Reactions of alkyl and alkenyl zirconocene complexes
by Klark Thor Hanson

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Chemistry
Montana State University

Abstract:
Zirconacycles have been. demonstrated to react sluggishly with acyl chlorides even at elevated temperatures . Studies were undertaken to detertmine whether or not this reaction could be facilitated via transmetallation of one or both of the carbon-zirconium bonds of the zirconacycle to a more suitable metal. This research demonstrates that zirconacycles will react with acyl chlorides in the presence of secondary metallic reagents. Cuprate reagents and catalytic palladium complexes have been demonstrated to function in this capacity, presumably via stoichiometric and catalytic transmetallation respectively.

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in

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APPROVAL

of a thesis submitted by

Klark Thor Hanson

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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ABSTRACT

Zirconacycles have been demonstrated to react sluggishly with acyl chlorides even at elevated temperatures. Studies were undertaken to detertmine whether or not this reaction could be facilitated *via* transmetallation of one or both of the carbon-zirconium bonds of the zirconacycle to a more suitable metal. This research demonstrates that zirconacycles will react with acyl chlorides in the presence of secondary metallic reagents. Cuprate reagents and catalytic palladium complexes have been demonstrated to function in this capacity, presumably *via* stoichiometric and catalytic transmetallation respectively.

INTRODUCTION

For many years zirconocene reagents have been the subject of extensive study. The wide range of controlled reactivity that these reagents display, coupled with their relatively low cost and toxicity, have made them ideal reagents for many transformations[1]. The two most synthetically useful and widely studied classes of reactions involving reagents of this type are the hydrozirconation[2,3,4] of alkenes and alkynes and the intramolecular reductive coupling of carbon-carbon multiple bonds to form bicyclic products[1] (Figure 1).

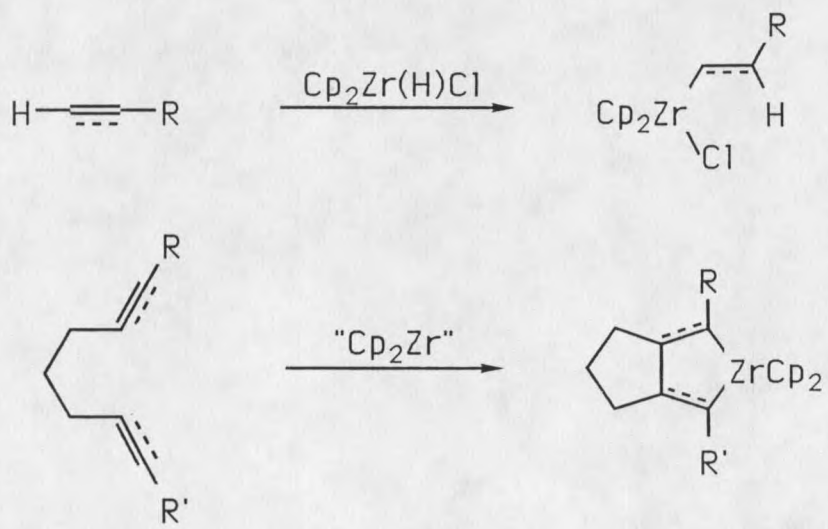


Figure 1. General Zirconium Mediated Processes

Hydrozirconation

Methods

The reagent for effecting hydrozirconation, $Cp_2Zr(H)Cl$, is known as Schwartz's reagent[2]. Unfortunately, it readily decomposes when subjected to air or water. It has been shown that Schwartz's reagent can be formed *in situ* by treating zirconocene dichloride with one equivalent of lithium triethylborohydride[5]. This reagent mixture has been shown to give results similar to Schwartz's reagent in many cases but is more desirable than Schwartz's reagent in that it can be prepared immediately before use from readily available and stable precursors. This *in situ* formation of Schwartz's reagent may not always be preferable, however. The presence of stoichiometric quantities of lithium chloride and triethylborane may complicate or impede some processes.

Scope and Limitations

One of the notable factors governing the outcome of these reactions is the propensity of zirconocene to migrate to the terminal carbon during the hydrozirconation of internal, straight chain oleins[6] (Figure 2).

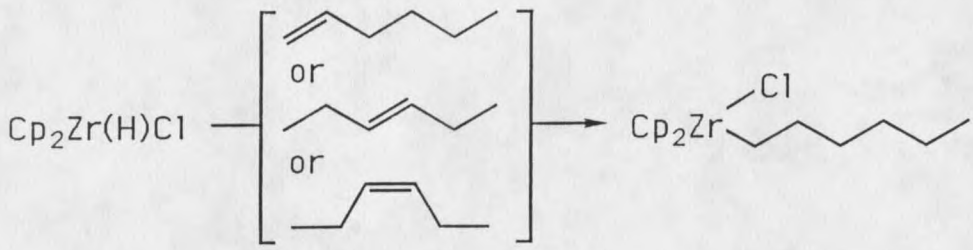


Figure 2. Zirconocene Migration

The order of reactivity for various types of olefins is: terminal > cis internal > trans internal > exocyclic > cyclic, as well as the general trend: monosubstituted > disubstituted > trisubstituted[7]. Tetrasubstituted olefins and trisubstituted cyclic olefins fail to react[7]. Additions to disubstituted alkynes are *cis* with the bulky zirconocene preferring the less hindered terminus[7]. Mixtures of regioisomers readily equilibrate in the presence of a small excess of $Cp_2Zr(H)Cl$ to a mixture greatly favoring the less hindered product[7].

Reductive Bicyclization

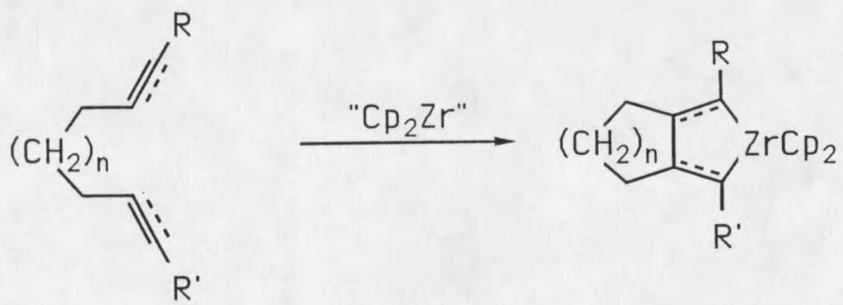
Methods

Intramolecular reductive couplings using zirconocene equivalents are carried out by the *in situ* reduction of zirconocene dichloride by sodium/mercury amalgam[8], magnesium/mercuric chloride[9] or, most conveniently, with two

equivalents of n-butyllithium followed by reductive elimination of butane[10]. The diyne, enyne or diene is then added to this solution and allowed to react to form either the ziconacyclopentadiene, zirconacyclopentene or zirconacyclopentane. Other methods for the *in situ* generation of zirconocene or ziconocene equivalents also exist although they are less frequently applied[11,12].

Scope and Limitations

The size of the carbocycle formed can vary from four to seven carbons when coupling diynes to form, following protonation, E,E exocyclic dienes[13]. However, dienes[14,15] and enynes[16] are limited to forming five and six membered carbocycles when reductively coupled (Figure 3).



diyne: n = 0, 1, 2, 3
enyne: n = 1, 2
diene: n = 1 (*trans*), 2 (*cis*)

Figure 3. General Intramolecular Reductive Coupling

The stereochemistry of the organic products of diene cyclizations is interesting; when 1,6-heptadiene is cyclized and protonated the product is almost exclusively *trans*-1,2-dimethylcyclopentane (*cis*:*trans*, 3:97) while 1,7-octadiene affords predominantly cis-1,2-dimethylcyclohexane (*cis*:*trans*, 83:17)[14,15]. Nugent has shown that by cyclizing 1,6-heptadiene with the reagent formed by treating Cp^*ZrCl_3 with sodium/mercury amalgam, *cis*-1,2-dimethylcyclopentanes (*cis*:*trans*, 99:1) can be formed[14] (Figure 4).

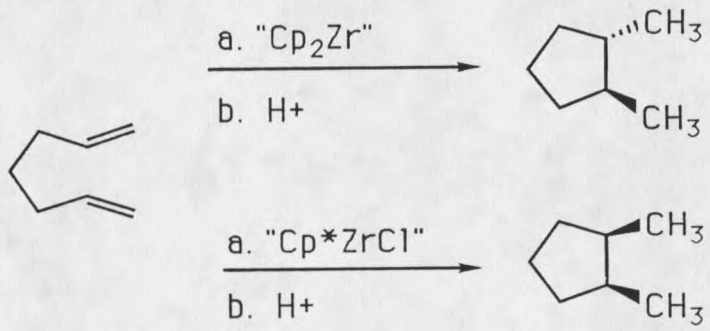
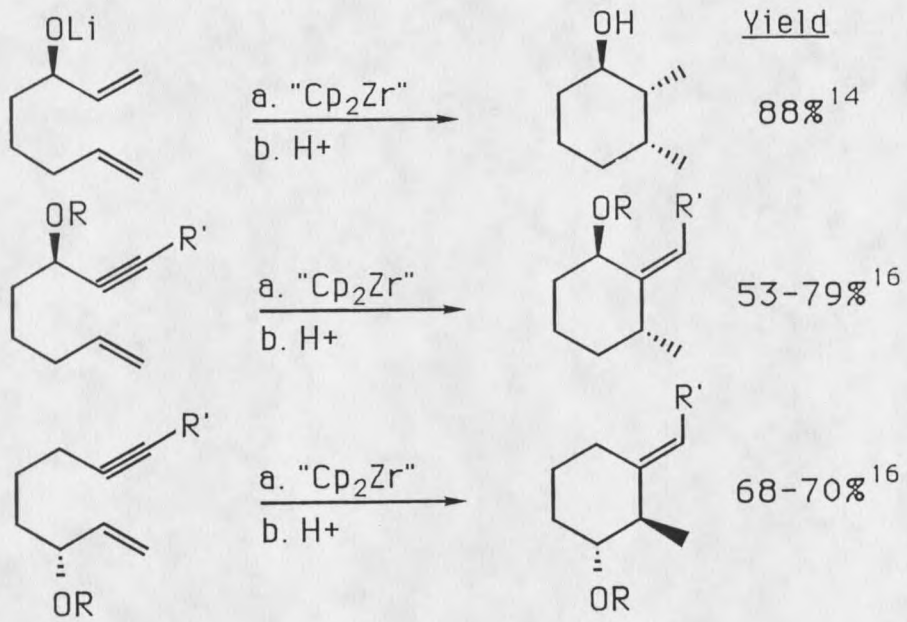


Figure 4. Stereochemistry of Diene Cyclization

These reactions will tolerate a variety of functionality in the precyclic substrate including allylic or propargylic silyl ethers[16], ketals[14], lithium alkoxides[14,16], tertiary amines[1], thioethers[16], alkyl silicon, tin and germanium groups[1], and dithio ketals. Nugent[14] and Livinghouse[16] have shown that, when the precyclic diene or

enyne contains an allylic or propargylic oxygen substituent, the cyclization will proceed in a diastereoselective fashion *via* 1,2 or 1,3-stereoinduction (Figure 5).



R = TMS, TBDMS R′ = TMS, SMe

Figure 5. 1,2 and 1,3-Stereoinduction

Functionalization of Carbon-Zirconium Bonds

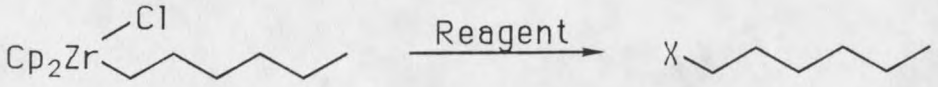
The literature contains many examples of how zirconocene reagents become incorporated into organic molecules and the nature of the carbon-metal bonds formed. In initial studies, many of the "transformed" organic products were isolated following protonation of the carbon-

metal bonds with acid, water or methanol. However, the reactivity of these carbon-metal bonds with electrophiles more elaborate than H^+ has received some attention and has been significantly expanded. Today, many processes involving zirconocene reagents exploit the capability of these carbon-metal bonds to produce more varied and more highly functionalized organic products[1].

