Mechanisms of Metal-Mediated Cyclizations

by

Benjamin Peter Warner

Submitted to the Department of
Chemistry in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
in Organic Chemistry

at the

Massachusetts Institute of Technology

February 1995

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Abstract

A complex of zirconocene with two η^2-alkynyl ligands is described. This complex is the first isolated example of the postulated intermediate in the zirconocene-mediated reductive coupling of alkynes.

The development of a Bergman cyclization controlled by metal-ligand interactions is described. Upon complexation with palladium or platinum, phosphine-substituted enediynes rearrange to the aromatic diradical quickly at room temperature. Upon complexation with mercury, the Bergman cyclization is not observed at temperatures up to 450 °C. The ligand undergoes a Bergman cyclization at 243 °C in the absence of metals. A mechanism for this reaction is proposed.

A new synthetic method for the catalytic conversion of organosilanes to organostannanes is described. This process utilizes the inexpensive bis(tributyltin) oxide, and produces the stannanes cleanly and in quantitative yield.

Thesis Supervisor: Stephen L. Buchwald

Title: Professor of Chemistry

Acknowledgments

Many people have greatly influenced the course of my graduate career, and I thank each of them. A full list of these people would be very long, so I will abbreviate it with the knowledge that everyone not mentioned knows who they are.

Three professors are at the top of this list. Steve Buchwald has provided me with guidance and freedom to explore the chemical world during my time at MIT. Bill Wulff gave me my first opportunity to conduct research. Both of them took a chance in accepting me into their laboratories virtually sight-unseen. Jim Lowe, who taught me how to think critically, was my mentor at the University of the South.

I need to acknowledge two very good friends as well. Chris Willoughby and I entered MIT together. Throughout our time here, he has provided constant intellectual stimulation and moral support. Rick Broene helped me maintain whatever sanity I still possess.

Most importantly, I must acknowledge my family. My parents, Jack and Deborah Warner, have always supported me and encouraged me to strive. Ellen McBee has been my closest friend and will be forever. Finally, my brother Tim Warner was and always will be in my heart.

To my parents for their encouragement.

To Ellen, for her friendship.

To Tim, for his inspiration.

Preface

Parts of this thesis have been adapted from the following articles co-written by the author:

Warner, B. P.; Davis, W. M.; Buchwald, S. L. "Synthesis and X-ray Structure of a Zirconocene Complex of Two Alkynes" *J. Am. Chem. Soc.* **1994**, *116*, 5471-5472.

Warner, B. P.; Buchwald, S. L. "A Catalytic Method for the Conversion of Silanes to Stannanes" *J. Org. Chem.* **1994**, *59*, 5822-5823.

Table of Contents

Introduction

Complexes of metals and ligands often have different properties than either of the partners. Seemingly small differences in the nature of either can result in large differences in the overall complex. The conformation or electronic structure of an organic fragment can be manipulated with a great deal of control by the selection of the proper metal. The work described here is based on these properties.

This thesis will discuss three projects to which I have devoted some time. The underlying rationale of this work has been the synthesis and manipulation of organo-main group compounds. The theme that developed, by chance, is the investigation of the mechanisms of two cyclization reactions.

The first chapter is devoted to the zirconocene-mediated reductive coupling of alkynes to form zirconacyclopentadienes. This reaction is well known and widely used in synthetic chemistry. However, no one had yet isolated the presumed intermediate zirconocene-bis(alkyne) complex. The isolation of such an intermediate and the molecular orbital description of the reductive coupling reaction are discussed in this chapter.

The second chapter concerns the synthesis of main group based enediynes, and their use in host-guest interactions. The goal, which was achieved, was the design of a controlled Bergman cyclization.

The third chapter describes a new synthetic method for the conversion of organosilanes to stannanes.

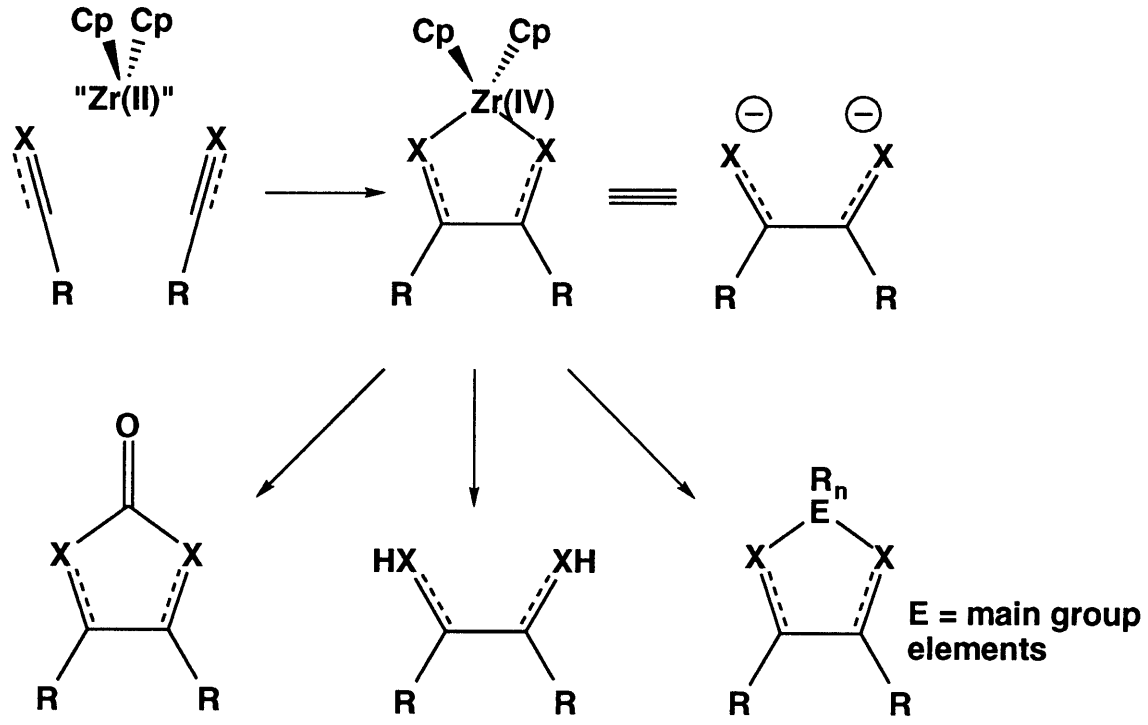
Chapter 1

A Complex of Zirconium and Two Alkynes

Introduction

The zirconocene-mediated reductive coupling reaction has found wide use in organic and organometallic synthesis. This family of reactions consists of the coupling of two unsaturated ligands by a zirconocene(II) equivalent (Scheme 1). In the product, the zirconocene is formally oxidized to the +4 oxidation state, and the ligands are each reduced by one bond order.[1,2,3] This reaction has been used in organic synthesis to form complex molecules, especially highly substituted aromatic and heterocyclic compounds, from simple precursors. It has also found use in the synthesis of organo-main group compounds which are otherwise difficult, if not impossible, to prepare.

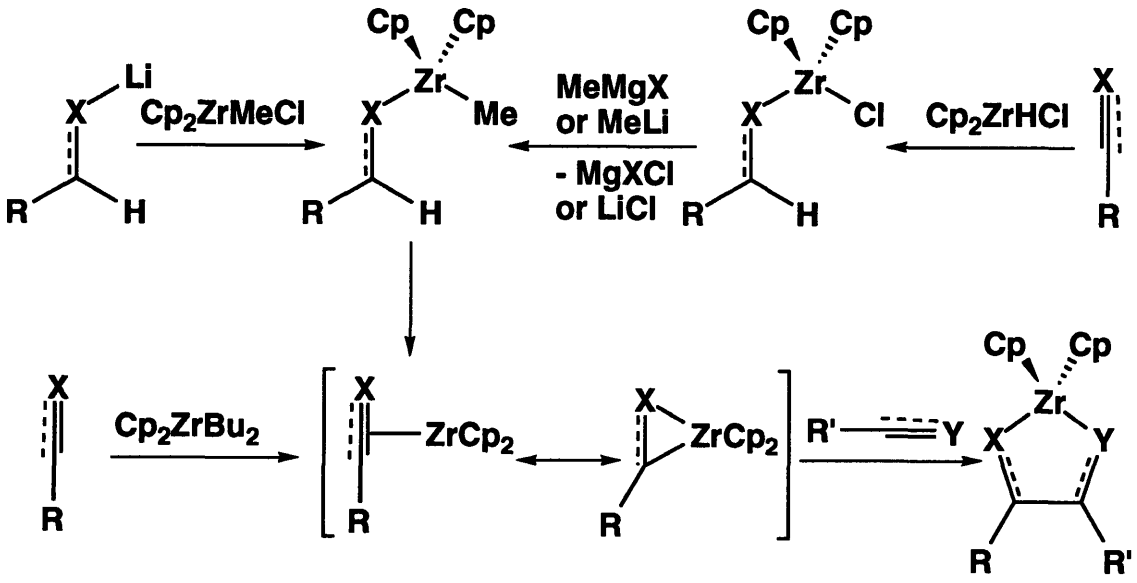
Scheme 1: The Zirconocene-Mediated Reductive Coupling Reaction



There are several advantages to using zirconocene-mediated coupling reactions in synthesis. These reactions are versatile, and allow the coupling of

a wide variety of simple unsaturated organic fragments including ketones,[4] nitriles,[4,5] olefins,[6,7] alkynes,[4,8,9] imines,[10,11] and thioaldehydes.[12,13,14] These fragments can be used directly, or generated from more stable precursors, such as the generation of thioaldehyde complexes from thiols or small cycloalkyne complexes from cyclic olefinic halides. A zirconocene equivalent, usually zirconocene dichloride under reducing conditions, can be used to homocouple ligands or perform intramolecular coupling reactions. This reaction is very easy to carry out, especially since the discovery that a reactive zirconocene(II) equivalent can be generated from the addition of *n*-butyllithium to zirconocene dichloride.[15] However, since these conditions do not allow selective cross-coupling of unsaturated molecules, alternative methods for the generation of reactive intermediates already bound to the metal were developed.[8,16] These methods involve the generation of dialkylzirconocene molecules, which undergo a β-hydrogen abstraction reaction to form the zirconocene-substrate complex *in situ* (Scheme 2). The zirconocene reagents are inexpensive, since

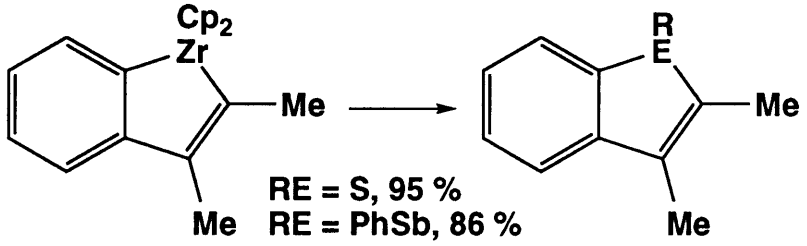
Scheme 2: Formation of Zirconocene-Unsaturated Ligand Complex



zirconocene dichloride costs only $0.36/mmole;[17] the more complex zirconocene precursors can be synthesized on a large scale from zirconocene dichloride in one ($Cp_2Zr(H)Cl$, Schwartz's reagent)[18] or two ($Cp_2Zr(Me)Cl$) high yielding steps. Finally, the product of the reaction, a zirconacyclopentane derivative, can be converted to many useful products (Scheme 1).

This reaction has been extensively used by our group to synthesize cyclic organo-main group compounds,[19,20,21,22] since the discovery, by researchers at DuPont, that zirconacycles will undergo a transmetallation reaction with main group halide reagents.[23,24,25] This simple reaction occurs in high yields upon mixing the two reagents (Scheme 3).

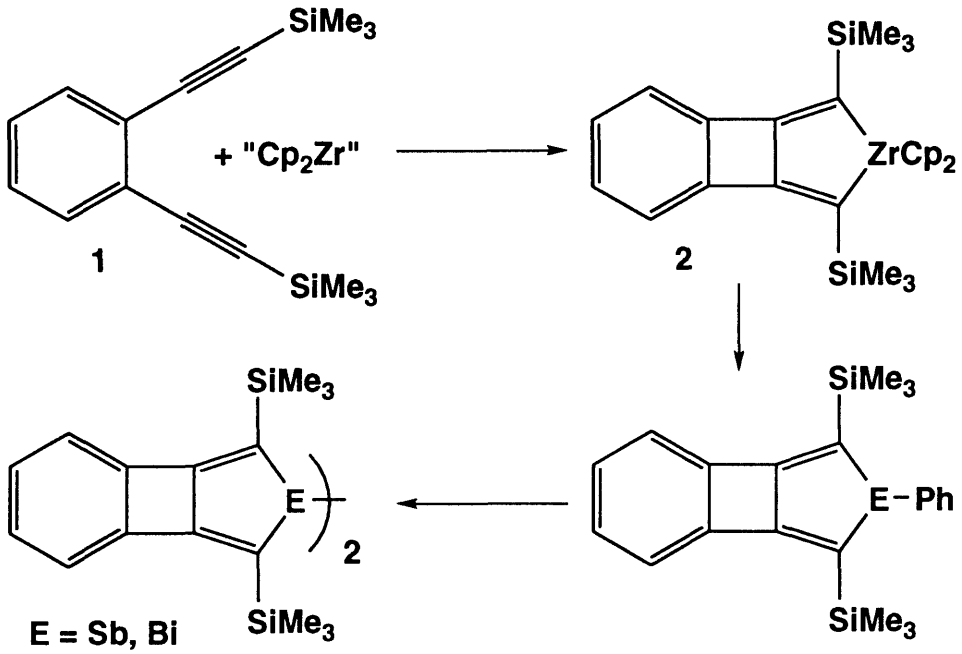
Scheme 3: Examples of Zirconium to Main Group Ligand Transfer



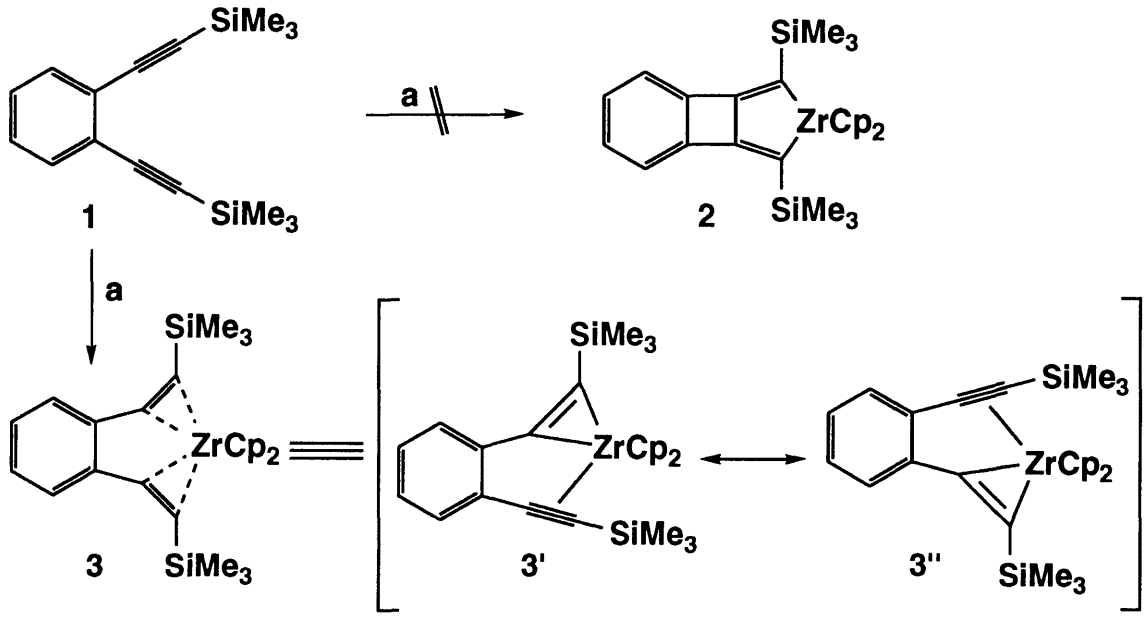
Results and Discussion

We had originally intended to synthesize examples of a new class of highly conjugated, tricyclic stiboles and bismoles, which we would convert to the corresponding distibines and dibismuthines. Compound **1**, synthesized by the palladium-catalyzed coupling of trimethylsilylacetylene and diiodobenzene,[26] was treated with zirconocene dichloride and two equivalents of *n*-butyllithium[15] in an attempt to generate the zirconacyclopentadiene, which would then be converted to the stibole or bismole, and then to the distibine or dibismuthine (Scheme 4).

Scheme 4: Attempted Synthesis of Highly Conjugated Distibines and Dibismuthines



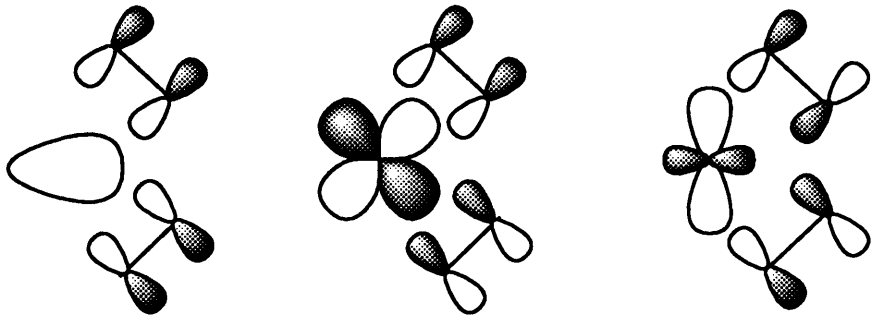
Scheme 5: Result of Attempted Reductive Coupling Reaction



a. Cp_2ZrCl_2/2 *n*BuLi/THF/-78 °C to RT, then hexane to 70 °C (55 %)

However, the zirconocene-mediated reductive coupling reaction of **1** failed to give **2**, but instead, complex **3** was isolated in 55% yield as air-sensitive, orange, crystals (Scheme 5).

Figure 1: Molecular Orbital Description of a Metallocene with Two η2 Alkyne Ligands



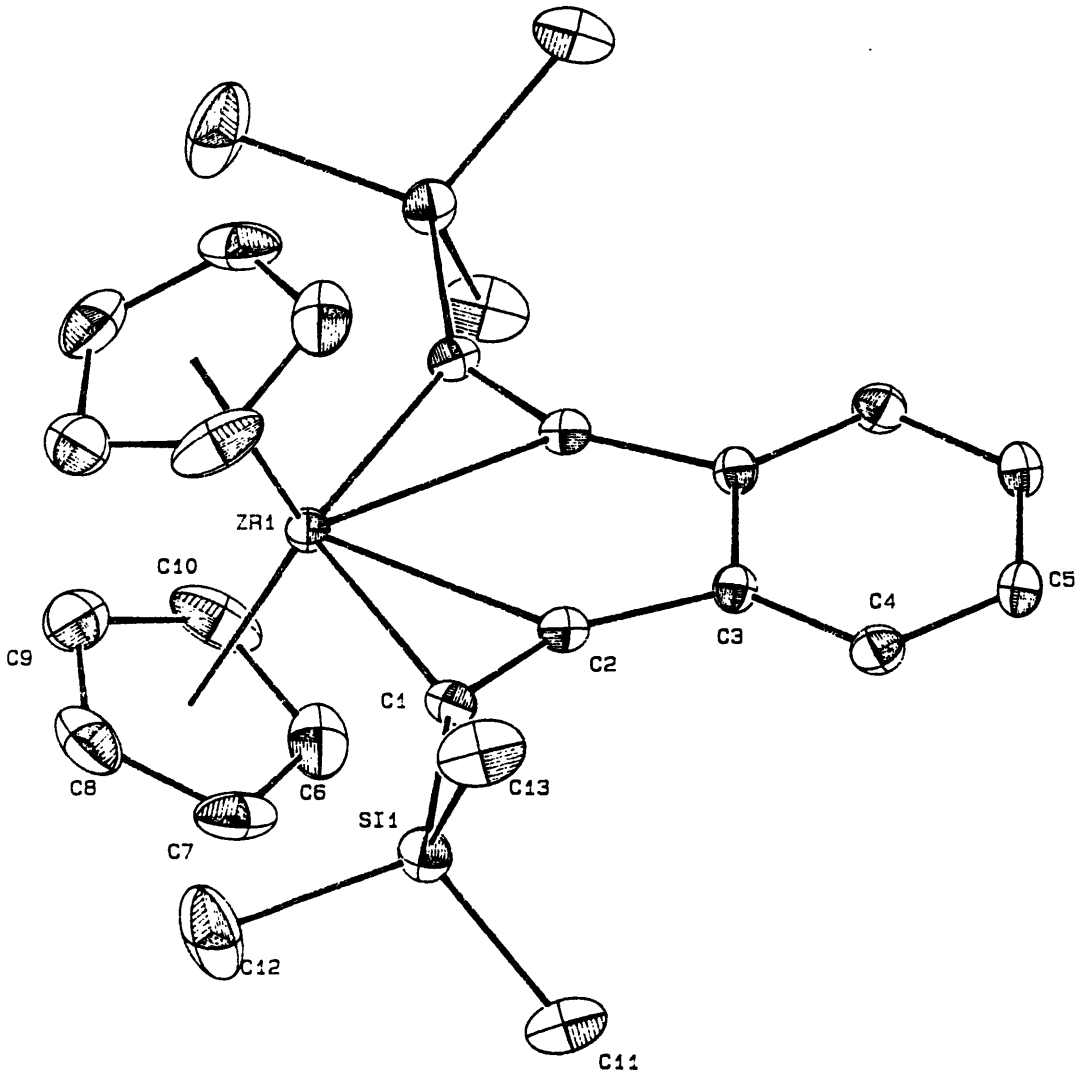
$a_1+\pi$ $b_2+\pi$ $a_1+\pi^*$

The nature of **3** is best described by the molecular orbital picture where there are three alkyne to metal interactions, two of which involve donation from the two alkyne π-systems to the metal ($a_1+\pi$, $b_2+\pi$), and one of which is backbonding from the metal to the π^* system of the alkynes ($a_1+\pi^*$) (Figure 1).[27,28] One ramification of this orbital description is that each alkyne possess full σ-bonding to the zirconium center, but there is only half the normal π-backbonding than is seen in the more conventional metallacyclopropenes; the two electrons in the $a_1+\pi^*$ orbital are shared equally between the two alkynes. This π-backbonding is manifested in the characteristics of the identical alkynyl ligands, both of which display spectroscopic and structural features almost exactly half-way between free alkynes and zirconacyclopropenes (which have 2 e^- worth of backbonding). A consequence of this data (*vide infra*) is that **3** is difficult to describe by a single Lewis structure. Complex **3** can be best

represented as the superposition of the degenerate resonance contributors **3'** and **3''**, each of which implies a Zr(IV) with one dative alkyne ligand and one zirconacyclopropene moiety. That we were unable to "freeze out" any discrete zirconacyclopropene-alkyne complex by either low temperature NMR or solid phase IR supports the notion that **3'** and **3''** are equivalent resonance forms and not in rapid equilibrium.

