Preparing and Tuning the Reactivity of Palladium Carbenes and an Unusual Catalytic Isomerization of Diphenylcyclopropanes

By

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ABSTRACT

The preparation of palladium carbene intermediates from diphenylketene is proposed. Experiments to trap these intermediates with alkenes have been conducted and optimized, with cyclopropanes being prepared in up to 69% yield. This methodology has shown to be compatible with olefins, ethers, esters, anhydrides and various benzannulated norbornyl derivatives. In addition, an unusual palladium(II) catalyzed cyclopropane isomerization has been observed. Various substrates have undergone this isomerization affording two different olefin products in up to 61% yield. A catalytic cycle for this process is proposed.

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Dedicated to my Mom and Dad

who told me I had the potential to do anything

and to

my first high school chemistry teacher Mr. Kuldip Bachher

who first interested me in chemistry

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LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Ar	aryl group
PhH	benzene
Bn	benzyl
*n*BuLi	*n*-butyllithium
*t*BuLi	*tert*-butyllithium
*t*BuOK	potassium *tert*-butoxide
COSY	correlation spectroscopy
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
dppe	diphenylphosphinoethane
dppf	diphenylphosphinoferrocene
EI	electron impact
GC-MS	gas chromatography – mass spectrometry
h	hour(s)
HMQC	heteronuclear multiple quantum coherence
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry

LUMO	lowest unoccupied molecular orbital
min	minute(s)
N/A	not applicable
NMR	nuclear magnetic resonance
NOSY	nuclear Overhauser enhancement spectroscopy
Pd/C	palladium on charcoal
Ph	phenyl
R	carbon-based group (also used for silyl-based group)
rt	room temperature
rxn	reaction
TBDPS	*tert*-butyldiphenylsilyl
temp	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	*para*-toluenesulphonic acid
X	halogen or trifluoromethanesulfonyl (or used to indicate variable groups)

Abbreviations for multiplicities of ^{1}H NMR and ^{13}C NMR signals

br s	broad singlet
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
dt	doublet of triplets
m	multiplet
q	quartet
s	singlet
t	triplet

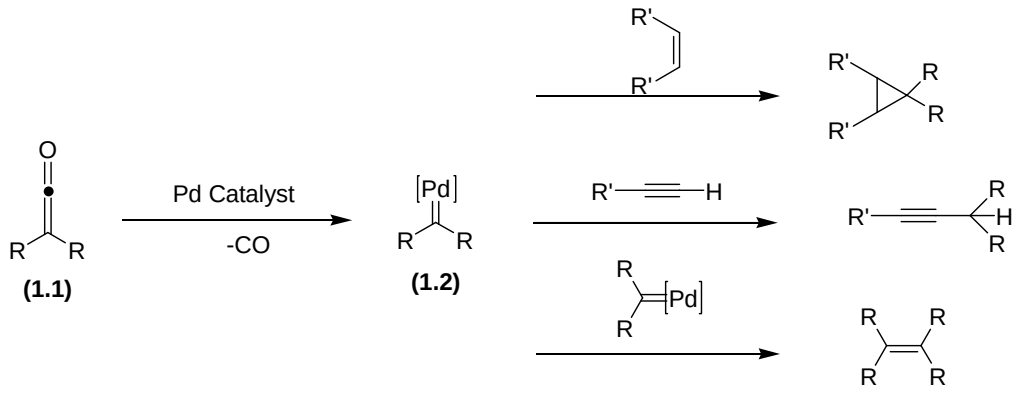
CHAPTER ONE

1.0 INTRODUCTION AND LITERATURE REVIEW

The formation and use of metal carbenes has been studied, and a large number of carbon-carbon bond forming processes have been developed.[1] The reactivity of these carbenes is dictated by the adjacent functionality on the carbene itself as well as the ligands on, and identity of, the metal involved. Metal carbene chemistry has predominantly focused on rhodium, ruthenium and copper complexes; compared to these, palladium-carbenes remain relatively unexplored, and detailed investigations into their reactivity are lacking.

The objective of this research is to study the preparation of palladium carbenes and explore their reactivity. It is proposed that palladium carbenes can be formed via the decomposition of ketene species **1.1** as illustrated in Scheme 1.1.[2] Upon loss of carbon monoxide, the palladium carbene **1.2** can then undergo reactions typical of metal carbenes such as cyclopropanation, C-H insertion and dimerization.

Scheme 1.1



These studies will further establish the use of palladium carbenes in organic synthesis and advance the field of metal carbenes.

1.1 CARBENES

1.1.1 Structural Considerations

A carbene is an uncharged reactive intermediate containing a divalent carbon atom bearing an unshared pair of electrons. The bond angles observed for most carbenes are between 100 º and 150 º, suggesting a trigonal (sp^2) hybridization state.[3] The six electrons can thus be distributed between three sp^2 orbitals and one p orbital. Since two of the sp^2 orbitals are occupied in bonding with various groups, the unshared pair of electrons can be dispersed between the remaining sp^2 orbital and the higher energy p orbital in one of two ways, generating a singlet state or a triplet state carbene. A singlet state carbene has both electrons paired in the sp^2 orbital (**1.3**, Figure 1.1). While a triplet state carbene has one electron occupying the sp^2 orbital and the other electron, with a parallel spin to the first, in the p orbital (**1.4**, Figure 1.1).

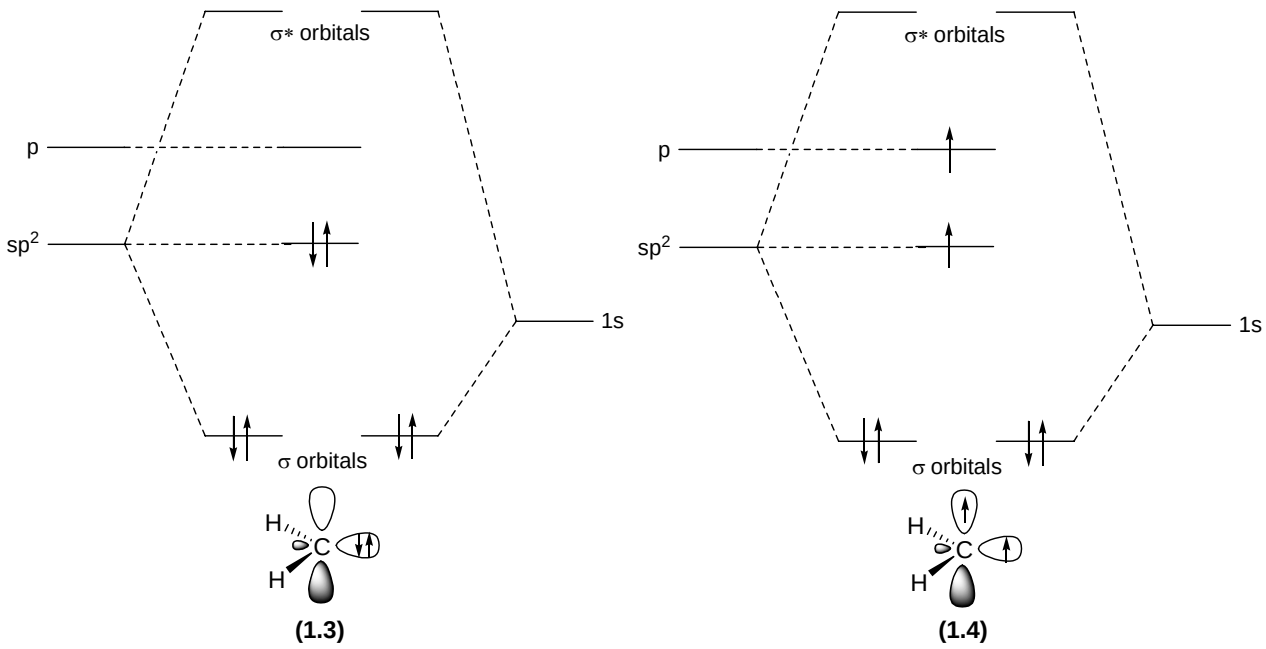


Figure 1.1: Energy diagrams for singlet (1.3) and triplet (1.4) carbenes.