Reactions of Hydrozirconation Products

Organic Electrophiles

Alkyl and alkenyl carbon-zirconium bonds in hydrozirconation products are known to undergo many reactions. Schwartz, in some of his initial work, has demonstrated several derivatizations. These compounds have been shown to react with *t*-butyl peroxide to yield alcohols, following protonation, and with iodine, bromine or other halogenating reagents such as *N*-bromosuccinimide and *N*-chlorosuccinimide to give the corresponding halides[6] (Figure 6). These reactions are thought to proceed through a closed transition state leading to retention of configuration at the carbon bound to zirconium[6].

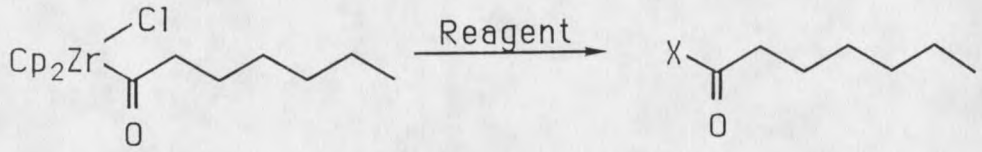


Reagent	X
t-C_4H_9OOH	OH
NCS	Cl
NBS or Br_2	Br
I_2	I

Figure 6. Reactions of Hydrozirconation Products

Carbonylation

The ability of these compounds to undergo carbon-carbon bond forming reactions is of greater synthetic interest. These compounds can be carbonylated with carbon monoxide and then protonated to yield one carbon homologated aldehydes[6]. Treatment of the carbon monoxide insertion product with N-bromosuccinimide will allow the isolation of the acid bromide[6]. Alternatively, the acid halide can be formed *in situ* by treatment with bromine and then "quenched" with alcohols to form esters or with peroxides to form carboxylic acids[6] (Figure 7).



Reagent	X
H+	H
Br_2 in MeOH	OMe
H_2O_2	OH
NBS	Br

Figure 7. Reactions of Carbonylation Products

It has been shown that carbon dioxide does not insert into carbon-zirconium bonds. Schwartz rationalized this observation by noting that carbon monoxide is both nucleophilic and electrophilic while carbon dioxide is electrophilic but not significantly nucleophilic[4].

Isocyanide Insertion

Also of note regarding carbon-carbon bond formation is the research of both Negishi[18] and Buchwald[19] concerning the insertion of isocyanides into carbon-zirconium bonds. These investigators, respectively, have shown that isocyanide insertion products can provide aldehydes when quenched with acid (Figure 8) or nitriles, *via* rearrangement, when quenched with iodine (Figure 9).

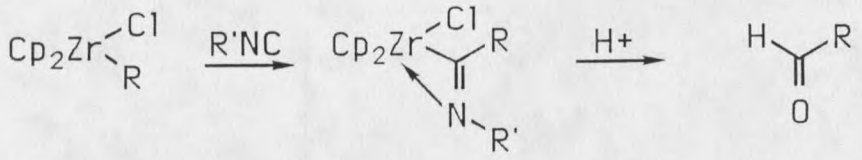


Figure 8. Aldehyde Formation *via* Isocyanide Insertion

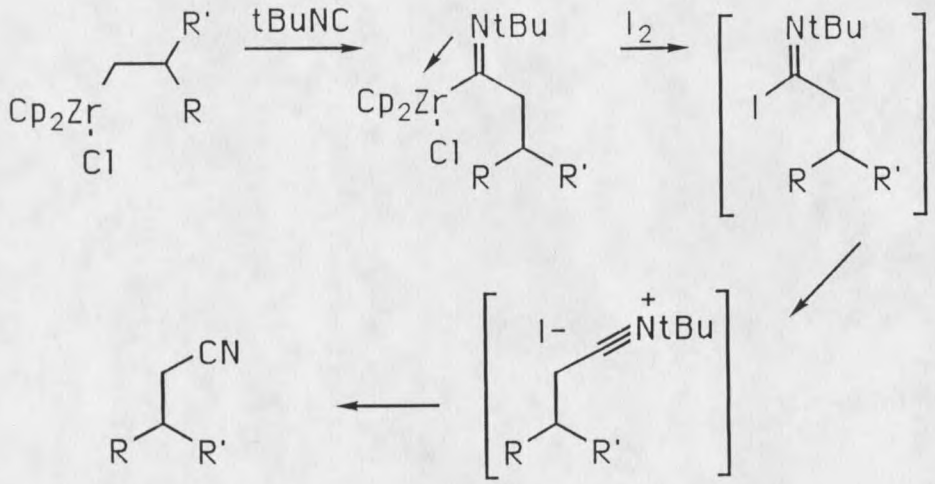


Figure 9. Nitrile Formation *via* Isocyanide Insertion

Acyclic diorganozirconocene complexes have been shown to undergo insertion reactions with ketenes, isocyanates, carbodiimides and diazo compounds[1], and; hydrozirconation products are known to insert nitric oxide and sulfur dioxide[4]. However, these reactions have not yet been developed into synthetically useful organic transformations.

Catalytic and Stoichiometric Transmetallation

Several nickel or palladium catalyzed carbon-carbon bond forming reactions of carbon-zirconium bonds have been demonstrated. Schwartz has demonstrated that alkenyl carbon zirconium bonds can undergo 1,4-addition to enones in the presence of a nickel catalyst[20,21,22]. Schwartz also demonstrated that alkenyl zirconium bonds will "couple" with stoichiometric quantities of pi-allyl palladium compounds[23]. Negishi has demonstrated that, in the presence of catalytic nickel or palladium compounds and stoichiometric quantities of zinc chloride, alkenyl zirconium bonds can be coupled with aryl[24], acetylenic[25] and vinyl[25,26] halides. Schwartz also noted that a carbon-zirconium bond, following treatment with Ag(I), can react with ethylene oxide to form a two carbon homologated alcohol following protonation[4].

Hydrozirconation products have a much larger body of chemistry associated with their derivatization than do zirconacycles. This may be due to the fact that the hydrozirconation process has been known for a longer period of time. Also, the reactions of these products would be inherently easier to investigate than the reactions of zirconacycles because there is only one carbon-zirconium bond per molecule.

Reactions of Zirconacycles

Organic Electrophiles

Zirconacycles have been shown to react with halogenating reagents (bromine or iodine) to produce dihalogenated carbocycles[14]. Diols can also be accessed by reaction with oxygen followed by protonation[14]. The diols can also be diacylated without isolation of the diol[14].

Carbonylation

Some carbon-carbon bond forming reactions of zirconacycles do exist in the literature. Negishi has demonstrated the carbonylation of a zirconacyclopentene to form a cyclopentenone[27,28]. He has also shown that zirconacyclopentanes will insert carbon monoxide and produce cyclopentanones when quenched with iodide or, alternatively, cyclopentanols when quenched with acid[15] (Figure 10).

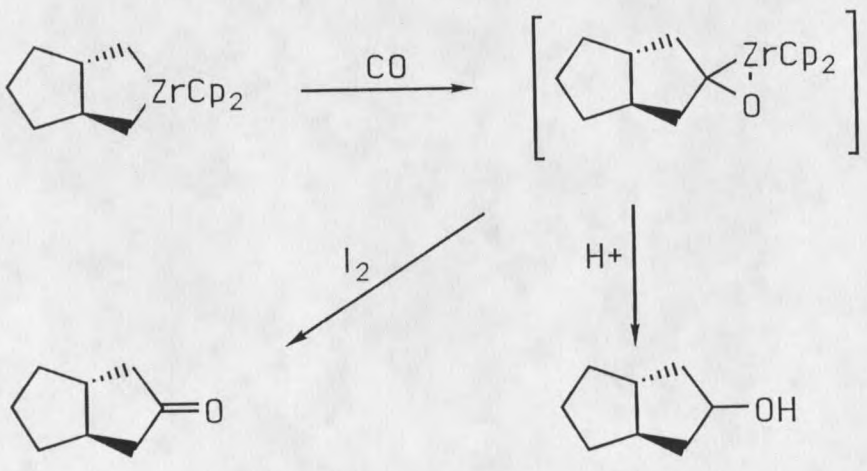


Figure 10. Carbonylation of Zirconacycles

Isocyanide Insertion

An interesting example of bifunctionalization of a zirconacycle comes from Negishi's work with isocyanides[18]. In one example, it was shown that sequential treatment of a zirconacycle with an isocyanide (which selectively inserts into the alkyl zirconium bond), one equivalent of iodine (which selectively halogenates the alkenyl zirconium bond), and finally acid (which quenches the new carbon-zirconium bond formed and hydrolyzes the resulting imine) produced the iodoaldehyde shown in Figure 11.

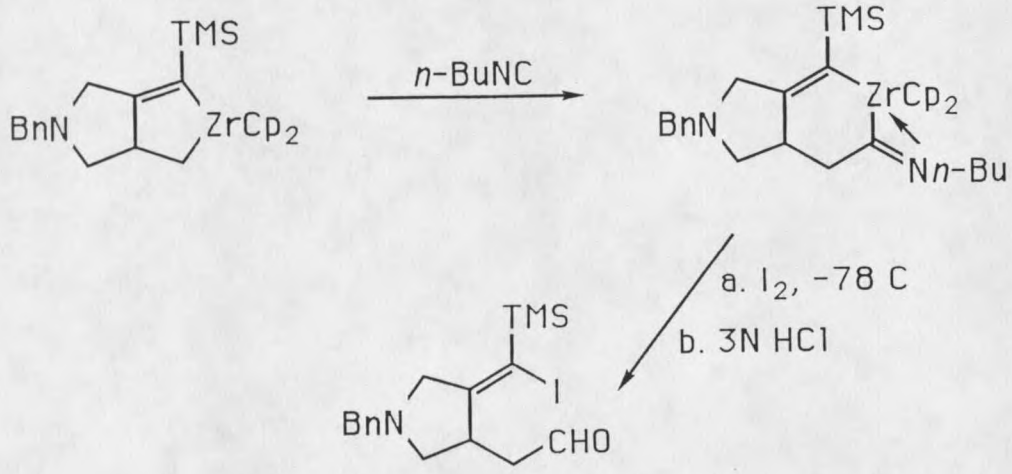


Figure 11. Bifunctionalization of a Zirconacycle

Transfer to Main Group Elements

The most significant work regarding the derivatization of zirconacycles is that of Fagan and Nugent. In a series of articles, these researchers have shown that the transfer

of zirconacycles to main group elements to form new heterocycles is quite general[13,14,17,29]. Zirconacycles have been successfully transferred to: antimony, arsenic, bismuth, boron, gallium, germanium, indium, phosphorus, sulfur, selenium and tin (Figure 12). This work is quite intriguing due to the greatly expanded reactivity these "transferred" zirconacycles might display.