An ORTEP of the structure resulting from an X-ray diffraction determination is shown in Figure 2. The molecule possesses a crystallographic C_2 axis of symmetry. The effects of partial π-backbonding are manifested by the fact that the C_1-C_2 bond distance of 1.258(5) Å in **3** is approximately halfway between the value of 1.195(3) Å seen in hexakis(trimethylsilylethynyl)benzene[29] and the length of 1.302(9) Å in zirconacyclopropene **6**,[30] and similar to the distance of 1.25 Å in **7**.[31] Further, the C_2-C_1-Si and C_1-C_2-C_3 bond angles in **3** are similar to the analogous angles in **4**,[32] **5**,[33] and **6** (Table 1). Consistent with this representation, no change, other than slight broadening, is observed in the ^{1}H NMR spectrum at temperatures as low as -92 °C (toluene-d_8). The IR spectrum exhibits only a single stretch in the alkyne region at 1816 cm^{-1}. This signal is approximately mid-way between that observed for **1** at 2161 cm^{-1}, and that seen in normal group 4 metallacyclopropenes in **4** at 1620 cm^{-1}, **5** at 1686 cm^{-1}, and **6** at 1581 cm^{-1}. The alkyne stretch is similar to that of **7**, which is 1755 cm^{-1}. Similarly, in the ^{13}C NMR spectrum of **3**, signals for only two alkynyl carbons are present at 143.3 and 154.2 ppm. These resonances are roughly equidistant from those observed for their counterparts in **1** (98.4 and 103.3 ppm), and **4** (177.4 and 181.0 ppm), **5** (213.0 and 219.6 ppm), and **6** (212.9 ppm), and similar to the relevant signal for **7** (151 ppm).

Figure 2: ORTEP Diagram of 3

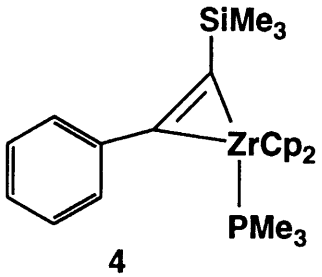


Selected Bond Distances (Å): Zr_1-C_1, 2.346(4); Zr_1-C_2, 2.390(4); Si_1-C_1, 1.854(4); C_1-C_2, 1.255(5); C_2-C_2', 2.319(7); C_2-C_3, 1.460(5). Selected Bond Angles (°): Si_1-C_1-C_2, 140.0(3); C_1-C_2-C_3, 155.2(4); C_2-C_3-C_3', 108.9(2); Zr_1-C_1-C_2, 76.6(2); Zr_1-C_2-C_1, 72.7(2); C_1-Zr_1-C_2, 30.7(1).

The above data suggests that the bond order of the ligated alkyne corresponds to the average number of electrons involved in a backbonding type interaction. Free alkynes have a bond order of three, which is reduced to approximately two in zirconacyclopropenes. Zirconocene(III)-alkyne complexes have a bond order approximately mid-way between these extremes. The

zirconocene-bis(alkyne) complex has two electrons involved in backbonding interactions with two alkynes, for an average of one electron per alkyne, and thus its alkyne ligands are similar to those in the zirconocene(III)-alkyne complex.

Table 1: Comparison of Physical Data of Several Compounds



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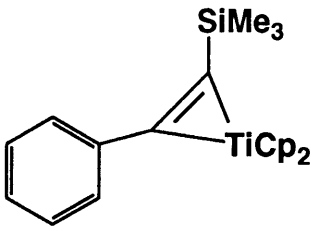

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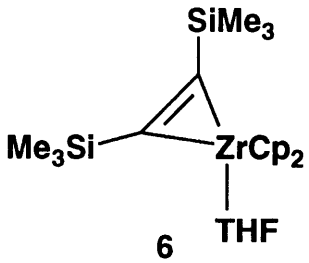

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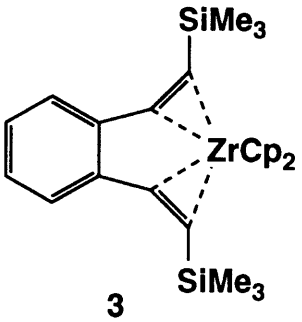
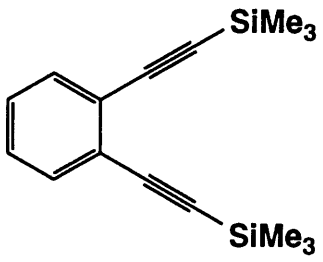
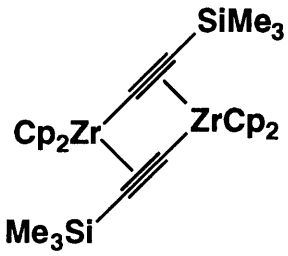


3



1

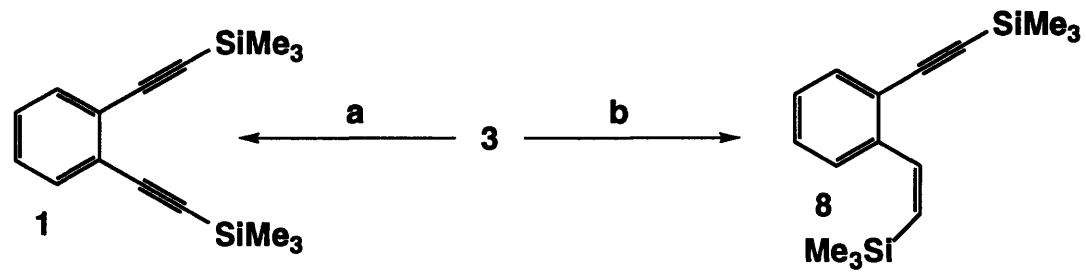


7

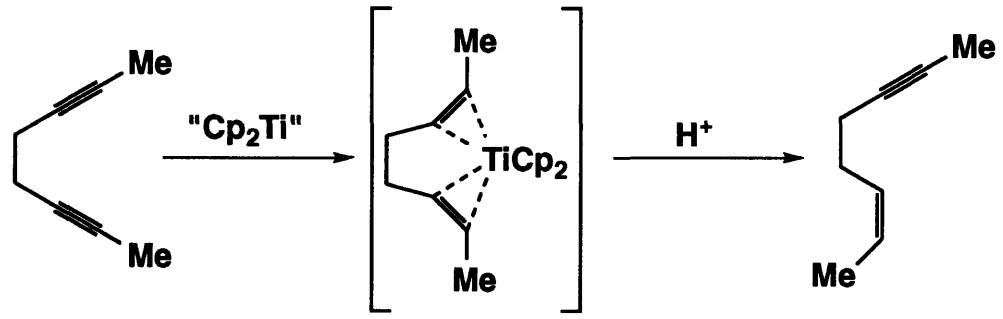
Compound	C_2-C_1-Si bond angles °	C_1-C_2-C_3 bond angles °
3	140.0(3)	155.2(4)
4	148.2(2)	141.0(2)
5	140.8(3)	151.9(3)
6	143.5(6) / 134.4(6)	--
7	144	--

Compound	IR / Alkyne (cm^{-1})	^{13}C (ppm)
3	1816	143.3, 154.2
4	1620	177.4, 181.0
5	1686	213, 219
6	1581	212
1	2161	98, 103
7	1755	151, 245

Scheme 6: Reactions of 3



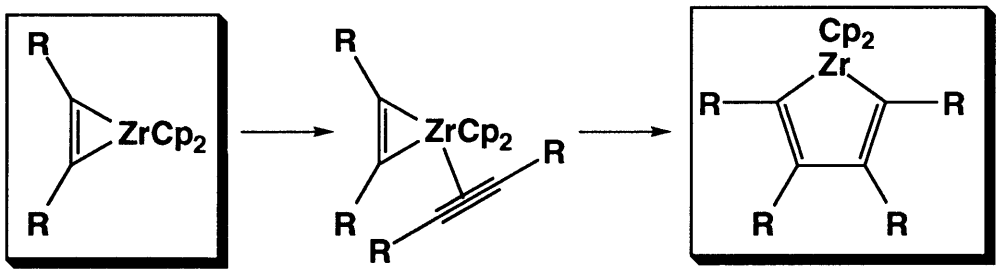
a. I_2/THF/-78 °C (88 %) b. H_2SO_4/H_2O/THF (92 %)



The reactions of **3** are also consistent with the above structural description (Scheme 6). For example, treatment of **3** with I_2 produces zirconocene diiodide and reforms **1** in 88% yield.[34] Treatment of **3** with aqueous sulfuric acid gives enyne **8**, in 92% yield.[9,34] This result is similar to that seen by Nugent, where hydrolysis of the product of the reaction of "titanocene" and 2,6-octadiyne yielded *Z*-6-octene-2-yne, while the corresponding zirconacycle was isolated and structurally characterized.[9]

The structure and reactivity of compound **3** address the mechanism of zirconocene-mediated reductive coupling.[9,28,27] This process is thought to have three principal intermediates, only two of which had been isolated: a zirconacyclopropene,[30,32,4,35,16] a postulated intermediate zirconocene-bis(alkyne) complex, and a zirconacyclopentadiene (Scheme 7).[9,36] Molecular orbital descriptions of each of these intermediates have been calculated.

Scheme 7: Mechanism and Intermediates of Zirconium-Mediated Alkyne Coupling



not previously isolated

The first step in the zirconocene-mediated reductive coupling is formation of the alkyne complex. This intermediate can be formed in one of two fashions: addition of a zirconocene source to an alkyne, or β-hydrogen elimination or abstraction from a vinyl(methyl)zirconocene species (Scheme 8). The zirconocene-alkyne complex can be described by the Dewar-Chatt-Duncanson model, where the alkyne π-orbital interacts with an empty zirconium orbital in a σ-type interaction, and the filled zirconium orbital interacts with the alkyne π^*-orbital in a π-type interaction (Figure 3). Overall, the effect of these interactions is to lower the bond order of the alkyne from three to two. Thus a zirconocene-alkyne complex is best described as a zirconacyclopropene.

Scheme 8: Formation of Zirconocene-Alkyne Complexes

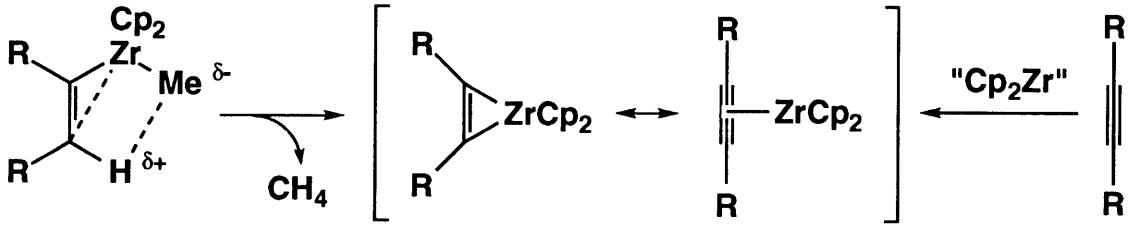
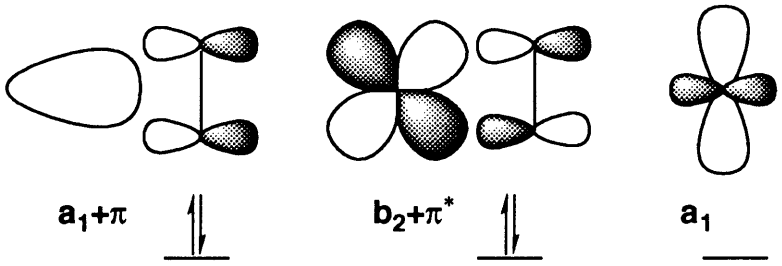
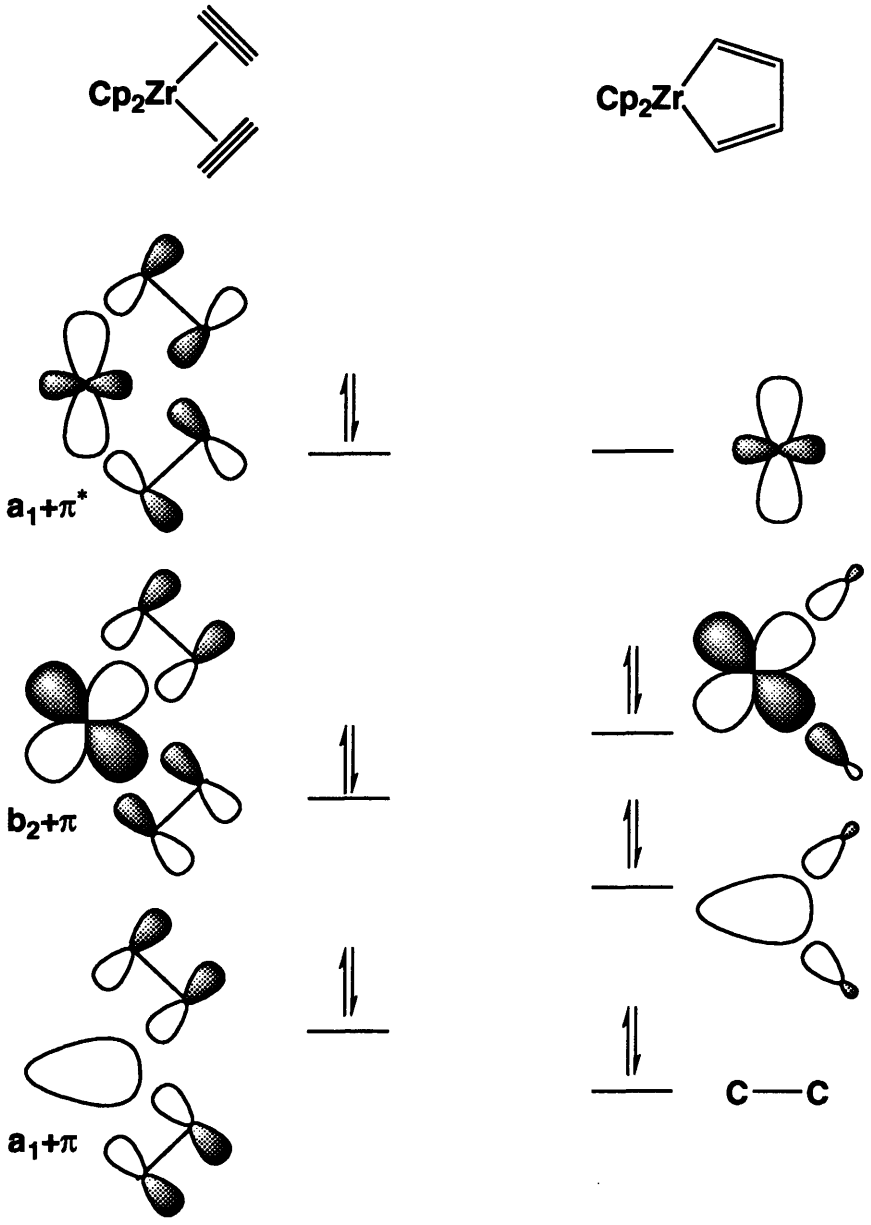


Figure 3: Orbital Description of a Zirconocene-Alkyne Complex



The zirconacyclopropene is a 16 electron species, with an empty orbital available for complexation of a second alkyne. This complexation occurs spontaneously, to form a bis-alkyne complex, the properties of which have been described above. This sort of complex is usually unstable relative to the zirconacyclopentadiene, and generally cannot be isolated (Scheme 9). The thermodynamic parameters of the reaction can be easily calculated. The zirconocene-bis(alkyne) complex has three zirconium-carbon interactions, while the zirconacyclopentadiene has two carbon-zirconium bonds and one carbon-carbon bond. The net difference in energy between the two species should be the difference between a carbon-carbon and a carbon-zirconium bond (~12 kcal/mol).[37,38] However, under circumstances where the carbons involved in the incipient carbon-carbon bond are held too far apart to interact fully, the zirconacyclopentadiene is destabilized relative to the zirconocene-bis(alkyne) complex, and that species can be isolated (Scheme 10). The thermodynamic argument is supported by the fact that **3** is not converted to **2** even when heated to 195 °C for 5 h.

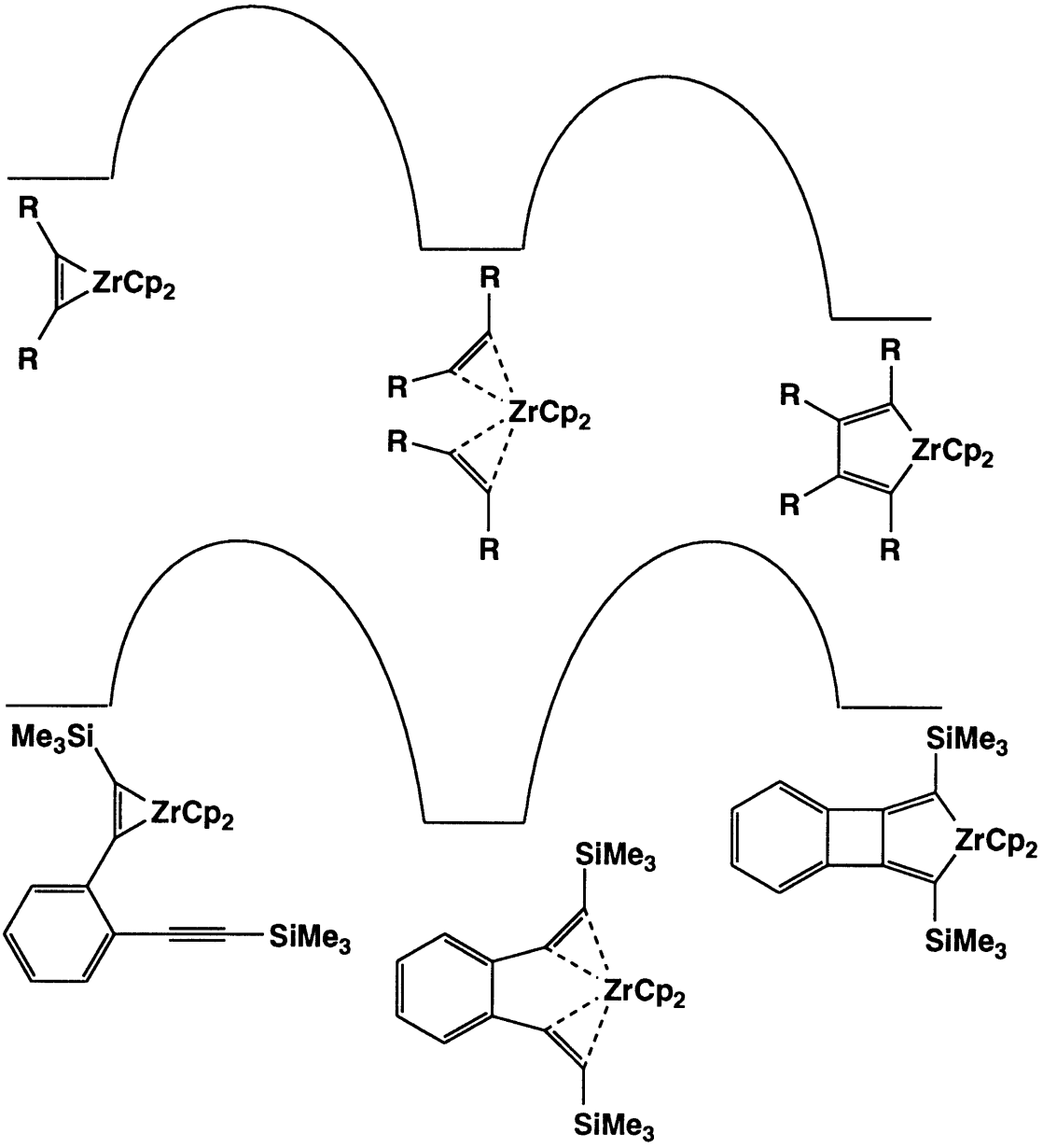
Scheme 9: Orbital Description of Coupling Reaction



In conclusion, we have prepared and isolated the first complex where zirconocene is bound to two alkynyl ligands. Compound **3** demonstrates the viability of a zirconocene-bis(alkyne) complex, which has been proposed as an intermediate in the zirconocene-induced reductive coupling of alkynes. The structural and spectroscopic data shows that **3** is best described by the orbital

depiction calculated by Hoffmann. Further, the structural and spectroscopic data of **3** supports the idea that the physical properties of complexed alkynes correlate to the amount of backbonding from the metal to the alkyne.

Scheme 10: Profile of Zirconocene-Mediated Reductive Coupling



Experimental Section

General Considerations

All reactions were carried out under an atmosphere of argon or nitrogen using standard Schlenk and glove box techniques. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity-300, Varian XL-300 or Bruker AC-250 Fourier transform spectrometer. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 series Fourier transform spectrometer. Gas chromatography (GC) analyses were performed on a Hewlett-Packard model 5890 gas chromatograph with a flame ionization detector and a model 3392A integrator using a 25 meter capillary column with polymethylsiloxane (Hewlett-Packard) as a stationary phase. The electron impact high resolution mass determination (HRMS) of **8** was recorded on a Finnegan MAT System 8200. A sample of **3** was sent in a sealed vial under nitrogen to Oneida Research Services, Inc. for elemental analysis. Melting points were determined with a Haake Buchler melting point apparatus and are uncorrected.

Tetrahydrofuran (THF) was dried and deoxygenated by refluxing and distilling from sodium / benzophenone ketyl under an argon atmosphere. Hexane was dried and deoxygenated by refluxing and distilling from sodium / benzophenone ketyl under a nitrogen atmosphere. Preparative flash chromatography was performed on silica gel (E. M. Science Kieselgel 60, 230-400 mesh). All reagents, unless otherwise stated, are commercially available and were used as received.

Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as determined by capillary GC and/or ^{1}H NMR spectrometry.

Preparation of 3

Original Procedure

A dry Schlenk flask was charged with zirconocene dichloride (0.973 g, 3.33 mmol) in the glove box. The flask was removed from the glove box and attached to a Schlenk line, and tetrahydrofuran (30 mL) was added. The flask was cooled to -78 °C and n-butyllithium (4.24 mL, 1.57 M in hexane) was added dropwise.[15] After 15 min, a degassed solution of **1**[26] (0.900 g, 3.33 mmol) in tetrahydrofuran (10 mL) was added *via* cannula, and the mixture was allowed to warm to room temperature over 1 h. The tetrahydrofuran was removed in vacuo and hexane (20 mL) was added to the remaining solid. The hexane was removed in vacuo (to remove the last traces of tetrahydrofuran) and the solid was redissolved in hexane (50 mL). The solution was cannula filtered into a second dry Schlenk flask and the solvent was removed until crystals began to form. The compound was then allowed to crystallize overnight at -20 °C, yielding **3** as air sensitive, orange, crystals (0.848 g, 52 %): Mp 193-195 °C. ^{1}H NMR (300 MHz, C_6D_6) δ 0.51 (s, 18 H), 5.19 (s, 10 H), 7.00 (dd, J = 3.0 Hz, 5.5 Hz, 2 H), 7.80 (dd, J = 3.0 Hz, 5.5 Hz, 2 H). ^{13}C NMR (75 MHz, C_6D_6) δ 1.66, 104.37, 127.25, 127.65, 129.17, 143.32, 154.16. IR (KBr) 3061, 2953, 2346, 1816, 1700, 1696, 1685, 1653, 1636, 1617, 1576, 1534, 1459, 1448, 1404, 1258, 1242, 1165, 1090, 1010, 866, 830, 785, 749, 691, 614, 589, 505. Anal. Calcd. for $C_{26}H_{32}Si_2Zr$: C, 63.48; H, 6.56. Found: C, 63.73; H, 6.73.

The ^{1}H NMR spectrum did not change when a sample of **3** was placed in toluene-d_8 and cooled to -92 °C. A sample of **3** was placed in toluene-d_8 and heated for 195 °C for 5 h, then allowed to cool. The ^{1}H NMR spectrum was identical to that of the sample before heating.

Modified Procedure

A flame dried Schlenk flask was charged with zirconocene dichloride (0.535 g, 1.8 mmol) in the glove box. The flask was removed from the glove box and attached to a Schlenk line, **1** (0.495 g, 1.8 mmol) was added as a solid, then tetrahydrofuran (20 mL) was added *via* syringe. The flask was cooled to -78 °C and n-butyllithium (2.6 mL, 1.38 M in hexane) was added dropwise. After 15 min the mixture was warmed to room temperature by submersion of the Schlenk flask in a water bath. The tetrahydrofuran was removed in vacuo and the solid was dissolved in hexane (50 mL). The solution was cannula filtered into a second flame dried Schlenk flask and the solvent was removed. As judged by ^{1}H NMR, the reaction was incomplete, so hexane (30 mL) was added and the solution was heated at 70 °C for 30 min. The solvent was then removed in vacuo until crystals began to form. The compound was then crystallized overnight at -80 °C, to yield **3** as orange crystals (0.524 g, 59 %).

Protonation of 3

A flame dried Schlenk flask was charged with **3** (0.253 g, 0.514 mmol) in the glove box. The flask was removed from the glove box and attached to a Schlenk line, and tetrahydrofuran (5 mL) was added. 10 % Aqueous sulfuric acid (5 mL) was added rapidly by syringe; the orange solution immediately turned pale yellow. The reaction was allowed to stir for 20 min, then water (50 mL) was added, and the mixture was extracted with hexane (2 x 50 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed at reduced pressure to afford a yellow oil. The oil was purified by flash chromatography (hexane) yielding **8** as a colorless oil (0.129 g, 92 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ .-0.01 (s, 9 H), 0.22 (s, 9 H), 5.88 (d, J = 15 Hz, 1 H), 7.14-7.29 (m, 3 H), 7.31 (dd, J = 1.2 Hz, 6.7 Hz, 1 H), 7.51 (d, J = 15 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ .04, .11, 99.08, 103.71, 122.26, 127.15, 127.81,

128.11, 132.19, 133.64, 142.54, 145.13. IR (Film) 3061, 3022, 2959, 2898, 2157, 1591, 1558, 1471, 1444, 1408, 1375, 1294, 1248, 1200, 1094, 1038, 949, 878, 758, 693, 667, 645. HRMS Calcd. for $C_{16}H_{24}Si_2$: 272.1416. Found: 272.1418.

Iodination of 3

A flame dried Schlenk flask was charged with complex **3** (0.250 g, 0.508 mmol) in the glove box. The flask was removed from the glove box and attached to a Schlenk line, tetrahydrofuran (5 mL) was added, and the solution was cooled to -78 °C. A solution of iodine (0.258 g, 1.02 mmol) in tetrahydrofuran (5 mL) was added dropwise *via* cannula, and the orange solution rapidly turned dark purple. The reaction was allowed to stir for 90 min at -78 °C, then warmed to room temperature. The excess iodine was removed by the addition of aqueous sodium thiosulfate (100 mL, saturated). The mixture was extracted with dichloromethane (3 x 50 mL), and the combined organics were dried ($MgSO_4$) and filtered. The solvent was removed at reduced pressure to yield a yellow oil, which was purified by flash chromatography (hexane) to afford **1** (0.123 g, 90 %).

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(17) Note The price of Cp_2ZrCl_2 is taken from the 1993-1994 catalog of Strem Chemicals, Inc.

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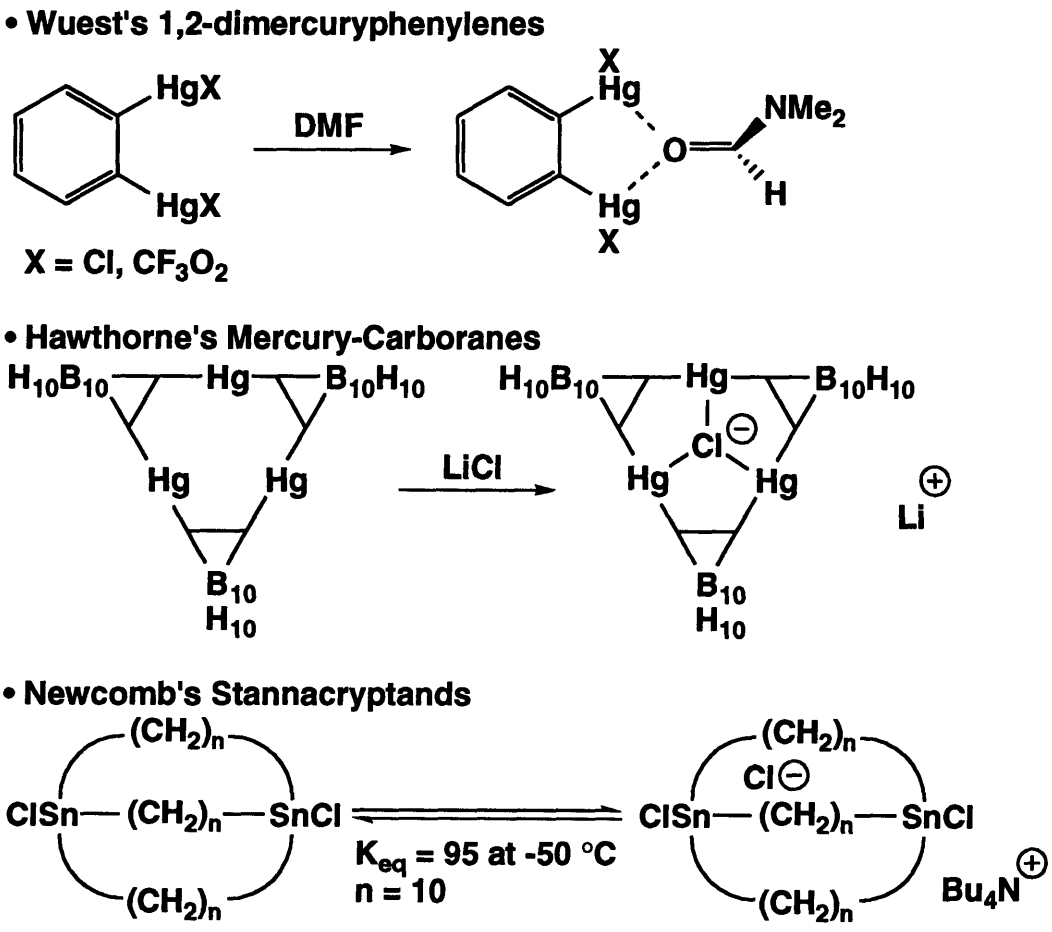
Chapter 2

Control of the Bergman Cyclization by Non-Covalent Interactions

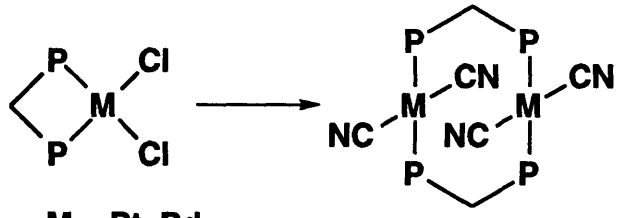
Introduction

The use of organo-main group compounds has provided opportunities in the binding of small organic molecules, main group elements, and metals.[1] Some researchers in this area have focused on the recognition of Lewis bases by Lewis acidic hosts, such as in the systems developed by Katz (rigid diborones)[2,3,4,5] Wuest (1,2-phenylene-bis(mercury)-based systems),[6,7,8] Hawthorne (carborane-mercury-based systems),[9,10] and Newcomb (tin analogs of crown ethers and cryptands)[11,12,13,14,15] (Figure 1). Chelating phosphines have been developed to complex metals in novel fashions.[16,17] Shaw has examined the properties of bis(phosphino)alkanes which form dinuclear metal complexes.[18,19]

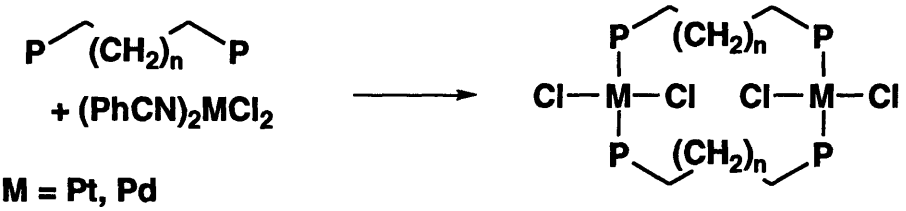
Figure 1: Examples of Main Group-Based Host Molecules



• **Shaw's Bridging Phosphines**



M = Pt, Pd
P = PPh_2



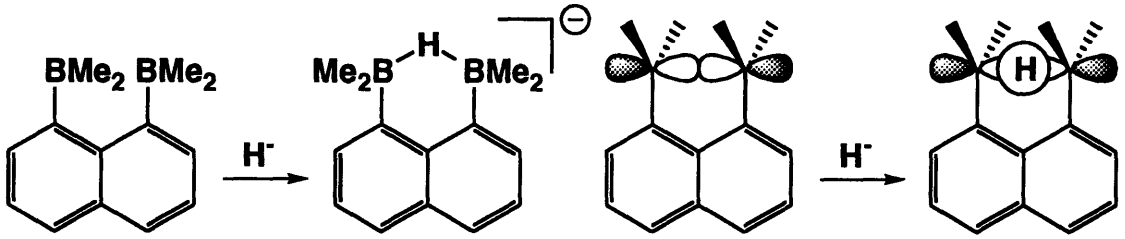
M = Pt, Pd
P = P*t*Bu_2
n = 9, 10, 12

The main group elements offer flexibility over more traditional organic components, usually at the price of air-sensitivity. Different main group elements exhibit varying degrees of acidity or basicity, so that ligands can be designed to coordinate basic or acidic guests. These elements vary in size, with covalent radii from 0.85 Å in boron to 1.33 Å in iodine, to 1.41 Å in antimony.[20] Further, some of these elements provide unusual geometries. Two examples of this are antimony[21] and iodine,[22] in which the s-orbital essentially does not mix with the p-orbitals, resulting in bond angles of close to 90°. Organo-main group compounds are easily synthesized by the reaction of an alkylmetal reagent with the desired main group halide. Finally, vinyl- and alkynyl-main group compounds are generally stable. This point is in contrast to oxygen or nitrogen, two traditional organic Lewis bases, which do not generally form stable compounds in these circumstances.

Several main group based hosts have influenced our research. Our principal inspiration was the work of Howard Katz. One of his compounds was 1,8-bis(dimethylboryl)naphthalene,[3] called "hydride sponge" in analogy with the

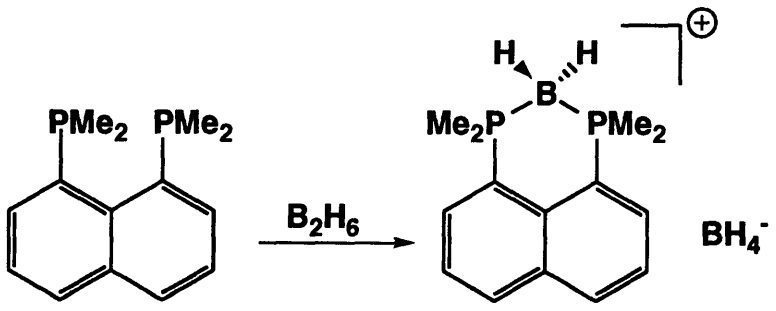
nitrogen-based "proton sponge." This compound abstracts a hydride from many sources.[2] Its high affinity for complexation of small anionic guests was explained by cooperativity between the two Lewis acidic boron atoms. In this molecule, the empty p-orbitals of the two boron atoms were forced to overlap with each other in order to minimize the steric interactions between the methyl ligands. This overlap increased the acidity of the pocket beyond that of a lone boron atom (Figure 2).

Figure 2: Katz's "Hydride Sponge"



The phosphine analog was also synthesized; its affinity for boron was strong enough to cause diborane to disproportionate into BH_2^+ and BH_4^- (Figure 3).[16]

Figure 3: Phosphine Analog of "Proton Sponge"



Katz has also studied 1,8-bis(catacholborylethynyl)anthracene (Figure 4).[5] The pocket in this molecule was the correct size to bind pyrimidines cooperatively between the two boron atoms, increasing the binding constant of the borane with 5-methylpyrimidine from 70 (in the non-cooperative analog where one of the catecholboranes was replaced by a hydrogen) to 130. The 1:1 complex was only displaced with a large excess of the pyrimidine (binding constant for 2:1 complex was 40).

Figure 4: Katz's 5-Methylpyrimidine Binder

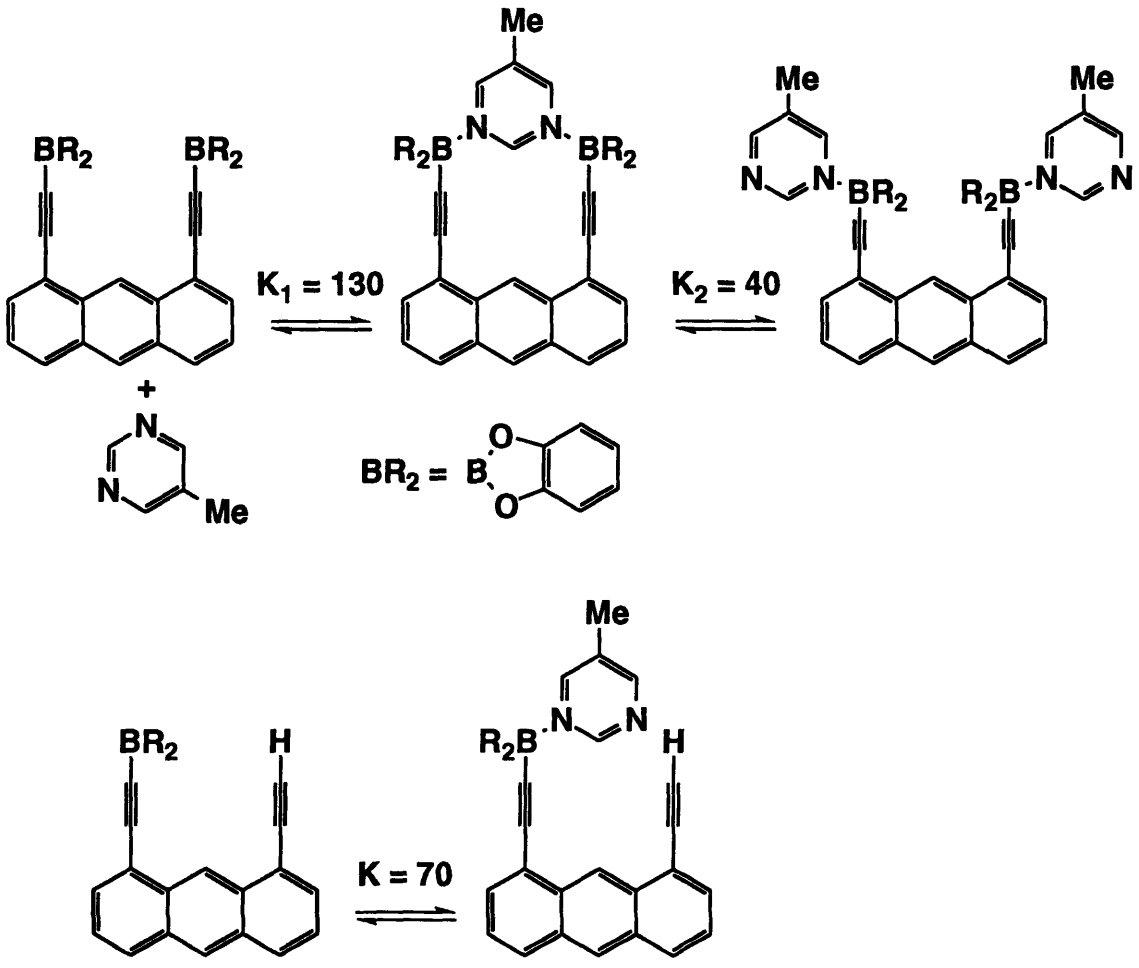
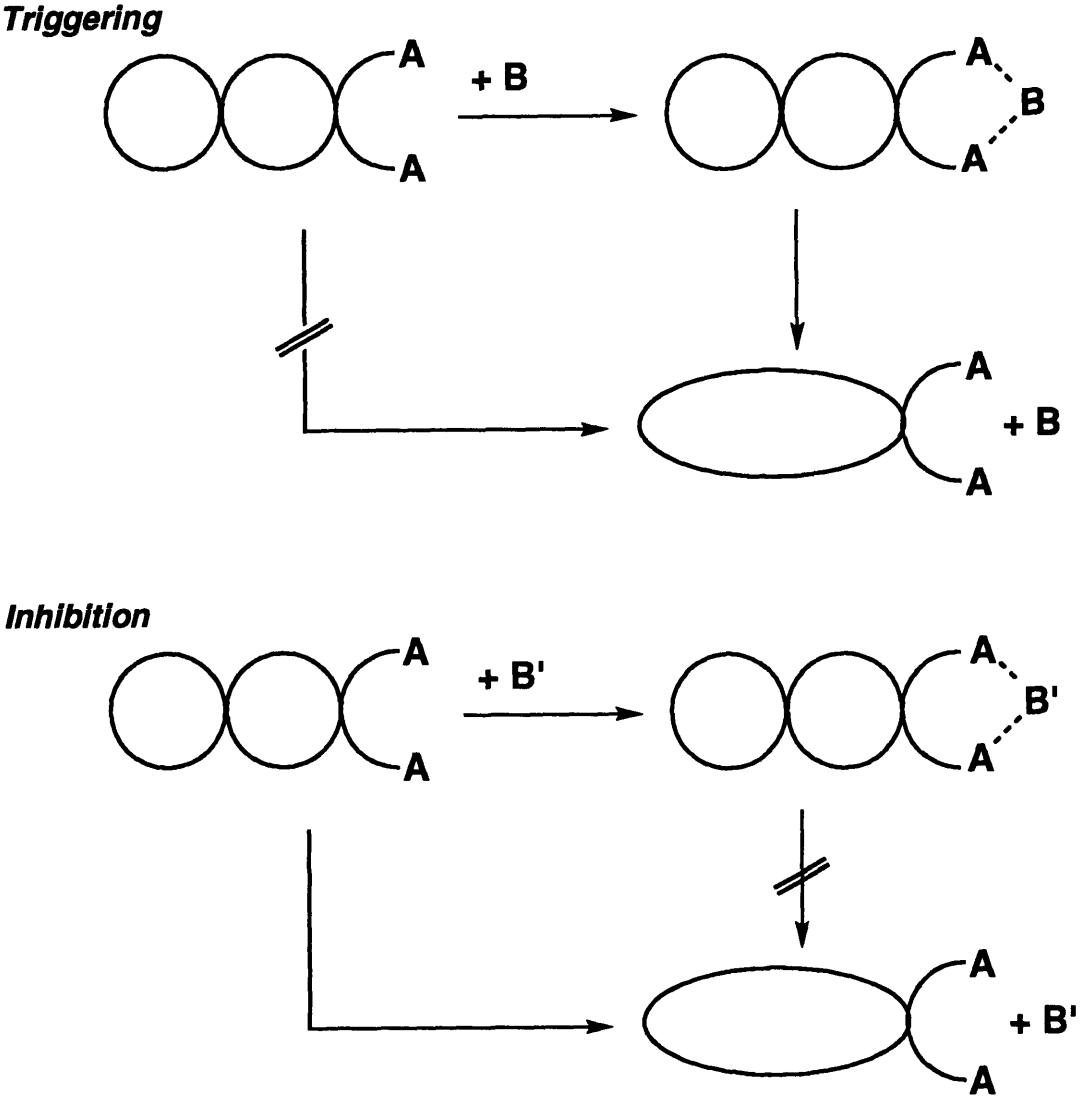


Figure 5: Schematic Description of Project Goals

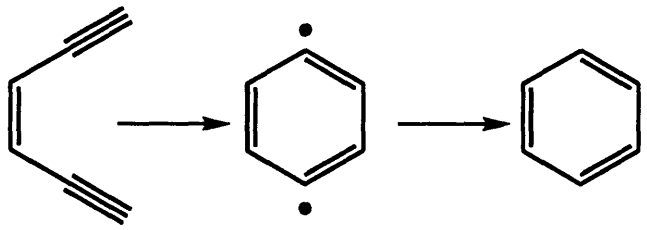


With this background in mind, I decided to investigate the next generation of organo-main group hosts. In contrast to many systems that had previously been studied, I wished to use the intermolecular interactions to effect reactivity. The ultimate goal was to develop compounds in which conformational changes induced by metal-ligand interactions would lead to a chemical of physical change in the material (Figure 5).

