91**: δ 7.20 (t, J = 7.7 Hz, 1 H), 7.09 (d, J = 7.7 Hz, 1 H), 7.01 (d, J = 7.6 Hz, 1 H), 3.80 (s, 1 H), 3.63 (d, J = 22.7 Hz, 1 H), 3.49 (d, J = 22.6 Hz, 1 H), 2.88 (sept, J = 6.9 Hz, 1 H), 1.34 (sept, J = 7.5 Hz, 3 H), 1.26 (d, J = 6.9 Hz, 3 H), 1.22 (d, J = 6.9 Hz, 3 H), 1.10 (d, J = 7.5 Hz, 9 H), 1.00 (d, J = 7.5 Hz, 9 H); For **92**: δ 7.18 (d, J = 7.5 Hz, 1 H), 7.05 (s, 1 H), 7.04 (d, J = 7.8 Hz, 1 H), 3.75 (s, 1 H), 3.66 (d, J = 22.7 Hz, 1 H), 3.47 (d, J = 22.6 Hz, 1 H), 2.88 (sept, J = 6.9 Hz, 1 H), 1.34 (sept, J = 7.5 Hz, 3 H), 1.26 (d, J = 6.9 Hz, 3 H), 1.24 (d, J = 6.9 Hz, 3 H), 1.11 (d, J = 7.5 Hz, 9 H), 1.01 (d, J = 7.5 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) for **91**: δ 217.3, 145.0, 142.0, 134.5, 127.7, 122.2, 121.2, 47.3, 43.9, 31.5, 23.3, 22.7, 18.8, 17.9, 11.4; For **92**: δ 217.6, 148.1, 142.1, 134.1, 124.7, 124.2, 121.9, 46.8, 45.1, 34.4, 24.5, 24.2, 18.8, 18.6, 11.5; Anal. Calcd for $C_{21}H_{34}OSi$: C, 76.30; H, 10.37. Found: C, 76.22; H, 10.25.


Si(i-Pr)3
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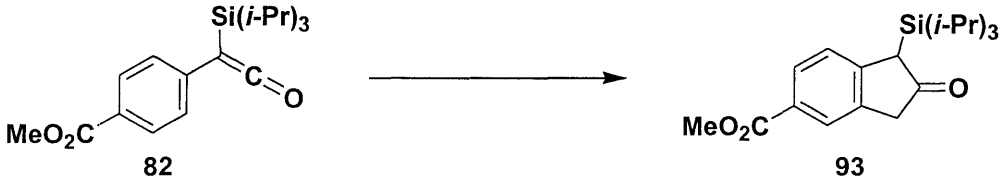
91

+

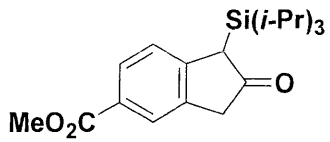
Si(i-Pr)3
O
92

9
8
7
6
5
4
3
2
1
0
ppm

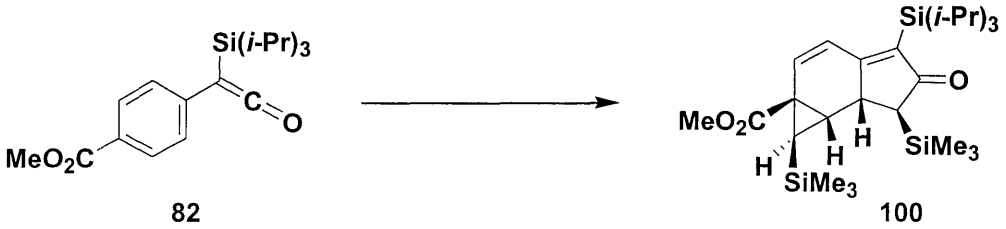


5-Carbomethoxy-1-(triisopropylsilyl)indan-2-one (93).

A 10-mL, two-necked flask equipped with a rubber septum and argon inlet adapter was charged with a solution of ketene **82** (0.161 g, 0.484 mmol) in 2.0 mL of CH_2Cl_2 and *i*-Pr_2EtN (0.042 mL, 0.031 g, 0.242 mmol) was added in one portion followed by a solution of (trimethylsilyl)diazomethane (2.0 M in hexanes, 0.266 mL, 0.53 mmol) added dropwise by syringe over 3 min. The reaction mixture was stirred at room temperature for 13.5 h and then concentrated to give 0.235 g of an orange-brown oil. This material was immediately dissolved in CH_2Cl_2, deposited onto 0.5 g of silica gel, and purified by column chromatography on 20 g of silica gel (elution with 10% *t*-BuOMe-hexanes) to provide 0.105 g (36% yield over 2 steps from **75**) of indanone **93** as a pale yellow solid: mp 120-121 °C; IR (CH_2Cl_2) 3054, 2987, 1717, 1422, 1267 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1 H), 7.92 (d, J = 8.1 Hz, 1 H), 7.24 (d, J = 8.1 Hz, 1 H), 3.92 (s, 3 H), 3.84 (s, 1 H), 3.74 (d, J = 22.7 Hz, 1 H), 3.55 (d, J = 22.8 Hz, 1 H), 1.34 (sept, J = 7.6 Hz, 3 H), 1.11 (d, J = 7.5 Hz, 9 H), 1.00 (d, J = 7.5 Hz, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.7, 167.3, 148.2, 137.0, 128.9, 127.9, 126.0, 123.7, 52.3, 47.6, 45.1, 18.8, 18.6, 11.4; LRMS (EI): *m/z* 346 (M^+); Anal. Calcd for $C_{20}H_{30}O_3Si$: C, 69.32; H, 8.73. Found: C, 69.19; H, 8.59.



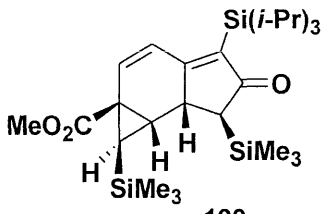
93



82 100

Tricyclic enone (100).

A 10-mL, two-necked flask equipped with a rubber septum and argon inlet adapter was charged with a solution of ketene **82** (0.119 g, 0.358 mmol) in 0.70 mL of CH_2Cl_2 and a solution of (trimethylsilyl)diazomethane (2.0 M in hexanes, 0.376 mL, 0.75 mmol) was then added in one portion. The reaction mixture was stirred at room temperature for 14 h and then concentrated to give 0.187 g of an orange oil. Column chromatography on 19 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) provided 0.101 g of a colorless oil. This material was further purified by preparative HPLC (95:5 hexanes-EtOAc) to afford 0.084 g (27% yield over 2 steps from **75**) of tricyclic enone **100** as a colorless oil which solidified on standing at room temperature: mp 76-78°C; IR (film) 2950, 1730, 1674, 1249 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, J = 10.1 Hz, 1 H), 6.48 (d, J = 10.1 Hz, 1 H), 3.74 (s, 3 H), 3.12 (t, J = 4.1 Hz, 1 H), 2.36 (dd, J = 8.9, 4.3 Hz, 1 H), 1.82 (d, J = 4.3 Hz, 1 H), 1.49 (sept, J = 7.6 Hz, 3 H), 1.03 (d, J = 7.5 Hz, 9 H), 1.01 (d, J = 7.5 Hz, 9 H), 0.27 (d, J = 8.9 Hz, 1 H), 0.17 (s, 9 H), 0.03 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.6, 174.5, 172.7, 138.2, 137.0, 121.2, 52.2, 46.0, 42.5, 32.7, 31.8, 31.3, 19.0, 18.9, 11.7, -0.8, -2.2; HRMS (ESI) Calcd for $C_{27}H_{49}O_3Si_3$ $(M+H)^+$: 505.2984. Found: 505.2972; Anal. Calcd for $C_{27}H_{48}O_3Si_3$: C, 64.23; H, 9.58. Found: C, 64.15; H, 9.47.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MeO2C
H
H
H
SiMe3
SiMe3

100

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8
7
6
5
4
3
2
1
0
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0.86
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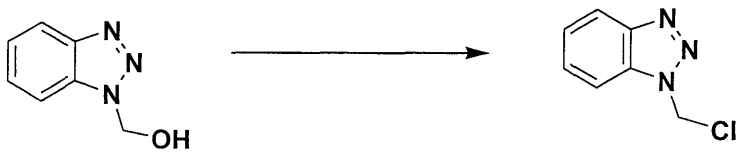
0.91
8.66
18.41

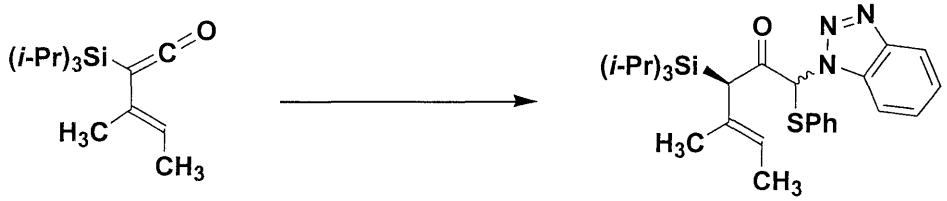


158 159

1-(Chloromethyl)benzotriazole (159).

A 250-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with benzotriazole **158**[134] (6.768 g, 45.38 mmol) and 115 mL of toluene, then thionyl chloride (9.93 mL, 16.2 g, 136 mmol) was carefully added. The rubber septum was replaced with a reflux condenser (vented to a water trap) and the heterogeneous reaction mixture was heated at reflux for 2 h. The resulting solution was allowed to cool to rt, the reflux condenser was replaced with a short path distillation head, and approximately 30 mL of excess thionyl chloride (and toluene) was distilled away from the reaction flask (bp 108 °C). The solution remaining in the reaction flask was allowed to cool to rt and the remaining toluene was removed by rotary evaporation to afford 7.56 g (99%) of benzotriazole **159** as a white solid in ≥96% purity based on ^{1}H NMR analysis.[82,83]

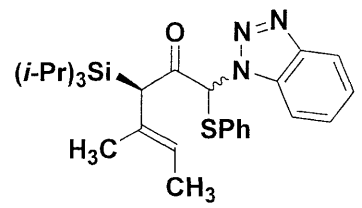
[134] Benzotriazoles **158** and **159** are commercially available from Aldrich.



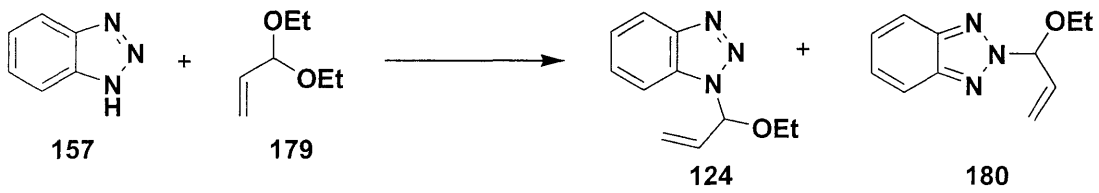
1 166

1-(Benzotriazol-1-yl)-4-methyl-1-phenylthio-3-triisopropylsilyl-hex-4-en-2-one (166).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of 1-(phenylthiomethyl)benzotriazole (0.082 g, 0.340 mmol) in 3.4 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.35 M in hexanes, 0.145 mL, 0.340 mmol) was added dropwise over 1 min. The resulting mixture was stirred at -78 °C for 1 h and then a solution of silylketene **1** (0.082 g, 0.324 mmol) in 1.1 mL of THF was added dropwise via cannula over 1 min. The reaction mixture was stirred for 1 h at -78 °C and then quenched by the addition of 1 mL of saturated aq NH_4Cl. The resulting mixture was diluted with 15 mL of Et_2O and 5 mL of saturated NaCl solution, and the organic phase was separated, dried over $MgSO_4$, filtered, and concentrated to afford 0.176 g of a pale yellow oil. Column chromatography on 12 g of silica gel (elution with 10% EtOAc-hexanes) provided 0.153 g (96%) of ketone **166** (57:43 mixture of diastereomers by ^1H NMR analysis) as a pale yellow oil: IR (film) 2946, 2868, 1709, 1614, 1584, 1451 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): for major: δ 7.76 (dt, J = 8.5, 0.9 Hz, 1 H), 4.99 (qd, J = 6.7, 1.2 Hz, 1 H), 3.52 (s, 1 H), 1.33 (t, J = 1.0 Hz, 3 H), 1.12 (d, J = 7.3 Hz, 9 H), 1.09 (d, J = 7.3 Hz, 9 H); for minor: δ 7.84 (dt, J = 8.3, 0.9 Hz, 1 H), 7.00 (s, 1 H), 5.56 (qd, J = 6.7, 1.3 Hz, 1 H), 3.81 (s, 1 H), 1.87 (t, J = 1.1 Hz, 3 H), 1.68 (dd, J = 6.8, 1.0 Hz, 3 H), 1.03 (d, J = 7.4 Hz); for major and minor: δ 8.00-8.03 (m, 2 H), 7.46-7.51 (m, 2 H), 7.37 (t, J = 7.7, 2 H), 7.20-7.24 (m, 2 H), 7.13-7.17 (m, 4 H), 7.07-7.10 (m, 5 H), 1.19-1.27 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): for major and minor: δ 199.0, 198.1, 146.91, 146.87, 133.4, 133.1, 132.5, 132.1, 131.3, 131.1, 130.0, 129.6, 129.5, 129.4, 129.3, 129.1, 127.63, 127.59, 124.4, 124.3, 123.43, 123.36, 120.1, 120.0, 113.4, 112.8, 75.6, 74.9, 50.3, 50.0, 19.11, 19.07, 19.01, 18.96, 18.9, 18.1, 14.1, 13.6, 12.24, 12.15. HRMS (ESI) Calcd for $C_{28}H_{39}N_3OSSi$ $(M+Na)^+$: 516.2475. Found: 516.2487.