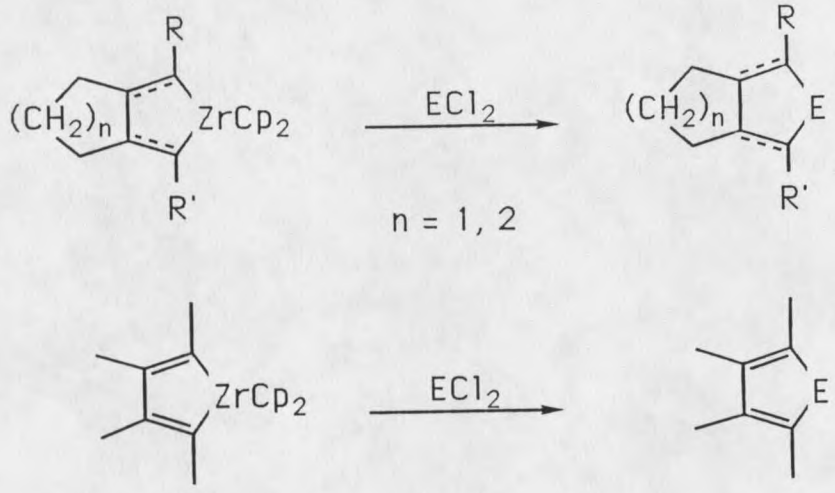


Figure 12. Zirconacycle Transfer to Main Group Elements

Catalytic Cyclization, Stoichiometric Transmetallation

Recently, investigators from Stanford have reported that the intramolecular reductive coupling of a diene with zirconocene dichloride and butylmagnesium bromide is catalytic in zirconium[30]. The product of these reactions appears to be the di-grignard. These results are noteworthy in that they will quite likely provide (when fully

exploited) products not available directly from zirconacyclopentanes. These conditions do not produce the stereospecificity of the stoichiometric zirconocene method when cyclizing 1,6-heptadiene to 1,2-dimethylcyclopentane (36:64 *cis*:*trans* vs 3:97). However, these conditions do show selectivity very similar to the stoichiometric method when cyclizing 1,7-octadiene to 1,2-dimethylcyclohexane (82:18 *cis*:*trans* vs 83:17). Unfortunately, these results seem to be specific for dienes; the researchers note that when attempting to cyclize an enyne the major product is the carbometallation product of the alkyne moiety.

Acyl Halides as Electrophiles for Carbon-Metal Bonds

Many organometals are known to react with acid halides to form acylation products. Examples from the literature include organometallic compounds of aluminum[31], boron[32], cadmium[33], copper[34], iron[35], magnesium[33], manganese[36], mercury[37], silicon[38], rhodium[39] and zinc[33]. In demonstrating the facility of transferring hydrozirconation products to aluminum in order to functionalize them with acid chlorides, Schwartz demonstrated in two examples that a direct reaction of a carbon-zirconium bond with acetyl chloride is possible, but slow[40]. Schwartz states that this reaction is affected significantly by steric congestion and fails for more hindered acid chlorides[40]. A related procedure in the literature is that of Negishi[41]. In order to form a ketone

from a hydrozirconation product, Negishi found it necessary to quench the hydrozirconation product with iodine, isolate the iodide, insert zinc metal into the carbon-iodine bond, and then treat this vinyl zinc iodide with an acid chloride in the presence of a palladium catalyst.

We have shown that zirconacycles react very sluggishly, with acid chlorides even at elevated temperatures. We investigated whether or not we could effect this reaction *via* transmetallation of one or both of the carbon-zirconium bonds of the zirconacycle to a more suitable metal. It seemed plausible that some of the existing methods for the functionalization of hydrozirconation products might serve as model processes for the functionalization of zirconacycles. The method detailed in the Results and Discussion section demonstrates that a one pot reaction of a zirconacycle with an acid chloride is possible in the presence of catalytic palladium.

Cuprate Mediated Functionalization

In 1990 researchers at Searle[42] and in Lipschutz's group[43] discovered that hydrozirconation products of alkynes, when modified with the cuprate reagent $Me_2CuCNLi_2$, could undergo 1,4-addition to enones (Figure 13).

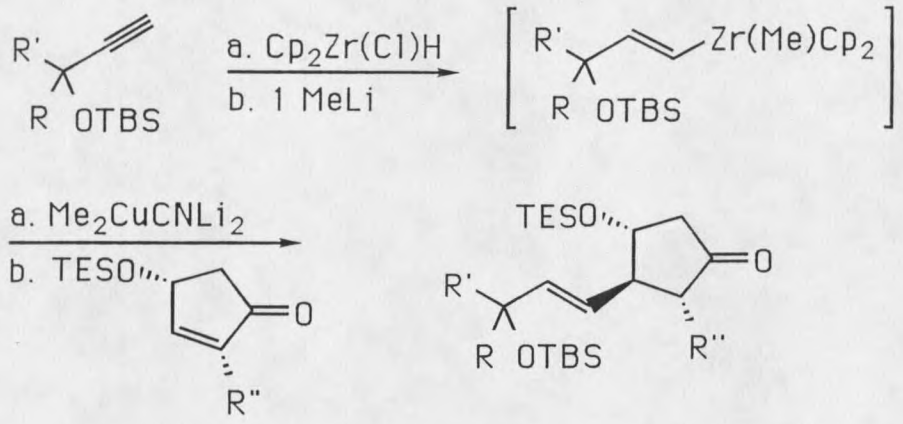


Figure 13. Cuprate Mediated 1,4-Addition

Because cuprate reagents are known to form ketones when treated with acid chlorides[34], we thought that carbon-zirconium bonds, following treatment with a cuprate reagent might react with acid chlorides to form a ketones.

RESULTS AND DISCUSSION

Cuprate Mediated Acylation

Model Substrate

The zirconacyclopentene constructed from the enyne **1** was chosen as a model in this study due to the ease of preparation and the ready availability of the starting materials. Enyne **1** was produced in satisfactory yield by alkylating lithium phenylacetylide with 5-bromo-1-pentene (Figure 14)[45].

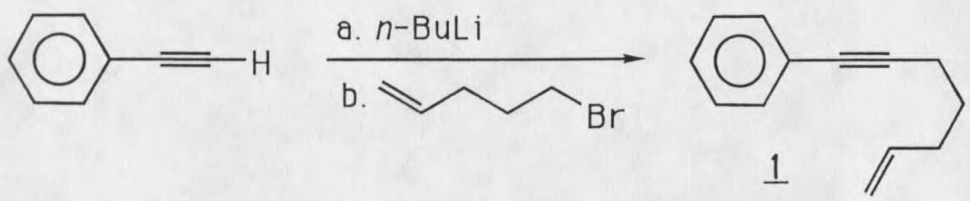


Figure 14. Preparation of **1**

Samples of the corresponding protonated and deuterated cycles of enyne **1**, compounds **2** (92% yield) and **3** (82% yield) respectively, were prepared at this time to test the efficiency of cyclization and recovery of products (Figure 15).

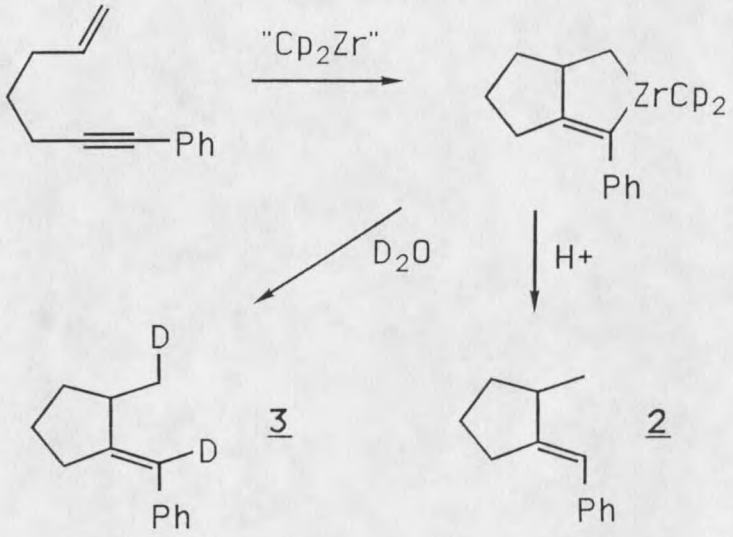


Figure 15. Preparation of 2 and 3

Model Reagents

The initial study employed trimethylacetyl chloride because it lacks acidic alpha protons and because it possesses a simple NMR signal that served to probe whether or not it had become incorporated into the organic products of our reactions. Our simplest reaction used the conditions of the researchers at Searle[42] and in Lipschutz's[43] group to treat the model zirconacycle with one equivalent of $Me_2CuCNLi_2$ and then treat this mixture with one equivalent of trimethylacetyl chloride.

Initial Results

In this preliminary reaction, a small amount of functionalized product was isolated, which proved to be **4**.

In addition, a reaction where two equivalents of $Me_2CuCNLi_2$ were used provided 5 as the major functionalized product (Figure 16).

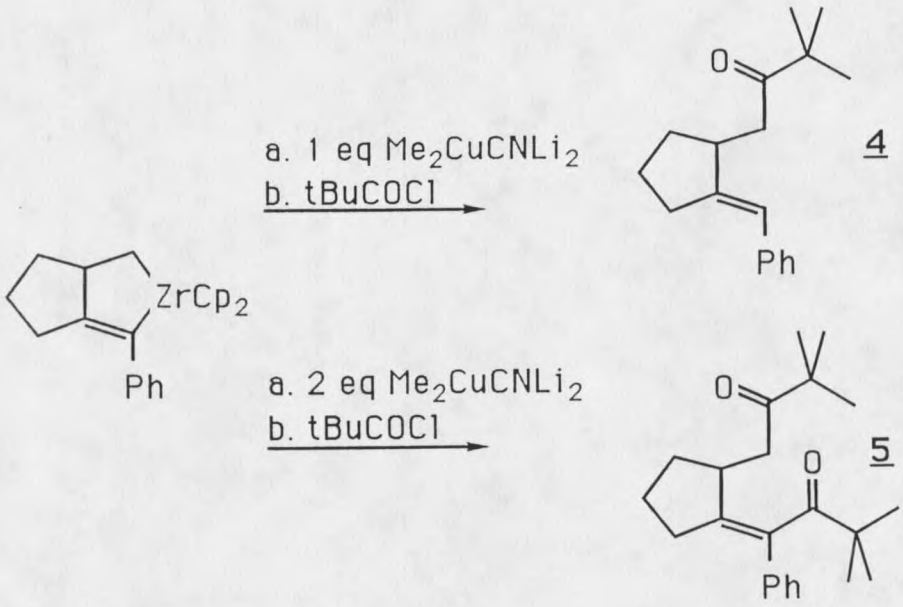


Figure 16. Cuprate Mediated Preparation of 4 and 5

In both reactions the major product was unfunctionalized (protonated) metallacycle. Both 4 and 5 presumably result from the transmetallation of the carbon-zirconium bond(s) to the cuprate reagent and subsequent reaction of this new cuprate reagent with the acid chloride. $Me_2CuCNLi_2$, while being very easy to prepare and use (prepared by adding two equivalents of methyllithium to a one molar solution of copper(I) cyanide in tetrahydrofuran[45]), did not appear capable of efficiently providing functionalized material.

This reagent did, however, show selectivity for the alkyl zirconium bond over the alkenyl zirconium bond.

Other Cuprate Reagents

Many other types of cuprate reagents were then screened in this process. Cuprates which possess something in addition to, or in place of, cyanide as a "non-transferable ligand" are known to display modified reactivity in other processes[46]. Cuprate reagents of the sort $Me(R)CuCNLi_2$, where R = NCy_2[46], PCy_2[46], and Me(R)CuLi, where R = 1-pentynyl[47,48] were substituted for the original reagent in this process, but failed to show equal or enhanced reactivity.

Problems

An inherent problem with the cuprate mediated acylation process might be the excess equivalents of carbanions present in the reaction vessel. If the process is not 100 percent selective for the alkyl zirconium bond, one may have a vinyl carbanion and a ketone in the same molecule even when only one equivalent of the cuprate reagent is used. A possible product of the condensation of this intermediate would be the alcohol **6**. This alcohol was observed as a by-product in both the cuprate mediated mono- and di-acylation reactions (Figure 17).