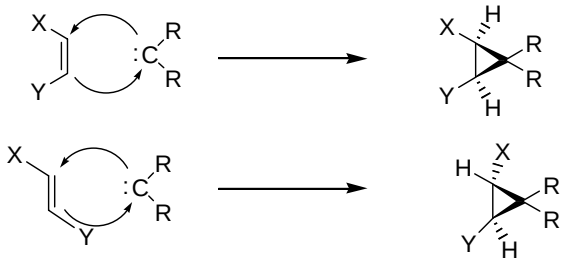
Most carbenes are more stable in the triplet state since the energy required to overcome the repulsion between two electrons is greater then the energy gained by bringing an electron from the higher energy p orbital to the lower energy sp^2 orbital. In any event, carbenes have the potential to exist in either state and the adopted state depends on such factors as the groups bonded to the carbene carbon and the process in which the carbene is prepared. In general, carbenes having a singlet ground state possess electron-rich substituents containing lone electron pairs adjacent to the carbene center. These lone pairs can interact with the p orbital of the carbene generating a new, lower-energy orbital allowing the carbene electron in the p orbital to pair with the electron in the sp^2 orbital, forming a singlet state carbene. Carbenes having electron-donating substituents, which are usually in the singlet state, tend to behave as nucleophiles, rather then electrophiles, while triplet state carbenes mimic radical reactivity.

1.1.2 Reactivity of Carbenes

In general, carbenes proceed as electrophiles due to their electron deficiency. They react with the highest occupied molecular orbital (HOMO) of almost any compound and unlike carbocations are not limited to electron-rich species. Most of these reactions are referred to as "insertion reactions" which denotes the outcome of the reaction and not the mechanism itself.

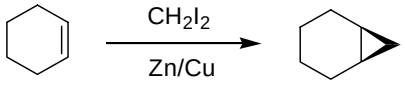
One of the most important reactions of carbenes is the cyclopropanation of double bonds. Both singlet and triplet carbenes are capable of this reaction; however the mechanism in which they undergo this transformation is different. Singlet carbenes cyclopropanate olefins in a concerted manner as shown in Scheme 1.2. The result of this concerted mechanism is a stereospecific cyclopropanation reaction, such that *Z*-alkenes generate *cis*-cyclopropanes and *E*-alkenes afford *trans*-cyclopropanes.

Scheme 1.2



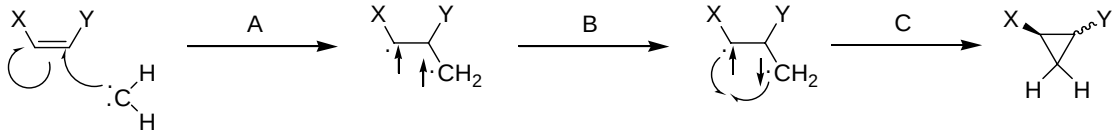
One of the most common methods used for cyclopropanation in organic synthesis utilizing a singlet carbene is the Simmons-Smith reaction (Scheme 1.3).[4]

Scheme 1.3



Triplet carbenes follow a radical mechanism and therefore undergo a step-wise process (Scheme 1.4). These reactions provide mixtures of *cis*- and *trans*-cyclopropanes.

Scheme 1.4



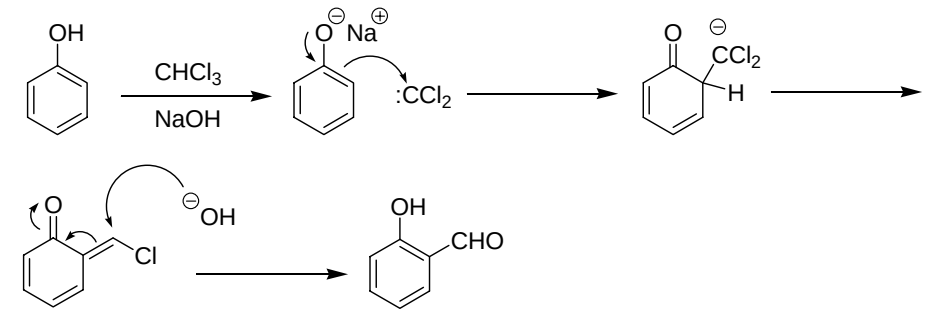
The first step of this stepwise process (A, Scheme 1.4) generates a diradical in which both electron spins are parallel. A slow spin inversion step (B, Scheme 1.4) is required so that the radicals can recombine (C, Scheme 1.4) to afford the cyclopropane product. The intermediate formed after step A has the time (slow step) and the ability to undergo free rotation which results in product mixtures. Upon the electron spin inversion, recombination occurs quickly, leaving little time for rotation to occur.

The utility of carbenes in synthetic organic chemistry goes beyond cyclopropanation. For instance, prior to the use of ortho-lithiation, the generation of ortho-substituted phenols could be achieved by the Reimer-Tiemann reaction shown in Scheme 1.5, which proceeds via a

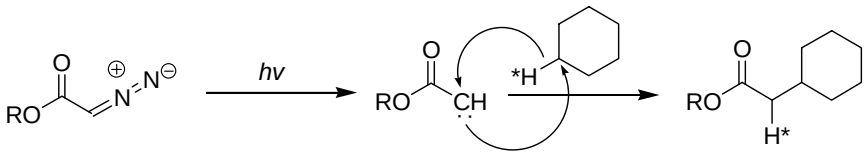
dichloromethyl carbene. Another common transformation employing carbenes are C-H insertion reactions.[1,3] In these reactions the empty p orbital (or LUMO) of the carbene interacts with the HOMO of a C-H bond and inserts itself into the C-H bond (Scheme 1.5). Finally, a common rearrangement observed as the result of carbene formation is the Wolff rearrangement (Scheme 1.5). In this reaction the formation of the carbene species leads to a rearrangement resulting in a ketene intermediate. This intermediate is highly reactive and undergoes facile hydration as shown in Scheme 1.5.

Scheme 1.5

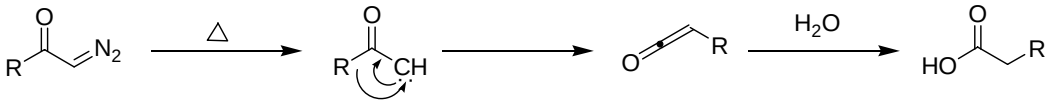
a) Reimer-Tiemann Reaction



b) C-H Insertion Reactions



c) Wolff Rearrangement



1.2 METAL CARBENES

The typical procedure for the generation of free carbenes via the photochemical decomposition of diazo compounds was first recognized in 1941 by Meerwein and co-workers.[5,6,7] In the presence of a transition metal, the p orbital of the carbene can be stabilized by the delocalization of the metal d orbital electrons, via back bonding, generating a carbenoid species (Figure 1.2).

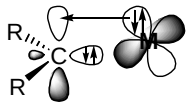


Figure 1.2: Back bonding between metals and carbenes.