166

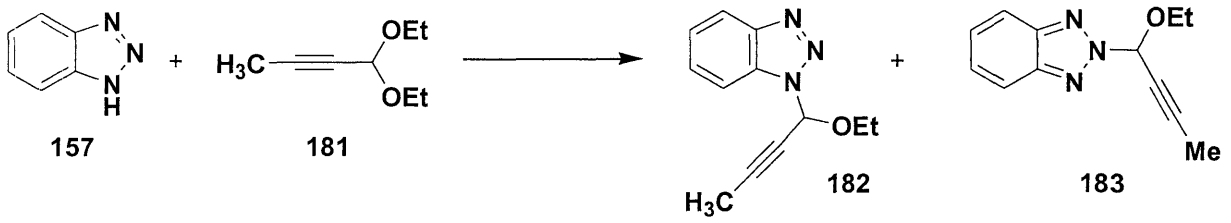


157 179 124 180

3-(Benzotriazol-1-yl)-3-ethoxy-1-propene (124).[135]

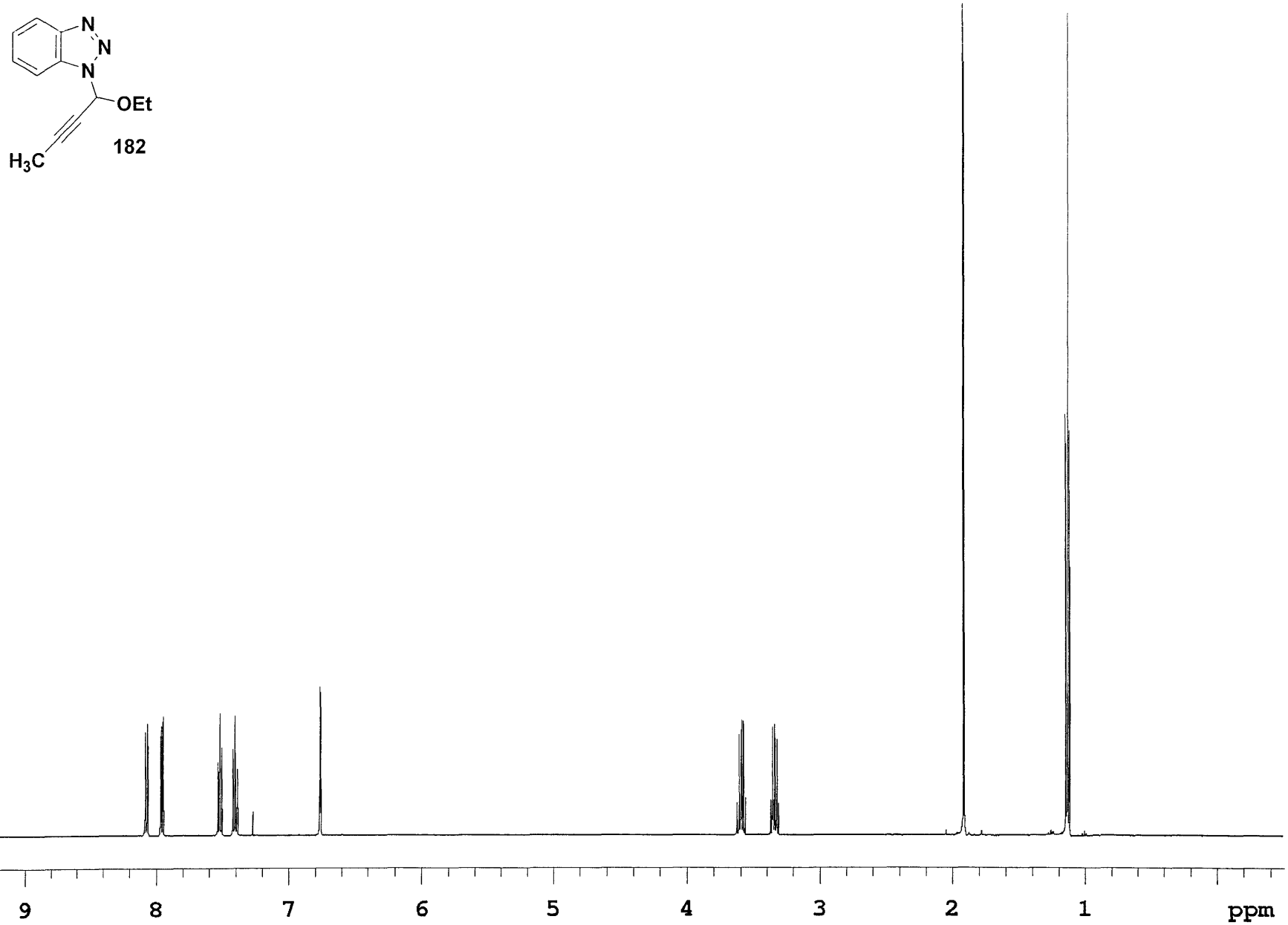
A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with benzotriazole (0.415 g, 3.48 mmol), 3 mL of toluene, and then 3,3-diethoxy-1-propene (0.35 mL, 0.30 g, 2.3 mmol). The rubber septum was replaced with a reflux condenser and the heterogeneous reaction mixture was heated at reflux for 24 h. The resulting homogeneous pale yellow mixture was allowed to cool to rt and then diluted with 30 mL of Et_2O and washed with two 15-mL portions of saturated aq Na_2CO_3, 15 mL of H_2O, dried over Na_2SO_4, filtered, and concentrated to afford 0.442 g of a yellow oil. This material was dissolved in CH_2Cl_2 and concentrated onto 1 g of silica gel which was transferred to the top of a column of 15 g of silica gel. Elution with 1% Et_3N-10% EtOAc-hexanes provided 0.280 g (59%) of benzotriazole **124** as a pale yellow oil, 0.024 g (5%) of 3-(Benzotriazol-2-yl)-3-ethoxy-1-propene (**180**) as a pale yellow oil, and 0.105 g (22%) of a mixture of **124** and **180** (88:12 by ^1H NMR analysis) as a pale yellow oil. Spectral characteristics for **124** are consistent with those previously reported. [136]

[135] This procedure is a modification of a procedure in which **124** is prepared by the reaction of benzotriazole with 3,3-diethoxy-1-propene in refluxing hexanes, see reference 97.
[136] A. R. Katritzky, G. Zhang, J. Jiang, *J. Org. Chem.* **1995**, *60*, 7589.



4-(Benzotriazol-1-yl)-4-ethoxy-2-butyne (182).

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with benzotriazole (1.114 g, 9.351 mmol), 5 mL of toluene, and then 1,1-diethoxy-2-butyne (0.99 mL, 0.89 g, 6.3 mmol). The rubber septum was replaced with a reflux condenser and the heterogeneous reaction mixture was heated at reflux for 14 h. The resulting homogeneous orange mixture was allowed to cool to rt and then diluted with 30 mL of Et_2O and washed with two 15-mL portions of saturated aq Na_2CO_3, 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.512 g of an orange oil. This material was dissolved in CH_2Cl_2 and concentrated onto 3 g of silica gel which was transferred to the top of a column of 53 g of silica gel. Elution with 1% Et_3N-10% EtOAc-hexanes provided 1.065 g (79%) of benzotriazole **182** as a pale yellow oil, 0.051 g (4%) of 4-(Benzotriazol-2-yl)-4-ethoxy-2-butyne (**183**) as a colorless oil, and 0.094g (7%) of a mixture of **182** and **183** (91:9 by ^1H NMR analysis) as a pale yellow oil. For **182**: IR (film) 2979, 2922, 2251, 1614, 1493, 1450, 1334, 1277 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 1 H), 7.96 (d, J = 8.4 Hz, 1 H), 7.52 (app t, J = 7.7 Hz, 1 H), 7.40 (app t, J = 7.7 Hz, 1 H), 6.76 (q, J = 2.1 Hz, 1 H), 3.56-3.63 (m, 1 H), 3.30-3.38 (m, 1 H), 1.92 (d, J = 2.1 Hz, 3 H), 1.14 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 131.3, 127.9, 124.6, 120.1, 111.8, 85.7, 78.9, 72.5, 64.5, 14.8, 3.8. HRMS (ESI) Calcd for $C_{12}H_{13}N_3O$ $(M+H)^+$: 216.1131. Found: 216.1141. For **183**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.91-7.95 (m, 2 H), 7.40-7.44 (m, 2 H), 6.68 (q, J = 2.0 Hz, 1 H), 3.56-3.68 (m, 2 H), 1.98 (d, J = 2.1 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 3 H).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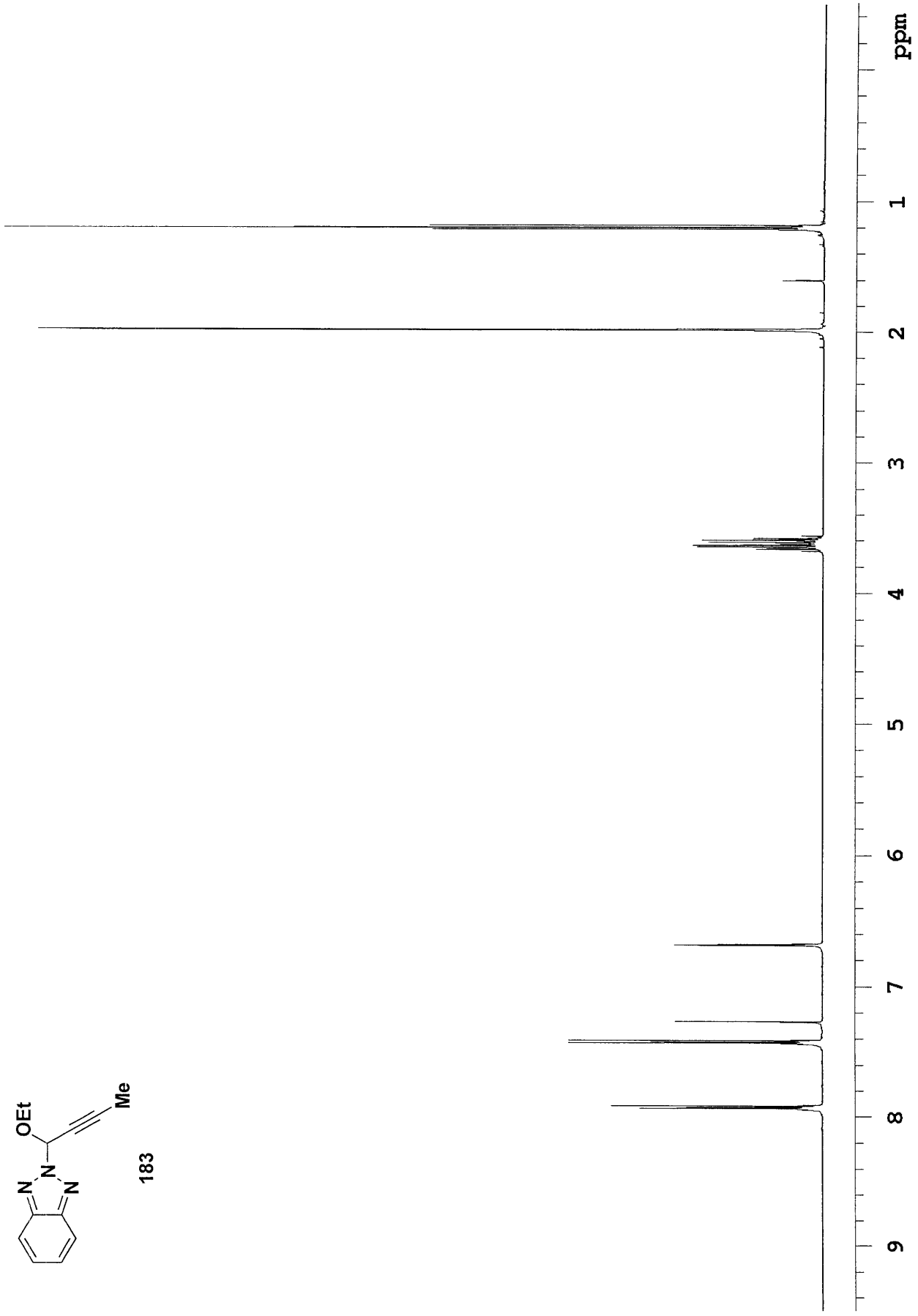
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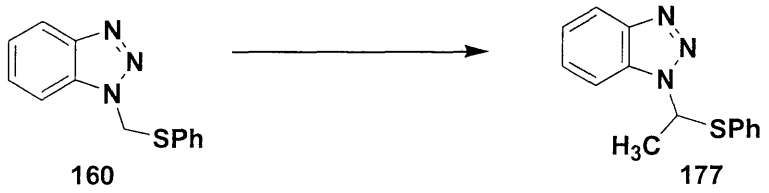
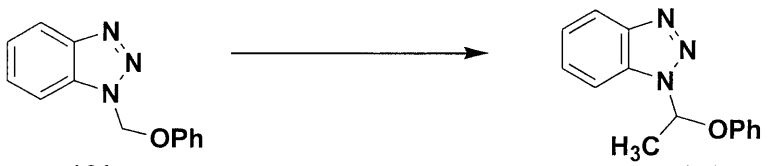