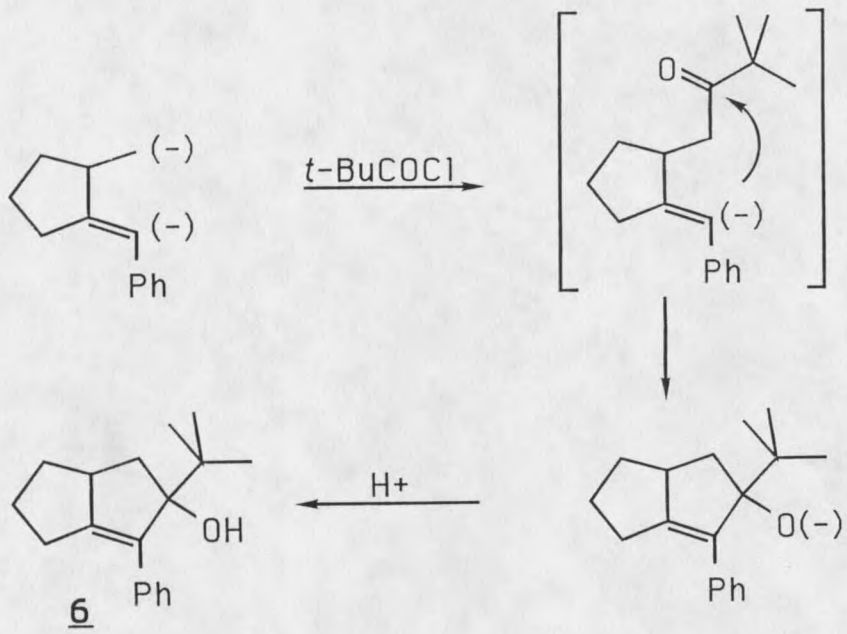


Figure 17. Formation of Cuprate By-product 6

Copper Halides

Later we thought that it might be interesting to try a reaction with the tetrahydrofuran soluble copper(I) halide complex, CuCl·2LiCl as the source of copper. In the presence of trimethylacetyl chloride, acylation proceeded rather slowly. However, with the addition of a palladium complex, bis(triphenylphosphine)palladium(II) chloride, the reaction did provide 5 as the major product, but; the reaction was not clean. The action of this palladium compound will be discussed in detail later in this thesis.

Zincates

Compounds of the type R_3ZnLi, zincates, are known to behave similarly to cuprates in that they undergo 1,4-addition rather than 1,2-addition to enones[49,50]. Also, there is precedence for the transmetallation of organic groups between zirconium and zinc[51]. So, it seemed reasonable to assess the usefulness of zincates in this process. The zincates $Et_2(Me)ZnLi$ and $Et_2(n\text{-}Bu)ZnLi$ were formed by treating a solution of diethylzinc in tetrahydrofuran with one equivalent of the appropriate alkyl lithium. The zincate Me_3ZnLi was also prepared by treating a tetrahydrofuran solution of $ZnCl_2 \cdot TMEDA$ with three equivalents of methyllithium. These reagents, when used in place of $Me_2CuCNLi_2$ failed to produce isolable quantities of acylated material.

Palladium Catalyzed Acylation

Rationale

Palladium compounds are known to oxidatively insert into the carbon-chlorine bond of acid chlorides[52] and have demonstrated catalytic behavior in the transmetallative functionalization of carbon-zirconium bonds (see Introduction). Stille's work[52] has demonstrated palladium catalysis of the reaction of organotin compounds with acid chlorides and other electrophiles. Accordingly, it seemed

reasonable to attempt an analogous reaction in this system. Assuming that organozirconium compounds would behave similarly in this process, a possible mechanism[52] is shown in Figure 18.

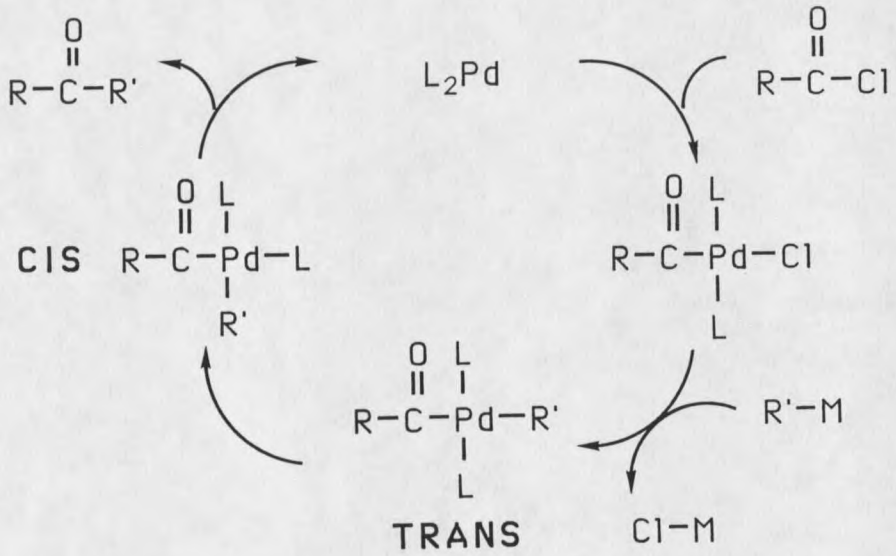
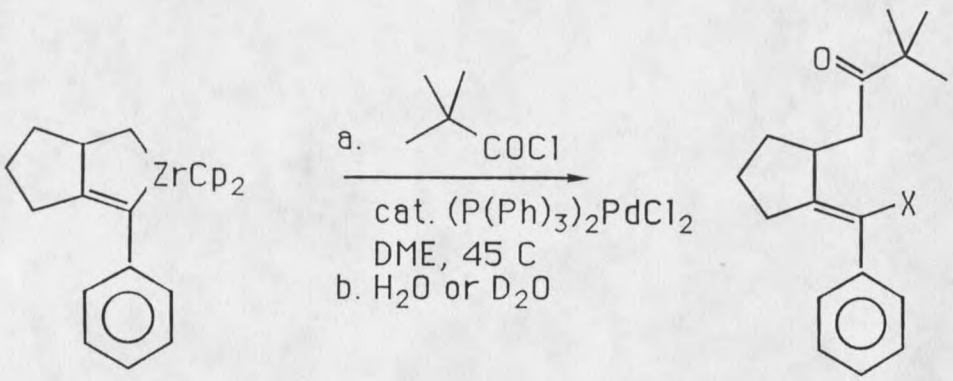


Figure 18. Palladium Catalyzed Acylation Mechanism

Model Reaction

A reaction was performed in which the zirconacyclopentene constructed from enyne **1** was allowed to react with two equivalents of trimethylacetyl chloride in the prescence of ten mole percent of bis(triphenylphosphine)-palladium(II) chloride. The amount of functionalized product observed was quite promising. Further study led to optimized conditions which use dimethoxyethane as the reaction solvent and require heating of the reaction mixture to 45 °C for 30 minutes. These conditions provided **4** in 75% isolated yield (Figure 19).



4 X = H
7 X = D (80%)

Figure 19. Palladium Catalyzed Preparation of **4** and **7**

In order to determine whether or not a carbon-metal bond still existed at the vinyl position (i.e. had it become quenched by a proton source in the flask and thus become inert to functionalization), deuteration experiments were performed. When excess D_2O was added following palladium catalyzed acylation, the product **7** (78% yield) displayed significant (80%) incorporation of deuterium at the vinyl position (Figure 20). This percentage was determined by integrating the vinyl proton signal region relative to the five proton aromatic signal.

Other Acylating Reagents

At this point, we decided to try another acid chloride. We thought that isobutyryl chloride (due to its similarity to the initial reagent) would have an excellent chance of

working in this process. Indeed, when the zirconacycle constructed from enyne **1** was reacted with two equivalents of isobutyryl chloride in the presence of catalytic palladium, the monofunctionalized product **8** was formed and isolated in 71% yield. Interestingly, when excess D_2O was added following functionalization, the product **9**, isolated in 64% yield, had significant incorporation of deuterium at the vinyl site and at the methine alpha to the carbonyl. No evidence for deuterium incorporation at the alpha methylene was observed (Figure 20).

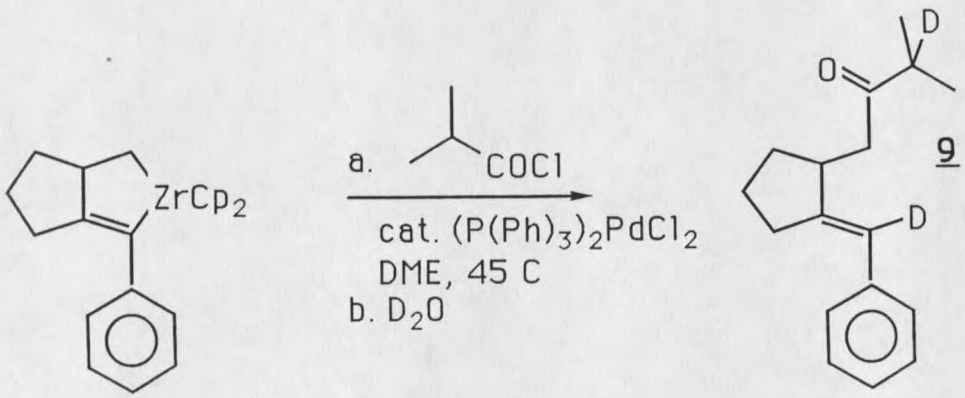
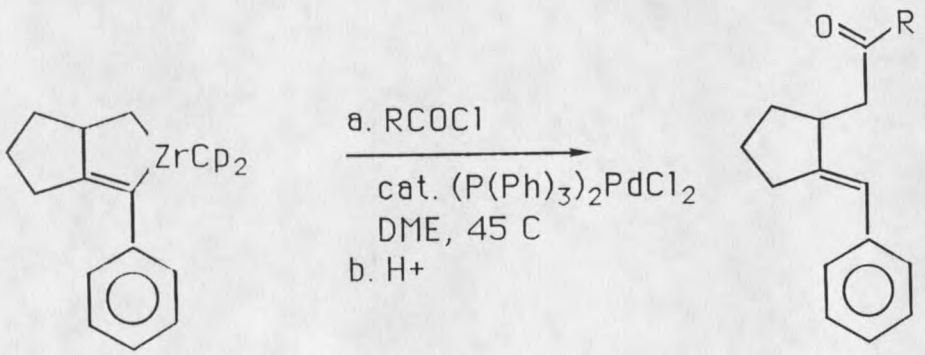


Figure 20. Preparation of **9**

It has not been determined if this carbonyl was formally enolized in solution or if the alpha deuterium was incorporated *via* some exchange process during the D_2O quench itself. However, due to the significant deuterium incorporation at the vinyl position and the fact that a majority of the alkyl carbon-zirconium bonds were

functionalized, we do not believe the carbonyl experienced significant enolization in this reaction or that any organometals acted as bases prior to the deuterium quench.

Trimethylacetyl chloride and isobutyryl chloride were the only acid chlorides that produced synthetically useful quantities of the corresponding ketones. Acetyl chloride, acryloyl chloride, phenylacetyl chloride, cinnamoyl chloride and methyl chloroformate failed to produce isolable quantities of acylated material. Isovaleryl chloride and benzoyl chloride reacted noticeably better than these alternative reagents but did not compare to the two best. Satisfactory ^{1}H and ^{13}C data were obtained for the benzoyl chloride product **10** while the isovaleryl product **11** was identified primarily by nominal MS. Both compounds were isolated in less than 30% yield in these trials (Figure 21).



10 R = Ph
11 R = *i*-Bu

Figure 21. Preparation of **10** and **11**

Bifunctionalization

A more interesting experiment would be one in which bifunctionalization was achieved. The ability to form three new bonds in "one pot" is a very powerful synthetic tool. Indeed, when a solution of iodine was added following the initial acylation, the bifunctionalized product **12**, iodinated at the vinyl position, was isolated in 40% overall yield (Figure 22).