The first transition metal carbene complex, $(CO)_5Cr=C(OMe)Me$, was synthesized in 1964 by Fischer and Maasböl.[1,8] This class of compound proved useful and versatile in organic and organometallic synthesis and was referred to as a Fischer carbene. Ten years later, in 1974, Schrock introduced a different type of metal carbene complex, $(CH_3CCH_2)_3Ta=C(H)CCH_3$, which came to be known as the Schrock carbene.[9,10] The two types of carbenes behaved, chemically, very differently, with the Fischer carbene illustrating electrophilic reactivity and the Schrock carbene behaving as a nucleophile. The reactivity and stability of the metal-carbene complex (**1.6**, Figure 1.3) is largely determined by the degree of σ-donation from the ligand to the metal and π-donation from the metal to the ligand, termed π-back bonding, that occurs. When the π-back bonding is strong, such that the metal is a good σ-acceptor and a good π-donor, then the interaction between the metal and the carbene is strong, resulting in a nucleophilic carbene. These types of metal-stabilized carbenes are Schrock carbenes (**1.8**, Figure 1.3). On the contrary, if the metal is both a poor σ-acceptor and poor π-donor then the interaction between the metal and the carbene is weak. The reactivity of these carbenes will be close to that of an uncomplexed free carbene (**1.5**, Figure 1.3) resulting in electrophilic behaviour. Like the uncomplexed free carbene, Fischer carbenes (**1.7**, Figure 1.3) also display electrophilic character.

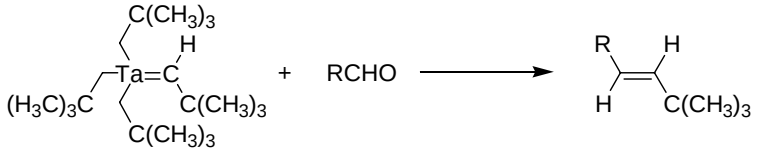
(**1.5**) (**1.6**) (**1.7**) (**1.8**)

Figure 1.3: Carbenes in order of increasing nucleophilicity (free carbene, metal carbenoid, Fischer carbene and Schrock carbene).

1.2.1 Schrock Carbenes

Schrock carbenes are nucleophilic alkylidene complexes formed by the coordination of strong donor ligands (i.e. alkyl or cyclopentadienyl) to metals having high oxidation states. The nucleophilic nature of these carbenes has often been compared to that of Wittig's ylides as Wittig-type alkenylation of a carbonyl group is possible using Schrock carbene compounds (an example is seen in Scheme 1.6).[1]

Scheme 1.6



Schrock carbenes can be characterized by the interaction of a triplet carbene ligand with a transition metal fragment that is also in the triplet state (Figure 1.4). The outcome of this interaction is nearly covalent σ and π bonds.

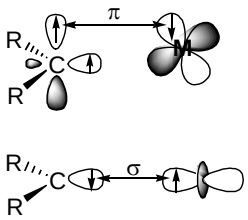


Figure 1.4: Dominant orbital interactions in Schrock carbenes.

The nucleophilic behaviour of these carbenes is attributed to these orbital interactions due to the more covalent double bond character as compared to electrophilic carbenes. The shorter metal-carbon bond observed in Schrock carbenes has been credited by the smaller radius of the metal atom due to its higher oxidation state.[1,11] Natural bond orbital (NBO) calculations, which focus on orbital structure, have illustrated that both the σ and π bonds are polarized towards the carbon end of the carbene, explaining their nucleophilic reactivity.

1.2.2 Fischer Carbenes

Fischer carbene complexes are electrophilic heteroatom-stabilized carbenes that are coordinated to metals in low oxidation states. These carbenes are generally characterized by the formula $(CO)_5M=C(X)R$, where M = Cr, Mo, W; X = π-donor substituent; R = alkyl, aryl or unsaturated alkenyl or alkynyl. Fischer carbene complexes are formed by coordination of a singlet carbene ligand to a transition metal also in the singlet state (Figure 1.5). These complexes have significant carbene to metal σ donation and metal to carbene π back donation.

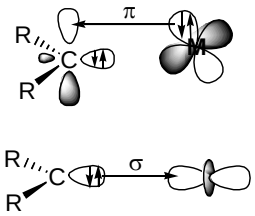
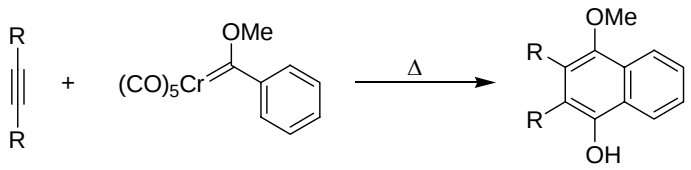


Figure 1.5: Dominant orbital interactions in Fischer carbenes.

One of the most prominent synthetic applications of Fischer carbenes is the Dötz benzannulation reaction (Scheme 1.7) which affords alkoxyphenol derivatives.[1,12]

Scheme 1.7



1.3 PALLADIUM CARBENES

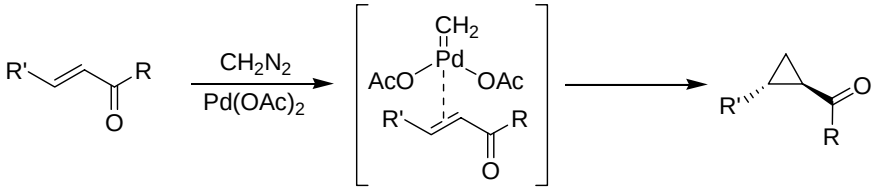
In the last few decades the synthesis and use of metal carbenes has flourished with a plethora of reagents and preparations available for their use. The classical metal carbenes chromium, tungsten, molybdenum, ruthenium and thallium have proven valuable tools in synthetic organic chemistry. The use of other transition metals, such as copper and rhodium, in the synthesis of metal carbenes has become an avid topic in organic chemistry. Recently, palladium carbenes

have engendered much attention. They have been proposed intermediates in numerous reactions, specifically; the Pd(II)-catalyzed diazomethane cyclopropanation of alkenes,[13,14,15,16,17,18] the cine substitution pathway in the Stille reaction,[19,20,21,22] the metathesis of 1,6-enynes,[23,24] a variety of intramolecular cyclization reactions, namely the cyclization of α-sulfonyl ε-acetylenic esters and nitriles,[25] palladium-catalyzed carbene transfer reactions,[26,27] the [2+1] cycloaddition of terminal alkynes to norbornylene derivatives,[28] dimerization and cyclopropanation reactions via (α-(tributylstannyl)-π-allyl)palladium(II) species,[29] and the C-H insertion of terminal alkynes.

1.3.1 Pd(II)-Catalyzed Diazomethane Cyclopropanation of Alkenes

The reaction between diazoalkanes and olefinic substrates in the presence of transition metal complexes is one of the most important procedures for the cyclopropanation of electron-deficient and electron-rich double bonds.[13-15] The parent diazo compound, diazomethane, has been utilized as a source of methylene because of the ease in which it loses nitrogen in the presence of many metal complexes.[13-15] Of the various metals that are capable of this reaction, palladium, rhodium and copper derivatives are the most common and efficient reagents for the reliable methylenation of alkenes by diazomethane.[13-17] The use of palladium(II) acetate for this transformation is a widely used synthetic method (Scheme 1.8).[13-16]

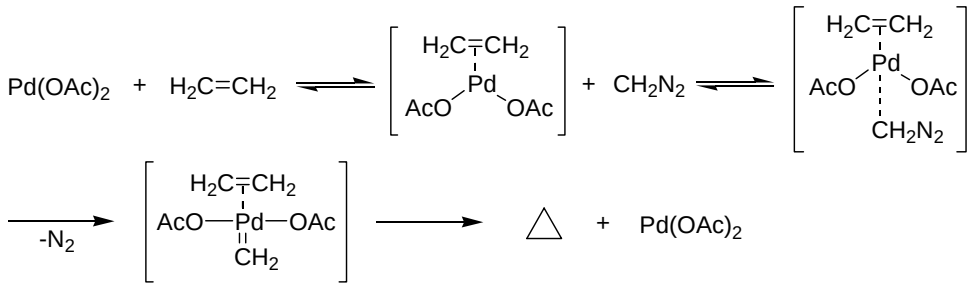
Scheme 1.8



Currently, it is thought that these reactions proceed via a palladium carbene intermediate which results from a reaction between the palladium(II) acetate and diazomethane.[15] Earlier work done by Anciaux and co-workers exemplified that palladium(II) carboxylates were effective catalysts

for cyclopropanating alkenes. They proposed that the reaction proceeded by coordination of the olefin substrate, followed by coordination of diazomethane (Scheme 1.9). Loss of nitrogen afforded the proposed palladium carbene intermediate that induced cyclopropanation of the coordinated olefin (Scheme 1.9).