1-(Benzotriazol-1-yl)ethyl phenyl sulfide (177).[95]

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of 1-(phenylthiomethyl)benzotriazole (**160**) (0.302 g, 1.25 mmol) in 5 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.50 M in hexanes, 0.60 mL, 1.5 mmol) was added dropwise over 2 min. The resulting orange-brown mixture was stirred at -78 °C for 1 h and then a solution of MeI (0.09 mL, 0.21 g, 1.5 mmol) in 1.3 mL of THF was added dropwise via cannula over 1 min. The resulting yellow-brown mixture was allowed to slowly warm to rt over 20 h. The reaction mixture was then concentrated to afford a yellow-orange oil which was dissolved in 50 mL of CH_2Cl_2 and washed with 10 mL of water. The aqueous phase was separated and extracted with 10 mL of CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 0.358 g of a yellow oil. This material was dissolved in CH_2Cl_2 and concentrated onto 0.8 g of silica gel which was transferred to the top of a column of 36 g of silica gel. Gradient elution with 33% Et_2O-hexanes provided 0.204 g (64%) of benzotriazole **177** as a pale yellow oil with spectral characteristics consistent with those reported previously.[84]



161 178

1-(Benzotriazol-1-yl)ethyl phenyl ether (178).[137]

A 100-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of 1-(phenoxymethyl)benzotriazole (**161**)[138] (1.075 g, 4.772 mmol) in 48 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.45 M in hexane, 2.14 mL, 5.24 mmol) was added dropwise over 2 min. The resulting deep green solution was stirred at -78 °C for 30 min and then a solution of MeI (0.33 mL, 0.75 g, 5.3 mmol) in 5 mL of THF was added dropwise via cannula over 3 min. The resulting dark brown solution was allowed to slowly warm to rt over 15 h. The reaction mixture was then diluted with 50 mL of water and the aqueous phase was separated and extracted with three 50-mL portions of ether. The combined organic layers were washed with 50 mL of half-saturated aq $Na_2S_2O_3$ solution and 50 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 1.174 g of a brown oil. This material was dissolved in CH_2Cl_2 and concentrated onto 2.4 g of silica gel which was transferred to the top of a column of 120 g of silica gel. Gradient elution with 20-30% EtOAc-hexanes provided 0.981 g (86%) of benzotriazole **178** as an off-white solid:[139] mp 66-68 °C (lit.[139] mp 60-62 °C); IR (film) 3064, 2996, 1590, 1492 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.02 (app dt, J = 8.4, 0.9 Hz, 1 H), 7.81 (app dt, J = 8.4, 0.9 Hz, 1 H), 7.44-7.48 (m, 1 H), 7.33-7.37 (m, 1 H), 7.16-7.20 (m, 2 H), 7.05 (q, J = 6.2 Hz, 1 H), 6.92-6.98 (m, 3 H), 2.07 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 146.7, 131.0, 129.7, 127.7, 124.3, 122.9, 120.2, 116.2, 111.1, 84.6, 21.3. Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.53; H, 5.47; N, 17.45.

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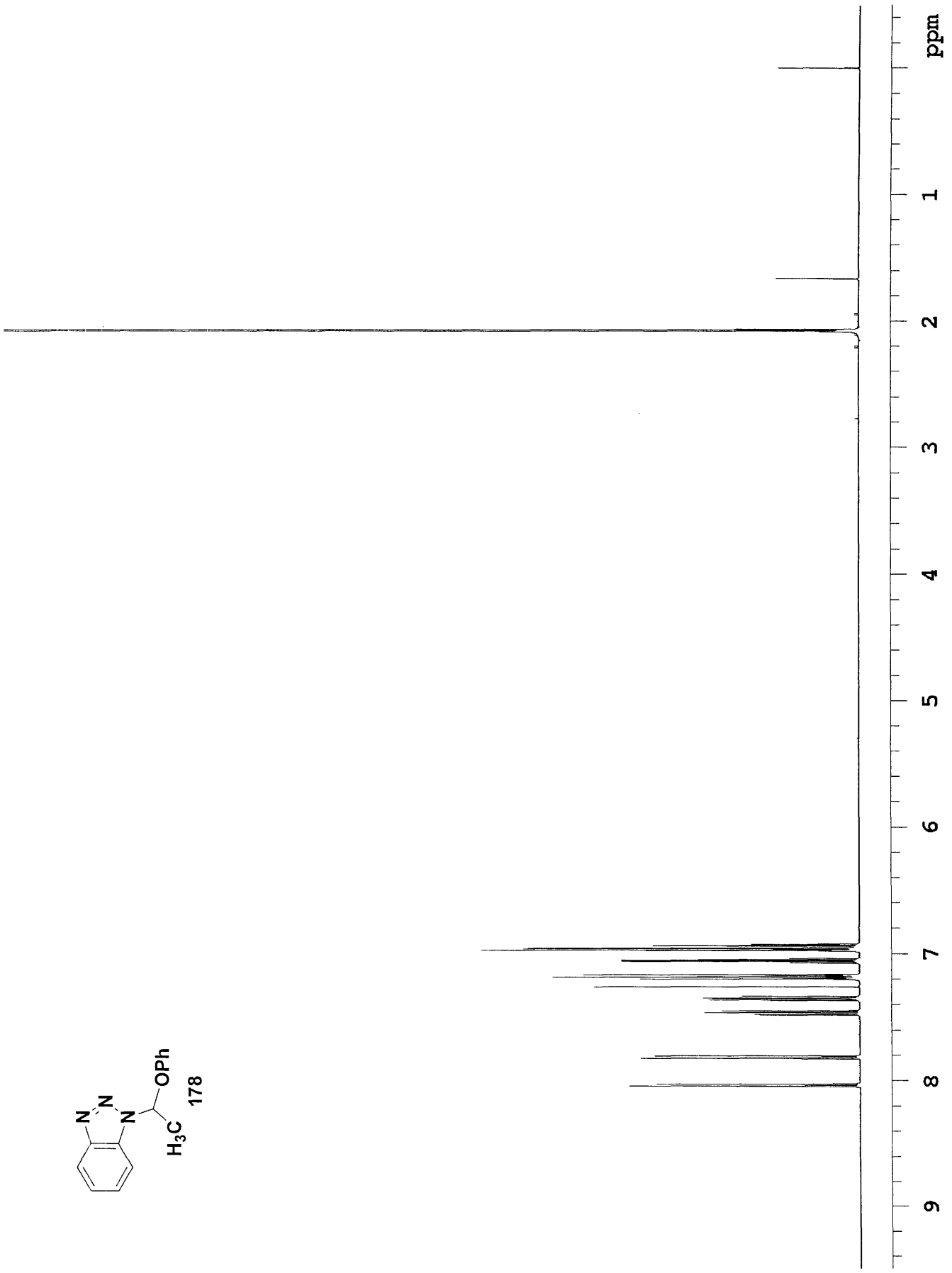
[137] This procedure is a modification of a procedure in which **178** is prepared and used in a subsequent step without purification, see reference 87.

[138] Prepared according to the procedure reported in reference 87.

[139] For previously reported melting point and spectral data, see: A. R. Katritzky, D. Feng, M. Qi, *J. Org. Chem.* **1998**, *63*, 1473.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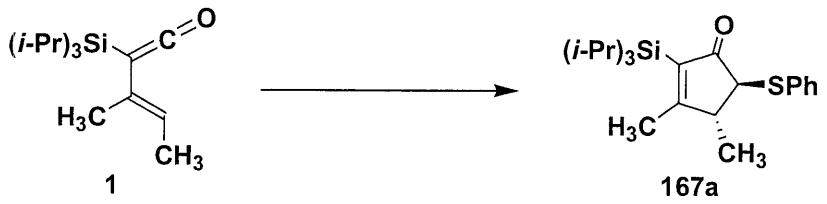
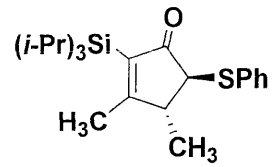
N
OPh
H3C
178

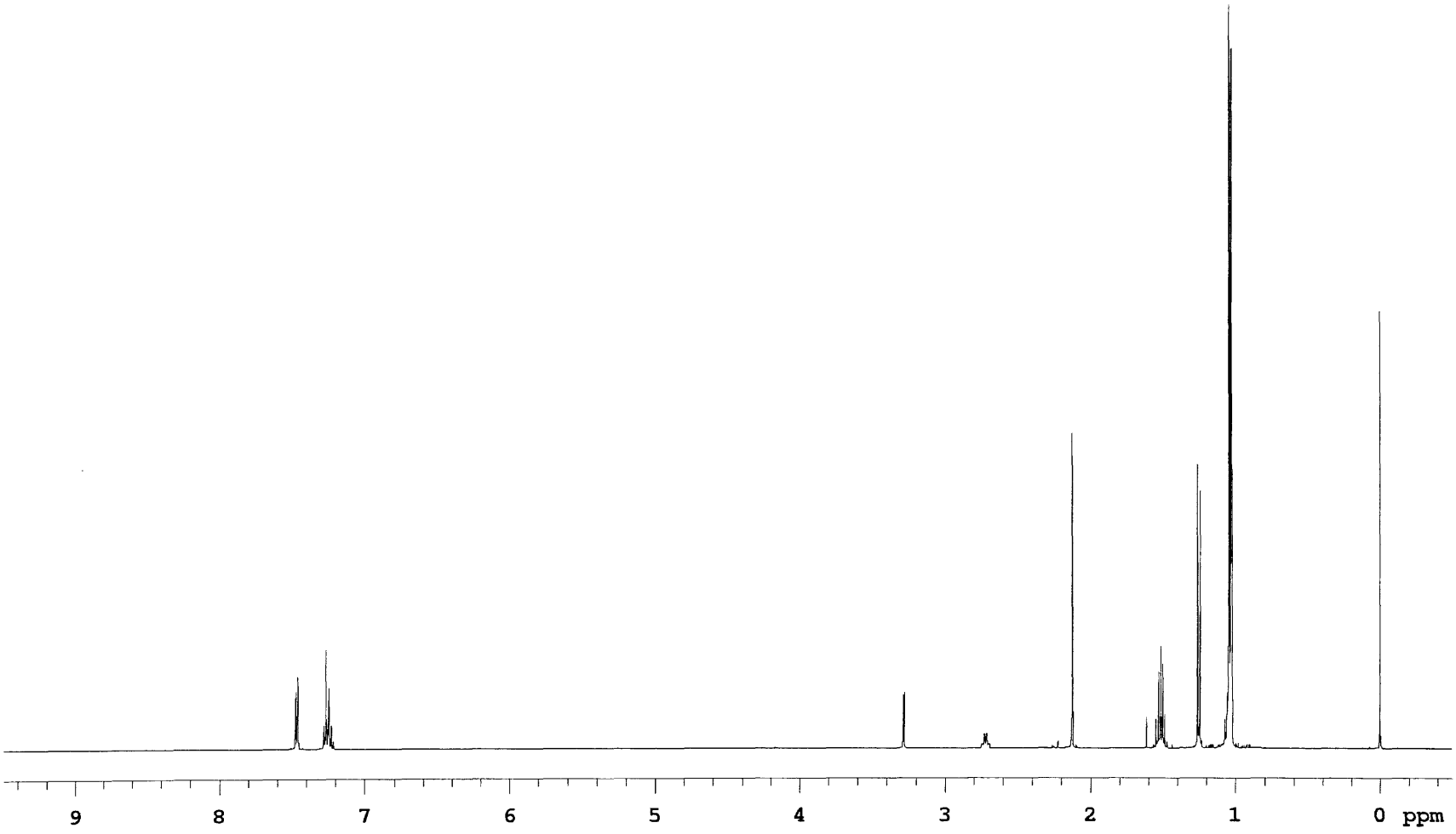


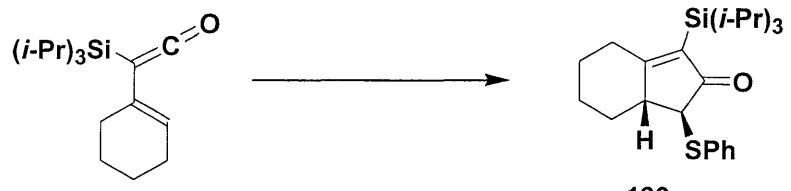
***trans*-3,4-Dimethyl-5-phenylthio-2-(triisopropylsilyl)cyclopent-2-enone (167a).**

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of 1-(phenylthiomethyl)benzotriazole (**160**) (0.086 g, 0.356 mmol) in 3.6 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.39 M in hexane, 0.149 mL, 0.356 mmol) was added dropwise over 1 min. The resulting orange-brown mixture was stirred at -78 °C for 1 h and then a solution of silylketene **1** (0.087 g, 0.345 mmol) in 1.1 mL of THF was added dropwise via cannula over 1 min. After 1 h, a solution of $ZnBr_2$ (1.00 M in THF, 1.02 mL, 1.02 mmol) was added dropwise over 2 min and the resulting bright yellow mixture was allowed to slowly warm to rt over 18.5 h. The reaction mixture was then filtered through Celite with the aid of 30 mL of Et_2O and the filtrate was washed with 15 mL of 1 N aq HCl solution. The aqueous phase was extracted with 10 mL of Et_2O, and the combined organic phases were washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.199 g of a yellow oil. This material was dissolved in CH_2Cl_2 and concentrated onto 0.5 g of silica gel which was transferred to the top of a column of 20 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.089 g (69%) of cyclopentenone **167a** (98:2 mixture of *trans*:*cis* isomers by ^1H NMR and GC analysis) as a colorless oil which partially solidified on standing: IR (film) 2944, 2865, 1696, 1574, 1463, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): for *trans* isomer: δ 7.44-7.48 (m, 2 H), 7.20-7.28 (m, 3 H), 3.28 (d, J = 3.1 Hz, 1 H), 2.72 (qd, J = 7.1, 3.1 Hz, 1 H), 2.12 (s, 3 H), 1.52 (sept, J = 7.6 Hz, 3 H), 1.25 (d, J = 7.3 Hz, 3 H), 1.04 (app dd, J = 7.8, 2.5 Hz, 18 H); for *cis* isomer (partial): δ 4.16 (d, J = 6.8 Hz, 1 H), 3.09 (app quint, J = 7.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.2, 188.8, 134.8, 134.2, 132.4, 129.0, 127.5, 57.7, 49.4, 19.1, 18.95, 18.93, 18.8, 11.8. Anal. Calcd for $C_{22}H_{34}OSSi$: C, 70.53; H, 9.15. Found: C, 70.37; H, 9.10.