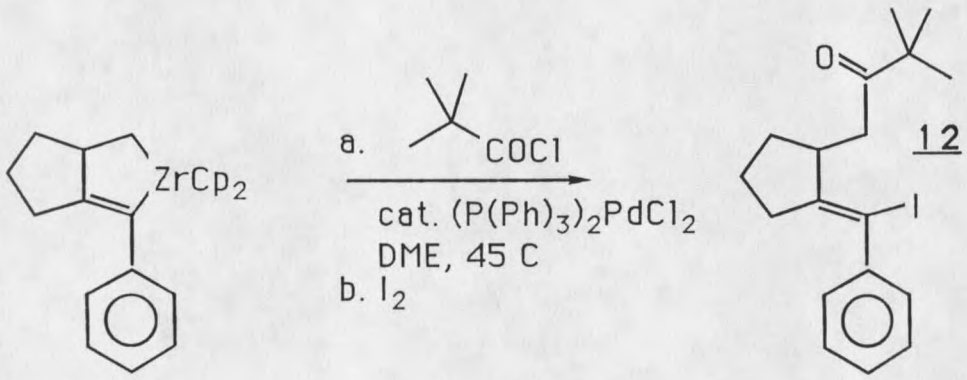


Figure 22. Preparation of **12**

To our knowledge, this is only the second example of heterobifunctionalization of a zirconacyclopentene. The first and the only other example of heterobifunctionalization would be the iodo aldehyde produced in Negishi's laboratories *via* isocyanide insertion followed by iodinolysis (Figure 11).

Lithium Chloride

In all of these reactions it is important to remember that there are always two equivalents of lithium chloride in the reaction mixture due to the initial reduction of zirconocene dichloride with two equivalents of *n*-butyllithium. Lithium chloride has been shown to be necessary for certain palladium catalyzed processes[52]. Whether or not the yield of product or the rate of the reaction could be enhanced with a halide other than chlorine was determined by running a reaction with zirconocene dibromide (prepared by treating zirconocene dichloride with two equivalents of boron tribromide[53]) and trimethylacetyl bromide (prepared from the corresponding carboxylic acid and phosphorus tribromide). This reaction proceeded noticeably slower than the "chloride" system and did not proceed to completion even after 48 hours.

Palladium(II) vs Palladium(0)

In catalytic processes involving palladium(II), the first step of the mechanism usually necessitates the reduction of palladium(II) to palladium(0) via reductive elimination. It has been shown in many cases that use of a palladium(0) complex directly can be beneficial. Tetrakis-(triphenylphosphine)palladium(0) was shown to be an effective catalyst in this reaction but not superior to our original choice. This fact coupled with the catalysts

sensitive nature precluded its further investigation. However, we did choose to investigate other palladium(0) complexes that were formed *in situ*.

One method for preparing phosphine complexes of palladium(0) is to displace labile ligands from a soluble palladium(0) complex with phosphines. A palladium(0) phosphine complex precursor now seeing widespread use is tris(dibenzylideneacetone)dipalladium(0), $Pd_2(dba)_3$. Reseachers at Bristol-Meyers Squibb have used this reagent to prepare a variety of palladium phosphine catalysts *in situ* and study their efficacy in Stille type couplings[54]. This complex's relative stability is noteworthy in comparison to the extremely sensitive tetrakis(triphenylphosphine)palladium(0). These researchers have noted the superior reactivity of a complex formed *in situ* from tri-α-furyl phosphine and $Pd_2(dba)_3$. However, this complex did not show enhanced reactivity in our system.

Another method for preparing phosphine complexes of palladium(0) is to reduce the bis(phosphine)palladium(II) chloride complex *in situ* with diisobutylaluminum hydride. Negishi has shown this catalyst mixture to be preferable to the dichloride complex[25]. In our reaction this catalyst was shown to be equal to but not better than the dichloride complex.

Other Phosphines

Modifying the steric and electronic character of the phosphines in a palladium complex can quite markedly alter the complex's reactivity. At this point we decided to examine the effect that different phosphines might have on the catalytic behaviour of palladium(II) chloride complexes in this reaction. The desired complexes were prepared by first forming bis(acetonitrile)palladium(II) chloride by dissolving palladium dichloride in refluxing acetonitrile and subsequent displacement of the labile acetonitrile ligands with two equivalents of the appropriate phosphine. Of the complexes prepared in this manner, only one is particularly noteworthy. The palladium(II) chloride complex of tri-o-tolylphosphine, compound **13**, did favor the formation of the diacylated product **5** over the monoacylated product **4** when substituted for bis(triphenylphosphine)-palladium(II) chloride in the standard palladium catalyzed acylation reaction.

Another Precycle

In order to probe the scope of this mono alkyl acylation reaction of zirconacyclopentenes, another precycle was synthesized in which the alkyne was substituted with an alkyl (*n*-propyl) chain rather than an aryl group. 1-Pentyne was metallated with *n*-butyllithium and alkylated with 5-bromo-1-pentene to produce **14** in satisfactory yield[44]. As

before, the protonated and deuterated cycles of enyne **14**, compounds **15** (73% yield) and **16** (64% yield) respectively, were prepared at this time. The zirconacycle constructed from enyne **14** produced the monofunctionalized product **17** using the conditions developed with enyne **1**, although in considerably lower (38%) yield (Figure 23).

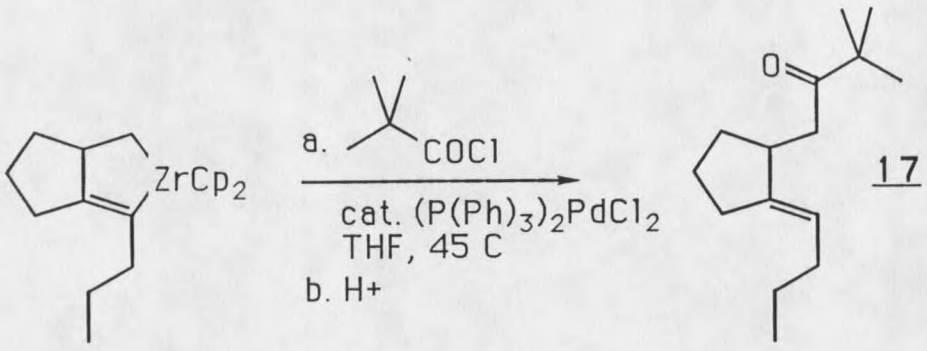


Figure 23. Preparation of **17**

Two other precycles that we briefly examined were not particularly promising. The zirconacyclopentene constructed from 1-trimethylsilylhept-1-yn-6-ene slowly provided small amounts of two unidentified products when subjected to the standard palladium catalyzed conditions. Also, the zirconacyclopentadiene constructed from 2,8-decadiyne appeared to be inert to the reaction conditions.

β-Elimination

The principle limitation of the palladium catalyzed method might be the propensity of alkyl palladium compounds to undergo β-elimination. When attempting to expand this methodology to include zirconacyclopentanes, it was realized that β-elimination may be a real problem. The diene, **18**, containing a protected carbonyl group was readily prepared *via* the dialkylation of 1,3-dithiane with allyl bromide[56,57] (Figure 24).

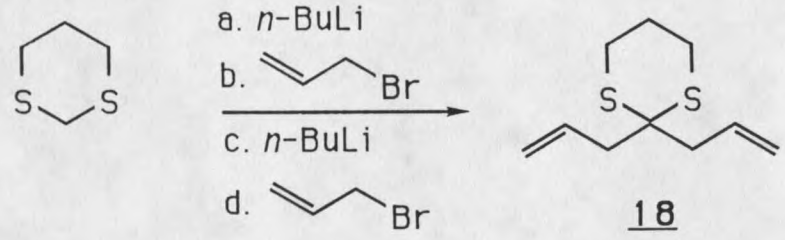


Figure 24. Preparation of **18**

As before, the protonated and deuterated cycles of diene **18**, compounds **19** (69% yield) and **20** (75% yield) respectively, were also prepared. We then investigated whether or not the zirconacyclopentane formed from the diene **18** would undergo palladium catalyzed acylation. The mono-acylated product **21** was formed, although in low (34%) yield. The major by-product of the palladium catalyzed acylation of this zirconacyclopentane was the β-elimination product **22** (Figure 25).

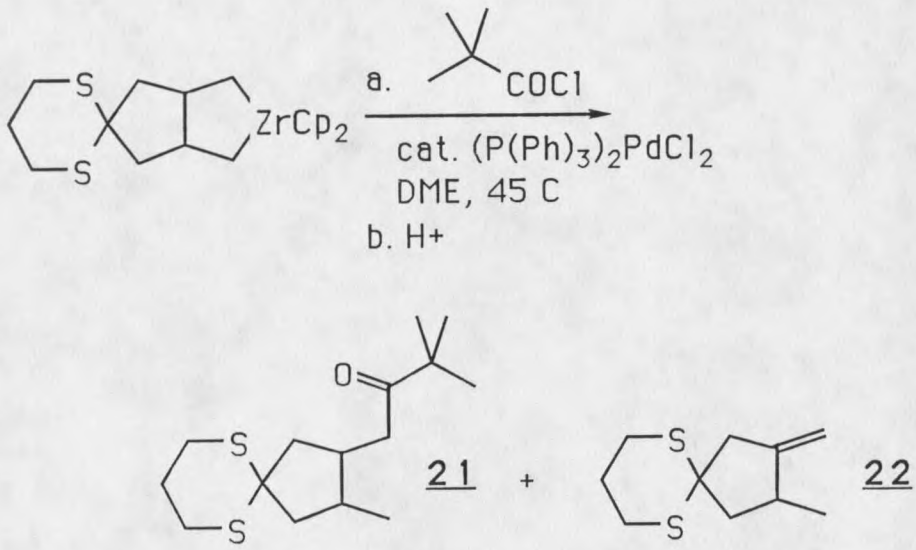


Figure 25. Zirconacyclopentane Functionalization

A reaction was also performed in which phenylacetylene, which had been hydrozirconated following the modified Lipschutz[5] procedure, was subjected to the standard palladium catalyzed acylation conditions. In this reaction, the major functionalized product was determined to be the disubstituted acetylene **23** instead of the expected enone (Figure 26).

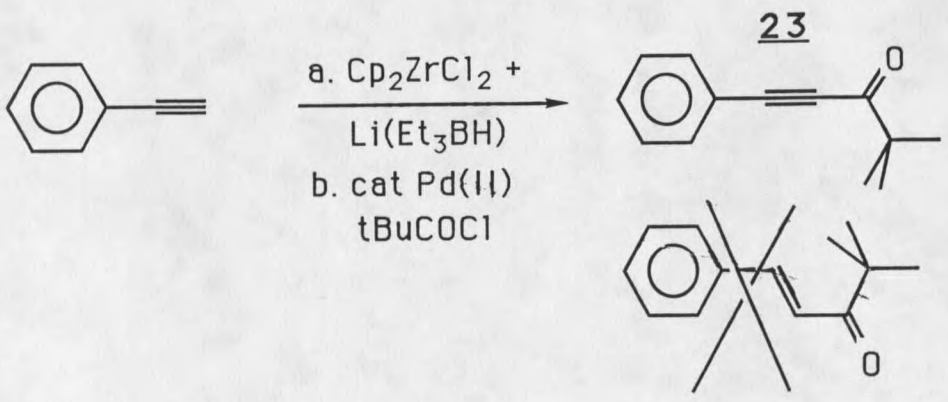


Figure 26. Preparation of **23**

Differential Reactivity in Zirconacyclopentenes

Alkyl vs Alkenyl Bonds

After obtaining these initial results, we thought that other electrophiles (e.g. H^+) may also react in a selective fashion with zirconacyclopentenes. An experiment was performed in which one equivalent of D_2O was added to a solution of the zirconacycle constructed from enyne **1**. Following an acidic work up, **24** was isolated in 78% yield. This strongly suggested the intermediate depicted in Figure 27.