Scheme 1.9



In 1980, Puddephatt and co-workers revisited Ancieux's results and proposed three mechanisms for metal carbene cyclopropanation (Figure 1.6). Each of these reaction pathways were initiated by attack of diazomethane onto the metal complex and, upon loss of nitrogen, the formation of the carbene species.

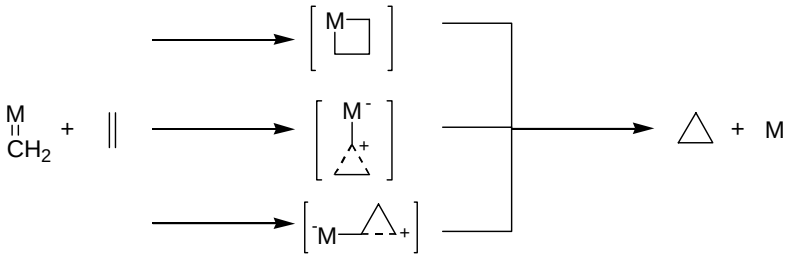
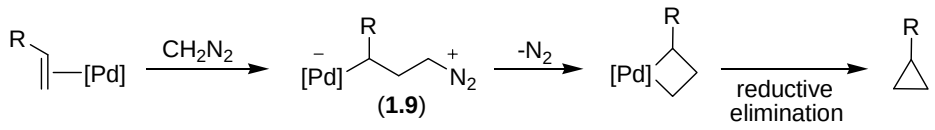


Figure 1.6: Three mechanisms for metal-carbene cyclopropanation.

It has also been proposed that due to the strong coordinating power of palladium(II) towards alkenes, electrophilic addition of the metal olefin complex onto diazomethane, forming **1.9** can occur (Scheme 1.10). Intermediate **1.9** could then undergo expulsion of nitrogen via a metallocyclobutane intermediate followed by reductive elimination to afford the cyclopropane (Scheme 1.10).[1,13]

Scheme 1.10



In 1997, Denmark and co-workers proposed an enantioselective diazomethane-based cyclopropanation reagent derived from bis(oxazoline)palladium(II) complexes (Figure 1.7).

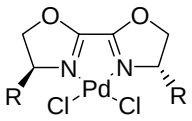


Figure 1.7: Bis(oxazoline)palladium(II) complex.

Cyclopropanation reactions were performed on various electron-deficient alkenes in good yields; however, the products were all racemic. The resulting racemic products gave some insight into the reaction mechanism. One could envision that the formation of a palladium-carbene intermediate would require dissociation of a ligand (either an oxazoline nitrogen or a chlorine) in order to coordinate the alkene. Due to the higher affinity of chloride relative to an oxazoline nitrogen, it is likely that partial or full dissociation of the chiral bis(oxazoline) ligand occurs, resulting in the formation of racemic cyclopropanes (Figure 1.8).[13]

In addition to the experimental evidence supporting the formation of palladium carbene complexes, computational studies on the reaction of diazomethane with ethylene in the presence of palladium diformate have also been performed and support the formation of a palladium-carbene intermediate.

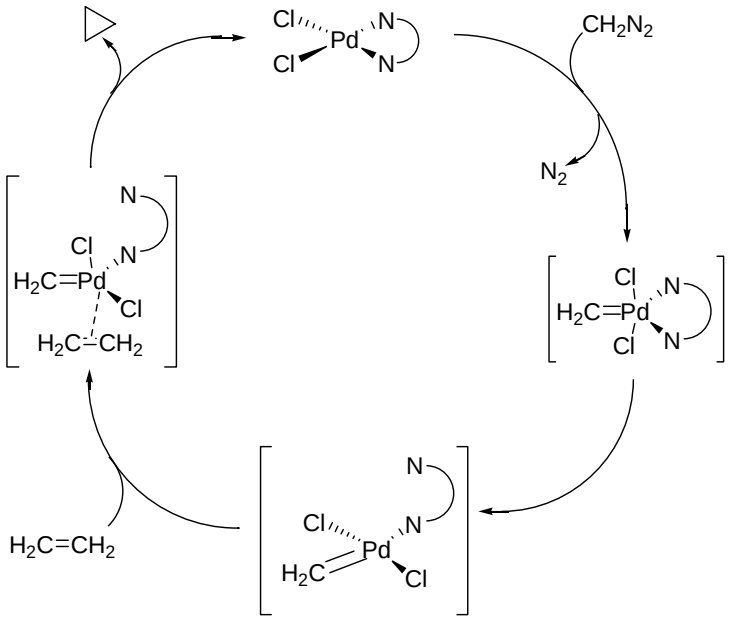
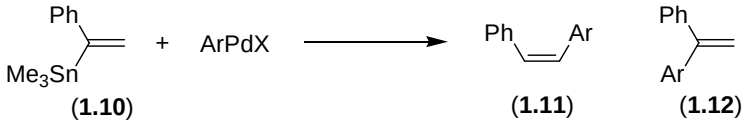


Figure 1.8: Proposed catalytic cycle for bis(oxazoline)palladium cyclopropanation.

1.3.2 Cine Substitution Pathway in the Stille Reaction

The Stille reaction is a powerful method for the stereospecific and chemoselective formation of carbon-carbon bonds. One of the constraints of this reaction is the tendency of some α-substituted olefinic stannanes to undergo cine substitution. The formation of the cine product was first reported in 1986 by Kikukawa and co-workers when they attempted a Stille coupling of α-styryltins (**1.10**) with various aryl diazonium salts (Scheme 1.11). The product obtained were (*Z*)-stilbenes (**1.11**) as opposed to the expected (*E*)-stilbenes (**1.12**) (Scheme 1.11).

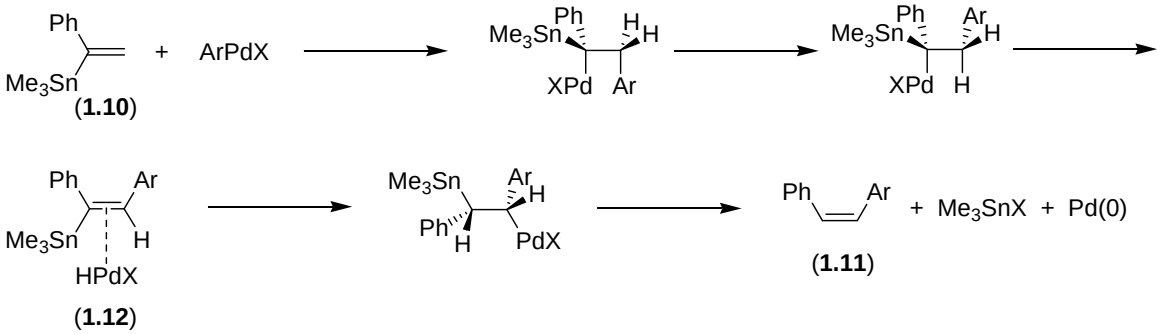
Scheme 1.11



The cine product (**1.11**) is observed when the carbon bearing the trialkylstannyl group is substituted. Kikukawa and co-workers proposed a mechanism for the formation of the cine product in which the first step is a carbopalladation rather then a transmetallation (Scheme 1.12).