Enediynes compose a class of compounds known to respond to small changes in geometry (Figure 6). These compounds undergo the Bergman

cyclization to the 1,4-benzene diradical,[23] with a rate dependent on the distance between the alkynes.[24]

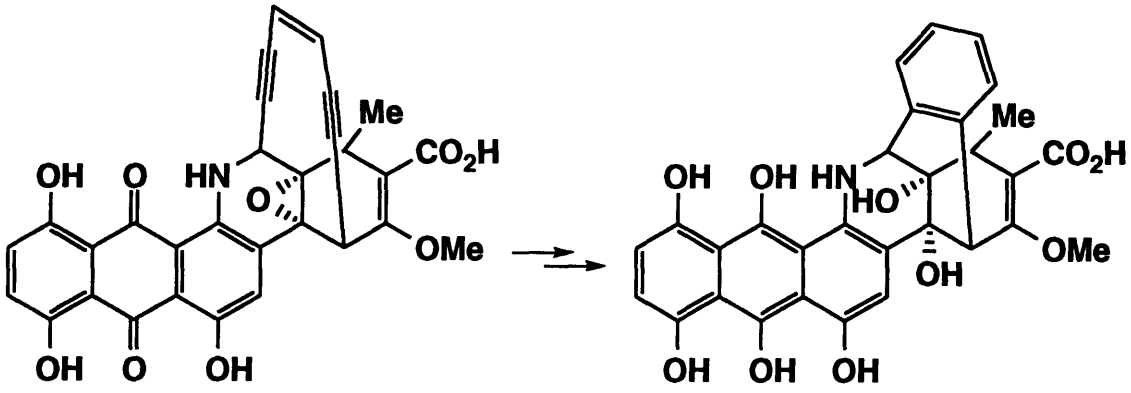
Figure 6: Bergman Cyclization of Enediynes



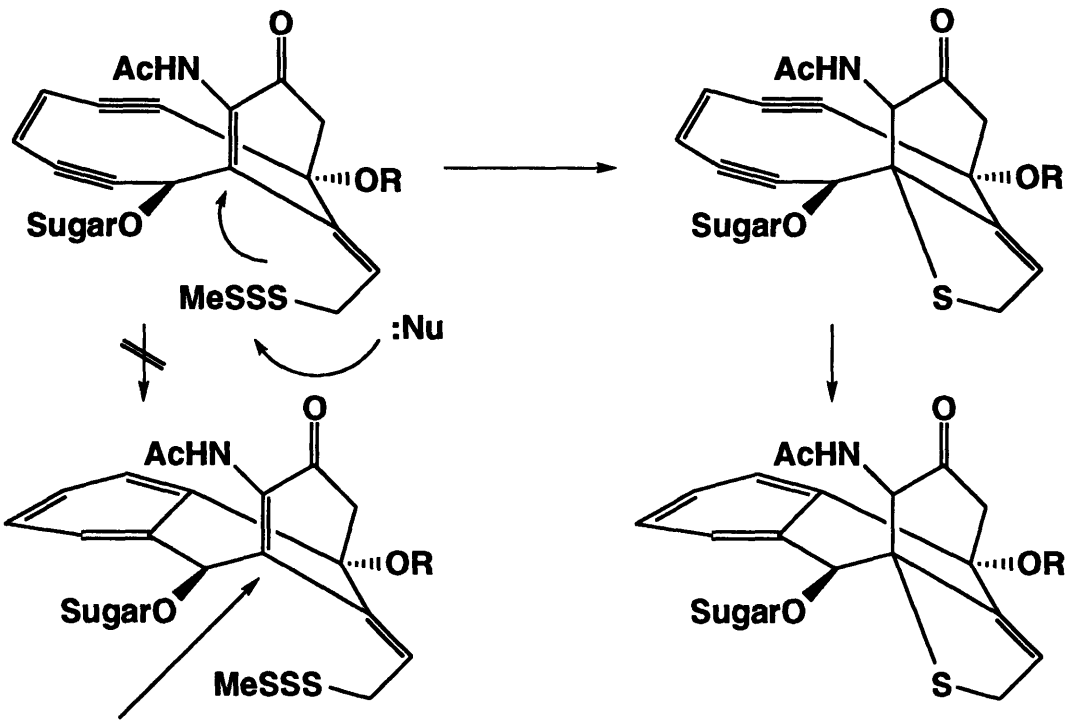
The discovery that the enediyne moiety was the pharmacologically active component of several naturally occurring[25,26] and designed[27,28,29,30] compounds with anti-tumor properties has stimulated renewed interest in the Bergman cyclization. These compounds include the calicheamicins / esperamicins, and the dynemicins (Figure 7).

Figure 7: Naturally Occurring Enediynes

Dynemicin A



Calicheamicins and Esperamicins



The synthesis of analogs of these agents has yielded several insights into the requirements of the Bergman cyclization. The most prominent of these is the correlation of the distance between the alkynes (**d** in Figure 8) with the propensity of a cyclic enediyne to undergo a Bergman cyclization (Table 1). Enediynes with distances of less than 3.34 Å were found to cyclize, while cyclization was not observed in those with distances greater than 3.4 Å.[24,31] A short alkyne-alkyne distance, however, is not sufficient to ensure cyclization, as demonstrated by the failure of calicheamicin or esperamicin (**d** = 3.35 Å) to cyclize before the Michael addition to the enone removes the incipient bridgehead double bond (Figure 7). Enediynes with distances of less than 3.2 Å have not been isolated, presumably due to their extreme reactivity.

Table 1: Cyclization Rate vs. Alkyne Termini Distance of Enediynes[31,24]

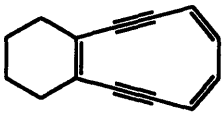
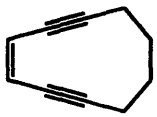
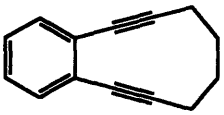
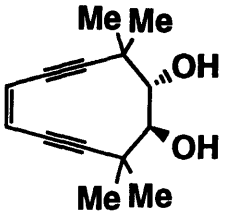
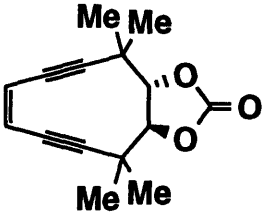
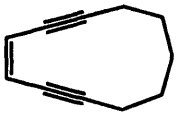
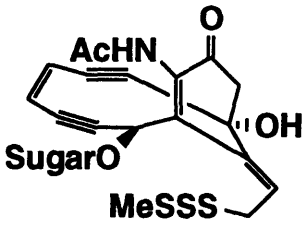
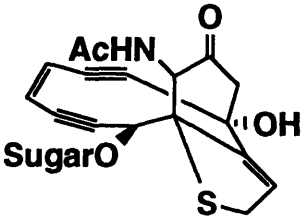
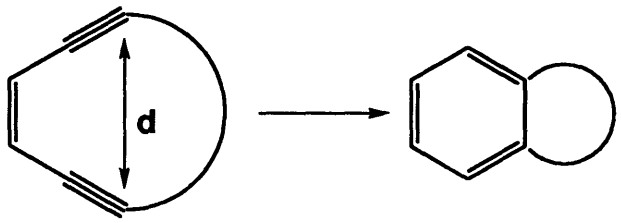
Compound	Ring Size	Distance	Rate ($t_{1/2}$)
	10	2.99 Å	"Spontaneous"
	10	3.25 Å	18 h at 37 °C
	10		24 h at 84 °C
	10	3.34 Å	2 h at 50 °C
	10	3.42 Å	Stable at 25 °C
	11	3.61 Å	no cyclization
	10	3.35 Å	Stable at 25 °C
	10	3.16 Å	"Spontaneous"

Figure 8: Conformational Dependence of the Bergman Cyclization



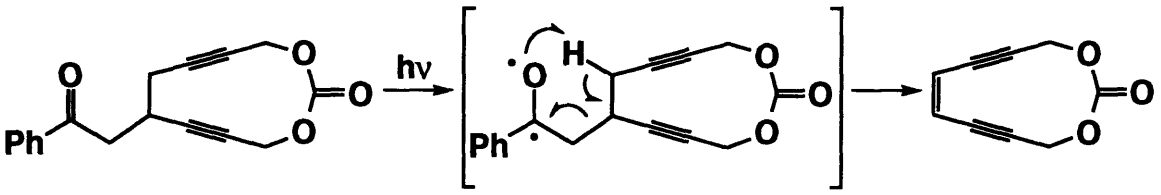
d ≥ 3.34 Å, cyclization observed

d < 3.4 Å, no cyclization observed

d > 3.2 Å, "spontaneous" cyclization

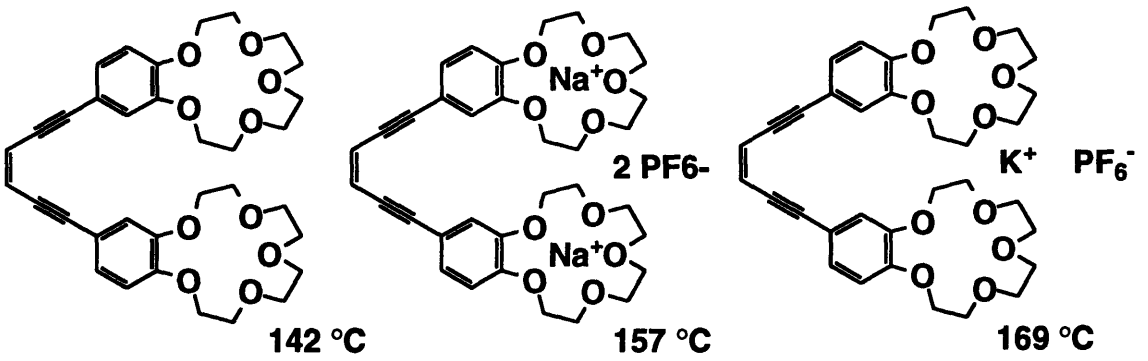
Several strategies to control the Bergman cyclization have been explored in order to design pharmacologically useful compounds. Nuss has used a photochemical Norrish type II reaction to generate a cyclic enediyne from a cyclic diyne carbonate. However, the eleven-membered ring generated, as expected, did not undergo a cyclization (Figure 9).[32]

Figure 9: Photochemical Generation of Enediyne



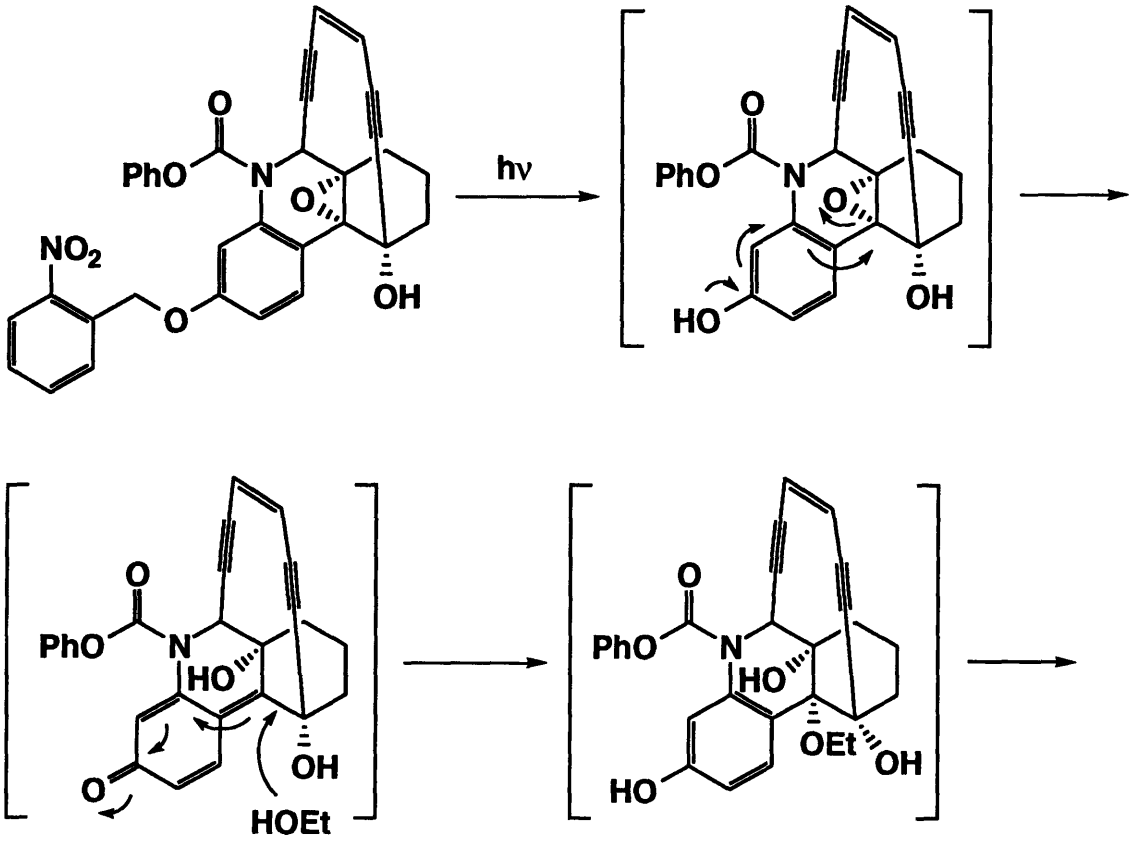
König has synthesized a bis(crown ether) based enediyne, which was complexed to sodium and potassium cations. This had the effect of raising the temperature needed to effect cyclization, as monitored by differential scanning calorimetry (DSC) (Figure 10).[33]

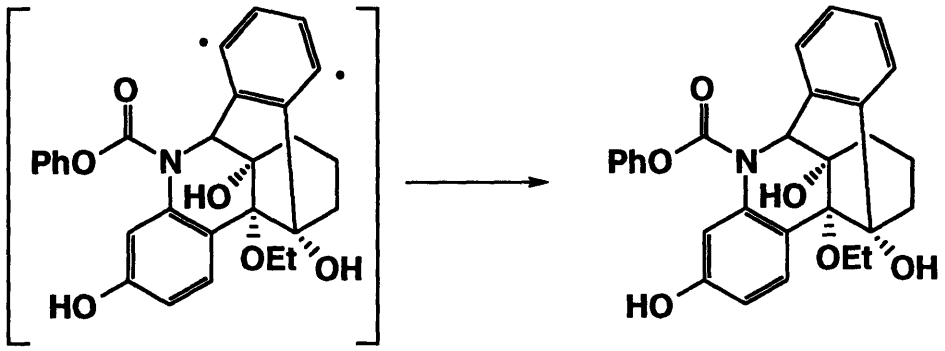
Figure 10: Bis(Crown Ether) Based Enediynes



Nicolaou has investigated several triggering systems for enediynes modeled after dynemicin (Figure 11).[28]

Figure 11: Photochemical Triggering of Bergman Cyclization





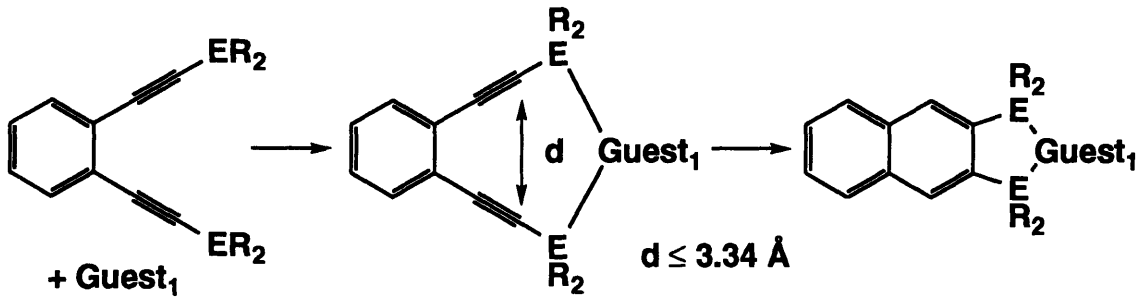
As part of my study into viable means for controlling the reactivity of enediynyl ligands, I identified five attributes for an enediyne which would facilitate its exploitation in biological systems: the molecule must be stable enough to store, compatible with biological systems, able to bind to various targets, and easy to synthesize. It must also cyclize readily at ambient temperatures. A candidate is an acyclic enediyne capable of chelating a metal. Upon complexation, the termini of the alkynes are brought close enough to effect cyclization. Given the wide choice of size among the metals, One should be able to control the size of the ring, and thus the speed of cyclization, by choice of chelated metal. A metal complex compatible with biological conditions, such as *cis*-platin,[34] could be used for triggering the Bergman cyclization.

Definitions

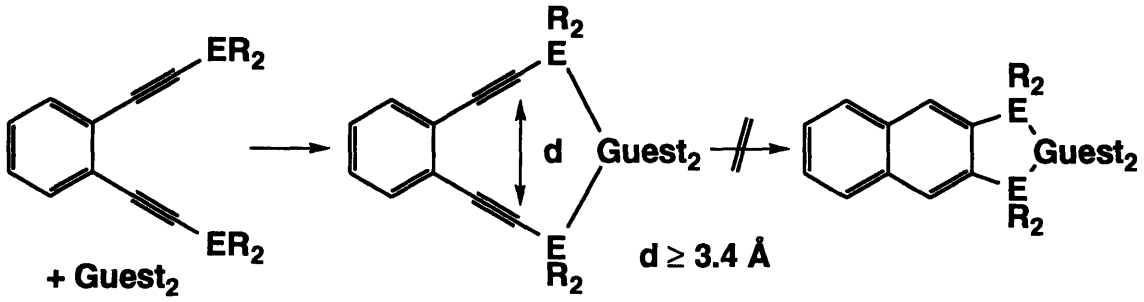
Since the work described below involves the study of chelating metal-phosphine complexes, for clarity, I define **#/M** to mean a 1:1 mixture of compound **#** and metal **M**, while **#•M** refers to a complex where both phosphorus atoms on ligand **#** are bound to metal **M**. The specific goal of the research was to develop systems where the size and geometry of the guest molecule would influence the alkyne-alkyne distance **d** enough to control the Bergman cyclization reaction as shown in Scheme 1.

Scheme 1: General Scheme for Complexation-Controlled Bergman Cyclization

Triggering of Bergman Cyclization by Formation of Small Rings



Inhibition of Bergman Cyclization by Formation of Large Rings



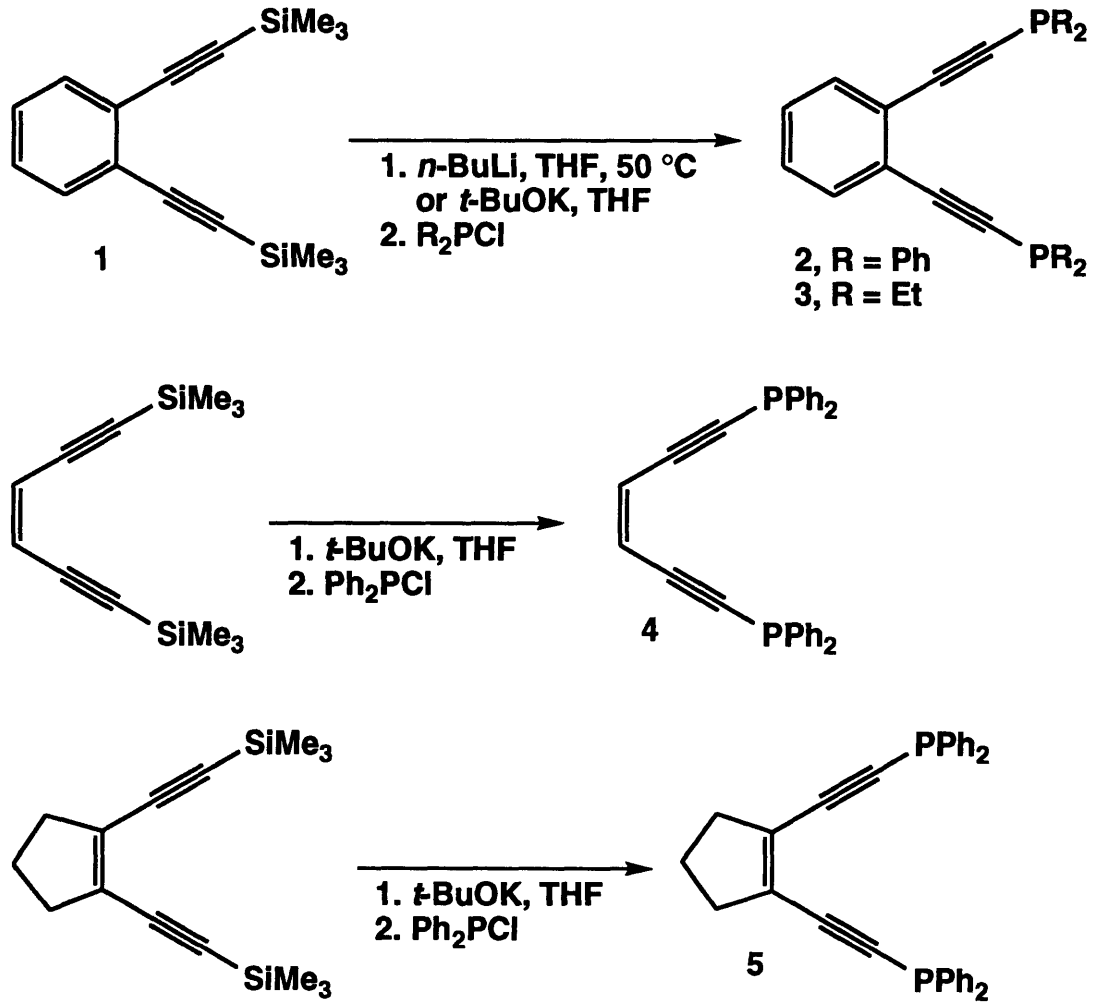
Results and Discussion

Two strategies were pursued in the course of this research. The first involved the binding of metals by phosphorus-substituted, acyclic enediynes. The second involved the binding of amines by a boron-based ligand. Compound **1**[35] was utilized as the starting point, which allowed the synthesis of the enediyne targets in only two steps from commercially available materials.