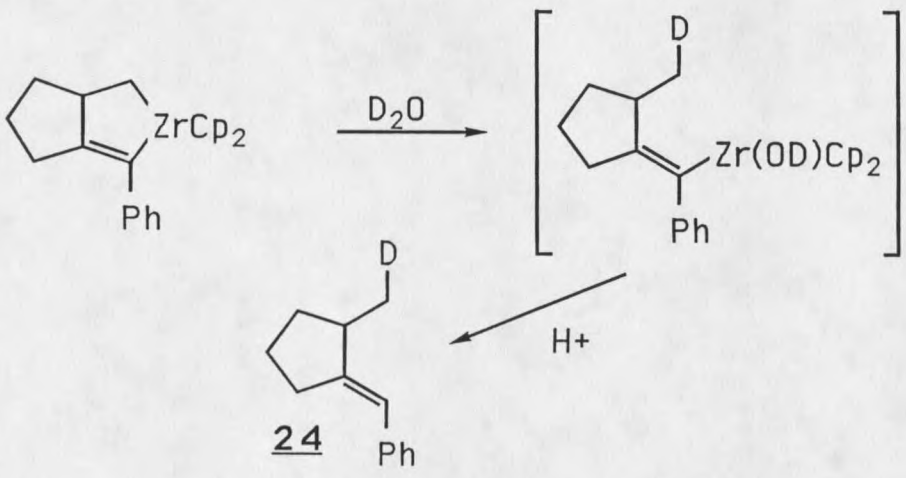


Figure 27. Preparation of **24**

Material isolated from the complementary experiment in which one equivalent of H_2O was first added and the reaction later quenched with excess D_2O failed to show quantitative deuterium incorporation at the vinyl site. However, if one equivalent of methanol is used as the initial proton source

and the reaction is later quenched with excess D_2O, quantitative deuterium incorporation at the vinyl site can be realized. In this way, the benzylidenecyclopentane **25** was isolated in 82% yield (Figure 28).

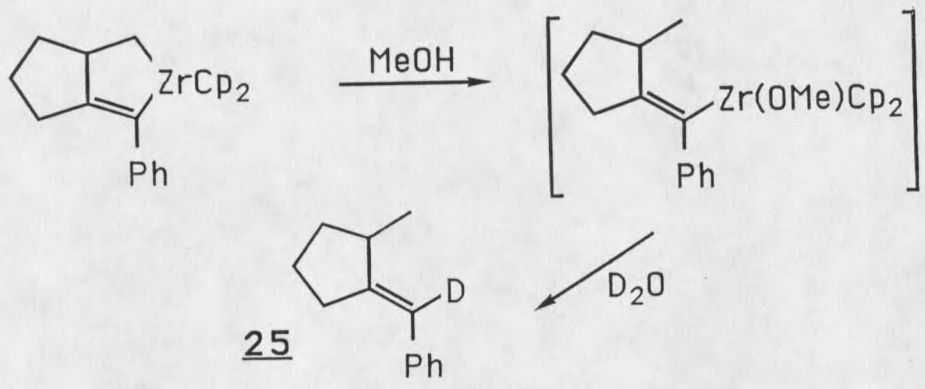


Figure 28. Preparation of **25**

Hydrohalogenation

These results suggested the possibility of installing something other than hydrogen or deuterium at the vinyl position. Indeed, following the reaction of the zirconacyclopentene constructed from enyne **1** with one equivalent of D_2O, treatment with one equivalent of an iodine solution in benzene provided **26** as the major product in reasonable (53%) yield (Figure 29).

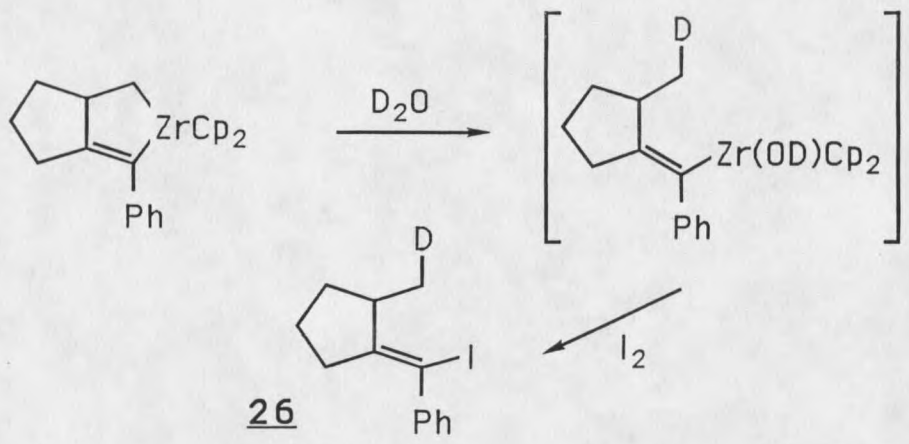


Figure 29. Preparation of 26

Alkyl vs Aryl Substitution

The zirconacyclopentene constructed from enyne **14** was shown to react in an analogous fashion to produce molecules which were cyclized and specifically monodeuterated at either the methyl or vinyl positions (compounds 27 (69% yield) and 28 (70% yield) respectively). These results suggest a basic difference in reactivity between alkyl and alkenyl carbon-zirconium bonds that appears to be general for zirconacyclopentenes. The alkyl carbon-zirconium bonds in zirconacyclopentenes are more nucleophilic (reactive) than the alkenyl carbon-zirconium bonds.

Summary

In summary, it has been shown that several useful organic transformations can be accomplished with zirconocene

based reagents. This body of chemistry has been expanded by the developement of methods involving the transmetallation of carbon-zirconium bonds to metals of greater or different reactivity. The transformations examined in this thesis demonstrate the scope and limitations of a novel palladium catalyzed acylation of organozirconium compounds. Additionally, a basic difference in reactivity between alkyl and alkenyl carbon-zirconium bonds in zirconacyclopentenes has been examined. Alkyl carbon-zirconium bonds have been shown to be more reactive than alkenyl carbon-zirconium bonds.

EXPERIMENTAL

General Information

^{1}H and ^{13}C nuclear magnetic resonance spectra were measured at 300 MHz and 75 MHz respectively on a Bruker model WM-300 spectrometer. ^{1}H chemical shifts are reported in ppm relative to the residual proton of $CDCl_3$ (δ: 7.24 ppm). ^{1}H coupling constants, reported in Hz, refer to apparent multiplicities and are not true coupling constants. ^{13}C chemical shifts are reported in ppm relative to $CDCl_3$ (δ: 77.0 ppm). Infrared spectra were recorded on a Perkin-Elmer model 1800 FTIR spectrophotometer. Nominal mass spectra were obtained by Dr. L. J. Sears using a VG Analytical model 7070E spectrometer.

Tetrahydrofuran and 1,2-dimethoxyethane were distilled under nitrogen from potassium metal. All acid chlorides were distilled under argon from calcium hydride. Alkyl lithium concentrations were determined by titration with 2-butanol.

All reactions were carried out in flame dried vessels under an atmosphere of argon. All organic solutions were dried with anhydrous magnesium sulfate and concentrated under reduced pressure with a Büchi rotary evaporator.

Flash chromotography was performed according to Still[57] using EM Science 230-400 mesh silica.

Compound Preparations

1-Phenyl-6-hepten-1-yne (**1**) A solution of phenylacetylene (4.1 g, 40 mmol), hexamethylphosphoramide (7 mL, 40 mmol) in tetrahydrofuran (60 mL) was cooled to 0 °C. *n*-Butyllithium (19 mL, 40 mmol, 2.1 M in heptane) was added dropwise and the mixture was stirred for 30 minutes. The 0 °C bath was then replaced with a -78 °C bath. After 15 minutes, 4-bromo-1-pentene (4.7 mL, 40 mmol) was added. The bath was removed, and the reaction mixture was allowed to warm to room temperature. After stirring overnight, the reaction mixture was transferred to a separatory funnel, diluted with diethyl ether (60 mL), washed with saturated aq. ammonium chloride (4 x 30 mL) and brine (30 mL) and finally dried with anhydrous magnesium sulfate. Filtration and concentration of the organic phases provided a yellow oil which was Kugelrohr distilled to afford the title compound in good yield as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (m, 2H), 7.26 (m, 3H), 5.81 (m, 1H), 5.01 (m, 2H), 2.41 (t, J = 7 Hz, 2H), 2.21 (apparent q, J = 7 Hz, 2H), 1.69 (m, J = 7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.84, 131.50, 128.14, 127.46, 115.16, 89.90, 80.84, 32.82, 27.90, 18.77. IR (film) cm^{-1}: 3096-2839, 1642, 1598, 1490, 1442, 1330, 1070, 992, 914, 756, 692, 528. Nominal GCMS,

m/e (relative intensity): 170 M+ (29), 169 (30), 155 (52), 142 (80), 128 (63), 115 (100), 103 (26), 91 (34), 77 (22), 63 (20), 51 (17), 39 (25).

(E)-1-Phenylmethylidine-2-methylcyclopentane (2) A solution of zirconocene dichloride (300 mg, 1.03 mmol) in tetrahydrofuran (8 mL) was cooled to -78 °C. *n*-Butyllithium (0.66 mL, 2.05 mmol, 3.1 M solution in heptane) was added dropwise and the mixture was stirred for 15 minutes at -78 °C. To this solution was added 1 (180 µl, 1 mmol). After 15 more minutes at -78 °C, the bath was removed and the reaction allowed to warm to room temperature. After 1 hour at room temperature formation of the zirconacyclopentene was complete as evidenced by GLC analysis of an aliquot. Sulfuric acid (10 mL, 10% aq. solution) was added at room temperature and the mixture allowed to stir for 5 minutes. The mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 20 mL). The organic phases were washed with saturated aq. sodium bicarbonate (20 mL) and dried with anhydrous magnesium sulfate. Filtration and concentration of the organic phases provided crude 2 as a yellow oil. Chromatography (hexanes) afforded the title compound (158 mg, 92%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (m, 4H), 7.08 (m, 1H), 6.15 (m, 1H), 2.53 (m, 3H), 1.80 (m, 2H), 1.54 (m, 1H), 1.17 (m, 1H), 1.11 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.67,

138.96, 128.14, 128.07, 125.61, 120.11, 40.92, 34.58, 31.52, 24.71, 19.38.

(E)-1-Phenyldeuteromethylidine-2-deuteromethyl-cyclopentane (3) After formation of the zirconacyclopentene as previously detailed (see preparation of 2), deuterium oxide (0.25 mL) was added at room temperature. The mixture was then heated at 45 °C for 3 hours, concentrated (dryness) and the solids triturated with hexane (3 x 20 mL). Filtration and concentration of the hexane extracts provided crude 3 as a yellow oil. Chromatography (hexanes) afforded the title compound (143 mg, 82%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (m, 4H), 7.14 (m, 1H), 2.59 (m, 3H), 1.86 (m, 2H), 1.64 (m, 1H), 1.24 (m, 1H), 1.15 (apparent dt, J = 6.8 Hz, 1.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.36, 138.86, 128.08, 128.03, 125.57, 120.14 (t, J = 23 Hz), 40.79, 34.53, 31.45, 24.68, 19.03 (t, J = 19.6 Hz). IR (film) cm^{-1}: 3089-2839, 1716, 1642, 1600, 1494, 1444, 908, 768, 696. Nominal GCMS, *m/e* (relative intensity): 174 M+ (97), 158 (53), 146 (17), 130 (70), 118 (53), 92 (53), 82 (100), 51 (11).

General Cuprate Mediated Acylation After formation of the zirconacyclopentene (see preparation of 2) the mixture was cooled to - 78 °C and a solution of $Me_2CuCNLi_2$ (1 mmol, see preparation at end) in tetrahydrofuran was then added. The reaction mixture was kept at - 78 °C for 10 minutes,

warmed to 0 °C for 10 minutes and finally recooled to - 78 °C. Trimethylacetyl chloride (0.125 mL, 1 mmol) was added at -78 °C and the reaction was allowed to warm to room temperature overnight. The major functionalized product 4 was isolated in undetermined yield following an acidic work up (see preparation of 2) and chromatography (10% diethyl ether in hexanes). $Me_2CuCNLi_2$: a suspension of copper(I) cyanide (90 mg, 1 mmol) in tetrahydrofuran (2 mL) was cooled to - 78°C. Following addition of methyllithium (1.19 mL, 2 mmol, 1.68 M solution in diethyl ether), the suspension was warmed to 0 °C until it became homogeneous and was then recooled to - 78 °C and used. These conditions will provide 5 as the major functionalized product if the amounts of $Me_2CuCNLi_2$ and trimethylacetyl chloride are doubled.