167a

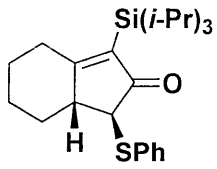




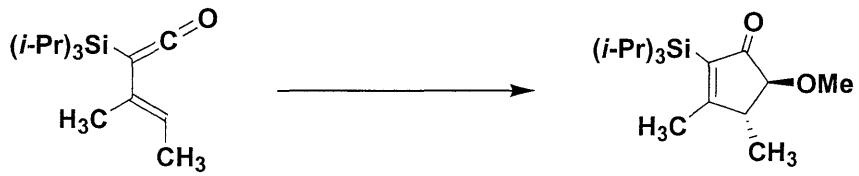
3 193a

***trans*-7-Phenylthio-9-(triisopropylsilyl)bicyclo[4.3.0]non-1(9)-en-8-one (193a).**

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of 1-(phenylthiomethyl)benzotriazole (**160**) (0.098 g, 0.406 mmol) in 4.1 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.34 M in hexane, 0.174 mL, 0.406 mmol) was added dropwise over 1 min. The resulting orange-brown mixture was stirred at -78 °C for 1 h and then a solution of silylketene **3** (0.109 g, 0.391 mmol) in 1.3 mL of THF was added dropwise via cannula over 1 min. After 1 h, a solution of $ZnBr_2$ (1.00 M in THF, 1.16 mL, 1.16 mmol) was added dropwise over 2 min and the resulting bright yellow mixture was allowed to slowly warm to rt over 20 h. The reaction mixture was diluted with 30 mL of Et_2O and washed with 15 mL of 1 N aq HCl solution. The aqueous phase was extracted with 10 mL of Et_2O, and the combined organic phases were washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.193 g of a yellow oil. This material was dissolved in CH_2Cl_2 and concentrated onto 0.4 g of silica gel which was transferred to the top of a column of 19 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.080 g (51%) of cyclopentenone **193a** (≥98:2 mixture of *trans*:*cis* isomers by ^1H NMR analysis) as a colorless oil: IR (film) 2941, 2864, 1696, 1573, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): for *trans* isomer: δ 7.44-7.49 (m, 2 H), 7.20-7.28 (m, 3 H), 3.27 (d, J = 3.3 Hz, 1 H), 2.98 (d, J = 13.8 Hz, 1 H), 2.60 (ddd, J = 12.3, 5.4, 3.3 Hz, 1 H), 2.21-2.28 (m, 1 H), 2.18 (td, J = 13.4, 5.4 Hz, 1 H), 1.96-2.03 (m, 1 H), 1.83 (d, J = 13.2 Hz, 1 H), 1.50 (sept, J = 7.5 Hz, 3 H), 1.08-1.47 (m, 3 H), 1.03 (app t, J = 7.6 Hz, 18 H); for *cis* isomer (partial): δ 4.07 (d, J = 7.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.2, 190.7, 134.4, 132.24, 132.18, 129.0, 127.5, 56.3, 51.9, 34.8, 32.7, 27.5, 25.4, 18.98, 18.96, 11.8. HRMS (ESI) Calcd for $C_{24}H_{36}OSSi$ $(M+Na)^+$: 423.2148. Found: 423.2145.



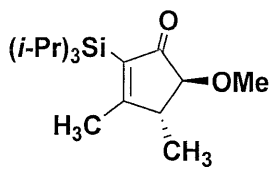
193a



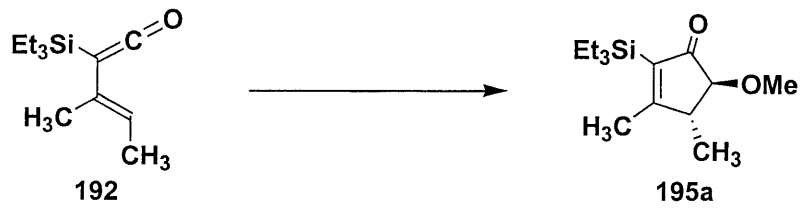
1 194a

***trans*-5-Methoxy-3,4-dimethyl-2-(triisopropylsilyl)cyclopent-2-enone (194a).**

A 50-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum and argon inlet adapter was charged with a solution of 1-(methoxymethyl)benzotriazole (**161**) (0.330 g, 2.02 mmol) in 10 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.31 M in hexane, 0.86 mL, 2.0 mmol) was added dropwise over 2 min. The resulting emerald green mixture was stirred at -78 °C for 1 h and then a solution of silylketene **1** (0.477 g, 1.89 mmol) in 3.5 mL of THF was added dropwise via cannula over 4 min. After 1h, a solution of $ZnBr_2$ (1.0 M in THF, 5.7 mL, 5.7 mmol) was added dropwise over 9 min and the resulting yellow-brown solution was allowed to slowly warm to rt over 15 h, during which time a white precipitate formed. The reaction mixture was diluted with 50 mL of Et_2O and filtered though a fritted glass funnel containing Celite. The filtrate was washed with 30 mL of 1 N aq HCl solution, and the aqueous phase was backextracted with 15 mL of Et_2O. The combined organic layers were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.660 g of an orange-yellow oil. This material was dissolved in CH_2Cl_2 and concentrated onto 1.3 g of silica gel which was transferred to the top of a column of 65 g of silica gel. Gradient elution with 0-8% EtOAc-hexanes provided 0.459 g (82%) of cyclopentenone **194a** (≥99:1 mixture of *trans*:*cis* isomers by ^1H NMR analysis) as a colorless oil which solidified upon standing: mp 47-49 °C; IR (film) 2944, 2866, 1699, 1574, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): for *trans* isomer: δ 3.59 (s, 3 H), 3.41 (d, J = 3.4 Hz, 1 H), 2.68 (qdd, J = 7.2, 3.5, 0.9 Hz, 1 H), 2.15 (d, J = 0.8 Hz, 3 H), 1.51 (sept, J = 7.5 Hz, 3 H), 1.30 (d, J = 7.3 Hz, 3 H), 1.04 (app dd, J = 7.5, 1.8 Hz, 18 H); for *cis* isomer (partial): δ 3.88 (d, J = 6.7 Hz, 1 H), 2.89 (app quint, J = 6.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.2, 186.6, 134.2, 87.8, 58.6, 47.0, 19.04, 18.96, 18.89, 17.5, 11.8. HRMS (ESI) Calcd for $C_{17}H_{32}O_2Si$ $(M+H)^+$: 297.2244. Found: 297.2239.

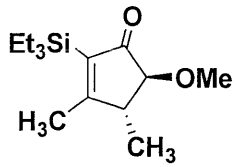


194a

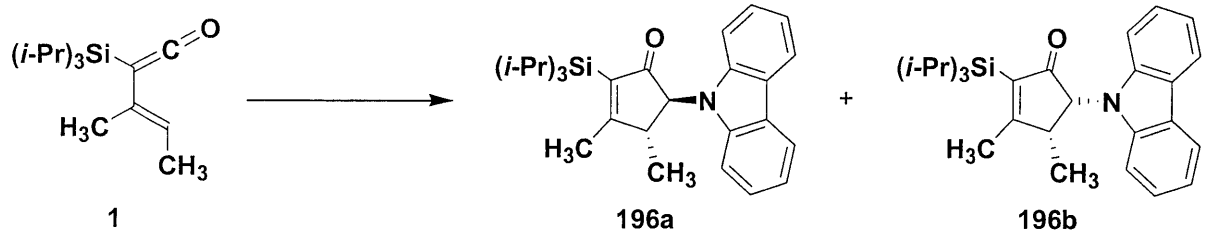


***trans*-5-Methoxy-3,4-dimethyl-2-(triethylsilyl)cyclopent-2-enone (195a).**

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with a solution of 1-(methoxymethyl)benzotriazole (**161**) (0.329 g, 2.02 mmol) in 20 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.42 M in hexane, 0.82 mL, 2.0 mmol) was added dropwise over 2 min. The resulting emerald green solution was stirred at -78 °C for 1 h and then a solution of silylketene **192** (0.399 g, 1.90 mmol) in 6.3 mL of THF was added dropwise via cannula over 5 min. After 1 h, a solution of $ZnBr_2$ (1.0 M in THF, 5.7 mL, 5.7 mmol) was added dropwise over 4 min and the resulting yellow-orange solution was allowed to slowly warm to rt over 19 h, during which time a white precipitate formed. The reaction mixture was then diluted with 50 mL of Et_2O and filtered though a fritted glass funnel containing Celite. The filtrate was washed with 30 mL of 1 N aq HCl solution, and the aqueous phase was backextracted with 15 mL of Et_2O. The combined organic layers were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.588 g of a yellow-orange oil. This material was dissolved in CH_2Cl_2 and concentrated onto 1.2 g of silica gel which was transferred to the top of a column of 60 g of silica gel. Gradient elution with 0-8% EtOAc-hexanes provided 0.336 g (70%) of cyclopentenone **195a** (≥99:1 *trans*:*cis* by ^{1}H NMR analysis) as a pale yellow oil. For the *trans* isomer **195a**: IR (film) 2955, 2875, 2826, 1698, 1582, 1457, 1376 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.60 (s, 3 H), 3.40 (d, J = 3.3 Hz, 1 H), 2.64-2.70 (m, 1 H), 2.11 (d, J = 1.0 Hz, 3 H), 1.29 (d, J = 7.3 Hz, 3 H), 0.91 (app t, J = 7.9 Hz, 9 H), 0.75-0.80 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.1, 186.3, 135.5, 87.8, 58.7, 46.9, 18.3, 17.3, 7.6, 3.6. HRMS (ESI) Calcd for $C_{14}H_{26}O_2Si$ $(M+Na)^+$: 277.1594. Found: 277.1583.



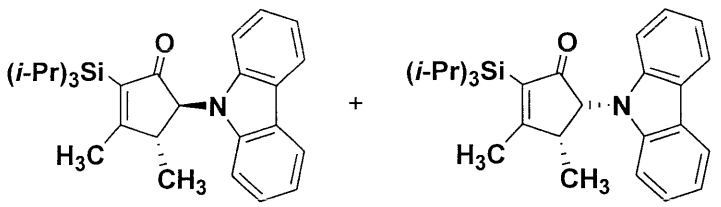
195a



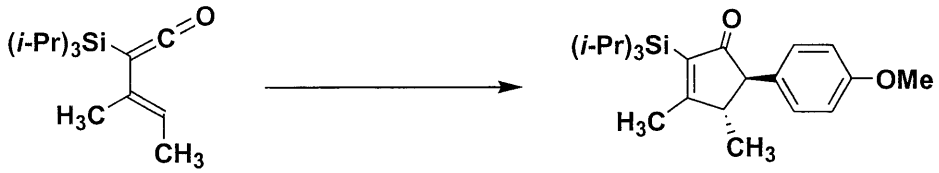
***trans*-5-(Carbazol-9-yl)-3,4-dimethyl-2-(triisopropylsilyl)cyclopent-2-enone (196a)** and ***cis*-5-(Carbazol-9-yl)-3,4-dimethyl-2-(triisopropylsilyl)cyclopent-2-enone (196b).**

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of 1-(carbazol-9-ylmethyl)benzotriazole (**162**) (0.129 g, 0.432 mmol) in 4.3 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.45 M in hexane, 0.177 mL, 0.434 mmol) was added dropwise over 1.5 min. The resulting orange solution was stirred at -78 °C for 1 h and then a solution of silylketene **1** (0.104 g, 0.412 mmol) in 1.4 mL of THF was added dropwise via cannula over 2 min. After 1 h, a solution of $ZnBr_2$ (1.0 M in THF, 1.2 mL, 1.2 mmol) was added dropwise over 2 min and the resulting yellow mixture was allowed to slowly warm to rt over 17 h, during which time a white precipitate formed. The reaction mixture was diluted with 30 mL of Et_2O and filtered though a fritted glass funnel containing Celite. The filtrate was washed with 15 mL of 1 N aq HCl solution, and the aqueous phase was backextracted with 15 mL of Et_2O. The combined organic layers were washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.202 g of a pale violet solid. This material was dissolved in CH_2Cl_2 and concentrated onto 0.5 g of silica gel which was transferred to the top of a column of 20 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.160 g of a pale violet solid. This material was dissolved in 25 mL of CH_2Cl_2, stirred with 0.3 g of decolorizing charcoal for several minutes, filtered, and concentrated to afford 0.152 g (85%) of a mixture of *trans*-cyclopentenone **196a** and *cis*-isomer **196b** (74:26 by ^1H NMR analysis) as a white solid. A pure sample of the major isomer was obtained by preparative TLC (elution with 5% EtOAc-hexanes and then with 2.5% EtOAc-hexanes). For **196a**: mp 164-167 °C; IR (film) 2943, 2865, 1703, 1563, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 7.9 Hz, 2 H), 7.25-7.54 (m, 4 H), 7.23 (t, J = 7.6 Hz, 1 H), 6.82 (br s, 1 H), 4.84 (d, J = 4.9 Hz, 1 H), 3.32-3.38 (m, 1 H), 2.34 (s, 3 H), 1.62 (sept, J = 7.5 Hz, 3 H), 1.43 (d, J = 7.0 Hz, 3 H), 1.16 (d, J = 7.5 Hz, 9 H), 1.16 (d, J =

7.5 Hz, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.2, 187.2, 136.3, 125.7 (2 C), 120.7 (2 C), 119.5, 109.0, 66.1, 45.6, 19.19, 19.17, 19.06, 17.9, 12.0. HRMS (ESI) Calcd for $C_{28}H_{37}NOSi$ $(M+H)^+$: 432.2717. Found: 432.2705. For **196b** (partial): ^1H NMR (500 MHz, $CDCl_3$): δ 6.93-6.99 (m, 1 H), 5.30 (d, J = 7.5 Hz, 1 H), 3.40 (app quint, J = 7.5 Hz, 1 H), 2.32 (s, 3 H), 1.18 (d, J = 7.5 Hz, 9 H), 0.81 (d, J = 7.5 Hz, 3 H).