Compound **2** was chosen as the first possible candidate for meeting the aforementioned five goals; it was found to be indefinitely stable under an inert atmosphere, stable in air for several hours with no sign of decomposition, and

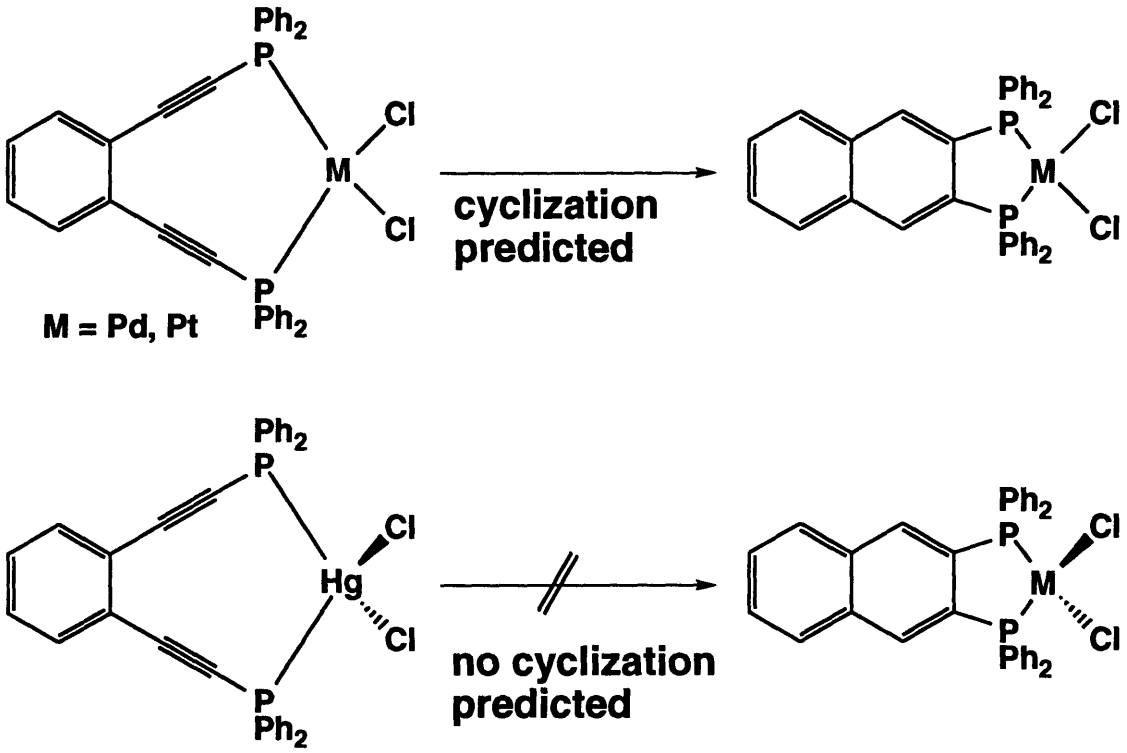
showed no change upon heating at 95 °C for 20 days in a sealed tube. It was readily synthesized from commercially available materials (Scheme 2). When complexed to a suitable metal, **2** undergoes a very rapid Bergman cyclization to provide the corresponding naphthalene. Compounds **3**, **4**, and **5** were also synthesized, and **3** was also found to undergo a metal-promoted cyclization. Under the same conditions, both **4** and **5** yielded intractable, insoluble products.

Scheme 2: Synthesis of Phosphine-Based Enediynes



Based on the expected size and geometry of several metal-ligand complexes of **2**,[36] I hypothesized that **2**•$PdCl_2$ and **2**•$PtCl_2$ would cyclize at moderate temperatures, while **2**•$HgCl_2$ would not cyclize at all.[24] These hypotheses were confirmed by generation of these complexes[37] and investigation of their properties by both NMR spectroscopy and differential scanning calorimetry (DSC).

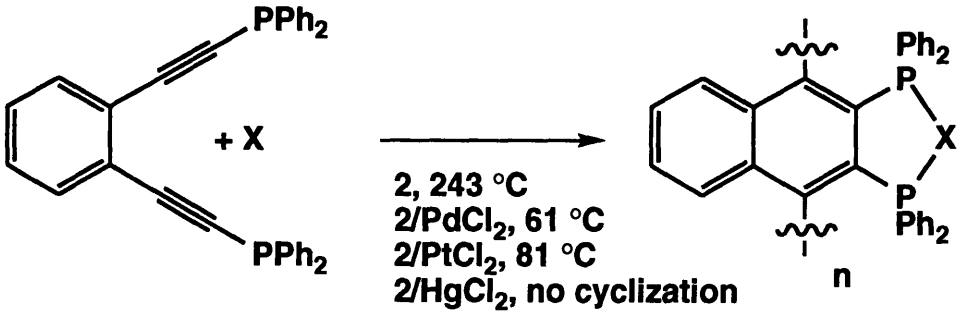
Scheme 3: Predicted Behavior of 2•MCl_2 Complexes



Kratz[38] and König[33] applied DSC in the investigation of enediyne cyclization, quantitatively measuring of the energy evolved in a reaction, and determining the reversibility of the reaction. Exothermic peaks (ΔG=24-39 kcal/mol) attributed to a Bergman cyclization to polymeric aromatic material[39] were observed for all enediynes studied. Subsequent re-analyses of the samples

showed no further peaks, indicating the reaction was irreversible. Compounds **2**, **2**/$PdCl_2$, and **2**/$PtCl_2$ displayed similar behavior by DSC.[40] Acyclic **2** showed an irreversible exothermic (ΔG=46 kcal/mol, $T_{cyclization}$=243 °C) peak attributable to Bergman cyclization. The temperature required for cyclization is similar to the reported values (286-317 °C) for other benzannulated, acyclic, enediynes.[38] Complex **2**/$PdCl_2$ showed an irreversible exothermic (26 kcal/mol, 61 °C) peak also attributable to cyclization, as did **2**/$PtCl_2$ (51 kcal/mol, 81°C). The temperature required for the cyclization of **1** was lowered by 182 °C upon complexation to $PdCl_2$, and by 162 °C upon complexation to $PtCl_2$. In contrast, **2**/$HgCl_2$ showed a phase change at 226 °C, but no evidence for cyclization was seen at up to 450 °C, which implied that complexation to $HgCl_2$ prevents the Bergman cyclization of **2**. These results support our hypothesis that the cyclization of **2** can be accelerated or slowed by judicious choice of the metal added (Scheme 4).

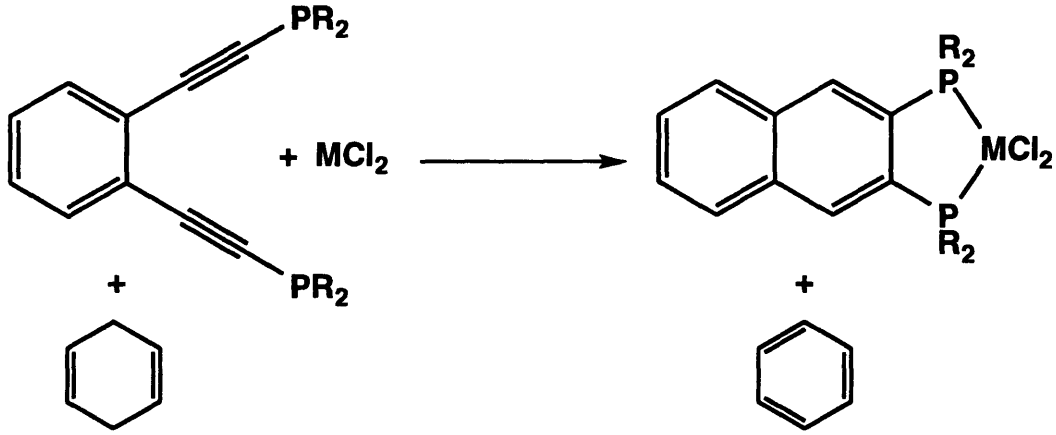
Scheme 4: Onset Temperature for Cyclization



The cyclization of **2**/MCl_2 (M=Pd, Pt) was carried out with cyclohexadiene (CHD) as a trapping agent,[41] to yield **6**•MCl_2 (Scheme 5). The cyclization of **2**/$PdCl_2$ was studied extensively to determine the rate, mechanism, and whether the conversion of **2**/$PdCl_2$ to **6**•$PdCl_2$ occurred via a Bergman-type 1,4-aromatic

diradical. The reaction order and activation parameters were determined, as was the kinetic isotope effect for the addition of hydrogen atoms to **9**•$PdCl_2$. The dependence of cyclization on the formation of a complex between Pd and **2** was also determined.

Scheme 5: Metal-Promoted Bergman Cyclization of 2



2 R = Ph, M = Pd, Pt
3 R = Et, M = Pd

6 R = Ph, M = Pd, Pt
7 R = Et, M = Pd

The cyclization reaction was monitored by ^{31}P NMR to determine the reaction order and activation parameters. The ^{31}P NMR spectra of solutions of **2**/$PdCl_2$ showed two species, which were assigned as the monomeric **2**•$PdCl_2$ and the dimeric **8**.[18,19] These species were found to be in equilibrium (K_{eq} =0.0058 M) by a ^{31}P NMR saturation transfer experiment.[46] Addition of 1 equiv of 1,2-bis(diphenylphosphino)ethane (dppe) to the reaction mixture caused the re-formation of **2** and the generation of dppe•$PdCl_2$. Added dppe and Ph_3P were both found to prevent the cyclization of **2**/$PdCl_2$ to **6**•$PdCl_2$.

The disappearance of **4** was followed by ^{31}P NMR to determine the rate of the reaction. The soluble $PdCl_2$ source, $(CH_3CN)_2PdCl_2$, and **2** were mixed in equimolar amounts, with CHD added as a trapping agent,[41] in CD_2Cl_2 (Scheme 6, M = Pd). The rate was found to be 1/2 order in **2**/$PdCl_2$ (Figure 12, Table 2), and essentially zero order in CHD (Figure 13, Table 3).[42,41,43] The rate

constant was found to be 0.0024 $mmol^{.5}$ min^{-1}. The empirical rate law is shown as equation 1:

(1) Rate ($mmol\ min^{-1}$) = 0.0024 ($mmol^{.5}\ min^{-1}$) [**2**/$PdCl_2$]$^{.5}$

The cyclization reaction was also run using 1,2,3,4,5,6-d_6-cyclohexadiene as the trapping agent.[44] The ratio of rates of trapping diradical **9** by hydrogen and deuterium (k_H/k_D), which are equal to the ratio of protonated and deuterated **6**•$PdCl_2$, was found to be 4.5 ± 0.2. This result is in agreement with studies by Bergman, who found k_H/k_D = 4.3 for the cyclization of *z*-4,5-diethynyl-4-octene to 1,2-dipropylbenzene.[41]

Table 2: Reaction Order in [2/$PdCl_2$]

Run	[**2**/$PdCl_2$] (M)	Rate (mmol/min)	k ($mmol^{1/2}$/min)
1	0.2	7.2E-04	2.2E-03
2	0.2	5.8E-04	1.7E-03
3	0.2	7.1E-04	2.1E-03
4	0.1	4.8E-04	2.0E-03
5	0.1	4.7E-04	2.0E-03
6	0.1	5.2E-04	2.2E-03
7	0.1	5.2E-04	2.2E-03
8	0.05	4.2E-04	2.4E-03
9	0.05	3.3E-04	1.9E-03
10	0.025	3.1E-04	2.5E-03
11	0.025	2.5E-04	2.0E-03

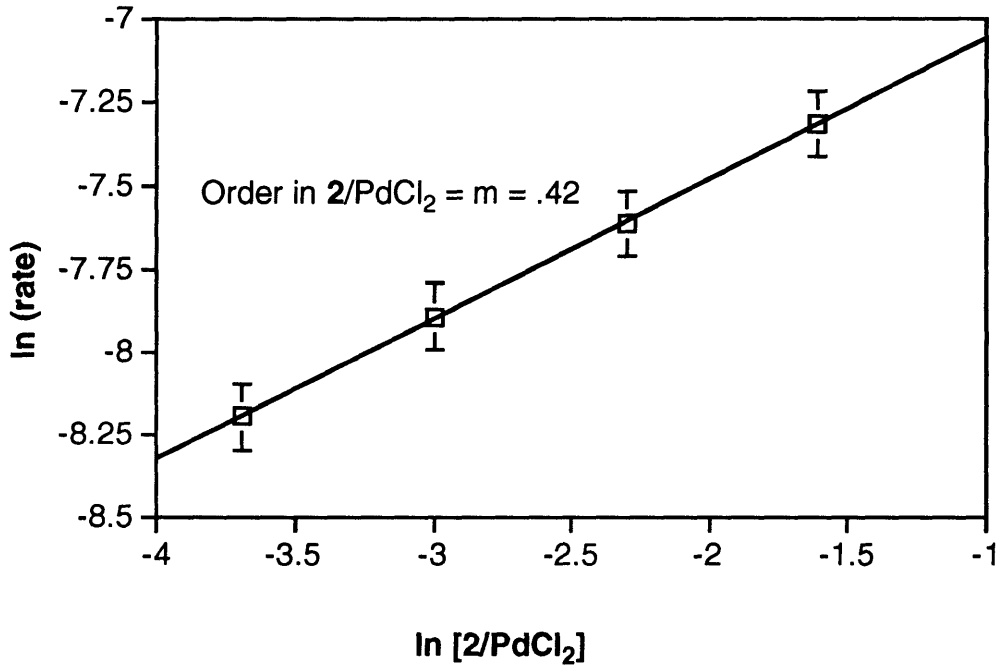
[CHD] = 0.5 M, T = 308 K

Table 3: Reaction Order in [CHD]

Run	[CHD] (M)	Rate (mmol/min)	k ($mmol^{1/2}$/min)
1	3	6.3E-04	3.1E-03
2	3	5.3E-04	2.6E-03
3	1	4.9E-04	2.7E-03
4	1	5.0E-04	2.7E-03
5	0.5	5.0E-04	2.9E-03
6	0.5	5.3E-04	3.1E-03
7	0.25	4.3E-04	2.7E-03
8	0.25	4.1E-04	2.5E-03
9	0.125	3.7E-04	2.5E-03
10	0.125	3.5E-04	2.3E-03
11	0.05	3.4E-04	2.5E-03
12	0.05	3.4E-04	2.5E-03

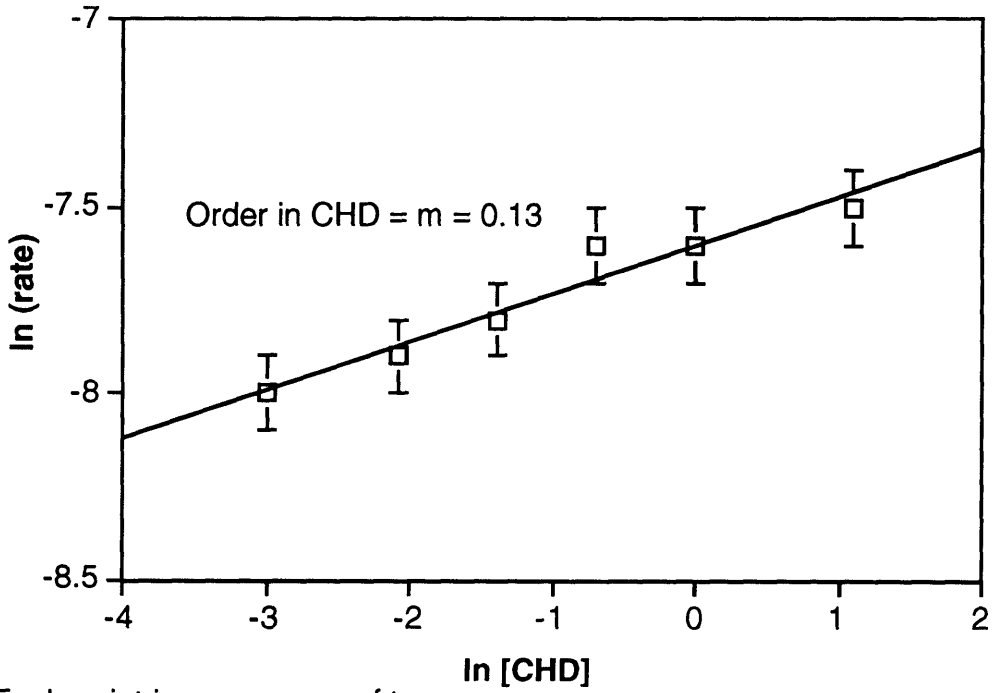
[**2**•$PdCl_2$] = 0.05 M, T = 308 K

Figure 12: Order of Cyclization in [2/$PdCl_2$]



Note: Each point is an average of two or more runs.

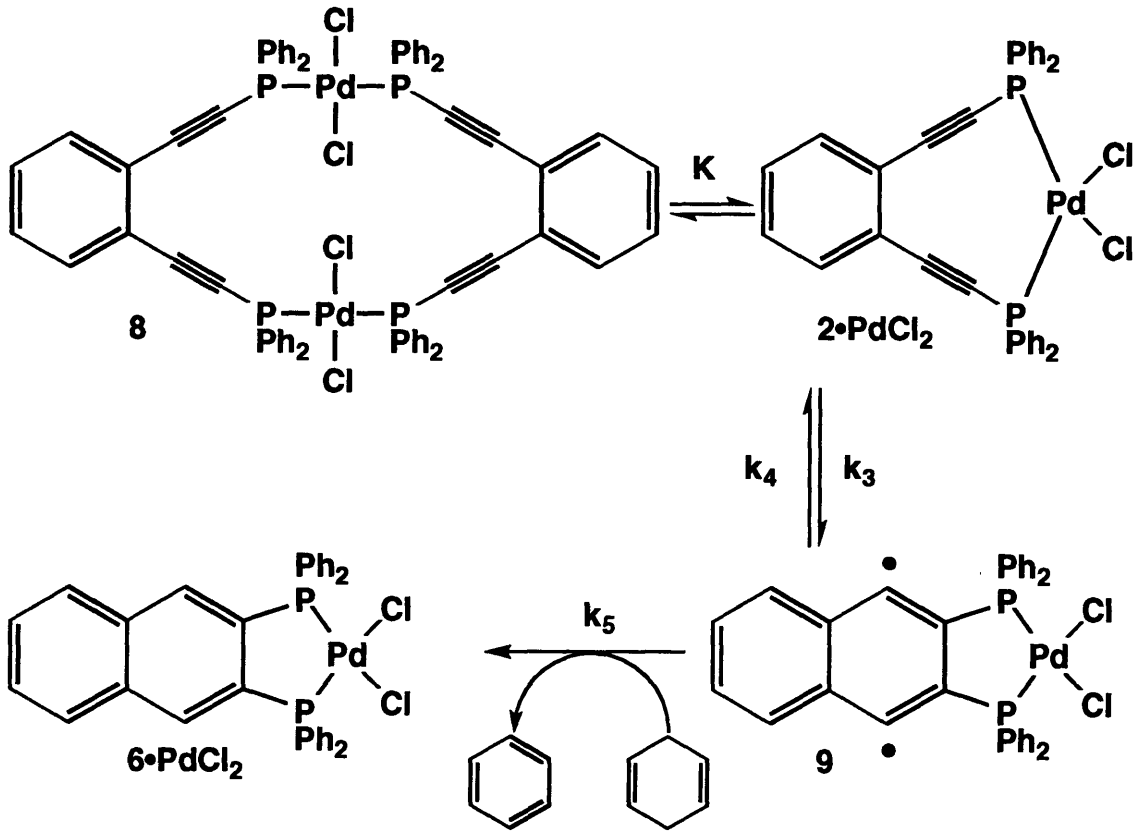
Figure 13: Order of Cyclization in [CHD]



Note: Each point is an average of two runs.

On the basis of this data, I propose that the mixture of **2** and $PdCl_2$ forms a dimeric species **8**,[18,19] which disproportionates to a monomeric species **2**•$PdCl_2$, and undergoes cyclization to the diradical **2**•$PdCl_2$ in a rate limiting step. The diradical is then rapidly trapped by cyclohexadiene to form **3**•$PdCl_2$ (Scheme 6).[41]

Scheme 6: Proposed Course of Palladium-Promoted Cyclization of 2



Assuming that the diradical **9** is at steady state, the calculated rate law for this process was derived (equation 2).

$$(2) \qquad \text{Rate} = \frac{k_5 k_3 [\text{CHD}] \sqrt{K[\mathbf{8}]}}{k_5[\text{CHD}] + k_4}$$

The ramifications of this proposed mechanism become apparent when the concentrations of the reagents are varied. If k_5[CHD] >> k_4, trapping of the diradical is fast, formation of the diradical (k_3) becomes rate limiting, and equation 2 reduces to equation 3, which is identical to equation 1.

$$(3) \quad \text{Rate} = k_3\sqrt{K[8]}$$

Substitution of known values for Rate, K, and [8] yields the value of 0.041 mL / min for k_3.