3,3-Dimethyl-1-((E)-2-phenylmethylidine)cyclopentyl-2-butanone (4) After formation of the zirconacyclopentene (see preparation of 2), but substituting 1,2-dimethoxyethane (8 mL) for tetrahydrofuran, the mixture was again cooled to -78 °C. Trimethylacetyl chloride (0.25 mL, 2 mmol, 2 eq.) and bis(triphenylphosphine)palladium(II) chloride (70 mg, 0.1 mmol, 0.1 eq.) were added at -78 °C. The reaction vessel was then placed in a 45 °C bath. After 45 minutes at 45 °C no further functionalization of the zirconacycle was observed via GLC analysis of aliquots. Sulfuric acid (10 mL, 10% aq. solution) was added at room temperature and

the mixture allowed to stir for 5 minutes. The mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 20 mL). The organic phases were washed with saturated aq. sodium bicarbonate (20 mL) and dried with anhydrous magnesium sulfate. Filtration and concentration of the organic phases provided crude **4** as a yellow oil. Chromatography (10% diethyl ether in hexanes) afforded the title compound (192 mg, 75%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23 (m, 4H), 7.08 (m, 1H), 6.12 (apparant q, J = 2 Hz, 1H), 3.13 (m, 1H), 2.60 (m, 4H), 1.90 (m, 1H), 1.73 (m, 1H), 1.60 (m, 1H), 1.11 (m, 1H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.99, 149.61, 138.50, 128.11, 128.06, 125.81, 120.67, 44.13, 42.09, 41.1, 32.45, 31.48, 26.30, 24.82. IR (film) cm^{-1}: 3096-2846, 1706, 1598, 1478, 1394, 1366, 1072, 996, 912, 860, 746, 696, 514. Nominal GCMS, *m/e* (relative intensity): 256 M+ (18), 165 (12), 129 (14), 91 (36), 85 (21), 57 (100), 41 (14).

Diacylated Product (**5**) This compound was prepared according to the general cuprate mediated acylation procedure using 2 equivalents of $Me_2CuCNLi_2$. Following an acidic work up, chromatography (15% diethyl ether in hexanes) afforded the title compound in undetermined yield as a yellow oil. IR (film) cm^{-1}: 3082-2839, 1706, 1678, 1478, 1394, 1366, 1314, 1264, 1264, 1098, 1074, 1032, 874,

788, 764, 702. Nominal GCMS, *m/e* (relative intensity): 340 M+ (2), 255 (48), 85 (51), 57 (100), 41 (24).

Tertiary Alcohol (**6**) This compound was isolated as a by-product in the initial cuprate mediated preparations of **4** and **5**. IR (film) cm^{-1}: 3420, 2985-2853, 1682, 1641, 702. Nominal GCMS, *m/e* (relative intensity): 256 M+ (16), 199 (100), 171 (73), 143 (27), 129 (53), 115 (35), 91 (47), 77 (12), 57 (16), 41 (14).

3,3-Dimethyl-1-((E)-2-phenyldeuteromethylidine) cyclopentyl-2-butanone (**7**) Following functionalization of the zirconacyclopentene with trimethylacetyl chloride (see preparation of **4**), deuterium oxide (0.25 mL) was added and the reaction allowed to stir overnight at room temperature. The reaction mixture was then concentrated (dryness) and triturated with 50% diethyl ether in hexanes (3 x 20 mL). Filtration and concentration of the organic extracts provided crude **7** as a yellow oil. Chromatography (10% diethyl ether in hexanes) afforded the title compound (201 mg, 78%) as a faint yellow oil. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.50, 149.07, 138.19, 127.85, 125.55, 120.50, 43.81, 41.78, 41.05, 32.20, 31.21, 26.03, 24.58. IR (film) cm^{-1}: 3110-2825, 1706, 1600, 1494, 1478, 1394, 1366, 1072, 998, 768, 698. Nominal GCMS, *m/e* (relative intensity): 257 M+ (14), 172 (10), 157 (22), 129 (22), 91 (30), 85 (35), 57 (100), 41 (18).

3-Methyl-1-((E)-2-phenylmethylidine)cyclopentyl-2-butanone (8) This compound was prepared following the procedure for 4 but substituting isobutyryl chloride (0.21 mL, 2 mmol, 2 eq.) for trimethylacetyl chloride. Chromatography (10% diethyl ether in hexanes) afforded the title compound (171 mg, 71%) as a faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18 (m, 4H), 7.05 (m, 1H), 6.10 (apparent q, J = 2.3 Hz, 1H), 2.90 (m, 1H), 2.67 (apparent dd, J = 5 Hz, 2H), 2.48 (m, 3H), 1.87 (m, 1H), 1.70 (m, 1H), 1.56 (m, 1H), 1.12 (buried m, 1H), 1.01 (apparent dd, J = 3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.70, 149.14, 138.32, 127.98, 127.95, 125.71, 120.69, 45.63, 41.29, 41.00, 32.30, 31.25, 24.68, 18.06, 17.96. IR (film) cm^{-1}: 3089-2846, 1712, 1466, 1382, 1030, 752, 696, 514. Nominal GCMS, *m/e* (relative intensity): 242 M+ (31), 199 (11), 171 (15), 156 (41), 141 (13), 129 (36), 115 (20), 91 (64), 71 (100), 43 (90).

3-Deutero-3-methyl-1-((E)-2-phenyldeuteromethylidine) cyclopentyl-2-butanone (9) This compound was prepared following the procedure for 7 but substituting isobutyryl chloride (0.21 mL, 2 mmol, 2 eq.) for trimethylacetyl chloride. Chromatography (10% diethyl ether in hexanes) afforded the title compound (156 mg, 64%) as a faint yellow oil. ^{13}C NMR (75 MHZ, $CDCl_3$) δ: 213.78, 149.01, 138.23, 127.97, 127.91, 125.69, 45.60, 41.21, 40.98, 32.27, 31.20,

24.65, 17.93 (t, J = 7.3 Hz). IR (film) cm^{-1}: 3082-2832, 1710, 1600, 1494, 1464, 1382, 1076, 772, 698. Nominal GCMS, *m/e* (relative intensity): 244 M+ (26), 172 (14), 157 (50), 142 (13), 129 (31), 116 (16), 92 (49), 71 (100), 43 (84).

Benzoyl Product (**10**) This compound was prepared following the procedure for **4** but substituting benzoyl chloride (0.23 mL, 2 mmol, 2 eq.) for trimethylacetyl chloride. Chromatography afforded the title compound as a faint yellow oil in undetermined yield. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.93 (m, 2H), 7.42 (m, 3H), 7.24 (m, 4H), 7.10 (m, 1H), 6.23 (apparent q, J = 2.3 Hz, 1H), 3.26 (apparent dd, J = 4.5 Hz, 1H), 3.16 (m, 1H), 2.99 (apparent dd, J = 8.7 Hz, 1H), 2.57 (m, 2H), 1.96 (m, 1H), 1.79 (m, 1H), 1.63 (m, 1H), 1.29 (m, 1H). ^{13}C NMR (75 MHZ, $CDCl_3$) δ: 199.66, 149.35, 138.48, 137.32, 132.96, 128.60, 128.18, 128.13, 125.94, 121.11, 44.09, 42.04, 32.48, 31.47, 24.87.

4-Methyl-1-((E)-2-phenylmethylidine)cyclopentyl-2-pentanone (**11**) This compound was prepared following the procedure for **4** but substituting isovaleryl chloride (0.24 mL, 2 mmol, 2 eq.) for trimethylacetyl chloride. Chromatography afforded the title compound as a faint yellow oil in undetermined yield. Nominal GCMS *m/e* (relative intensity): 256 M+ (18), 165 (21), 156 (41), 129 (23), 115 (15), 91 (48), 85 (100), 57 (70), 41 (16).

3,3-Dimethyl-1-((Z)-2-phenyliodomethylidine)-cyclopentyl-2-butanone (**12**) Following functionalization of the zirconacyclopentene with trimethylacetyl chloride (see preparation of **4**), a solution of iodine (2.9 mL, 1.5 eq., 0.52 M in benzene) was added and the reaction was maintained at room temperature for 30 minutes. This mixture was transferred to a separatory funnel, diluted with diethyl ether (50 mL), washed with saturated aq. sodium bisulfite (15 mL) and saturated aq. sodium bicarbonate (15 mL) and finally dried with anhydrous magnesium sulfate. Filtration and concentration of the organic phases provided crude **12**. Chromatography (10% diethyl ether in hexanes) afforded the title compound (80 mg, 20%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (m, 4H), 7.19 (m, 1H), 3.18 (m, 1H), 3.07 (apparent dd, J = 2.4 Hz, 18 Hz, 1H), 2.61 (apparent dd, J = 11 Hz, 18 Hz, 1H), 2.28 (m, 2H), 2.02 (m, 1H), 1.70 (m, 2H), 1.46 (m, 1H), 1.18 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.31, 154.68, 144.28, 128.62, 128.04, 127.42, 89.52, 45.86, 44.18, 39.84, 33.36, 31.97, 29.63, 26.48, 25.73. IR (film) cm^{-1}: 3082-2839, 1706, 1476, 1442, 1394, 1366, 1346, 1284, 1230, 1072, 1010, 988, 818, 784, 746, 700, 634. Nominal GCMS (CH_4 CI), *m/e* (relative intensity): 383 M+ (5), 283 (20), 255 (100), 199 (19), 105 (17).

General Palladium Complex Formation (Illustrated for bis(tri-o-tolylphosphine)palladium(II) chloride (**13**))
A suspension of palladium chloride (89 mg, 0.5 mmol) in acetonitrile (7 mL) was refluxed overnight resulting in an orange solution. Tri-o-tolylphosphine (305 mg, 1 mmol) suspended in tetrahydrofuran (7 mL), was added to the palladium solution. The reaction mixture was then refluxed for two hours. After cooling to room temperature, the reaction mixture was concentrated to dryness and the solids were triturated with diethyl ether (2 x 5 mL). The complex was dried under vacuum and analyzed *via* ^{1}H NMR to assure the absence of uncoordinated phosphine.

Dec-6-yn-1-ene (**14**) This compound was prepared following the procedure for **1** but using 1.2 equivalents of 1-pentyne in place of 1 equivalent of phenylacetylene. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.77 (m, 1H), 4.97 (m, 2H), 2.12 (m, 6H), 1.51 (m, 4H), .94 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.11, 114.88, 80.37, 79.89, 32.80, 28.35, 22.53, 20.75, 18.16, 13.44.

(E)-1-Butylidene-2-methylcyclopentane (**15**) **14** (170 µl, 1 mmol) was cyclized and protonated following the procedure for **2**. Chromatography (hexanes) afforded the title compound (101 mg, 73%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.13 (m, 1H), 2.24 (m, 3H), 1.96 (m, 2H), 1.85 (m, 1H), 1.72

(m, 1H), 1.51 (m, 1H), 1.38 (m, 2H), 1.14 (m, 1H), 1.04 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.81, 119.29, 38.90, 35.62, 31.57, 29.07, 24.06, 22.93, 19.13, 13.82.

(E)-1-(1-Deuterobutylidene)-2-deuteromethylcyclopentane (**16**) **14** (170 ul, 1 mmol) was cyclized and deuterated following the procedure for **3**. Chromatography (hexanes) afforded the title compound (90 mg, 64%) as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.25 (m, 3H), 1.95 (apparent t, J = 7.2 Hz, 2H), 1.83 (m, 1H), 1.71 (m, 1H), 1.52 (m, 1H), 1.37 (m, 2H), 1.14 (m, 1H), 1.02 (apparent dt, J = 1.8 Hz, 2H), 0.89 (t, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.72, 118.90 (t, J = 23 Hz), 38.79, 35.58, 31.44, 29.03, 24.04, 22.90, 18.83 (t, J = 19 Hz), 13.82.