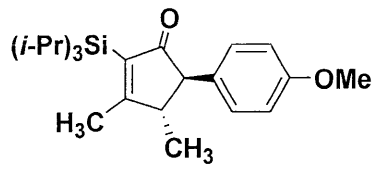


196a + 196b

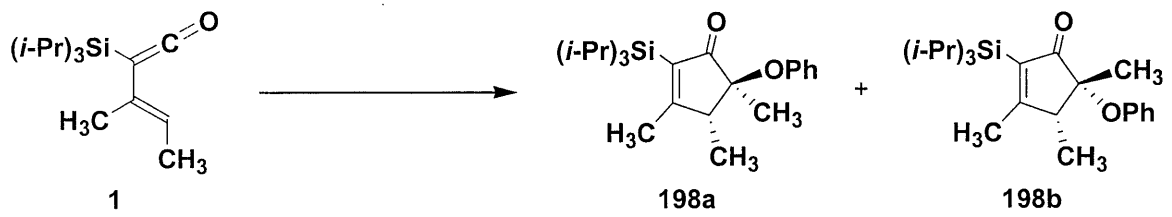


***trans*-5-(4′-Methoxy-phenyl)-3,4-dimethyl-2-(triisopropylsilyl)cyclopent-2-enone (197a).**

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of 1-[(4′-methoxy-phenyl)methyl]benzotriazole (**176**) (0.102 g, 0.426 mmol) in 4.3 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.33 M in hexane, 0.183 mL, 0.426 mmol) was added dropwise over 1 min. The resulting deep green mixture was stirred at -78 °C for 1 h and then a solution of silylketene **1** (0.103 g, 0.406 mmol) in 1.4 mL of THF was added dropwise via cannula over 2 min. After 1 h, a solution of $ZnBr_2$ (1.00 M in THF, 1.22 mL, 1.22 mmol) was added dropwise over 2 min. The resulting bright yellow mixture was allowed to slowly warm to rt over 10 h, after which time the reaction flask was equipped with a reflux condenser and the mixture was heated at reflux for 4 h. After cooling, the reaction mixture was diluted with 25 mL of Et_2O and washed with 10 mL of 1 N aq HCl solution, 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.252 g of an orange oil. This material was dissolved in CH_2Cl_2 and concentrated onto 0.5 g of silica gel which was transferred to the top of a column of 20 g of silica gel. Gradient elution with 0-8% EtOAc-hexanes provided 0.052 g (34%) of cyclopentenone **197a** (≥99:1 *trans*:*cis* by ^{1}H NMR analysis) as a pale yellow oil: IR (film) 2943, 2865, 1692, 1576, 1513, 1463, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 3.78 (s, 3 H), 3.06 (d, J = 3.2 Hz, 1 H), 2.81 (qd, J = 7.2, 3.3 Hz, 1 H), 2.26 (s, 3 H), 1.54 (sept, J = 7.5 Hz, 3 H), 1.31 (d, J = 7.1 Hz, 3 H), 1.08 (d, J = 7.5 Hz, 9 H), 1.05 (d, J = 7.5 Hz, 9 H); ^{13}C NMR (125 MHz, C_6D_6): δ 211.2, 188.8, 159.3, 135.4, 133.0, 129.5, 114.8, 61.6, 55.1, 51.9, 19.54, 19.50, 19.1, 18.9, 12.4. HRMS (ESI) Calcd for $C_{23}H_{36}O_2Si$ $(M+Na)^+$: 395.2377. Found: 395.2377.



197a

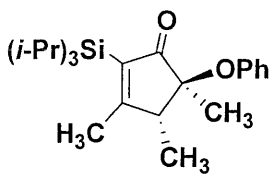


***trans*-3,4,5-Trimethyl-5-phenoxy-2-(triisopropylsilyl)cyclopent-2-enone (198a) and *cis*-3,4,5-Trimethyl-5-phenoxy-2-(triisopropylsilyl)cyclopent-2-enone (198b).**

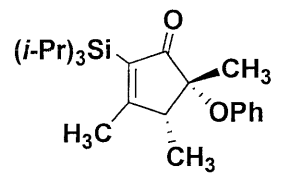
A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of the substituted benzotriazole **178** (0.081 g, 0.339 mmol) in 3.4 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.39 M in hexane, 0.14 mL, 0.33 mmol) was added dropwise over 1 min. The resulting deep red solution was stirred at -78 °C for 5 min[140] and then a solution of silylketene **1** (0.081 g, 0.321 mmol) in 1.1 mL of THF was added dropwise via cannula over 2 min. After 2 h, a solution of $ZnBr_2$ (1.0 M in THF, 0.97 mL, 0.97 mmol) was added dropwise over 2 min and the resulting yellow solution was allowed to slowly warm to rt over 14 h, during which time a white precipitate formed. The reaction mixture was then diluted with 30 mL of Et_2O and filtered though a fritted glass funnel containing Celite. The filtrate was washed with 15 mL of 1 N aq HCl solution, 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.166 g of a yellow oil. This material was dissolved in CH_2Cl_2 and concentrated onto 0.5 g of silica gel which was transferred to the top of a column of 17 g of silica gel. Gradient elution with 0-5% EtOAc-hexanes provided 0.078 g (65%) of a mixture of *trans*-cyclopentenone **198a** and *cis*-cyclopentenone **198b** (75:25 by ^1H NMR analysis) as a colorless oil. Pure samples of each isomer were obtained by preparative TLC (elution with 5% EtOAc-hexanes). The *trans* isomer **198a** was obtained as a colorless oil which partially solidified upon standing: IR (film) 2943, 2865, 1706, 1567, 1493 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.15-7.20 (m, 2 H), 6.94 (tt, J = 7.4, 1.0 Hz, 1 H), 6.74-6.78 (m, 2 H), 3.22 (qd, J = 7.4, 1.0 Hz, 1 H), 2.17 (d, J = 1.1 Hz, 3 H), 1.55 (sept, J = 7.5, 3 H), 1.33 (s, 3 H), 1.18 (d, J = 7.4 Hz, 3 H), 1.07 (d, J = 7.5 Hz, 9 H), 1.06 (d, J = 7.5 Hz, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.7, 186.4, 155.5, 134.1, 129.4, 122.2, 119.4, 85.8, 46.2, 21.1, 19.2, 19.04, 18.97, 12.4, 12.0. HRMS (ESI) Calcd for $C_{23}H_{36}O_2Si$

[140] In this case some decomposition of the lithiated benzotriazole derivative was observed when metallation was allowed to proceed for longer than 5 min.

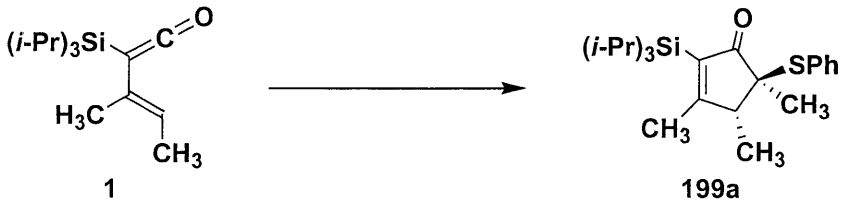
$(M+H)^+$: 373.2557. Found: 373.2556. The *cis* isomer **198b** was obtained as a colorless oil: IR (film) 2942, 2865, 1705, 1578, 1493, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.23-7.27 (m, 2 H), 7.03-7.07 (m, 2 H), 6.99 (tt, J = 7.3, 1.0 Hz, 1 H), 2.85 (q, J = 7.1 Hz, 1 H), 2.23(s, 3 H), 1.54 (sept, J = 7.5, 3 H), 1.39 (s, 3 H), 1.27 (d, J = 7.1 Hz, 3 H), 1.07 (app t, J = 7.5 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.7, 187.4, 155.8, 131.5, 129.2, 122.1, 120.3, 85.2, 54.3, 22.1, 20.1, 19.02, 18.99, 16.3, 11.9.



198a

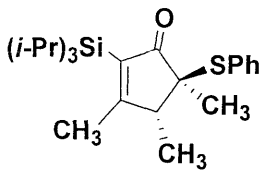


198b

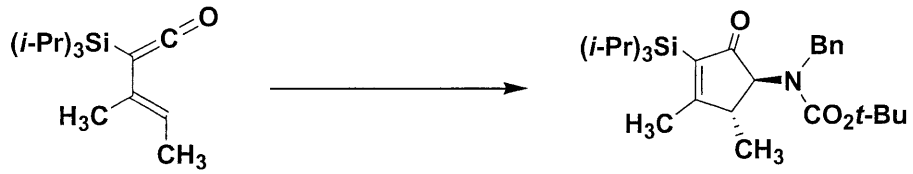


***trans*-3,4,5-Trimethyl-5-phenylthio-2-(triisopropylsilyl)cyclopent-2-enone (199a).**

An oven-dried, 25-mL, one-necked, round-bottomed flask equipped with a three-way stopcock adapter (fitted with a rubber septum and connected to a vacuum/Ar manifold) was charged with the benzotriazole derivative **177** (0.121 g, 0.474 mmol). Toluene (5 mL) was added and the resulting solution was concentrated at 0.2 mmHg with vigorous stirring. This process was repeated twice, and the residue was then dissolved in 4.7 mL of THF and cooled at -78 °C while *n*-BuLi solution (2.45 M in hexane, 0.18 mL, 0.44 mmol) was added dropwise over 1 min. The resulting deep purple solution was stirred at -78 °C for 1 h and then a solution of silylketene **1** (0.108 g, 0.428 mmol) in 1.4 mL of THF was added dropwise via cannula over 2 min. After 1 h, a solution of $ZnBr_2$ (1.0 M in THF, 1.3 mL, 1.3 mmol) was added dropwise over 2 min and the resulting bright yellow solution was allowed to slowly warm to rt over 15 h, during which time a white precipitate formed. The reaction mixture was diluted with 30 mL of Et_2O and filtered through a fritted glass funnel containing Celite. The filtrate was washed with 15 mL of 1 N aq HCl solution, and the aqueous phase was backextracted with 15 mL of Et_2O. The combined organic layers were washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.208 g of a yellow oil. This material was dissolved in CH_2Cl_2 and concentrated onto 0.5 g of silica gel which was transferred to the top of a column of 21 g of silica gel. Gradient elution with 0-2.5% EtOAc-hexanes provided 0.107 g (64%) of cyclopentenone **199a** (97:3 mixture of *trans*:*cis* isomers by ^1H NMR analysis) as a colorless oil which partially solidified upon standing. For *trans*-cyclopentenone **199a**: IR (film) 2943, 2865, 1694, 1580, 1464, 1254 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 7.63-7.67 (m, 2 H), 6.97-7.06 (m, 3 H), 2.69 (q, J = 7.3 Hz, 1 H), 1.68 (s, 3 H), 1.60 (sept, J = 7.5 Hz, 3 H), 1.26 (s, 3 H), 1.15 (app t, J = 7.5 Hz, 18 H), 0.77 (d, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6): δ 210.0, 186.4, 137.1, 133.1, 132.8, 129.2, 129.1, 58.5, 52.5, 19.9, 19.50, 19.48, 19.0, 15.1, 12.5. HRMS (ESI) Calcd for $C_{23}H_{36}OSSi$ $(M+Na)^+$: 411.2148. Found: 411.2164.