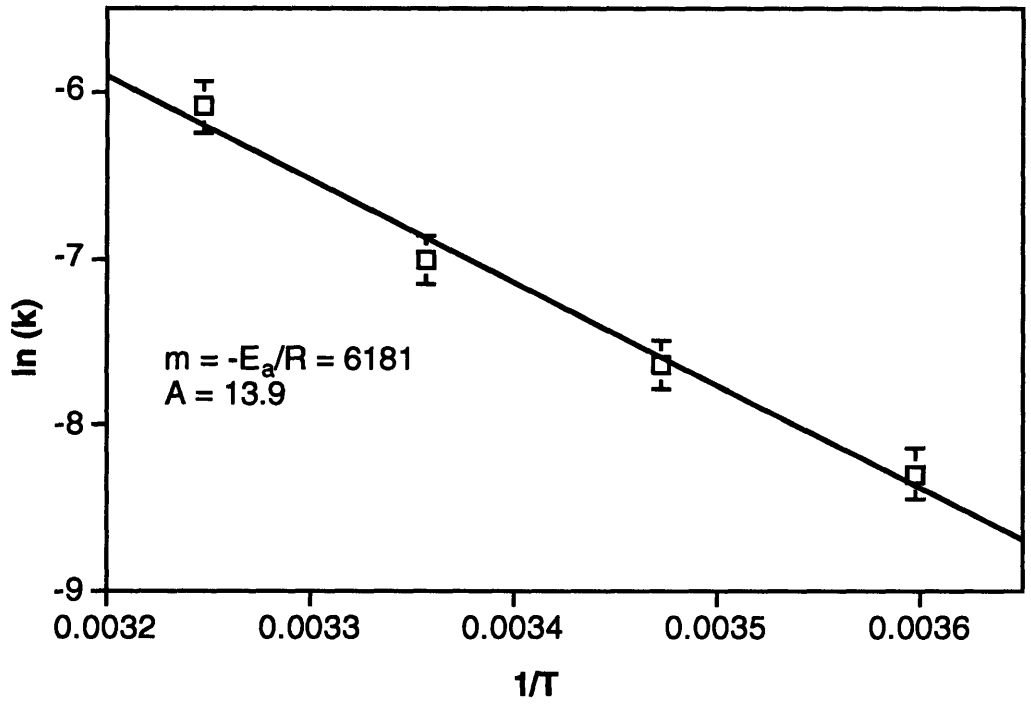
The rate of the palladium-promoted cyclization compares favorably to other enediynes that have been studied.[24,31,43] The reaction has a half-life of 42 min ([**2**/$PdCl_2$] = 0.025 M, [CHD] = 0.125 M, 35 °C), which is an acceleration of at least 30,000 times over the unpromoted reaction. The activation parameters for this process ([**2**/$PdCl_2$] = 0.025 M, [CHD] = 0.5 M, T = 278K-308K) are E_a = 12.3 kcal/mol and ln(A) = 13.9 (Figure 14, Table 4), reflecting the facility of the cyclization under these conditions.[45]

Table 4: Determination of Activation Parameters

Run	T (K)	Rate (mmol/min)	k ($mmol^{1/2}$/min)
1	308	3.1E-04	2.5E-03
2	308	2.5E-04	2.0E-03
3	298	1.2E-04	1.0E-03
4	298	9.9E-05	8.2E-04
5	288	5.1E-05	4.2E-04
6	288	6.7E-05	5.5E-04
7	278	3.1E-05	2.5E-04
8	278	3.0E-05	2.5E-04

[**2**•$PdCl_2$] = 0.05 M, [CHD] = 0.5 M

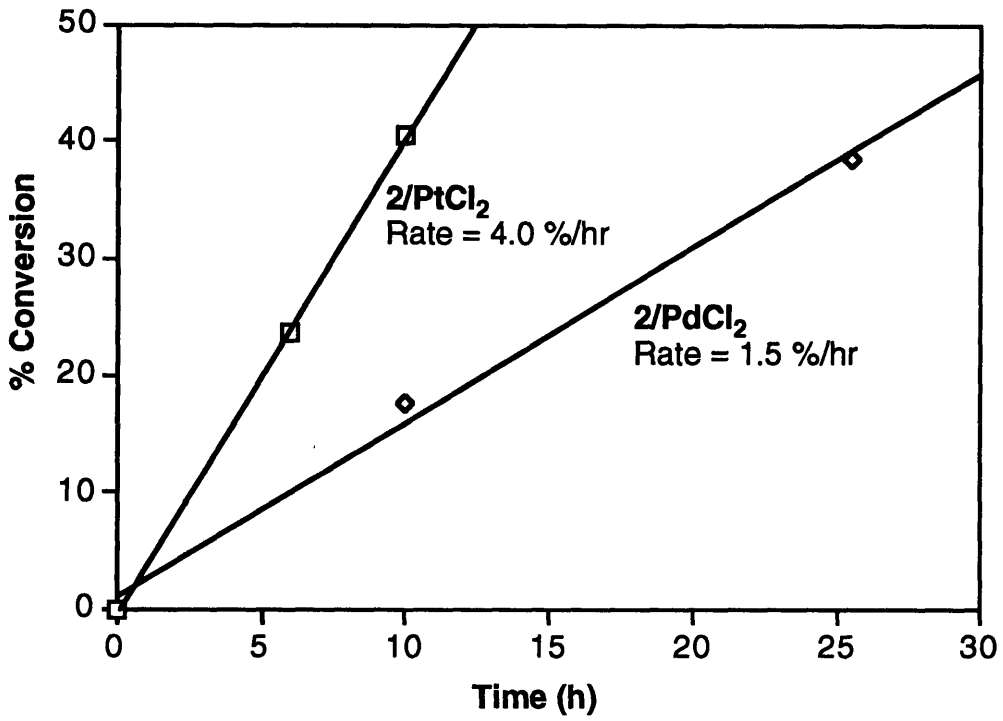
Figure 14: Arrhenius Plot of Cyclization of 2/$PdCl_2$



Note: Each point is an average of two runs.

The rate of cyclization of **2**/$PtCl_2$ was found to be approximately 2.7 times faster than that of **2**/$PtCl_2$, as determined by ^1H NMR (Figure 15), although **2**/$PdCl_2$ underwent cyclization at a lower temperature than **2**/$PtCl_2$ as monitored by DSC. However, the DSC-monitored reaction was run in the solid state while the NMR-monitored reaction was run in solution. Further, the reactions run in solution employed 1,4-cyclohexadiene as a radical trapping reagent,[41] while the solid-state reactions presumably yielded polymeric material.[39] These different conditions prevent the exact correlation of onset temperature and rate of cyclization in solution.

Figure 15: Relative Rates of Cyclization for 2/$PdCl_2$ and 2/$PtCl_2$

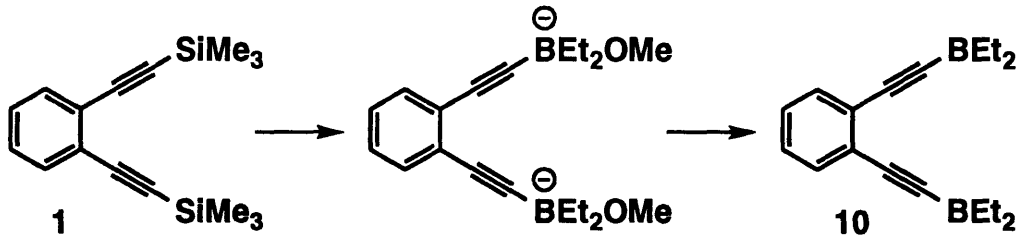


Note: Each point is an average of two runs.

In conclusion, I have developed a chelation-controlled cyclization of an enediyne-based diphosphine. Based on kinetic and other data, a mechanism for the palladium-promoted Bergman cyclization of **2** has been proposed. Upon coordination of **2** to palladium or platinum dichloride, the ligand undergoes a Bergman cyclization at an enormously enhanced rate, while complexation of **2** to mercuric chloride prevents this cyclization. This system meets the criteria of speed, compatibility, stability, and ease of synthesis. Under appropriate conditions, including in the presence of platinum dichloride, **2** undergoes rapid cyclization at low temperatures.

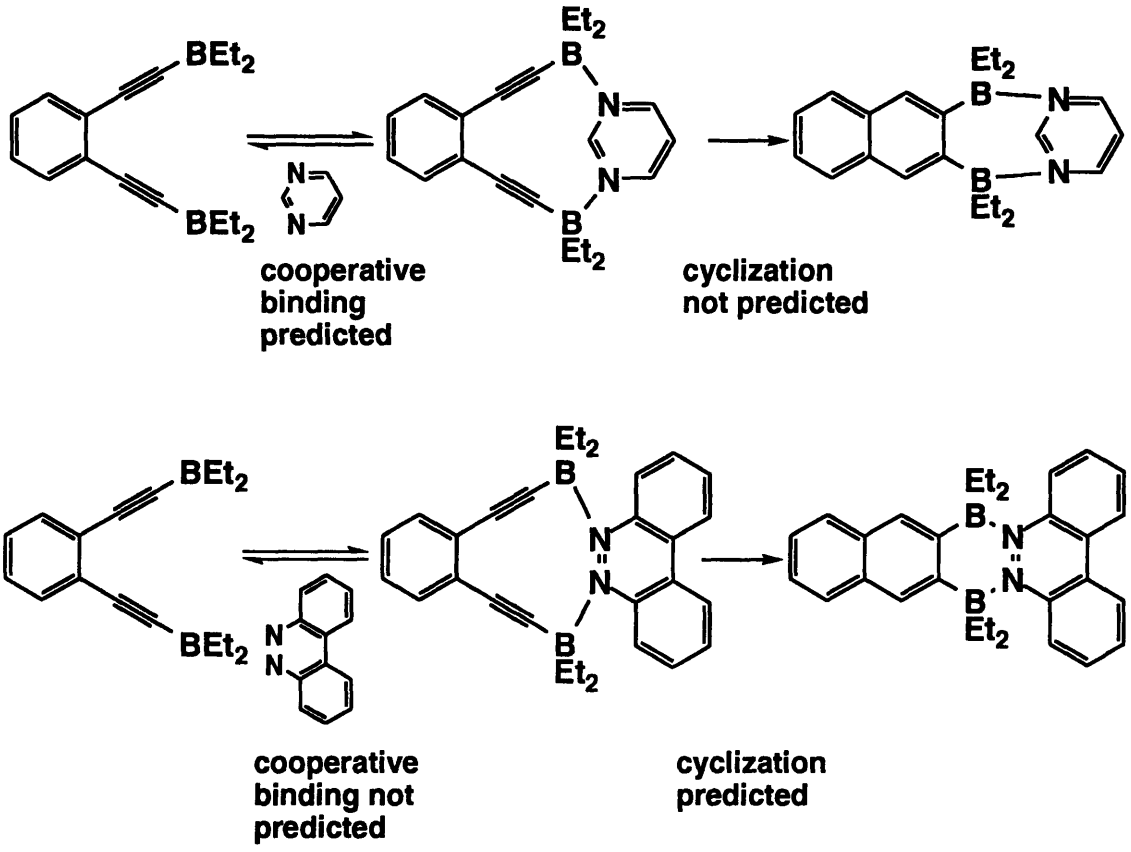
Borane **10** was synthesized in a manner similar to that used to make the phosphines. Compound **1** was treated with *n*-BuLi, then methyl diethylborinate to form the bis(borate), which was then treated directly with boron trifluoride etherate, to form the bis(borane) **10** in 95 % yield, after filtration through celite (Scheme 7). Compound **10** is a highly air-, and moisture-sensitive oil, which is indefinitely stable when stored under argon.

Scheme 7: Synthesis of a Boron-Based Host



A mixture of **10** and pyrimidine was hypothesized to form a 1:1 chelating complex **10**•pyrimidine. However, **10**•pyrimidine was not expected to undergo a Bergman cyclization because eleven-membered rings generally do not undergo these cyclizations; this enediyne, in particular, should not undergo a cyclization because the product would contain a seven-membered ring with a *trans*-double bond. Since ten-membered ring enediynes do usually undergo Bergman cyclizations, we examined the complex **10**•benzo[c]cinnoline (Scheme 8). Benzo[c]cinnoline was considered, rather than the simpler pyridazine, since the latter reacted (presumably in a Diels-Alder reaction) with the electron-deficient alkyne. Due to the air-sensitivity of the boranes, we did not perform DSC analyses on these compounds.

Scheme 8: Predicted Behavior of 10•Guest Complexes



Compound **10** was titrated with both pyrimidine and benzo[c]cinnoline to determine the nature of any host-guest complexes that would form (Figures 16-20). Pyrimidine was found to strongly complex to **10** in a 1:1 ratio, which was then displaced to form a 2:1 complex. The NMR signal for the pyrimidine 2-proton further suggests that the complex formed had two nitrogen-boron bonds. This signal was shifted to 12.4 ppm in the 1:1 complex, as opposed to 9.4 ppm in free pyrimidine or in the 2:1 complex. Benzo[c]cinnoline, in contrast, formed a 2:1 complex with **10** with a binding constant of 160. That there was only one discernible binding constant, suggests that there was no cooperative binding.

Figure 16: Titration Curve of 10 with Pyrimidine

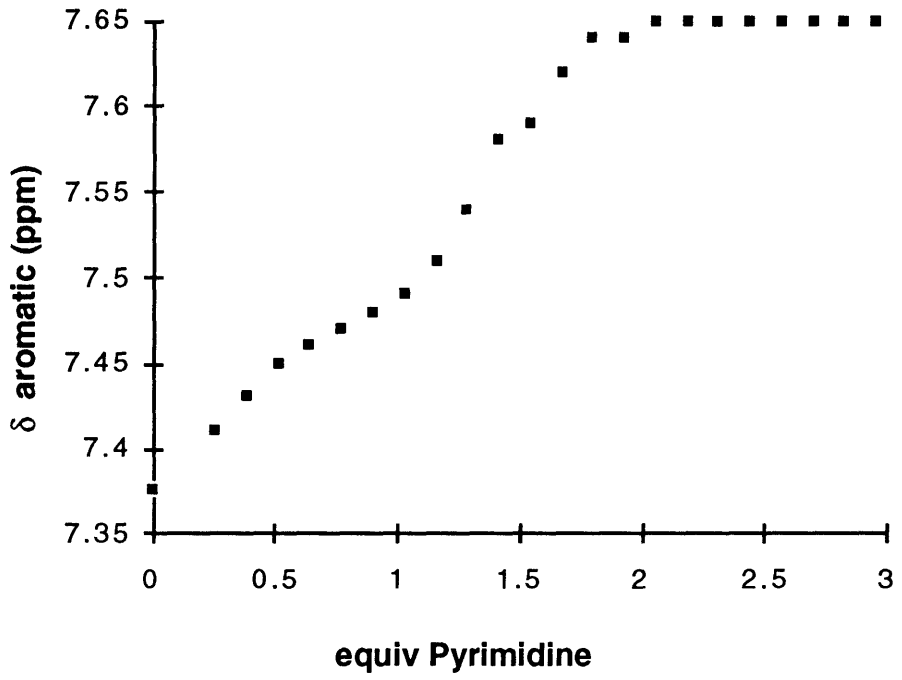


Figure 17: Binding Modes for 10•Pyrimidine

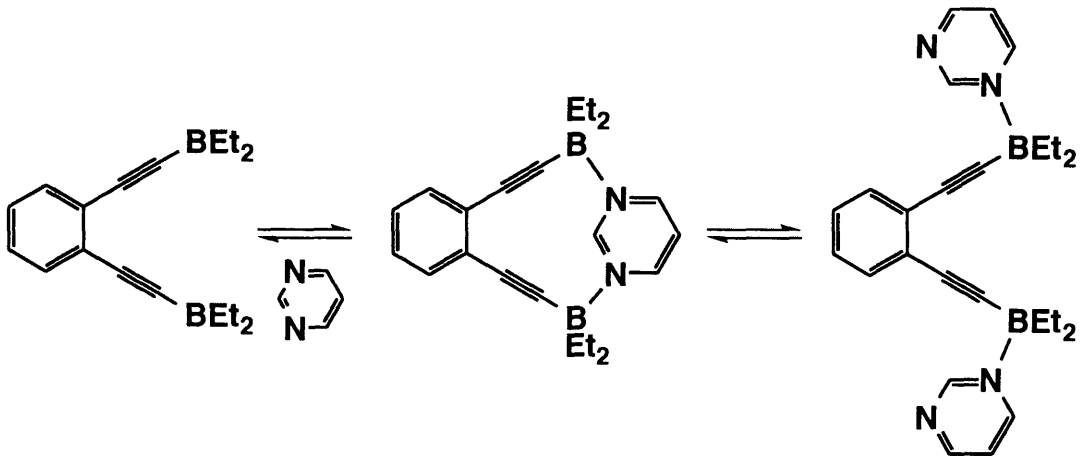


Figure 18: Titration Curve of 10 with Benzo[c]cinnoline

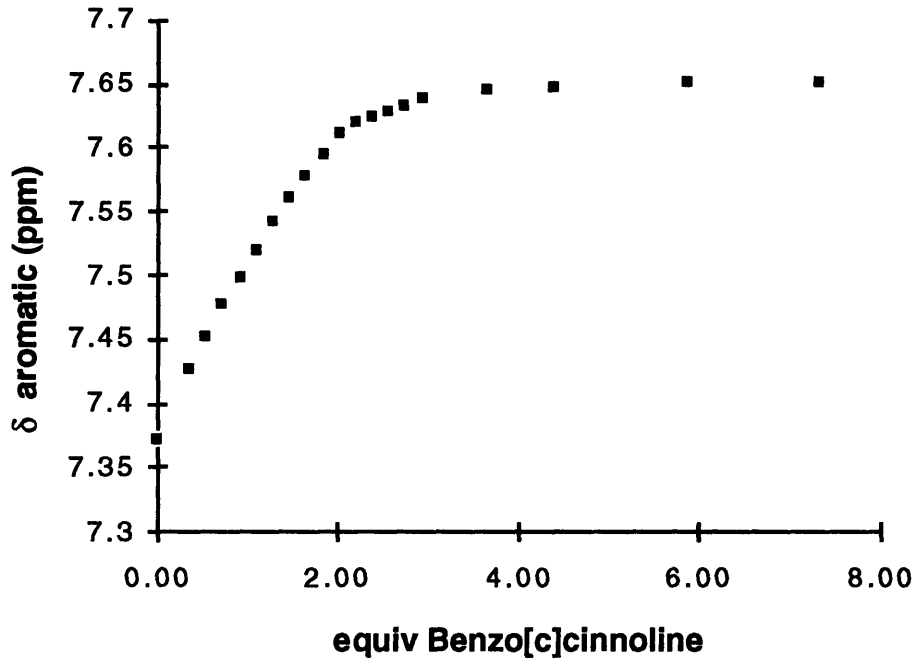


Figure 19: Binding Modes for 10•Benzo[c]cinnoline

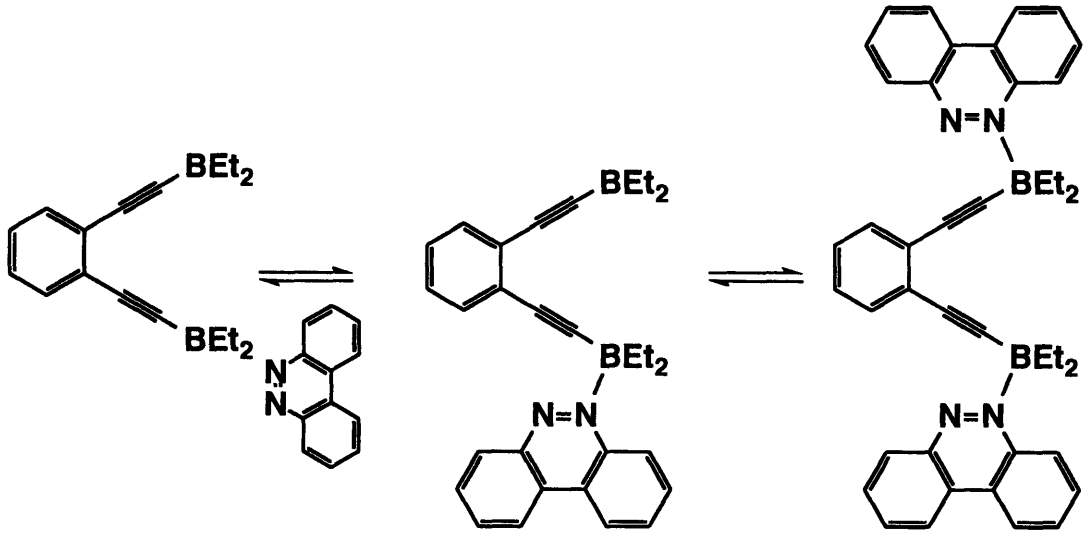
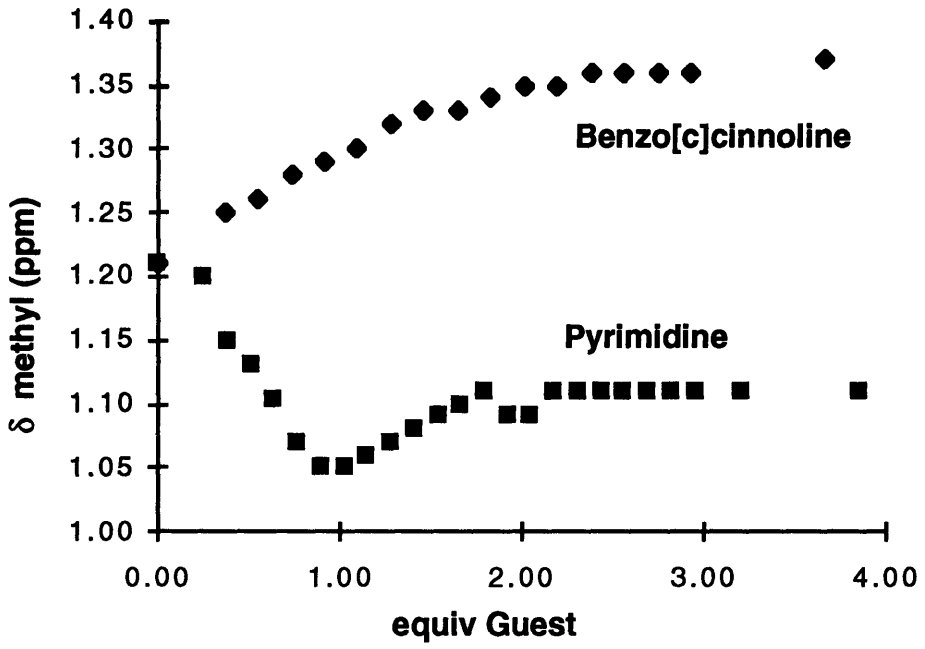


Figure 20: Titration Curves of 10 and Pyrimidine, and 10 and Benzo[c]cinnoline



In conclusion, we developed a very strong, cooperative, binder for pyrimidine based on a boron-substituted enediyne. This molecule did not cooperatively complex benzo[c]cinnoline, and no Bergman cyclizations were observed in this system.