3,3-Dimethyl-1-((E)-2-butylidene)cyclopentyl-2-butanone (**17**) The zirconacyclopentene used to prepare **15** was functionalized following the procedure for **4**. Chromatography afforded the title compound (78 mg, 38%) as a faint yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.04 (m, 1H), 2.79 (m, 1H), 2.59 (m, J = 4.9 Hz, 1H), 2.44 (m, J = 8.8 Hz, 1H), 2.20 (m, 3H), 1.88 (m, 3H), 1.67 (m, 1H), 1.51 (m, 1H), 1.30 (m, 2H), 1.11 (s, 9H), 0.84 (apparent t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 215.27, 145.77, 119.85, 44.05, 41.85, 39.32, 33.38, 31.48, 29.00, 26.31, 24.00, 22.73, 13.79.

2,2-Diallyl-1,3-dithiane (**18**) A solution of 1,3-dithiane (5 g, 42 mmol) in tetrahydrofuran (125 mL) was cooled to -30 °C. *n*-Butyllithium (16.7 mL, 42 mmol, 2.5 M in heptane) was added at a rate of 3-5 mL per minute. The reaction mixture was then stirred for 3 hours at -25 °C. After warming the mixture to -5 °C, allyl bromide (4 mL, 46 mmol) was added dropwise and the reaction mixture was maintained at 0 °C for 24 hours. The reaction mixture was again cooled to -30 °C and *n*-butyllithium (19.4 mL, 48.5 mmol, 2.5 M in heptane) was added at a rate of 3-5 mL per minute. The reaction mixture was stirred for 6 hours at -25 °C. After warming the mixture to -5 °C, allyl bromide (4.2 mL, 48.5 mmol) was added dropwise and the reaction mixture was maintained at 0 °C for 24 hours. The reaction mixture was transferred to a separatory funnel and diluted with diethyl ether (100 mL). This solution was washed successively with saturated aq. ammonium chloride (40 mL), water (40 mL) and brine (40 mL) and finally dried with anhydrous magnesium sulfate. Filtration and concentration of the organic phases provided a very faint yellow oil which was Kugelrohr distilled to afford the title compound in good yield as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.80 (m, 2H), 5.12 (m, 4H), 2.82 (m, 4H), 2.63 (apparent d, J = 7 Hz, 4H), 1.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 132.75, 118.42, 51.47, 42.70, 25.96, 25.02. IR (film) cm^{-1}: 3096-

2811, 1638, 1424, 1276, 1240, 994, 916, 626. Nominal GCMS, *m/e* (relative intensity): 200 M+ (18), 159 (100), 97 (10), 85 (72), 73 (16), 41 (46).

trans-1,2-Dimethyl-4-(1,3-dithiane)cyclopentane (**19**) **18** (190 µl, 1 mmol) was cyclized and protonated following the procedure for **2**. Chromatography (5% diethyl ether in hexanes) afforded the title compound (139 mg, 69%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.83 (apparent q, J = 4.8 Hz, 4H), 2.42 (apparent d, J = 6.7 Hz, 2H), 1.94 (m, 2H), 1.65 (apparent d, J = 7.3 Hz, 4H), .94 (d, J = 5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.68, 41.00, 28.78, 25.37, 17.46. Nominal GCMS, *m/e* (relative intensity): 202 M+ (76), 187 (51), 169 (10), 159 (40), 128 (74), 113 (41), 107 (12), 95 (100), 85 (30), 79 (15), 73 (15), 67 (13), 55 (22), 41 (50).

trans-1,2-Di-(deuteromethyl)-4-(1,3-dithiane)-cyclopentane (**20**) **18** (190 ul, 1 mmol) was cyclized and deuterated following the procedure for **3**. Chromatography (5% diethyl ether in hexanes) afforded the title compound (152 mg, 75%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.82 (m, 4H), 2.41 (apparent d, J = 6.6 Hz, 2H), 1.93 (m, 2H), 1.63 (apparent d, J = 7.5 Hz, 4H), .92 (broad s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.64, 40.88, 28.75, 25.34, 17.15 (t, J = 19.3 Hz). Nominal GCMS, *m/e* (relative intensity): 204 M+ (91), 188 (67), 171 (13), 160 (53), 145

(10), 130 (79), 114 (51), 107 (19), 97 (100), 86 (35), 80 (16), 73 (21), 68 (12), 56 (21), 41 (45).

trans-3,3-Dimethyl-1-(2-methyl-4-(1,3-dithiane)-cyclopentyl)-2-butanone (**21**) The zirconacyclopentane used to prepare **19** was functionalized following the procedure for **4**. Chromatography (15% diethyl ether in hexanes) afforded the title compound (62 mg, 22%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.82 (m, 4H), 2.61 (m, 2H), 2.41 (m, 2H), 2.10 (m, 1H), 1.94 (m, 2H), 1.83 (m, 1H), 1.62 (m, 2H), 1.1 (s, 9H), 0.96 (d, J = 6.5 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 215.05, 52.90, 50.69, 49.37, 44.00, 41.36, 40.92, 30.09, 28.72, 28.59, 26.28, 25.33, 17.87. Nominal GCMS, *m/e* (relative intensity): 286 M+ (61), 229 (38), 211 (20), 186 (70), 179 (35), 153 (18), 139 (13), 112 (100), 93 (22), 85 (39), 79 (21), 73 (21), 67 (11), 57 (85), 41 (66).

1-Methylene-2-methyl-4-(1,3-dithiane)cylopentane (**22**) This by-product was isolated during the chromatography of **19**. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.50, 105.96, 49.39, 48.98, 36.71, 28.48, 27.95, 25.49, 18.44. Nominal GCMS, *m/e* (relative intensity): 200 M+ (54), 185 (12), 126 (50), 106 (46), 93 (100), 77 (23), 73 (11), 67 (14), 59 (10), 53 (15), 41 (44).

4,4-Dimethyl-1-phenylpent-1-yn-3-one (**23**) To a solution of zirconocene dichloride (292 mg, 1 mmol, 1 eq.)

in tetrahydrofuran (8 mL) was added a solution of lithium triethylborohydride (1.1 mL, 1.1 mmol, 1 M in tetrahydrofuran). This mixture was allowed to stir at room temperature for one hour while being shielded from light. Phenylacetylene (0.11 mL, 1 mmol, 1 eq.) was added at room temperature and the mixture was stirred for ten minutes. At this point the hydrozirconation product was functionalized following the procedure for **4**. Chromatography (5% diethyl ether in hexanes) provided the title compound in undetermined yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 1.21 (s, 9H). Nominal GCMS, *m/e* (relative intensity): 186 M+ (3), 171 (4), 158 (23), 143 (18), 129 (100), 102 (11), 75 (14), 57 (39), 41 (19).

(E)-1-Phenylmethylidine-2-deuteromethylcyclopentane (**24**) After formation of the zirconacyclopentene (see preparation of **2**), deuterium oxide (18 µl, 1 mmol) was added at room temperature. The mixture was then allowed to stir at room temperature for 2 hours. Sulfuric acid (10 mL, 10% aq. solution) was added at room temperature and the mixture allowed to stir for 5 minutes. The mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 20 mL). The organic phases were washed with saturated aq. sodium bicarbonate (20 mL) and dried with anhydrous magnesium sulfate. Filtration and concentration of the organic phases provided crude **24** as a yellow oil.

Chromatography (hexanes) afforded the title compound (134 mg, 78%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (m, 4H), 7.20 (m, 1H), 6.28 (apparent q, J = 2.4 Hz, 1H), 2.65 (m, 3H), 1.92 (m, 2H), 1.70 (m, 1H), 1.28 (buried m, 1H), 1.22 (apparent dt, J = 1.7 Hz, 6.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.61, 138.94, 128.13, 128.06, 125.60, 120.11, 40.84, 34.54, 31.50, 24.71, 19.07, (t, J = 19.5 Hz). Nominal GCMS, *m/e* (relative intensity): 173 M+ (97), 157 (51), 144 (21), 129 (77), 117 (59), 104 (11), 91 (73), 82 (100), 77 (17), 65 (13), 51 (13).

(E)-1-Phenyldeuteromethylidine-2-methylcyclopentane (**25**) After formation of the zirconacyclopentene (see preparation of **2**), methanol (40 µl, 1 mmol) was added at room temperature. The mixture was stirred at room temperature for 2 hours. Deuterium oxide (0.25 mL) was added and the reaction stirred at 45 °C for 3 hours. The mixture was concentrated (dryness) and the residue triturated with hexanes (3 x 20 mL). Filtration and concentration of the hexane extracts provided crude **25**. Chromatography (hexanes) afforded the title compound (141 mg, 82%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 (m, 4H), 7.21 (m, 1H), 2.66 (m, 3H), 1.94 (m, 2H), 1.70 (m, 1H), 1.30 (buried m, 1H), 1.24 (apparent d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.50, 138.87, 128.11, 128.03, 125.58, 40.88, 34.57, 31.47, 24.69, 19.34. Nominal GCMS, *m/e* (relative

intensity): 173 M+ (96), 158 (53), 144 (23), 130 (76), 118 (51), 92 (57), 81 (100), 77 (16), 65 (10), 51 (12), 41 (13).

(Z)-1-Phenyliodomethylidine-2-deuteromethylcyclopentane (**26**) After formation of the zirconacyclopentene (see preparation of **2**), deuterium oxide (18 µl, 1 mmol) was added at room temperature. The mixture was stirred at room temperature for 2 hours. A solution of iodine (2.9 mL, 1.5 mmol, 0.52 M in benzene) was added and the reaction was maintained at room temperature for 30 minutes. This mixture was transferred to a separatory funnel, diluted with diethyl ether (50 mL), washed with saturated aq. sodium bisulfite (15 mL) and saturated aq. sodium bicarbonate (15 mL) and finally dried with anhydrous magnesium sulfate. Filtration and concentration of the organic phases provided crude **26**. Chromatography (hexanes) afforded the title compound in undetermined yield as faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (m, 4H), 7.18 (m, 1H), 2.82 (apparent q, J = 6.6 Hz, 1H), 2.58 (m, 1H), 2.35 (m, 1H), 2.21 (m, 1H), 1.80 (m, 4H), 1.51 (m, 1H), 1.15 (apparent dd, J = 1.2 Hz, 2H). Nominal GCMS, *m/e* (relative intensity): 299 M+ (18), 172 (100), 144 (23), 129 (54), 115 (31), 91 (49), 77 (11), 56 (18).

(E)-1-Butylidene-2-deuteromethylcyclopentene (**27**) The zirconacyclopentene used to prepare **15** was worked up following the procedure for **24**. Chromatography (hexanes)

afforded the title compound (96 mg, 69%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.12 (m, 1H), 2.24 (m, 3H), 1.95 (m, 2H), 1.84 (m, 1H), 1.72 (m, 1H), 1.52 (m, 1H), 1.38 (m, 2H), 1.14 (m, 1H), 1.02 (apparent dt, J = 1.8 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.81, 119.26, 38.82, 35.58, 31.55, 29.06, 24.04, 22.92, 18.83 (t, J = 19 Hz), 13.82. Nominal GCMS, *m/e* (relative intensity): 139 M+ (38), 110 (31), 96 (100), 82 (77), 67 (80), 56 (33).

(E)-1-(1-Deuterobutylidene)-2-methylcyclopentane (**28**)

The zirconacyclopentene used to prepare **15** was worked up following the procedure for **25**. Chromatography (hexanes) afforded the title compound (98 mg, 70%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.23 (m, 3H), 1.95 (apparent t, J = 7.2 Hz, 2H), 1.83 (m, 1H), 1.71 (m, 1H), 1.53 (m, 1H), 1.37 (m, 2H), 1.14 (m, 1H), 1.03 (d, J = 6.6 Hz, 2H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.70, 118.90 (t, J = 23 Hz), 38.86, 35.61, 31.45, 29.03, 24.04, 22.90, 19.12, 13.82. Nominal GCMS, *m/e* (relative intensity): 139 M+ (33), 110 (28), 96 (100), 82 (77), 67 (64), 55 (30).

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