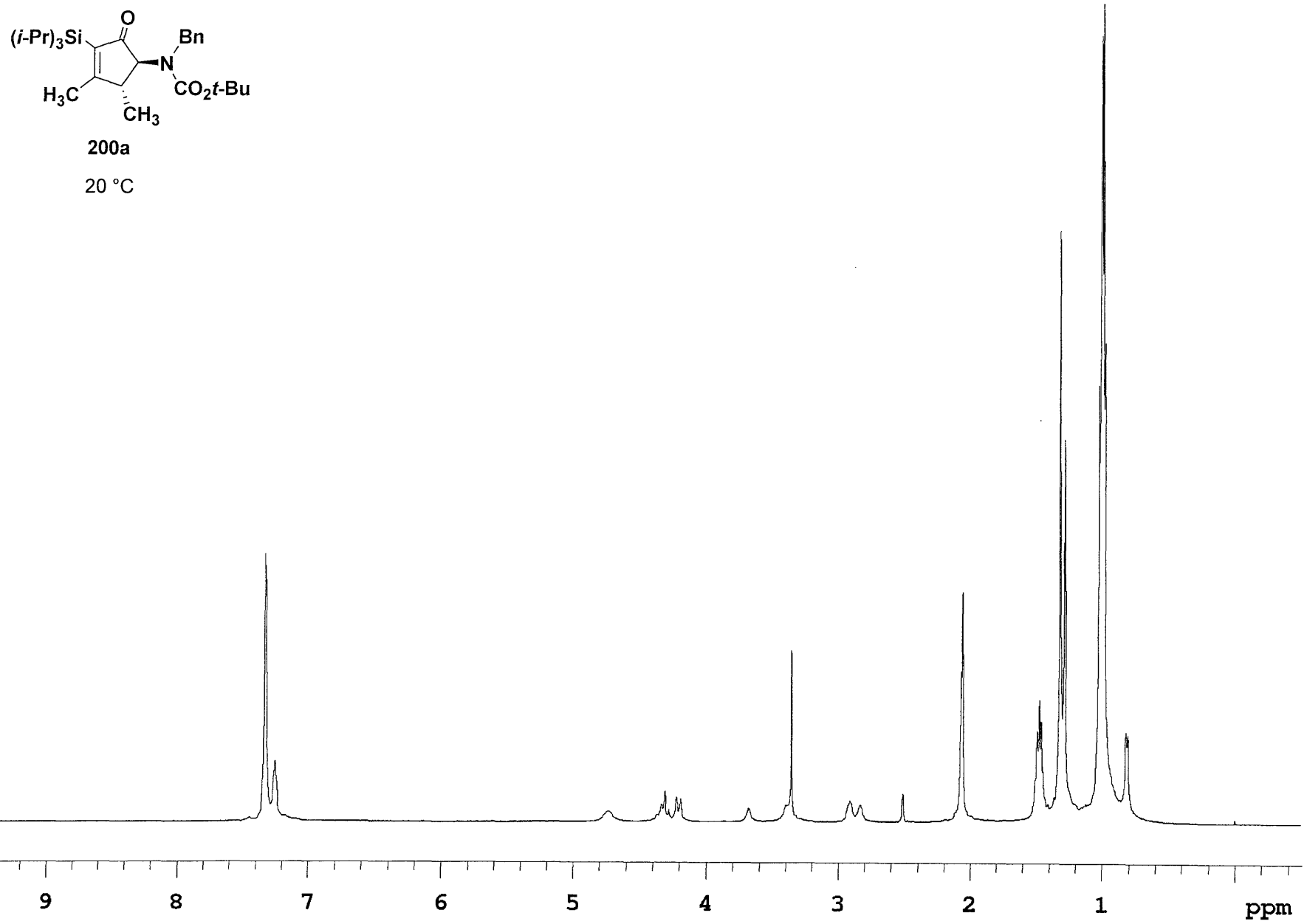
199a

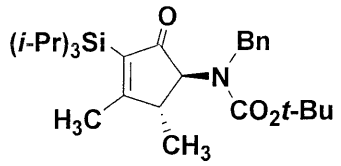


1 200a

***trans*-5-(*N*-benzyl-*N*-*tert*-butoxycarbonyl)amino-3,4-dimethyl-2-(triisopropylsilyl)cyclopent-2-enone (200a).**

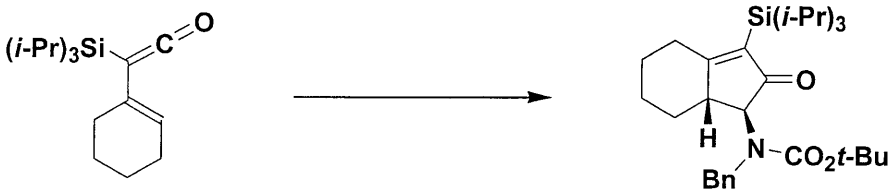
A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of the benzotriazole **174** (0.149 g, 0.440 mmol) in 4.4 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.35 M in hexane, 0.19 mL, 0.45 mmol) was added dropwise over 1 min. The resulting orange-yellow solution was stirred at -78 °C for 30 min and then a solution of silylketene **1** (0.105 g, 0.416 mmol) in 1.4 mL of THF was added dropwise via cannula over 1 min. The resulting orange-yellow solution was stirred at -78 °C for 2 h. The cooling bath was then removed and the reaction mixture was stirred for 2.5 h. The resulting mixture was diluted with 30 mL of Et_2O and washed with 15 mL of water, and the aqueous phase was backextracted with 10 mL of Et_2O. The combined organic layers were washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.221 g of a viscous yellow oil. Column chromatography on 16 g of silica gel (elution with 1-5% EtOAc-hexanes) provided 0.143 g (73%) of *trans*-cyclopentenone **200a** as a colorless oil (96% pure by ^{1}H NMR analysis; contains 4% of an impurity which is tentatively assigned as the *cis* isomer): IR (film) 2944, 2866, 1697, 1570, 1456 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, 135 °C): δ 7.26-7.31 (m, 4 H), 7.19-7.23 (m, 1 H), 4.41 (d, J = 15.7 Hz, 1 H), 4.35 (d, J = 15.6 Hz, 1 H), 3.61 (d, J = 4.5 Hz, 1 H), 2.84-2.90 (m, 1 H), 2.07 (s, 3 H), 1.46 (sept, J = 7.5 Hz, 3 H), 1.34 (s, 9 H), 1.00-1.06 (m, 21 H); ^{13}C NMR (125 MHz, DMSO-d_6, 135 °C): δ 205.5, 185.2, 154.1, 138.4, 133.3, 127.3, 126.7, 126.1, 78.9, 69.3, 51.0, 44.2, 27.3, 17.9, 17.8, 17.4, 15.7, 10.6. HRMS (ESI) Calcd for $C_{28}H_{45}NO_3Si$ $(M+Na)^+$: 494.3061. Found: 494.3073.


(i-Pr)3Si
O
Bn
N
CO2t-Bu
H3C
CH3
200a
20 °C
9
8
7
6
5
4
3
2
1
ppm



200a

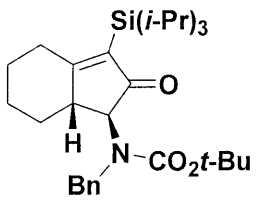
135 °C



3 201a

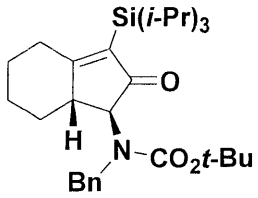
***trans*-7-(*N*-benzyl-*N*-*tert*-butoxycarbonyl)amino-9-(triisopropylsilyl)bicyclo[4.3.0]non-1(9)-en-8-one (201a).**

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of the benzotriazole **174** (0.153 g, 0.452 mmol) in 4.5 mL of THF and then cooled at -78 °C while *n*-BuLi solution (2.40 M in hexane, 0.19 mL, 0.45 mmol) was added dropwise over 1 min. The resulting orange-yellow solution was stirred at -78 °C for 30 min and then a solution of silylketene **3** (0.118 g, 0.424 mmol) in 1.4 mL of THF was added dropwise via cannula over 2 min. The resulting orange-yellow solution was stirred at -78 °C for 1 h. The cooling bath was then removed and the reaction mixture was stirred for 2.5 h. The reaction mixture was diluted with 30 mL of Et_2O and washed with 15 mL of water, and the aqueous phase was backextracted with 10 mL of Et_2O. The combined organic layers were washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.242 g of a yellow oil. This material was dissolved in CH_2Cl_2 and concentrated onto 0.6 g of silica gel which was transferred to the top of a column of 19 g of silica gel. Gradient elution with 1-5% EtOAc-hexanes provided 0.141 g (67%) of cyclopentenone **201a** (≥99:1 *trans*:*cis* by ^{1}H NMR analysis) as a viscous, pale orange oil: IR (film) 2939, 2864, 1701, 1569, 1456 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, 130 °C): δ 7.27-7.30 (m, 4 H), 7.19-7.24 (m, 1 H), 4.43 (d, J = 15.6 Hz, 1 H), 4.31 (d, J = 15.7 Hz, 1 H), 3.57 (d, J = 4.3 Hz, 1 H), 2.88 (d, J = 14.7 Hz, 1 H), 2.69-2.75 (m, 1 H), 2.18-2.26 (m, 1 H), 1.82-1.95 (m, 2 H), 1.65-1.72 (m, 1 H), 1.44 (sept, J = 7.5 Hz, 3 H), 1.33 (s, 9 H), 1.27-1.49 (m, 3 H), 1.04 (d, J = 7.5 Hz, 9 H), 1.02 (d, J = 7.4 Hz, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 130 °C): δ 205.9, 186.9, 154.1, 138.4, 127.4, 126.7, 126.2, 98.7, 78.9, 68.4, 51.1, 46.8, 32.5, 31.4, 27.4, 25.7, 23.8, 17.93, 17.86, 10.6. HRMS (ESI) Calcd for $C_{30}H_{47}NO_3Si$ $(M+H)^+$: 498.3398. Found: 498.3386.



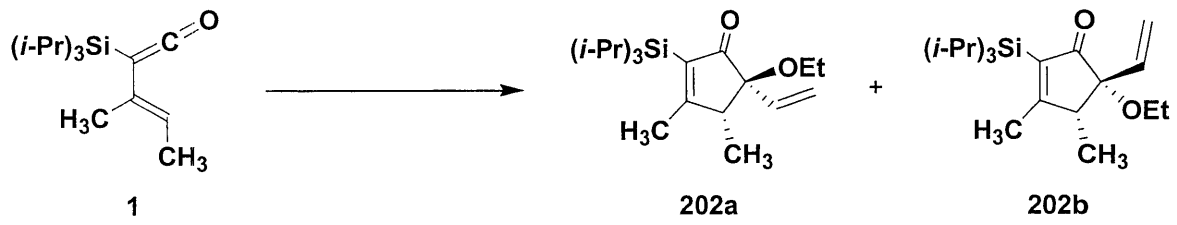
201a

20 °C



201a

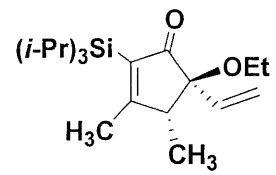
130 °C



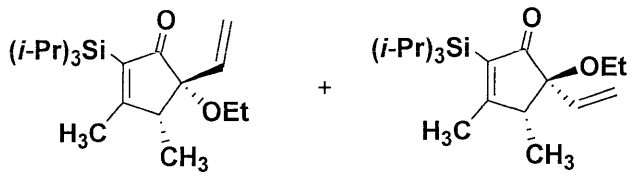
***trans*-5-Ethoxy-3,4-dimethyl-2-triisopropylsilyl-5-(vinyl)cyclopent-2-enone (202a)** and ***cis*-5-Ethoxy-3,4-dimethyl-2-triisopropylsilyl-5-(vinyl)cyclopent-2-enone (202b).**

An oven-dried, 25-mL, one-necked, round-bottomed flask equipped with a three-way stopcock adapter (fitted with a rubber septum and connected to a vacuum/Ar manifold) was charged with the benzotriazole derivative **124** (0.125 g, 0.615 mmol). Toluene (5 mL) was added and the resulting solution was concentrated at 0.2 mmHg with vigorous stirring. This process was repeated twice, and the residue was then dissolved in 6.2 mL of THF and cooled at -78 °C while *n*-BuLi solution (2.39 M in hexane, 0.25 mL, 0.60 mmol) was added dropwise over 1 min. The resulting deep green solution was stirred at -78 °C for 4 min and then a solution of silylketene **1** (0.141 g, 0.558 mmol) in 1.9 mL of THF was added dropwise via cannula over 2 min. The resulting orange-yellow solution was allowed to slowly warm to rt over 15 h. The reaction mixture was then diluted with 30 mL of Et_2O and washed with 15 mL of water, and the aqueous phase was backextracted with 20 mL of Et_2O. The combined organic layers were washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.218 g of an orange oil. This material was dissolved in CH_2Cl_2 and concentrated onto 0.5 g of silica gel which was transferred to the top of a column of 20 g of silica gel. Gradient elution with 0-2.5% EtOAc-hexanes provided 0.131 g (70%) of *trans*-cyclopentenone **202a** and *cis*-isomer **202b** (76:24 by ^{1}H NMR analysis) as a pale yellow oil. A pure sample of **202a** and an enriched sample of **202b** (77:23 **202b**:**202a** by ^{1}H NMR analysis) were obtained by preparative TLC (elution with 4% EtOAc-hexanes). For **202a** and **202b**: IR (film) 2944, 2866, 1698, 1574, 1463 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) for **202a**: δ 5.69 (dd, J = 17.5, 10.7 Hz, 1 H), 5.60 (dd, J = 17.4, 2.1 Hz, 1 H), 5.27 (dd, J = 10.7, 2.1 Hz, 1 H), 3.59-3.71 (m, 2 H), 2.74 (q, J = 7.4 Hz, 1 H), 1.75 (s, 3 H), 1.57 (sept, J = 7.6 Hz, 3 H), 1.14 (app d, J = 7.6 Hz, 18 H), 1.12-1.17 (m, 3 H), 0.84 (d, J = 7.6 Hz, 3 H); for **202b**: δ 5.85 (dd, J = 17.5, 10.9 Hz, 1 H), 5.31 (dd, J = 17.7, 1.2 Hz, 1 H), 5.12 (dd, J = 10.7, 1.2 Hz, 1 H), 3.85-3.92 (m, 1 H), 3.59-3.66 (m, 1 H), 2.43 (q, J = 7.2 Hz, 1 H), 1.76 (s, 3 H), 1.57 (sept, J = 7.6 Hz, 3 H), 1.13 (app d, J = 7.5 Hz, 18 H), 1.12-1.17