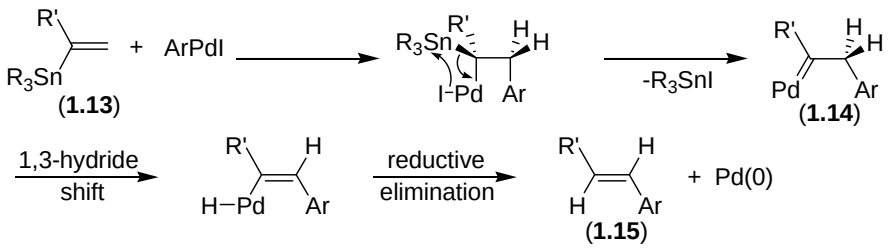
This permits rotation about the carbon-carbon single bond such that syn orientation is achieved and β-hydride elimination of X-Pd-H can occur (Scheme 1.12). The re-addition of HPdX across the double bond with the opposite regiochemistry, followed by the anti elimination of tin halide and Pd(0) would afford the cine product (Scheme 1.12).

Scheme 1.12



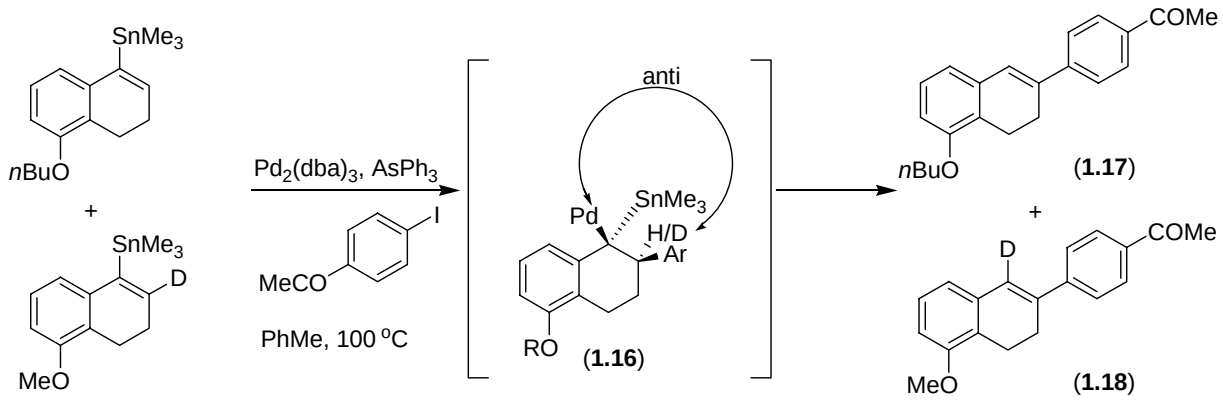
This potential reaction pathway has been cited in the literature; however, it raised concern that the intermediate vinyl stannane (**1.12**) was never observed as a side product. In 1994, Busacca and co-workers proposed an alternate route to the cine substitution product. Their reaction pathway involved the formation of a palladium carbene intermediate species (**1.14**) (Scheme 1.13). Like Kikukawa's mechanism, the first step was a carbopalladation reaction of the vinyl stannane (**1.13**) (Scheme 1.13). The palladium carbene could then be formed by loss of trialkylstannyliodide via a four-center transmetallation transition state. Upon formation of the palladium carbene a 1,3-hydride shift followed by reductive elimination affords the cine product (**1.15**) (Scheme 1.13).

Scheme 1.13



Busacca and co-workers illustrated strong evidence for this mechanism by performing deuterium labeling studies demonstrating a 1,3-hydride shift. In 1996, Farina and co-workers conducted further experiments confirming the reaction mechanism presented by Busacca and co-workers two years prior. In these studies, cyclic stannanes were utilized to prevent the β-hydride elimination pathway, as anti β-hydride elimination had no literature precedent at that time (see **1.16**, Scheme 1.14). Under the Stille reaction conditions the cine substitution product was still observed. Employing Kikukawa's proposed reaction pathway, anti-elimination of HPdI followed by readdition to the alkene would be required to obtain the cine product. Thus, in deuterium-labeled crossover studies, Kikukawa's route would generate crossover products. The Busacca mechanism involves an intramolecular 1,3-hydride shift and therefore the same crossover studies would not generate any crossover products. The results of these crossover experiments illustrated that only "intramolecular" products (**1.17** and **1.18**) were observed (Scheme 1.14). In particular, no deuterium incorporporation in product **1.17** or loss of deuterium in product **1.18** was observed. These results strongly suggest the formation of a palladium-carbene intermediate.

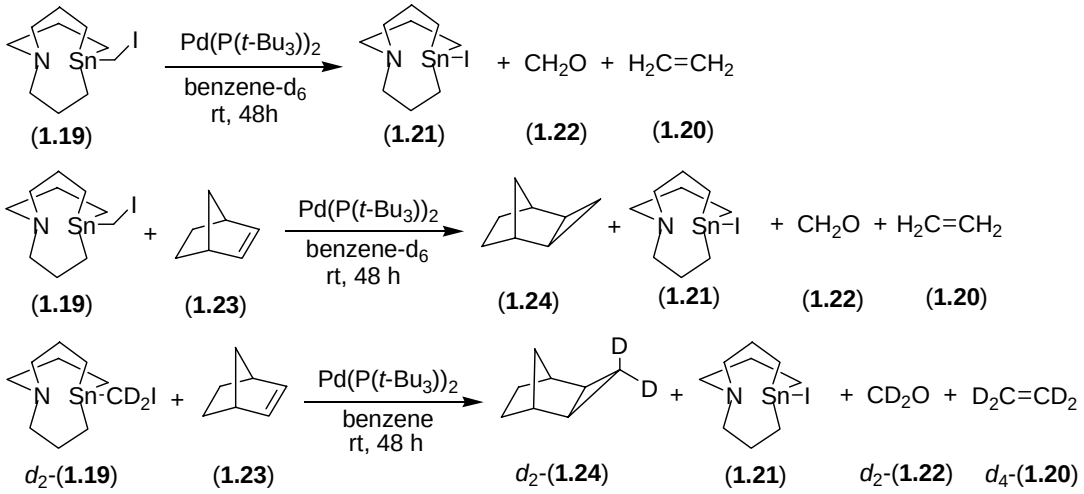
Scheme 1.14



In 2003, our group provided evidence for the intermediacy of dimetallics and their reactivity as palladium carbenes by means of trapping experiments. It was anticipated that the decomposition

of iodomethyl-trialkylstannanes by Pd(0) catalysts would lead to the formation of ethylene by dimerization of the carbene intermediate, which is typical of carbene species. This prediction was tested using iodomethylstannatrane (**1.19**) and $Pd(P(t\text{-}Bu)_3)_2$ in benzene-d_6 (Scheme 1.15). The formation of ethylene (**1.20**) and iodostannatrane (**1.21**) was observed as well as trace amounts of formaldehyde (**1.22**) resulting from the reaction of the palladium carbene with oxygen (Scheme 1.15). Furthermore, when this decomposition reaction was carried out in the presence of norbornene (**1.23**), the cyclopropanated product (*exo*-tricyclo[3.2.1.$0^{2,4}$]octane) (**1.24**) was formed (Scheme 1.15). Ethylene and formaldehyde were also observed as side-products.