EXPERIMENTAL SECTION

General Considerations

All reactions were carried out under an atmosphere of argon or nitrogen using standard Schlenk and glove box techniques. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity-300, Varian XL-300, Bruker AC-

300, or Bruker AC-250 Fourier transform spectrometer. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 series Fourier transform spectrometer. Gas chromatography (GC) analyses were performed on a Hewlett-Packard model 5890 gas chromatograph with a flame ionization detector and a model 3392A integrator using a 25 meter capillary column with polymethylsiloxane (Hewlett-Packard) as a stationary phase. Electron impact high resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Elemental Analyses were performed by E+R Microanalytical Laboratory, Inc.; air sensitive samples were sent in sealed vials under nitrogen. DSC was performed using a Perkin Elmer DSC 7 Differential Scanning Calorimeter. Melting points were determined with a Haake Buchler melting point apparatus and are uncorrected.

Tetrahydrofuran (THF), hexane, toluene, and pentane were dried and deoxygenated by refluxing and distilling from sodium / benzophenone ketyl under an argon or nitrogen atmosphere. Dichloromethane was dried and deoxygenated by refluxing and distilling from calcium hydride under nitrogen. Preparative flash chromatography was performed on silica gel (E. M. Science Kieselgel 60, 230-400 mesh). All reagents, unless otherwise stated, are commercially available and were used as received.

Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as determined by ^{1}H NMR spectrometry.

Preparation of 1,2-bis(diphenylphosphinoethynyl)benzene 2

A dry Schlenk flask under argon was charged with **1** (1.157 g, 4.28 mmol), and tetrahydrofuran (20 mL) was added. The solution was cooled to 0 °C, and a solution of n-butyllithium (5.35 mL, 1.6 M in hexane) was added. The solution was then warmed to 50 °C for 2 h, and a white precipitate developed. The

solution was cooled to 0 °C, chlorodiphenylphosphine (1.886 g, 8.55 mmol) was added by syringe, and the solution was allowed to warm to RT and stir for 1 h. The solvent was then removed under reduced pressure , and the resulting oil was purified by filtration through silica (methylene chloride) to leave **2** (1.866 g, 3.77 mmol, 88 %) as a mildly air sensitive brown oil, which is stable when stored under argon in the refrigerator, but decomposed substantially over 1 week in air. **2**: ^{1}H NMR (250 MHz, C_6D_6) δ 6.67 (dd, *J* = 3.4 Hz, 5.8 Hz, 2 H), 6.98-7.08 (m, 12 H), 7.19 (dd, *J* = 3.4 Hz, 5.8 Hz, 2 H), 7.78 (dd, *J* = 8.2 Hz, 8.2 Hz, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.94 (d, J_{CP}= 6.1 Hz), 135.92, 132.69, 132.41, 128.87, 128.63, 128.53, 125.23, 105.96, 90.54 (d, J_{CP}= 9 Hz). ^{31}P NMR (121 MHz) δ -33.2 (CH_2Cl_2), -32.0 (C_6D_6). IR (Film) 3285, 3053, 3002, 2954, 2278, 2161, 1954, 1890, 1811, 1752, 1585, 1477, 1434, 1327, 1305, 1274, 1247, 1230, 1204, 1182, 1158, 1097, 1068, 1026, 999, 951, 912, 873, 842, 809, 739, 695, 642, 632. Anal. Calcd. for $C_{34}H_{24}P_2$: C, 82.58; H, 4.89. Found: C, 82.48; H, 5.09.

Cyclization of 2 with Pd

A round bottom flask was charged with **2** (0.136 g, 0.275 mmol), $(CH_3CN)PdCl_2$ (0.071 g, 0.275 mmol), 1,4-cyclohexadiene (0.44 g, 5.5 mmol), and CH_2Cl_2 (5 mL). The mixture was then degassed, and stirred at RT for 24 h. Pentane (100 mL) was added, and **6**•$PdCl_2$ was isolated as a yellow precipitate by filtration (0.171 g, 0.254 mmol, 92 %). **6**•$PdCl_2$: Mp 324 °C (decomposes). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.46 (t, *J* = 6.7 Hz, 8 H), 7.54 (d, *J* = 7.5 Hz, 4 H), 7.66 (dd, *J* = 3.2 Hz, 6.2 Hz, 2 H), 7.78 (dd, *J* = 7.5 Hz, 12.4 Hz, 8 H), 7.89 (dd, *J* = 3.2 Hz, 6.2 Hz, 2 H), 8.08 (d, *J* = 11 Hz, 2 H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 134.43, 134.37, 134.30, 132.35, 130.06, 129.34, 129.24, 129.18, 129.11. ^{31}P NMR (121 MHz, CD_2Cl_2) δ 62.05. IR (Film) 1763, 1718, 1618, 1482, 1434,

1383, 1310, 1229, 1185, 1119, 1098, 1026, 998, 972, 896, 846, 784, 746, 689, 619, 607. Anal. Calcd. for $C_{34}H_{26}Cl_2P_2Pd$: C, 60.60; H, 3.89. Found: C, 60.64; H, 3.99.

Cyclization of 2 with Pt

A dry Schlenk flask was charged with **2** (0.117 g, 0.236 mmol), (1,5-cyclooctadiene)$PtCl_2$ (0.088 g, 0.236 mmol), 1,4-cyclohexadiene (0.381 g, 4.7 mmol), and toluene (10 mL). The mixture was stirred at 80 °C for 3 h, then pentane (50 mL) was added, and **6**•$PtCl_2$ was isolated as a white precipitate by filtration (0.135 g, 0.178 mmol, 75 %). **6**•$PtCl_2$: Mp > 400 °C. ^1H NMR (300 MHz, CD_2Cl_2) δ 7.42-7.50 (m, 8H), 7.50-7.55 (m, 4 H), 7.66 (dd, *J* = 3.2 Hz, 6.2 Hz, 2 H), 7.75-7.82 (m, 8 H), 7.89 (dd, *J* = 3.4 Hz, 6.4 Hz, 2 H), 8.11 (d, *J* = 12.2 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.54, 134.47, 134.39, 132.45, 130.20, 129.52, 129.42, 129.34, 129.27. ^{31}P NMR (121 MHz, CD_2Cl_2) δ 39.6 (d, $J_{P\text{-}Pt}$ = 3596 Hz). IR (Film) 3054, 1482, 1436, 1310, 1118, 1100, 998, 747, 691, 552, 506. Anal. Calcd. for $C_{34}H_{26}Cl_2P_2Pd$: C, 53.56; H, 3.44. Found: C, 53.85; H, 3.62.

Attempted Thermal Cyclization of 2

A sealable NMR tube was charged with **2** (0.031 g, 0.063 mmol), 1,4-cyclohexadiene (0.030 g, 0.31 mmol), and benzene-d_6 (1.2 mL). The sample was heated at 95 °C for 447.5 h, with no change observed by ^1H NMR.

Determination of Relative Rates of Cyclization of 2/$PdCl_2$ and 2/$PtCl_2$

A stock solution of **2** (0.021 g, 0.043 mmol), 1,4-cyclohexadiene (0.017 g, 0.213 mmol), and mesitylene (0.0086 g, 0.072 mmol), in CD_2Cl_2 (3.0 mL) was prepared. Two NMR tubes were charged with (COD)$PtCl_2$ (0.0037 g, 0.01

mmol), and two with $(CH_3CN)PdCl_2$ (0.0026 g, 0.01 mmol), and a portion (0.700 mL) of the stock solution was added to each NMR tube. The formation of **6**•$PtCl_2$ and **6**•$PdCl_2$ was monitored by ^1H NMR until 40% completion.

Time (hr)	**2**/$PtCl_2$ Run 1	**2**/$PtCl_2$ Run 2	Time (hr)	**2**/$PdCl_2$ Run 1	**2**/$PdCl_2$ Run 2
0	0 %	0 %	0	0 %	0 %
6	23 %	24 %	10	17 %	18 %
10	41 %	40 %	25.5	37 %	40 %
rate (%/hr)	4.0 %/hr	4.0 %/hr		1.4 %/hr	1.6 %/hr
rate Pt/rate Pd	2.7				

Determination of k_H/k_D for the Palladium-Promoted Cyclization of 2

A stock solution of **2** (0.015 g, 0.031 mmol), 1,2,3,4,5,6-*d*$_6$-1,4-cyclohexadiene (0.027 g, 72 % CHD, 28 % C_6D_6, 0.23 mmol), and mesitylene (0.0086 g, 0.074 mmol), in CD_2Cl_2 (1.4 mL) was prepared. Two NMR tubes were each charged with a portion (0.700 mL) of the stock solution, then $(CH_3CN)_2PdCl_2$ (0.004 g, 0.015 mmol) was added. The NMR tubes were heated to 35 °C for 12 h. The amount of deuterium incorporation was measured by integration of both the ^1H and ^{31}P NMR spectra. Reaction 1: k_H/k_D = 4.5 (^1H), 4.3 (^{31}P). Reaction 2: k_H/k_D = 4.3 (^1H), 4.7 (^{31}P).

1,2,3,4,5,6-*d*$_6$-1,4-Cyclohexadiene was prepared by Birch reduction of benzene-*d*$_6$ in a method similar to that used by Lewis.[44] Ammonia was condensed into a 2-neck flask fitted with at cold finger at -78 °C. Benzene-*d*$_6$ (9.51 g, 113 mmol) was added slowly by syringe to form a slurry, then 1-pentanol (10.93 g, 124 mmol) was added by syringe. Sodium was added portionwise until the solution remained blue for 15 min. Additional 1-pentanol was added until the

solution became colorless. The product was distilled to leave 1,2,3,4,5,6-d_6-1,4-cyclohexadiene (1.57 g, 72 % CHD, 28 % C_6D_6, 18.3 mmol, 16%).

Inhibition of Palladium-Promoted Cyclization of 2 with DPPE and PPh_3

A stock solution of **2** (0.027 g, 0.054 mmol), 1,4-cyclohexadiene (0.022 g, 0.27 mmol), $(CH_3CN)_2PdCl_2$ (0.0014 g, 0.054 mmol), and mesitylene (0.0086 g, 0.074 mmol), in CD_2Cl_2 (4.5 mL) was prepared. Two NMR tubes were charged with 1,2-bis(diphenylphosphino)ethane (0.0067 g, 0.017 mmol), two with Ph_3P (0.009 g, 0.034 mmol), and two NMR tubes were kept as control, and a portion (0.700 mL) of the stock solution was added to each NMR tube. The NMR tubes were left at RT for 6.5 h, then heated to 50 °C for 71 h. The amount of **6**•$PdCl_2$ formed was checked periodically by ^1H NMR. The control reactions were judged complete after 23.5 h. No cyclization products were observed in any NMR tube containing added phosphines.

A stock solution of **2** (0.078 g, 0.158 mmol) and triphenylphosphine oxide (0.33 g, 0.119 mmol), in CD_2Cl_2 (1.0 mL) was prepared. Three NMR tubes were charged with this solution (0.100 mL, 0.200 mL, 0.400 mL), and diluted to 0.600 mL each. $(CH_3CN)_2PdCl_2$ (1 equiv) was added, and the samples were examined by ^{31}P NMR. Two peaks (and an additional very small, very broad, peak at ~12 ppm), assigned to **8** (1.6 ppm) and **2**•$PdCl_2$ (5.1 ppm) were observed and integrated, yielding an equilibrium constants of 0.0058. When a solution of dppe (1 equiv) was then added to the samples (in a separate experiment), **2** was quantitatively regenerated in each case, as well as dppe•$PdCl_2$ as determined by ^{31}P NMR.

Saturation Transfer Experiment

A solution of **2** (0.0216 g, 0.043 mmol), $(CH_3CN)_2PdCl_2$ (0.0113 g, 0.043 mmol), and triphenylphosphine oxide (0.14 g, 0.05 mmol), in CD_2Cl_2 (0.87 mL) was prepared in an NMR tube, and examined by ^{31}P NMR. A spectrum in which no peak was irradiated was subtracted from a spectrum in which the peak assigned to **2**•$PdCl_2$ (5.1 ppm) was irradiated. The resulting spectrum showed two peaks, assigned to **2**•$PdCl_2$ (5.1 ppm) and **8** (1.6 ppm), indicating those species are in equilibrium.[46]

General Procedure for Determination of Rate of the Palladium-Promoted Cyclization of 2 (Table 5, Run 5)

A stock solution of **2** (0.4137 g, 0.837 mmol) and triphenylphosphine oxide (0.2341 g, 0.841 mmol) in CH_2Cl_2 (28.1 mL) / CD_2Cl_2 (5.4 mL) was prepared. An NMR tube was charged with a portion (3.5 mL) of the stock solution, then 1,4-cyclohexadiene (0.141 g, 1.75 mmol) and $(CH_3CN)_2PdCl_2$ (0.023 g, 0.088 mmol) was added. The solution was held at 288 K in the NMR probe, and ^{31}P NMR spectra were taken at approximately 15 min intervals. The disappearance of starting material was followed to 50 % completion by integration of the signal at 1.6 ppm vs. the signal for Ph_3PO. The temperature of the NMR probe was measured by the difference between the two chemical shifts of methanol by ^1H NMR (before, 499.8 Hz; after, 500.1 Hz) before and after the reaction.

DSC of 2, 2/$PdCl_2$, 2/$PtCl_2$, 2/$HgCl_2$

A sample of **2** (0.005476 g) was weighed into a sample pan, and heated from RT to 450 °C at 20 °C/min. An exothermic peak (391 J/g, Onset Temperature 243 °C) was observed. The sample was cooled to RT, and

reheated to 450 °C. This peak was not observed in a second analysis of the same sample.

A Schlenk flask was charged with **2** (0.132 g, 0.267 mmol), $(CH_3CN)PdCl_2$ (0.069 g, 0.267 mmol), and CH_2Cl_2 (1 mL), and the reaction was stirred for 5 min at 0 °C. The solvent was removed in vacuo, and the complex was stored at -78 °C until DSC analysis was carried out. A sample of **2**/$PdCl_2$ (0.003533 g) was weighed into a sample pan, and heated from -40 to 200 °C at 20 °C/min. An exothermic peak (164 J/g, Onset Temperature 60 °C) was observed. The sample was cooled to RT, and reheated to 200 °C. This peak was not observed in a second analysis of the same sample.

A Schlenk flask was charged with **2** (0.178 g, 0.360 mmol), $(COD)PtCl_2$ (0.135 g, 0.360 mmol), and CH_2Cl_2 (1 mL), and the reaction was stirred for 5 min at 0 °C. The solvent was removed in vacuo, and the complex was stored at -78 °C until DSC analysis was carried out. A sample of **2**/$PtCl_2$ (0.005718 g) was weighed into a sample pan, and heated from 20 to 450 °C at 20 °C/min. An exothermic peak (281 J/g, Onset Temperature 81 °C) was observed. The sample was cooled to RT, and reheated to 450 °C. This peak was not observed in a second analysis of the same sample.

A round bottom flask was charged with **2** (0.156 g, 0.315 mmol), $HgCl_2$ (0.085 g, 0.315 mmol), and CH_2Cl_2 (10 mL), and the reaction was stirred for 30 h at RT. By ^1H NMR, **2**/$HgCl_2$ was formed. A sample of **2**/$HgCl_2$ (0.005476 g) was weighed into a sample pan, and heated from RT to 450 °C at 20 °C/min. A phase change was observed at 226 °C, but no exothermic peak was observed.

Preparation of 1,2-bis(diethylphosphinoethynyl)benzene 3

In an argon-filled glovebox, a vial was charged with **1** (0.209 g, 0.77 mmol), potassium *tert*-butoxide (0.174 g, 1.55 mmol), and tetrahydrofuran (5 mL).

The solution, which immediately turned blue, was stirred for 6 h, at which time chlorodiethylphosphine (0.193 g, 1.55 mmol) was added dropwise. The solution turned brown quickly, and was stirred for 1 h. The solvent was removed, and the remaining black solid was extracted with pentane and filtered to leave **3** (0.165 g, 0.55 mmol, 71 %) as a brown oil. **3**: ^{1}H NMR (300 MHz, C_6D_6) δ 7.30 (dd, J = 3.4 Hz, 5.8 Hz, 2 H), 6.72 (dd, J = 3.4 Hz, 5.8 Hz, 2 H), 1.45-1.78 (m, 8 H), 1.19 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4, 128.1, 126.2, 103.50 (d, J_{CP}= 3.9 Hz), 94.21 (d, J_{CP}= 26.2 Hz), 19.62 (d, J_{CP}= 8.0 Hz), 10.29 (d, J_{CP}= 9.9 Hz). ^{31}P NMR (121 MHz, C_6D_6) δ -39.97. IR (Film) 2961, 2929, 2905, 2872, 2158, 1588, 1474, 1455, 1439, 1420, 1376, 1272, 1231, 1204, 1099, 1044, 870, 804, 757. Anal. Calcd. for $C_{18}H_{24}P_2$: C, 71.51; H, 8.00. Found: C, 71.43; H, 7.85.

Cyclization of 3 with Pd

A sealable Schlenk was charged with **3** (0.173 g, 0.57 mmol), $(CH_3CN)PdCl_2$ (0.148 g, 0.57 mmol), 1,4-cyclohexadiene (0.921 g, 11.5 mmol), and THF (5 mL) in an argon-filled glovebox. The mixture was then stirred at 100 °C for 24 h, and purified by flash chromatography (95:5 CH_2Cl_2:Et_2O) to yield **7**•$PdCl_2$ (0.200 g, 0.415 mmol, 73 %) as a white solid, 85 % pure by as estimated by ^{1}H NMR. This material was dissolved in hot ethanol, and allowed to cool slowly to leave **7**•$PdCl_2$•EtOH as yellow needle-shaped crystals (0.061 g, 0.127 mmol, 22 %). **7**•$PdCl_2$•EtOH: Mp 334 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.60 (d, J_{HP}= 10.3 Hz, 2 H), 8.16 (dd, J = 3.2 Hz, 6.3 Hz, 2 H), 7.80 (dd, J = 3.2 Hz, 6.3 Hz, 2 H), 3.61 (q, J = 7.1 Hz, 2 H), 2.62 (m, 4 H), 2.44 (m, 4 H), 1.04-1.20 (m, 15 H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 135.56, 134.72, 132.35, 129.99, 129.27, 58.57, 23.16, 18.76, 9.74. ^{31}P NMR (121 MHz, CD_2Cl_2) δ 96.22. IR (KBr) 3482, 3048, 2968, 2934, 2873, 1487, 1459, 1406, 1376, 1310, 1231, 1125, 1023,

948, 911, 785, 763, 705. Anal. Calcd. for $C_{20}H_{32}Cl_2OP_2Pd$: C, 45.52; H, 6.11. Found: C, 45.31; H, 6.12.

Preparation of *z*-1,6-bis(diethylphosphino)hex-3-ene-1,5-diyne 4

In an argon-filled glovebox, a vial was charged with *z*-1,6-bis(trimethylsilyl) hex-3-ene-1,5-diyne 4 (0.140 g, 0.63 mmol), potassium *tert*-butoxide (0.142 g, 1.27 mmol), and tetrahydrofuran (5 mL). The solution, which immediately turned dark brown, was stirred for 24 h, at which time chlorodiphenylphosphine (0.279 g, 1.27 mmol) was added. The solution was stirred for 1 h. The solvent was removed, and the remaining black solid was extracted with ether and filtered through alumina to leave **4** (0.260 g, 0.58 mmol, 93 %) as a brown oil. **4**: ^1H NMR (250 MHz, C_6D_6) δ 7.70 (td, J = 1.6 Hz, J_{PH} = 8.15 Hz, 8 H), 7.00 (m, 12 H), 5.50 (s, 2 H). ^{13}C NMR (75 MHz, C_6D_6) δ 136.23 (d, J_{CP}= 7.0 Hz), 133.02 (d, J_{CP}= 21.2 Hz), 129.20, 129.01 (d, J_{CP}= 7.5 Hz), 120.05, 105.65 (d, J_{CP}= 3.9 Hz), 96.78 (d, J_{CP}= 11.1 Hz). ^{31}P NMR (121 MHz, C_6D_6) δ -31.63. IR (Film) 3069, 2157, 2123, 1954, 1886, 1810, 1760, 1667, 1584, 1571, 1478, 1434, 1385, 1328, 1306, 1275, 1182, 1082, 1026, 998, 932, 846, 739, 693. Anal. Calcd. for $C_{30}H_{22}P_2$: C, 81.07; H, 4.99. Found: C, 81.01; H, 5.23.

Preparation of 1,2-bis(diphenylphosphinoethynyl)cyclopentene 5

In an argon-filled glovebox, a vial was charged with 1,2-bis(trimethylsilyl) cyclopentene (0.078 g, 0.30 mmol), potassium *tert*-butoxide (0.067 g, 0.60 mmol), and tetrahydrofuran (5 mL). The solution was stirred for 3 h, at which time chlorodiphenylphosphine (0.132 g, 0.60 mmol) was added. The solution was stirred for 1 h. The solvent was removed, and the remaining red-brown oil was extracted with CH_2Cl_2 and filtered through silica to leave **5** (0.130 g, 0.27 mmol, 89 %) as a red-brown oil. **5**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.61-7.67 (m,

8 H), 7.25-7.28 (m, 12 H), 2.68 (t, J = 7.5 Hz, 4 H), 2.00 (t, J = 7.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.00 (d, J_{CP}= 5.3 Hz), 132.48 (d, J_{CP}= 20.6 Hz), 131.21, 128.88, 128.58 (d, J_{CP}= 8.4 Hz), 104.12 (d, J_{CP}= 5.0 Hz), 93.78 (d, J_{CP}= 8.3 Hz), 37.03, 23.21. ^{31}P NMR (121 MHz, $CDCl_3$) δ -32.57. IR (Film) 3284, 3052, 2964, 2845, 2147, 1954, 1890, 1812, 1585, 1478, 1435, 1326, 1305, 1208, 1181, 1095, 1068, 1025, 999, 933, 842, 741, 692. HRMS: Calcd. for $C_{30}H_{22}P_2$: 484.1510. Found: 484.1508.