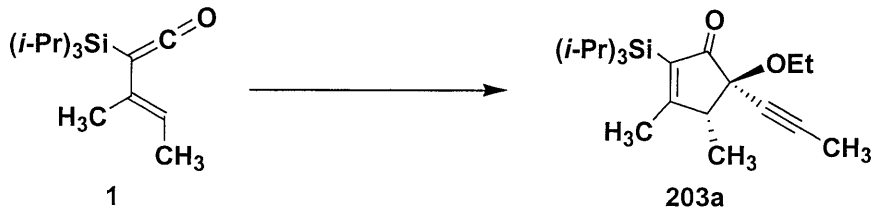
(m, 3 H), 1.09 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): for **202a** and **202b**: δ 209.2, 209.0, 187.8, 187.7, 138.0, 134.9, 134.1, 132.3, 118.0, 116.8, 87.0, 86.3, 60.7, 60.1, 51.2, 50.5, 19.8, 19.3, 19.02, 18.98, 18.95, 18.93, 16.0, 15.9, 15.1, 14.5, 11.92, 11.87. HRMS (ESI) Calcd for $C_{20}H_{36}O_2Si$ $(M+Na)^+$: 359.2377. Found: 359.2382.



202a

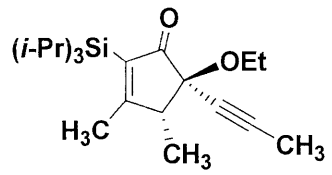


202b (77 : 23) 202a

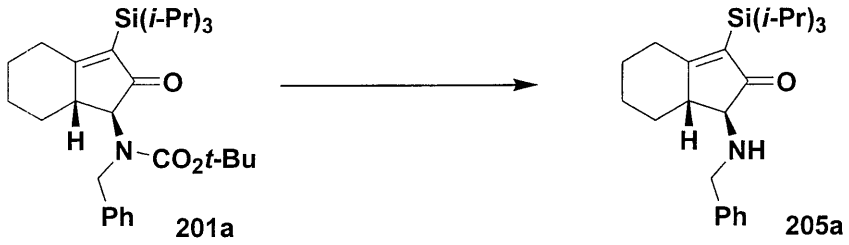


***trans*-5-Ethoxy-3,4-dimethyl-5-prop-1-ynyl-2-(triisopropylsilyl)cyclopent-2-enone (203a).**

An oven-dried, 25-mL, one-necked, round-bottomed flask equipped with a three-way stopcock adapter (fitted with a rubber septum and connected to a vacuum/Ar manifold) was charged with the benzotriazole derivative **182** (0.140 g, 0.650 mmol). Toluene (5 mL) was added and the resulting solution was concentrated at 0.2 mmHg with vigorous stirring. This process was repeated twice, and the residue was then dissolved in 6.5 mL of THF and cooled at -78 °C while *n*-BuLi solution (2.39 M in hexane, 0.26 mL, 0.62 mmol) was added dropwise over 1 min. The resulting deep blue solution was stirred at -78 °C for 5 min and then a solution of silylketene **1** (0.149 g, 0.590 mmol) in 2.0 mL of THF was added dropwise via cannula over 2 min. The resulting red-brown solution was allowed to slowly warm to rt over 15 h. The reaction mixture was then diluted with 30 mL of Et_2O and washed with 15 mL of water, and the aqueous phase was backextracted with 10 mL of Et_2O. The combined organic layers were washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.255 g of a brown oil. This material was dissolved in CH_2Cl_2 and concentrated onto 0.7 g of silica gel which was transferred to the top of a column of 25 g of silica gel. Gradient elution with 0-2.5% EtOAc-hexanes provided 0.111 g (54%) of cyclopentenone **203a** (97:3 mixture of *trans*:*cis* isomers by ^1H NMR analysis) as a yellow oil. For *trans*-cyclopentenone **203a**: IR (film) 2944, 2866, 2245, 1705, 1580, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.69-3.83 (m, 2 H), 2.72, (q, J = 7.4 Hz, 1 H), 2.16 (s, 3 H), 1.91 (s, 3 H), 1.50 (sept, J = 7.5 Hz, 3 H), 1.26 (d, J = 7.4 Hz, 3 H), 1.16 (app t, J = 7.05 Hz, 3 H), 1.06 (d, J = 7.3 Hz, 9 H), 1.05 (d, J = 7.3 Hz, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8, 187.3, 131.5, 86.9, 82.2, 74.4, 61.2, 52.8, 19.5, 18.94, 18.92, 16.5, 15.7, 11.9, 4.0. HRMS (ESI) Calcd for $C_{21}H_{36}O_2Si$ $(M+H)^+$: 349.2557. Found: 349.2559.

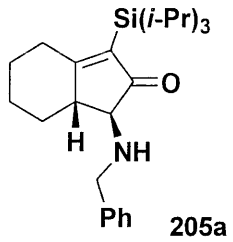


203a



***trans*-7-(*N*-benzyl)amino-9-(triisopropylsilyl)bicyclo[4.3.0]non-1(9)-en-8-one (205a).**

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of cyclopentenone **201a** (0.062 g, 0.125 mmol) in 2.5 mL of CH_2Cl_2. Trifluoroacetic acid (0.19 mL, 0.28 g, 2.5 mmol) was added via syringe over 30 sec, and the resulting pale yellow solution was stirred at rt for 1.5 h. The reaction mixture was then diluted with 20 mL of CH_2Cl_2 and 10 mL of saturated aq $NaHCO_3$ solution, and the aqueous phase was separated and extracted with 10 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 0.053 g of a yellow oil. Column chromatography on 3 g of silica gel (elution with 1% Et_3N-20% EtOAc-hexanes) provided 0.048 g (96%) of *trans*-cyclopentenone **205a** and *cis*-isomer **205b** (99:1 by ^1H NMR analysis) as a pale yellow oil. For *trans*-cyclopentenone **205a**: IR (film) 2935, 2863, 1694, 1572, 1496 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.31-7.36 (m, 4 H), 7.23-7.27 (m, 1 H), 3.94 (d, J = 13.1 Hz, 1 H), 3.83 (d, J = 13.2 Hz, 1 H), 3.03 (app d, J = 14.3 Hz, 1 H), 2.91 (d, J = 3.1 Hz), 2.56 (ddd, J = 12.5, 5.7, 3.2 Hz, 1 H), 2.17-2.31 (m, 3 H), 1.96-2.03 (m, 1 H), 1.82-1.89 (m, 1 H), 1.37-1.60 (m, 5 H), 1.22 (app qd, J = 12.9, 3.5 Hz, 1 H), 1.05 (d, J = 7.6 Hz, 9 H), 1.03 (d, J = 7.6 Hz, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.1, 190.7, 140.0 131.3, 128.6, 128.3, 127.3, 68.6, 53.2, 51.9, 34.8, 32.9, 27.2, 25.5, 19.0, 18.9, 11.8. HRMS (ESI) Calcd for $C_{25}H_{39}NOSi$ $(M+H)^+$: 398.2874. Found: 398.2876.

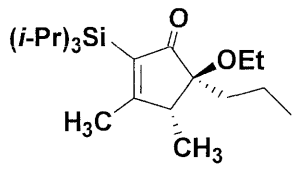


205a

203 207a

***trans*-5-Ethoxy-3,4-dimethyl-5-propyl-2-(triisopropylsilyl)cyclopent-2-enone (207a).**

A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of (triisopropylsilyl)cyclopentenone **203** (0.030 g, 0.086 mmol) in 8.6 mL of EtOH. Palladium on carbon (5 wt%, 0.018 g, 0.008 mmol) was added, and the rubber septum was replaced with a Claisen adapter (fitted with a gas outlet adapter and a thermometer adapter). A balloon filled with H_2 was attached to a disposable glass pipette, and the pipette was inserted through the thermometer adapter so that the tip of the pipette was submerged into the reaction mixture. The stopcock on the gas outlet adapter was carefully opened to obtain a modest rate of H_2 bubbling, and the reaction mixture was stirred at rt for 4 h (the H_2 balloon was refilled as necessary). The reaction mixture was then filtered through a fritted glass funnel containing Celite with the aid of ca. 20 mL of EtOH, and the filtrate was concentrated to afford 0.033 g of a colorless oil. Column chromatography on 5 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.030 g (100%) of cyclopentenone **207a** (96:4 mixture of *trans*:*cis* isomers by ^{1}H NMR analysis) as a colorless oil which partially solidified upon standing. For *trans*-cyclopentenone **207a**: IR (film) 2962, 2867, 1698, 1577, 1463 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.24-3.38 (m, 2 H), 2.83 (q, J = 7.3 Hz, 1 H), 2.16 (s, 3 H), 1.24-1.61(m, 7 H), 1.11-1.15 (m, 6 H), 1.04 (app d, J = 7.5 Hz, 18 H), 0.90 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.0, 187.6, 133.3, 86.0, 59.3, 48.8, 33.2, 19.5, 19.00, 18.99, 16.5, 15.9, 14.8, 13.6, 11.9. HRMS (ESI) Calcd for $C_{21}H_{40}O_2Si$ $(M+Na)^+$: 375.2690. Found: 375.2697.

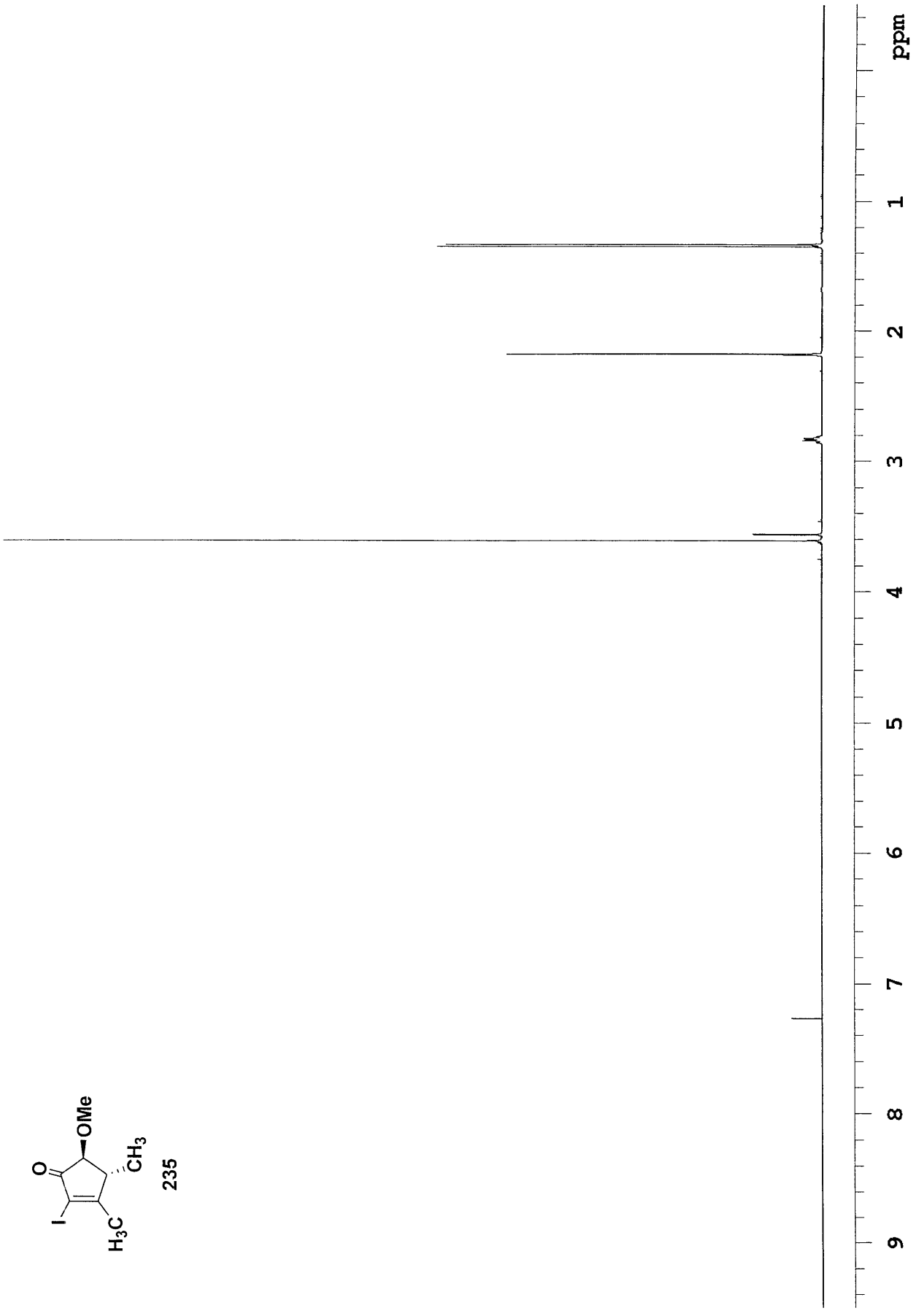


207a

195a 235

***trans*-2-Iodo-5-methoxy-3,4-dimethylcyclopent-2-enone (235).**

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of (triethylsilyl)cyclopentenone **195a** (0.215 g, 0.845 mmol) in 3 mL of CH_2Cl_2 and then cooled at 0 °C while a solution of ICl (1.0 M in CH_2Cl_2, 1.0 mL, 1.0 mmol) was added dropwise over 1 min. The resulting deep red solution was stirred at 0 °C in the dark for 2.5 h. The reaction mixture was then diluted with 30 mL of CH_2Cl_2 and washed with 25 mL of saturated $Na_2S_2O_3$ solution. The aqueous phase was extracted with two 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 25 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.311 g of a yellow oil mixed with some white solid. Column chromatography on 23 g of silica gel (elution with 10% EtOAc-hexanes) provided 0.200 g of iodocyclopentenone **235** (≥99:1 *trans*:*cis* by ^1H NMR analysis) as a pale yellow oil.