Scheme 1.15

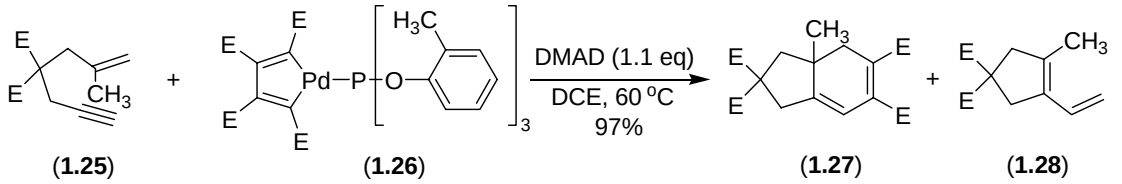


Further insights into the reaction mechanism were gained from the results obtained in deuterium-labeling studies. Using d_2-**1.19** and undeuterated benzene, cyclopropanation of norbornene was observed yielding d_2-**1.24**. This clearly illustrates the formation of a palladium carbene intermediate and further supports the Busacca-Farina cine mechanism.

1.3.3 Metathesis of 1,6-Enynes

In 1988, Trost and co-workers introduced a novel palladium catalyzed rearrangement of 1,6-enynes (**1.25**) (Scheme 1.16). They illustrated that in the presence of tetracarbomethoxy-palladacyclopentadiene (TCPC), tri-*o*-tolylphosphite (TOTPO) (complexed with palladium, **1.26**) and dimethyl acetylene-dicarboxylate (DMAD), 1,6-enynes generate the [2+2+2] cycloadduct (**1.27**) and vinylcyclopentene (**1.28**) in a 1:1.2 ratio, respectively (Scheme 1.16).

Scheme 1.16

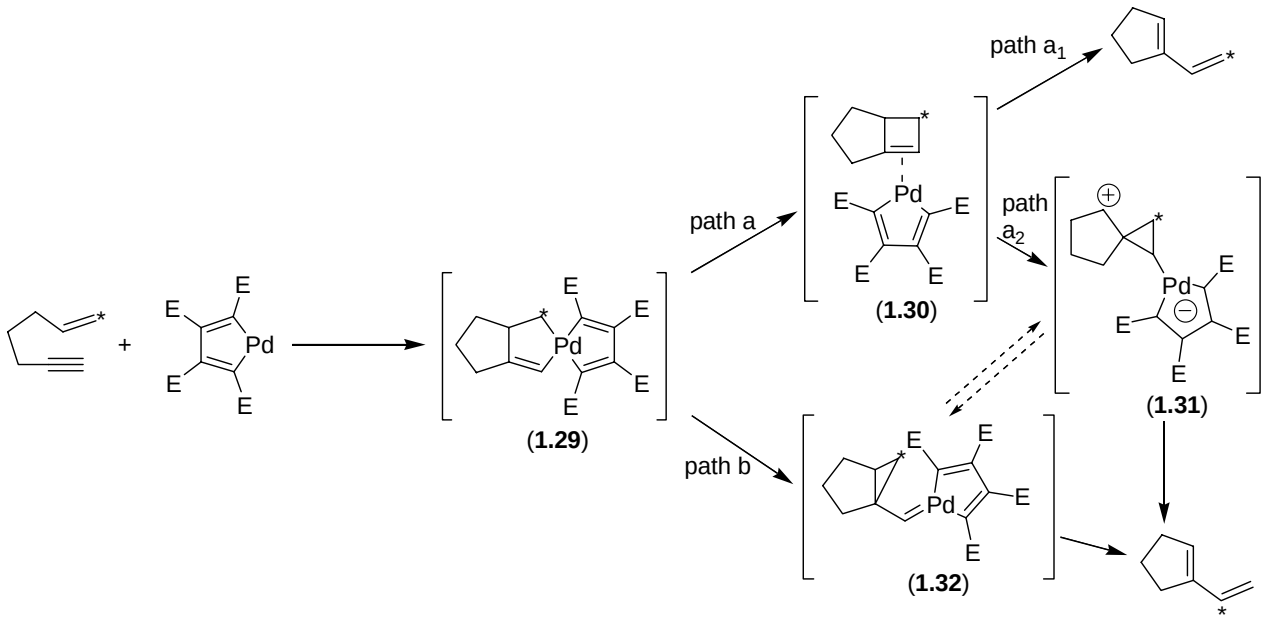


(**1.25**) (**1.26**) (**1.27**) (**1.28**)

E = CO_2CH_3

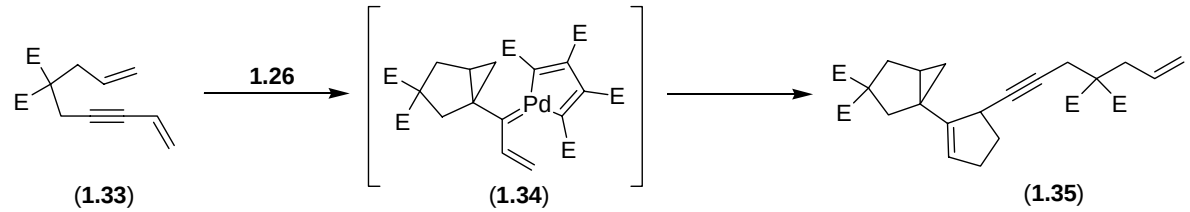
Labeling studies suggested that the reaction underwent two mechanistic pathways when terminal acetylenes were used (Scheme 1.17).[23,24]

Scheme 1.17



The formation of a cyclobutene intermediate, as illustrated in path a, has been validated by studies whereby the cyclobutenes were isolated. The formation of the cyclopropyl complexes (**1.31** or **1.32**) were based on the labeling patterns observed. Initially, **1.31** was favoured as seen in path a_2. Studies on the effects of substitution on the alkyne led to a new product whose structure strongly implicated **1.32** as shown in path b. The presence of a vinyl substituent on the alkyne (**1.33**) under the reaction conditions outlined in Scheme 1.16 afforded the expected [2+2+2] cycloadduct as well as dimer (**1.35**), which became the exclusive product in the absence of DMAD (Scheme 1.18).

Scheme 1.18



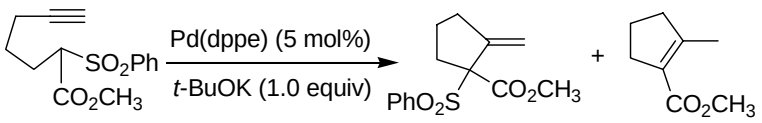
(**1.33**) (**1.34**) (**1.35**)

The formation of the dimer (**1.35**) was proposed to occur by the trapping of the palladium carbene intermediate (**1.34**) with the olefin starting material (**1.33**).

1.3.4 Intramolecular Cyclization Reactions

In 1994, Balme and co-workers reported strong evidence for the existence of a vinyl palladium carbene from enolates of α-sulfonyl ε-acetylenic esters (**1.36**).[25] In the presence of potassium *t*-butoxide and (diphenylphosphinoethane)palladium(0) the α-sulfonyl ε-acetylenic esters were expected to undergo cyclization to afford products **1.37** and **1.38** (Scheme 1.19).

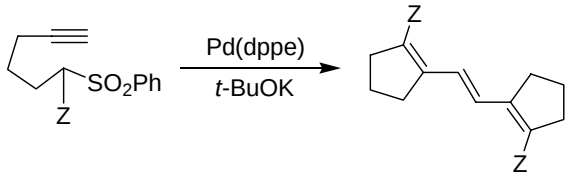
Scheme 1.19



(**1.36**) (**1.37**) (**1.38**)

However, the only product observed was the diester (**1.40a**) (Scheme 1.20). Under the same conditions the cyanosulfone (**1.39b**) generated the dinitrile (**1.40b**) (Scheme 1.20).