Derivation of Calculated Rate Law for Conversion of 2/$PdCl_2$ to 6•$PdCl_2$

Assume steady state for **9**

(a) $k_3[\mathbf{2}\bullet PdCl_2] = k_4[\mathbf{9}] + k_5[\mathbf{9}][CHD]$

which rearranges to

(b) $$[\mathbf{9}] = \frac{k_3[\mathbf{2}\bullet PdCl_2]}{k_4 + k_5[CHD]}$$

The equilibrium constant K is defined as

(c) $$K = \frac{[\mathbf{2}\bullet PdCl_2]^2}{[\mathbf{8}]}$$

which rearranges to

(d) $$[\mathbf{2}\bullet PdCl_2] = \sqrt{K[\mathbf{8}]}$$

The rate of the reaction is

(e) $$\frac{d[\mathbf{6}\bullet PdCl_2]}{dt} = k_5[\mathbf{9}][CHD]$$

Substituting for [**9**] (equation b)

(f) $$\frac{d[\mathbf{6}\bullet PdCl_2]}{dt} = \frac{k_3k_5[\mathbf{2}\bullet PdCl_2][CHD]}{k_5[CHD] + k_4}$$

Substituting for [**2**•$PdCl_2$] (equation d)

(g) $$\frac{d[\mathbf{6}\bullet PdCl_2]}{dt} = \frac{k_3k_5[CHD]\sqrt{K[\mathbf{8}]}}{k_5[CHD] + k_4}$$

Limiting Case [CHD]->0:

(h) $$\frac{d[\mathbf{6}\bullet PdCl_2]}{dt} = \frac{k_3k_5[CHD]\sqrt{K[\mathbf{8}]}}{k_4}$$

therefore rate α $[CHD]\sqrt{[\mathbf{8}]}$ at low [CHD]

Limiting Case [CHD]->∞:

(i) $$\frac{d[\mathbf{6}\bullet PdCl_2]}{dt} = k_3\sqrt{K[\mathbf{8}]}$$

therefore rate α $\sqrt{[\mathbf{8}]}$ at high [CHD]

Preparation of 1,2-bis(diethylborylethynyl)benzene 10

A dry Schlenk flask under argon was charged with **1** (0.541 g, 2 mmol), and tetrahydrofuran (20 mL) was added. A solution of n-butyllithium (2.5 mL, 1.6 M in hexane) was added. The solution was then warmed to 50 °C for 3 h, and a white precipitate developed. The solution was cooled to -78 °C, methyl diethylborinate was added, and the flask was allowed to warm to RT, then stirred for 30 min. The flask was cooled to -78 °C, and boron trifluoride etherate was added, and the flask was warmed to RT for 30 min. The solvent was removed in vacou, and the resulting oil was dissolved in pentane, and filtered through celite in the glovebox, to yield **10** as a dark oil. **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (m, 12 H), 1.31 (m, 8 H), 6.78 (dd, J = 2.4 Hz, 5.7 Hz, 2 H), 7.38 (dd, J = 2.4 Hz, 5.7 Hz, 2 H).

Titration of 10 with benzo[c]cinnoline and pyrimidine

An NMR tube was charged with **10** (0.013 g, 0.05 mmol), and C_6D_6 (0.500 mL), and fitted with a septum in the glovebox. A solution of pyrimidine (0.200 g, 2.5 mmol) in C_6D_6 (4.0 mL). The solution of **10** was titrated with the pyrimidine solution, and monitored by ^{1}H NMR.

An NMR tube was charged with **10** (0.015 g, 0.057 mmol), and C_6D_6 (0.500 mL), and fitted with a septum in the glovebox. A solution of benzo[c]cinnoline (0.375 g, 2.08 mmol) in C_6D_6 (5.0 mL). The solution of **10** was titrated with the benzo[c]cinnoline solution, and monitored by ^{1}H NMR.

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Chapter 3

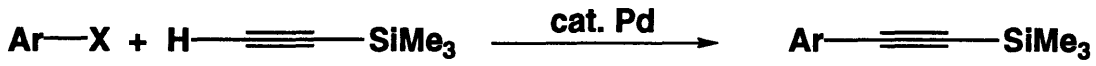
A Catalytic Method for the Conversion of Silanes to Stannanes

Introduction

In the course of our studies of organo-main group compounds, we desired ready access to aryl(alkynyl)boranes as host molecules for studies in molecular recognition. Our ultimate goal was to selectively recognize Lewis bases with conformationally rigid Lewis acids.[1] Our starting materials for these targets were bis(trimethylsilylethynyl)aromatic compounds, generated by the palladium-catalyzed cross-coupling reaction of trimethylsilylacetylene and dihaloaromatic compounds. These silylacetylene starting materials could be prepared easily on large scales, were indefinitely stable, and could be converted to the corresponding boranes (Scheme 1). While each step of this synthetic route was precedented, the synthesis of the alkynylboranes involved a four step process which necessitated the work-up and isolation of four compounds, including palladium-catalyzed cross-coupling; desilylation to form the terminal acetylene;[2,3] addition of bis(tributyltin)oxide to form the alkynylstannane;[4] and transmetallation from tin to boron[5] (Scheme 1).

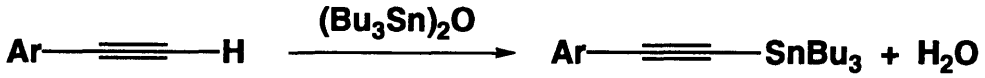
Scheme 1: Synthesis of Alkynylboranes from Aryl Halides

1) Cross-Coupling

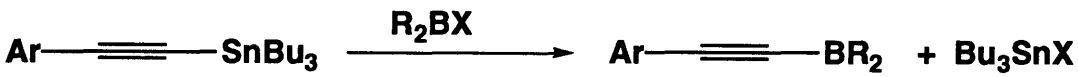


2) Desilylation

3) Formation of Stannane



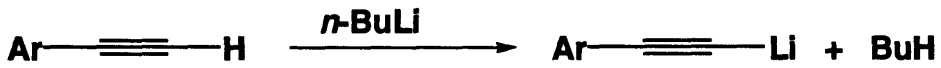
4) Formation of Borane



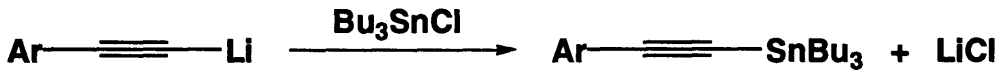
Alternatively, the alkynyl stannane could be generated by the reaction of a lithium acetylide with tributyltin chloride (Scheme 2).

Scheme 2: Alternative Route

3a) Deprotonation



3) Formation of Stannane



Results and Discussion

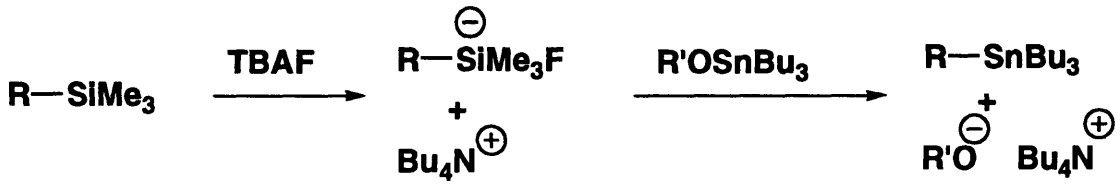
Rather than following either of these unnecessarily long procedures, we reasoned that steps (2) and (3) could be combined. This judgment was based on the reagents and products of each of these steps. In the first step, the trimethylsilyl group is removed by an alkoxide anion to generate an acetylide, which is protonated during work-up. It became apparent that the acetylide could be trapped with a tin alkoxide in a transmetallation step, to generate a stannylacetylene and a new reactive alkoxide. Overall, the reaction would be a metathesis of a silylacetylene and a tin alkoxide to form a alkoxysilane and a stannylacetylene. This reaction would be driven by the difference in energy (-9 kcal/mol) between the starting materials (Sn-O bond = 84 kcal/mol in Me_3SnOEt, Si-C bond = 91 kcal/mol in Me_4Si) and the products (Si-O bond = 111 kcal/mol in Me_3SiOEt, Sn-C bond = 73 kcal/mol in Me_4Sn),[6] and would eliminate the need to isolate any unstable intermediates.

The metathesis reaction was explored and was found to require a catalyst to initiate the process. The best catalyst was found to be tetrabutylammonium fluoride (TBAF). Both bis(tributyltin)oxide and tributyltin methoxide work well as tin sources. Allyl- and benzyltrimethylsilane were both found to work in this reaction as well. The catalytic cycle is shown in Scheme 3.

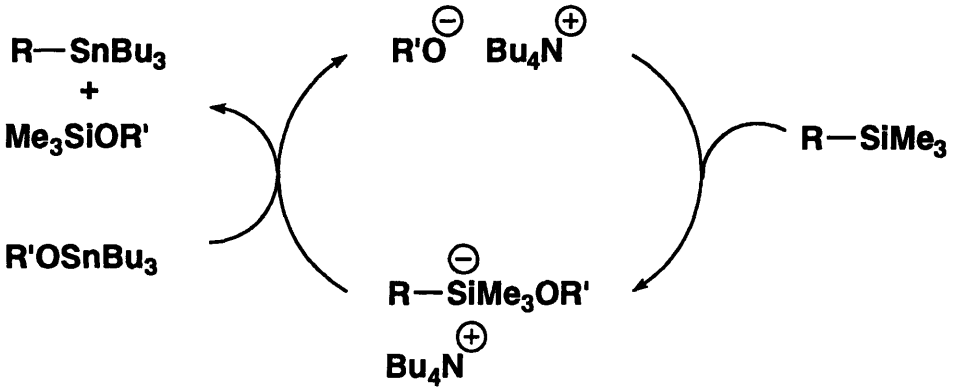
This process is similar to that of three other reactions. The first two are the fluoride catalyzed additions of silylacetylenes[7] and allylsilanes[8] to ketones. The third is the reaction of terminal acetylenes and bis(tributyltin)oxide to yield stannylacetylenes (Scheme 1, Reaction 3).

Scheme 3: Proposed Course of Reaction Catalytic Stannylation

Initiation



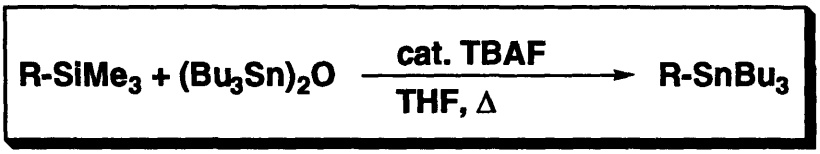
Catalytic Cycle

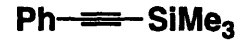
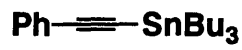
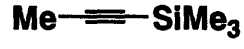
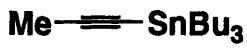
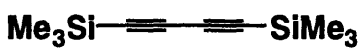
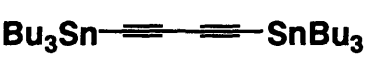
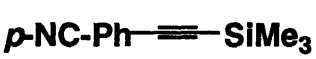
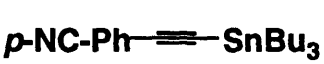
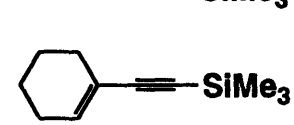
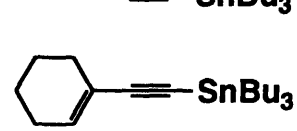
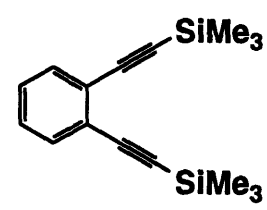
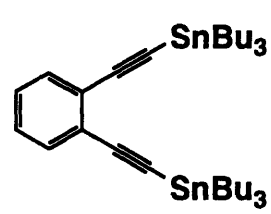


R' = Bu_3Sn or Me_3Si

The reaction was carried out by first charging a sealable Schlenk tube with an appropriate silane (1 equiv)[9], bis(tributyltin)oxide (0.5 equiv), and THF. A small amount of TBAF (0.02 equiv) was then added and the solution was heated at 60 °C for 2.5 h (16 h for allyl- and benzyltrimethylsilane), at which time the solvent and bis(trimethylsilyl)oxide are removed *in vacuo*. Allyltrimethylsilane, benzyltrimethylsilane, and alkynylsilanes all react to generate the corresponding stannanes in excellent yields without further purification (Table 1).

Table 1



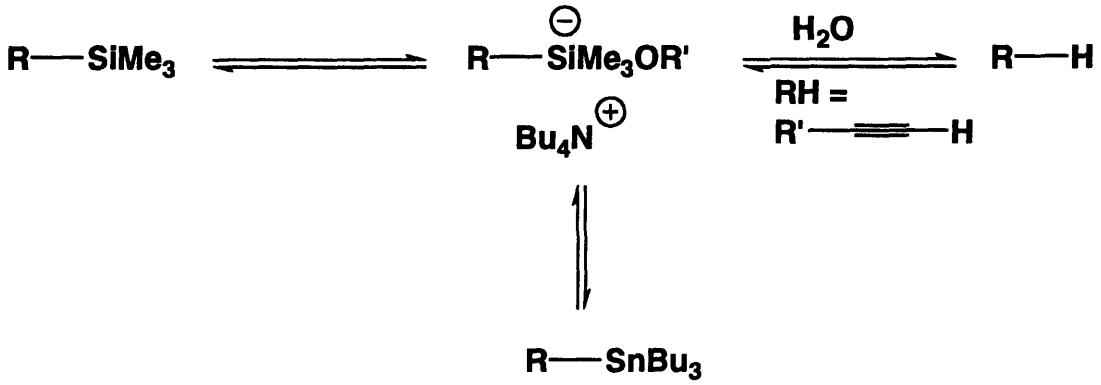
	Substrate[a]		Product	Yield[c]
1a		1b		97%
2a		2b		98%
3a		3b		98%
4a		4b		98%
5a		5b		99%
6a		6b		98%
7a		7b		97%
8a		8b		99%
9a[b]		9b		95%
10a[b]		10b		95%

[a] Reaction run for 2.5 h except as noted.
[b] Reaction run for 16 h.
[c] Yields refer to isolated product of >95% purity as estimated by ^{1}H NMR, and are based on the silane.

One aspect of the reaction that bears mentioning is the difference between alkynylsilanes and allyl- or benzylsilanes as substrates. Since solutions of TBAF contain 5% water, protonation of some of the silane or stannane is possible. For

alkynylstannanes, this reaction is reversible, but for allyl and benzyl trimethylsilane, a small amount of material is unavoidably lost (Scheme 4).

Scheme 4

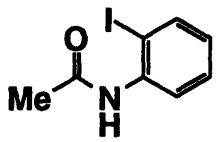
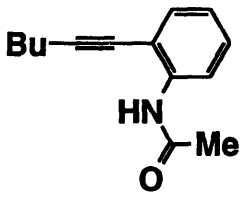


The utility of this reaction is further highlighted by the fact that the stannanes generated can be used without purification or removal of solvent and volatiles. This is demonstrated by the Stille coupling of the unpurified stannanes with aryl halides. For example, **1a** was converted to **1b**, then 1 equivalent of iodobenzene, 0.025 equivalents of palladium (II) acetate, and 0.05 equivalents of triphenylphosphine were added. After heating the reaction mixture to 60 °C for 14 h, aqueous work up, followed by flash chromatography afforded diphenylacetylene in 81 % isolated yield. Several other palladium-catalyzed cross-coupling reactions were also carried out to demonstrate that the stannanes generated from silanes can be generally be used in Stille couplings without any purification or isolation (Table 2).

The method developed here for generating stannanes from silanes has advantages in terms of cost and ease of use. The reaction utilizes inexpensive bis(tributyltin)oxide rather than the more costly and moisture-sensitive tributyltin chloride. The reaction allows the conversion of alkynylsilanes, as well as allyl- and benzyltrimethylsilane, to the corresponding tributylstannanes in one step, as opposed to desilylation and isolation of the terminal alkyne, followed by conversion to the stannane.

Finally, the product is isolated in quantitative yield with removal of the volatile bis(trimethylsilyl)oxide being the only purification needed.

Table 2

	Silane, Ar-I		Product	Yield
1a	Ph—≡—$SiMe_3$ PhI	1c	Ph—≡—Ph	80 % 81 %[a]
4a	Me_3Si—≡—≡—$SiMe_3$ PhI	4c	Ph—≡—≡—Ph	82 %
5a	NC—C6H4—≡—$SiMe_3$ I—C6H4—OMe	5c	NC—C6H4—≡—C6H4—OMe	78 %
11a	Bu—≡—$SiMe_3$ 	11c		70 %

[a] $(Bu_3Sn)_2O$ used instead of Bu_3SnOMe

In summary, we have developed an efficient method for the conversion of alkynyl, benzyl, and allyl silanes to the corresponding stannanes; and have shown that these products can be used in palladium couplings without any purification.

Experimental Section

General Considerations

All reactions were carried out under an atmosphere of argon using standard Schlenk techniques. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity-300, Varian XL-300, Varian XL 301, or Bruker AC-250 Fourier transform spectrometer. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 series Fourier transform spectrometer. The electron impact high resolution mass determination (HRMS) of **5b** was recorded on a Finnegan MAT System 8200. A sample of **8b** was sent, in a sealed vial under nitrogen, to Desert Analytics for elemental analysis.

Tetrahydrofuran (THF) was dried and deoxygenated by refluxing and distilling from sodium / benzophenone ketyl under an argon atmosphere. All reagents, unless otherwise stated, are commercially available and were used as received. Yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H NMR spectrometry, and are an average of two or more separate experiments.

Representative Procedure for Silicon to Tin Metathesis: A flame dried sealable Schlenk flask under Argon was charged with **1a** (0.348 g, 2.0 mmol), and $(Bu_3Sn)_2O$ (0.596 g, 1.0 mmol), and THF (5 mL). TBAF (0.040 mL, 1 M in THF) was added, and the flask was sealed and stirred at 60 °C for 2.5 h, at which time the volatiles were removed *in vacuo* to yield **1b** as a colorless oil with no further purification necessary (0.764 g, 98 %).

Representative Procedure for Stille Coupling: A flame dried sealable Schlenk flask under Argon was charged with **1a** (0.348 g, 2.0 mmol), and $(Bu_3Sn)_2O$ (0.596 g, 1.0 mmol), and THF (5 mL). TBAF (0.040 mL, 1 M in THF) was added, and the flask was sealed and stirred at 60 °C for 3 h. Iodobenzene (0.408 g, 2.0 mmol), palladium acetate (0.011 g, 0.05 mol), and triphenylphosphine (0.026 g, 0.1 mol) were added, and the reaction was heated to 60 °C for 14 h. Aqueous potassium fluoride (10 %, 50 mL)

was added, and the solution was stirred for 3 h. The volatiles were removed by rotary evaporation, then the aqueous layer was extracted with hexane (3 x 50 mL). The organic layer was dried ($MgSO_4$) and filtered to leave a white solid, which was purified by flash chromatography (hexane) to afford **1c** as a white crystalline solid (0.291 g, 82 %).

Compounds **1a-4a**, **9a**, and **10a** were purchased from Aldrich Chemical Co., Inc. Compounds **5a-8a** were prepared according to the literature. The spectral data for **6a**,[10] **1b**,[11] **2b**,[12], **5c**,[13] and **11c**[14] have been reported in the literature. Compounds **3b**, **9b**, **1c**, and **4c** were compared with material purchased from Aldrich Chemical Co., Inc.

5a:[2] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.26 (s, 9H), 7.54 (d, J = 18.0 Hz, 2H), 7.57 (d, J = 18.0 Hz, 2H); IR (Film): alkyne 2158, nitrile 2234.

7a:[15] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.18 (s, 9H), 1.59 (m, 4H), 2.11 (m, 4H), 6.18 (m, 1H); IR (Film): alkyne 2146.

8a:[2] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.34 (s, 18H), 7.28 (dd, J = 5.7, 3.3 Hz, 2H), 7.51 (dd, J = 5.7, 3.3 Hz, 2H); IR (Film): alkyne 2161.

4b:[16] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 9H), 1.00 (t, J = 8.3 Hz, 6H), 1.30 (m, 6H), 1.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 92.91, 83.94, 28.79, 26.97, 13.57, 11.36; IR (Film): alkyne 2036.

5b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, J = 7.3 Hz, 9H), 1.07 (t, J = 8.0 Hz, 6H), 1.36 (m, 6H), 1.6 (m, 6H), 7.51 (d, J = 8.2 Hz, 2 H), 7.53 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.2, 131.7, 128.7, 118.5, 110.5, 108.0, 99.9, 28.9, 27.0, 13.7, 11.3; IR (Film): nitrile 2363, alkyne 2228; HRMS: Calcd. for $C_{21}H_{31}NSn$: 417.1478. Found: 417.1476.

6b:[17] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 7.5 Hz, 9H), 0.99 (t, J = 8.1 Hz, 6H), 1.32 (m, 6H), 1.53 (m, 6H), 3.37 (s, 3H), 4.09 (s, 2H); IR (Film): alkyne 2149.

7b:[18] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 9H), 0.98 (t, J = 8.1 Hz, 6H), 1.34 (m, 10H), 1.57 (m, 10H), 2.09 (m, 4H), 6.10 (m, 1H); IR (Film): alkyne 2126.

8b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, J = 7.2 Hz, 18H), 1.06 (t, J = 12 Hz, 12H), 1.36 (m, 12H), 1.6 (m, 12H), 7.17 (dd, J = 5.7, 3.4 Hz, 2 H), 7.42 (dd, J = 5.8, 3.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.6, 127.2, 126.3, 108.5, 97.4, 28.9, 27.0, 13.6, 11.2; IR (Film): alkyne 2135; Anal: Calcd. for: $C_{34}H_{58}Sn_2$: C, 57.99; H, 8.3. Found: C, 57.97; H, 8.58.

10b:[19] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, J = 7.8 Hz, 6H), 0.87 (t, J = 7.4 Hz, 9H), 1.28 (m, 6H), 1.4 (m, 6H), 2.3 (t, J_{Sn-H} =27 Hz, 2H), 6.9 (m, 3 H), 7.16 (m, 2 H).

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(3) Note: The desilylation step was not carried out *in situ*, as is normally the case, because polyethynyl compounds are often unstable. See Ashe, A. J. III, Drone, F. J. *J. Am. Chem. Soc.* **1987**, *109*, 1879-1880.

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