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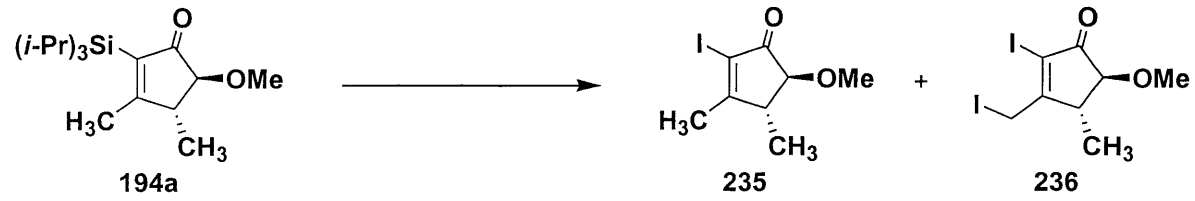

***trans*-2-Iodo-5-methoxy-3,4-dimethylcyclopent-2-enone (235).**

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of (triisopropylsilyl)cyclopentenone **194a** (0.324 g, 1.09 mmol) in 3 mL of CH_2Cl_2 and then cooled at 0 °C while a solution of ICl (1.0 M in CH_2Cl_2, 2.2 mL, 2.2 mmol) was added dropwise over 4 min. The resulting deep red solution was stirred at 0 °C in the dark for 2 h and then a second portion of ICl (1.0 M in CH_2Cl_2, 1.1 mL, 1.1 mmol) was added dropwise over 1 min. After 2 h, a third portion of ICl (1.0 M in CH_2Cl_2, 0.55 mL, 0.55 mmol) was added dropwise over 1 min. The deep red reaction mixture was stirred for an additional hour at 0 °C and then was diluted with 50 mL of CH_2Cl_2 and washed with 40 mL of saturated $Na_2S_2O_3$ solution. The aqueous phase was backextracted with three 15-mL portions of CH_2Cl_2, and the combined organic layers were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.512 g of an oily, yellow-green solid. Column chromatography on 50 g of silica gel (elution with 10% EtOAc-hexanes) provided 0.234 g of iodocyclopentenone **235** (≥99:1 *trans*:*cis* by ^{1}H NMR analysis; contaminated with ca. 3% of bis-iodide **236**) as a pale yellow oil: IR (film) 2966, 2931, 2829, 1724, 1597, 1452 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.61 (s, 3 H), 3.56 (d, J = 2.8 Hz, 1 H), 2.80-2.86 (m, 1 H), 2.18 (d, J = 1.2 Hz, 3 H), 1.34 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.5, 180.5, 100.8, 84.9, 58.8, 47.2, 20.4, 17.0. HRMS (ESI) Calcd for $C_8H_{11}IO_2$ $(M+Na)^+$: 288.9696. Found: 288.9695.

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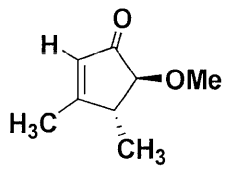
***trans*-5-Methoxy-3,4-dimethylcyclopent-2-enone (227).**

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with iodocyclopentenone **235** (0.141 g, 0.530 mmol). The reaction flask was purged with argon for 10 min, and then 2.5 mL of THF, Bu_3SnH (0.428 mL, 0.463 g, 1.59 mmol), and AIBN (0.50 M in THF, 0.11 mL, 0.06 mmol) were added. The rubber septum was replaced with a reflux condenser and the reaction mixture was heated at 55 °C for 1 h. The reaction mixture was allowed to cool to rt and then concentrated by rotary evaporation at ca. 20 mmHg (bath temperature 0-10 °C) to afford 0.492 g of a pale yellow liquid. Column chromatography on 12 g of silica gel (elution with 0-20% EtOAc-hexanes) provided 0.078 g of a pale yellow liquid. This material was dissolved in 15 mL of CH_3CN and washed with three 10-mL portions of hexanes to remove the last traces of tributyltin-containing impurities.[141] Concentration of the CH_3CN phase at 20 mmHg and 0-10 °C provided 0.065 g (88%) of cyclopentenone **227** (≥99:1 *trans*:*cis* by ^1H NMR analysis) as a pale yellow oil: IR (film) 2968, 2828, 1710, 1618, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.88 (s, 1 H), 3.59 (s, 3 H), 3.47 (d, J = 2.8 Hz, 1 H), 2.68-2.74 (m, 1 H), 2.08 (s, 3 H), 1.31 (d, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.6, 178.9, 128.4, 87.4, 58.6, 45.0, 17.5, 16.8. HRMS (ESI) Calcd for $C_8H_{12}O_2$ $(M+Na)^+$: 163.0730. Found: 163.0725.

[141] For a discussion of the removal of organotin impurities by this extraction procedure see reference 115.



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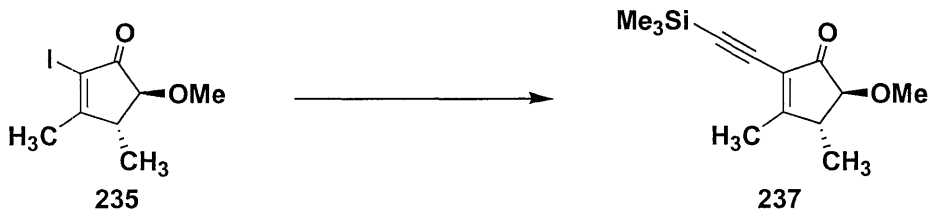
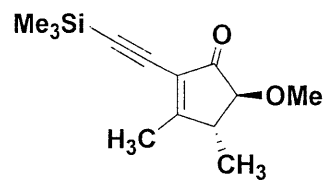


***trans*-5-Methoxy-3,4-dimethyl-2-(2-trimethylsilylethynyl)cyclopent-2-enone (237).**

A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with $(Ph_3P)_2PdCl_2$ (0.012 g, 0.017 mmol), CuI (0.002 g, 0.011 mmol), and a solution of iodocyclopentenone **235** (0.075 g, 0.282 mmol) in 2 mL of THF. Trimethylsilylacetylene (0.0.060 mL, 0.042 g, 0.428 mmol) was added, followed by *i*-Pr_2NH (0.395 mL, 0.285 g, 2.82 mmol), and the resulting mixture was stirred at rt for 3 h. The dark brown reaction mixture was diluted with 5 mL of Et_2O and filtered through a plug of 1 g of silica gel with the aid of 50 mL of Et_2O. The filtrate was washed with 25 mL of saturated $Na_2S_2O_3$ solution, and the aqueous phase was backextracted with 25 mL of Et_2O. The combined organic layers were washed with 25 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.100 g of a yellow-brown oil. Column chromatography on 14 g of silica gel (elution with 10% EtOAc-hexanes) provided 0.065 g (97%) of cyclopentenone **237** (≥99:1 *trans*:*cis* by ^1H NMR analysis) as a pale orange solid: mp 43-45 °C; IR (film) 2963, 2829, 2158, 1721, 1608, 1380 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.58 (s, 3 H), 3.46 (d, J = 3.1 Hz, 1 H), 2.68-2.75 (m, 1 H), 2.19 (d, J = 1.2 Hz, 3 H), 1.30 (d, J = 7.3 Hz, 3 H), 0.22 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 181.0, 124.1, 103.9, 94.7, 86.6, 58.6, 44.1, 17.0, 16.8, 0.1. HRMS (ESI) Calcd for $C_{13}H_{20}O_2Si$ $(M+Na)^+$: 259.1125. Found: 259.1113.



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Christopher P. Davie

Curriculum Vitae

Education

Ph.D., Organic Chemistry, *Massachusetts Institute of Technology* *June 2005*
Advisor: Professor Rick L. Danheiser
Thesis Title: "[4 + 1] Annulation Reactions of (Trialkylsilyl)ketenes: Synthesis of Substituted Indanones and Cyclopentenones."

Graduate Studies in Organic Chemistry, *Stanford University* *August 1999-March 2000*

B.S., Chemistry, *Boston College*, *magna cum laude* *May 1999*
Advisor: Professor William H. Armstrong
Thesis Title: "Vanadium(II) Thiolate Chemistry"

Research Experience

Graduate Research Assistant, *Massachusetts Institute of Technology* *January 2001-Present*
• Examined the scope and mechanism of a [4 + 1] annulation strategy for the synthesis of 2-indanone derivatives.
• Developed an annulation strategy for the synthesis of highly-substituted cyclopentenones based on the reaction of (trialkylsilyl)vinylketenes with α-benzotriazolyl organolithium compounds.

Research Internship, *Millennium Pharmaceuticals, Cambridge, MA* *Summer 2000*
Advisor: Dr. Shannon Chi
• Synthesized nitrogen heterocycles for biological evaluation.

Graduate Research Assistant, *Stanford University* *August 1999-October 1999*
Advisor: Professor Justin Du Bois
• Investigated transition metal catalysis of dioxirane-based epoxidation reactions.

Undergraduate Research Assistant, *Boston College* *May 1996-May 1999*
• Synthesized and characterized low-valent vanadium thiolate complexes and investigated their reactivity toward small, reducible molecules.
• Explored the vanadium(II)-promoted pinacol coupling of aldehydes.

Additional Experience

Chemistry Outreach Volunteer, *Massachusetts Institute of Technology* *January 2001-Present*
• Presented educational and exciting chemistry demonstrations to local high school students.
• Coordinated the program in 2003 and 2004, involving approximately 20 graduate student volunteers and 25 local high schools.

Teaching Assistant, *Massachusetts Institute of Technology* *September 2000-May 2001*
Teaching Assistant, *Stanford University* *September 1999-March 2000*
• Taught recitation sections for general chemistry and introductory organic chemistry.
• Organized and presented review sessions, and graded exams and problem sets.

Publications and Presentations

Davie, C. P.; Danheiser, R. L. Stereoselective Synthesis of Highly Substituted Cyclopentenones via [4 + 1] Annulation Reactions of (Trialkylsilyl)vinylketenes with α-Benzotriazolyl Organolithium Compounds. *Angew. Chem., Int. Ed.* **2005**, *in press*.

Dalton, A. M.; Zhang, Y.; Davie, C. P.; Danheiser, R. L. Synthesis of 2-Indanones via [4 + 1] Annulation Reactions of (Trialkylsilyl)arylketenes. *Org. Lett.* **2002**, *4*, 2465-2468.

Davis, J. A.; Davie, C. P.; Sable, D. B.; Armstrong, W. H. Directed Reactivity at a Vanadium(II) Thiolate Center: Synthesis and Structure of a Novel Vanadium Thiolate Complex and its Reaction Product with Azobenzene. *J. Chem. Soc., Chem. Commun.* **1998**, 1649-1650.

Davie, C. P.; Danheiser, R. L. Synthesis of Substituted Cyclopentenones via [4 + 1] Annulation Reactions of (Trialkylsilyl)vinylketenes. *Abstracts of Papers, Part 2*, 226th National Meeting of the American Chemical Society, New York, NY, September 7-11, 2003; American Chemical Society: Washington, DC, 2003; ORGN 298.

Davie, C. P.; Zhang, Y.; Dalton, A. M.; Danheiser, R. L. Synthesis of 2-Indanones via [4 + 1] Annulation Reactions of (Trialkylsilyl)arylketenes. *Abstracts of Papers, Part 2*, 224th National Meeting of the American Chemical Society, Boston, MA, August 18-22, 2002; American Chemical Society: Washington, DC, 2002; ORGN 080.

Davie, C. P.; Davis, J. A.; Armstrong, W. H. Synthesis, Structure and Reactivity of Vanadium(II) Thiolate Complexes. *Abstracts of Papers, Part 2*, 216th National Meeting of the American Chemical Society, Boston, MA, August 23-27, 1998; American Chemical Society: Washington, DC, 1998; INOR 164. (poster presentation)

Honors and Awards

MIT Outstanding Teaching Assistant Award, 2001
American Institute of Chemists Award, 1999
Scholar of the College, Boston College, 1999
Elected to Phi Beta Kappa, 1999
ACS Undergraduate Award in Analytical Chemistry, 1997

Affiliations

American Chemical Society, Organic Division