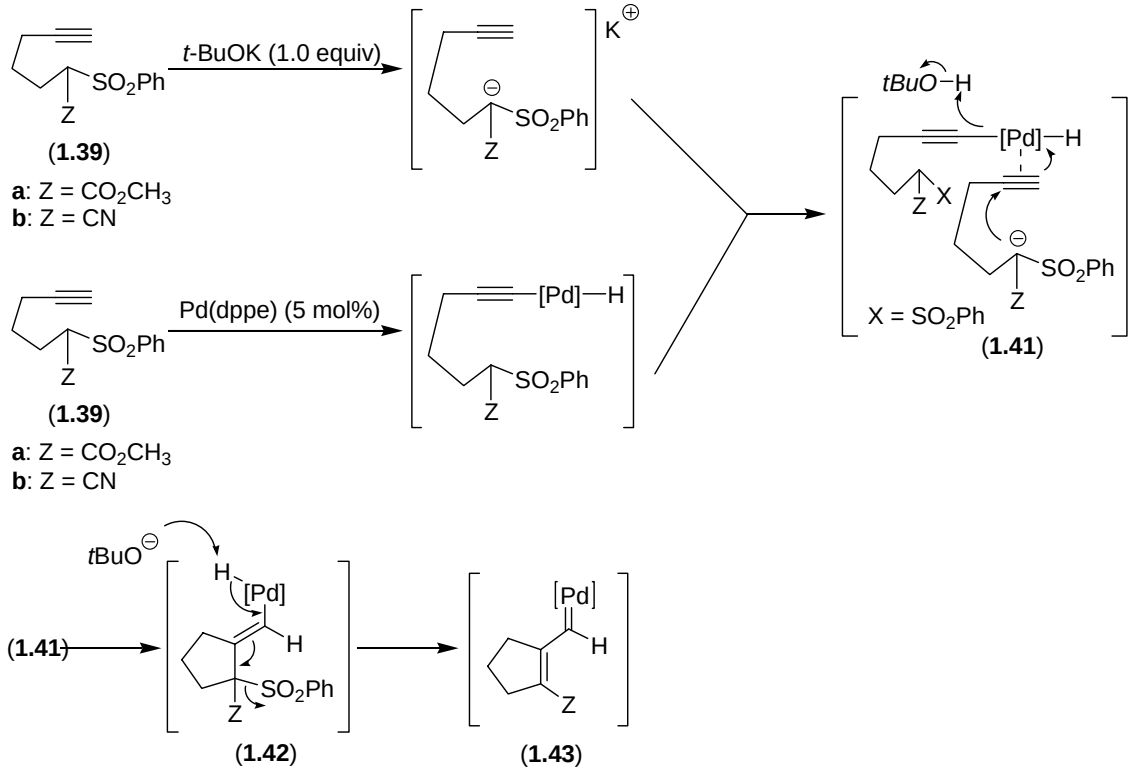
Scheme 1.20



1.39a: Z = CO_2CH_3 **1.40a**: Z = CO_2CH_3
1.39b: Z = CN **1.40b**: Z = CN

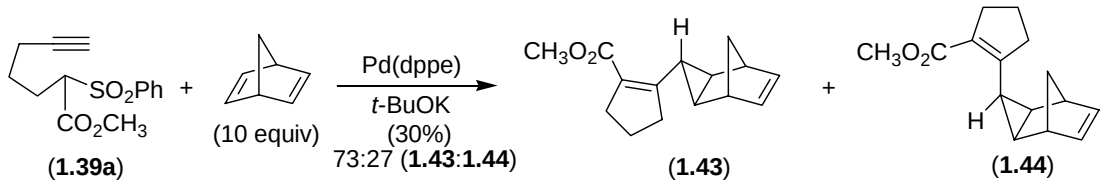
Balme and co-workers proposed the formation of a palladium carbene intermediate (**1.43**) as shown in Scheme 1.21.[30] They propose that this intermediate can arise from attack of base on the vinylic palladium hydride (**1.42**), which forms via the cyclization of the anion (**1.41**) onto the palladium(II)-activated alkyne (Scheme 1.21).

Scheme 1.21



In order to validate this intermediate, they conducted intermolecular trapping experiments with norbornadiene and the cyclopropanated adducts (**1.44a** and **1.44b**) were observed (Scheme 1.22).

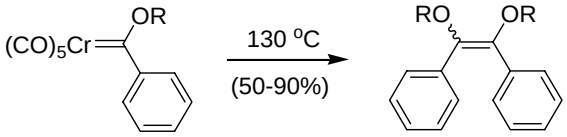
Scheme 1.22



1.3.5 Palladium-Catalyzed Carbene Transfer Reactions

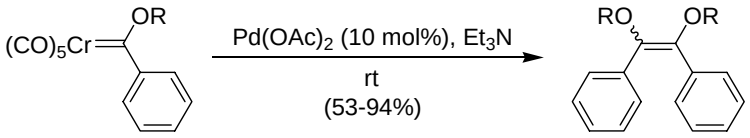
In the last decade Sierra and co-workers have illustrated the use of palladium as a catalyst in reactions involving group 6 Fischer carbene complexes.[26,27] They have described how the reactivity of these Fischer carbenes can be enhanced or modified in the presence of a catalytic amount of palladium, leading to new forms of reactivity not otherwise observed with these systems. The key step for these reactions being transmetalation from the stoichiometric Fischer carbene to the palladium catalyst whereby dimerization is observed and can be followed by other tandem reactions.[26,27] Initial studies were performed looking at self-dimerization reactions. Although these reactions will occur without the addition of another catalyst, they require harsh reaction conditions (Scheme 1.23).

Scheme 1.23



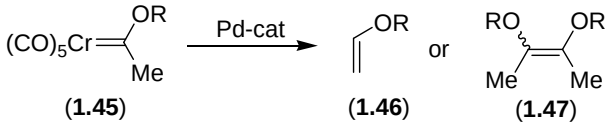
When they ran this reaction in the presence of catalytic amounts of palladium and triethylamine, the same reaction occurred with comparable yields, however, under much milder reaction conditions (Scheme 1.24).

Scheme 1.24



Besides chromium-based Fischer carbenes, tungsten also illustrated the same compatibility and reactivity in the presence of palladium. In addition to $Pd(OAc)_2$, other palladium(II) and palladium(0) catalysts were equally efficient in promoting the carbene ligand dimerization (i.e. $Pd_2(dba)_3 \bullet CHCl_3$, $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$). The nature of the reaction did depend on the catalyst when the substituents on the carbene carbon were methyl groups. Thus, alkyl carbene complex (**1.45**) gave exclusively vinyl ether (**1.46**) when $Pd(OAc)_2$ and Et_3N were used, in up to 65% yield (Scheme 1.25). However, when other palladium catalysts, such as $Pd_2(dba)_3 \bullet CHCl_3$, $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$, were used the expected dimerization product (**1.47**) was the only product observed, in 70-87% yield (Scheme 1.25).[26,27]

Scheme 1.25



(**1.45**) (**1.46**) (**1.47**)

To explain the observed results they proposed the following catalytic cycle shown in Figure 1.9.

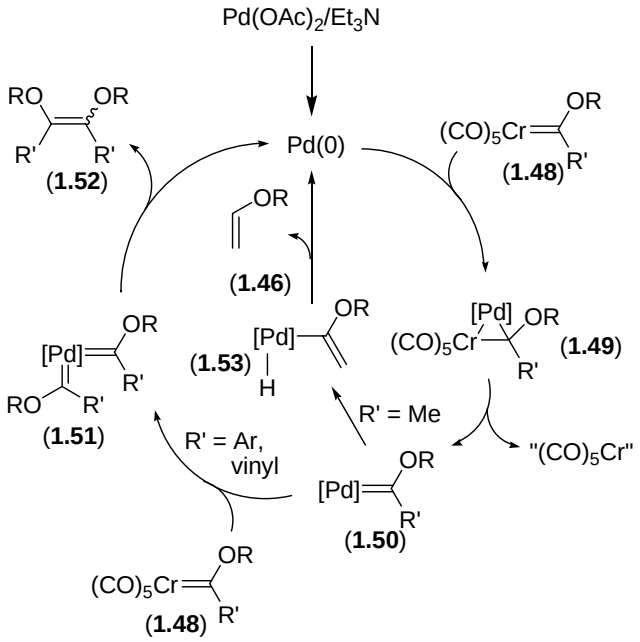
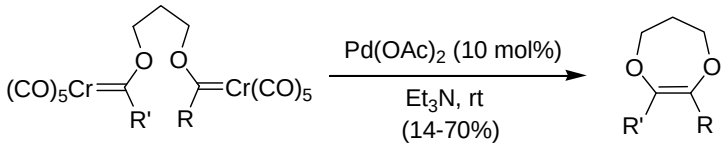


Figure 1.9: Proposed catalytic cycle for formation of dimer and vinyl ether.

The first step they proposed was transmetallation of the carbene ligand from **1.48** to the palladium catalyst, generating intermediate **1.49**. Loss of $(CO)_5Cr$ generates palladium carbene (**1.50**) which can then go through one of two potential reaction paths. When R' is an aryl or vinyl group, **1.50** can transmetallate with a second carbene ligand from another equivalent of **1.48** affording the palladium-bicarbene intermediate (**1.51**). Elimination of Pd(0) generates the dimer product (**1.52**). When R' is a methyl group, hydride transfer to the metal center to form a new palladium-hydrido complex (**1.53**), was proposed to occur. Reductive elimination affords the vinyl ether product (**1.46**) and the regeneration of the Pd(0) catalyst.

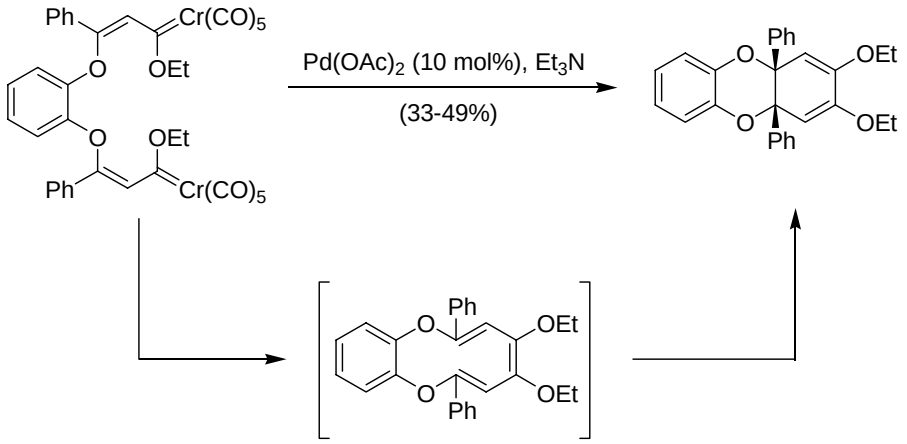
They then tested the intramolecular palladium-catalyzed dimerization (Scheme 1.26).

Scheme 1.26



Given these results, they devised a tandem reaction sequence involving dimerization followed by electrocyclic ring closure (Scheme 1.27).

Scheme 1.27

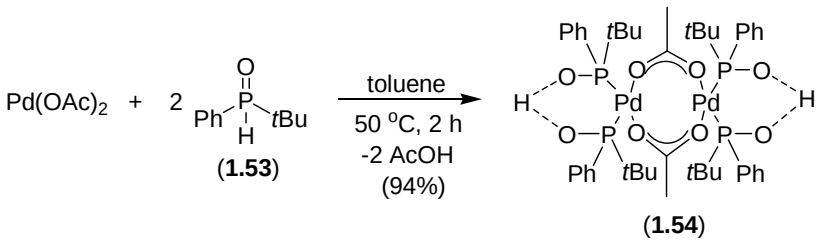


Attempts at utilizing this system for the cyclopropanation of electron-deficient olefins with palladium were unsuccessful and only the dimerization product was ever observed.

1.3.6 [2+1] Cycloadditions of Alkynes to Norbornylene Derivatives

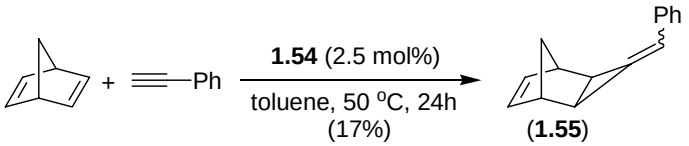
In 2005, Buono and co-workers illustrated a direct formation of alkylidenecyclopropanes via a palladium-catalyzed cyclopropanation of norbornylene derivatives with terminal alkynes. The palladium catalyst used (**1.54**) was prepared by treating $Pd(OAc)_2$ with 2 equivalents of *tert*-butyl(phenyl)phosphane oxide (**1.53**) in toluene at 50 ºC for 2 h (Scheme 1.28) .

Scheme 1.28



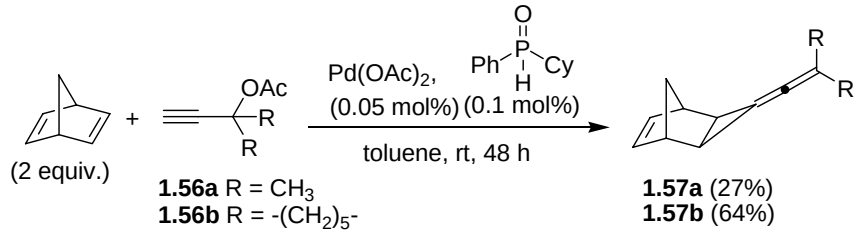
In the presence of 2.5 mol% of **1.54**, phenylethyne and excess norbornadiene reacted in toluene at 50 ºC for 24 h, to afford the benzylidenecyclopropane product (**1.55**) (Scheme 1.29).

Scheme 1.29



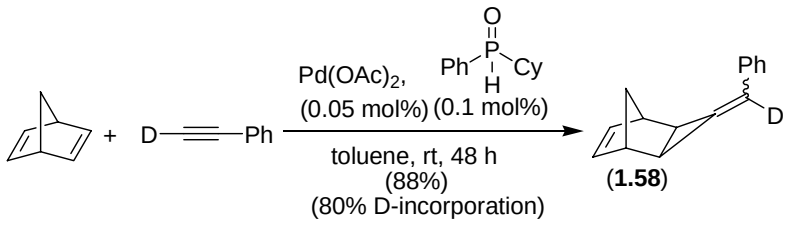
During a preliminary study they found that the addition of acetic acid was beneficial to the reaction and increased the yield from 17% to 26%. This finding prompted them to generate the catalyst in situ since acetic acid was released during its preparation. In an effort to optimize the reaction they prepared similar catalysts from different phosphinous acid ligands. They found that the catalyst generated from cyclohexyl(phenyl)phosphane oxide provided product **1.55** in a yield of 80% and at room temperature. They applied this method to various alkynes functionalized with groups including, benzyl ethers, esters, alcohols, sulfones and morpholine derivatives and successfully isolated the alkylidenecyclopropane products in yields ranging from 9-80%. When they applied these conditions to tertiary acetates (**1.56a, 1.56b**), they obtained allenylidenecyclopropanes (**1.57a, 1.57b**) (Scheme 1.30).

Scheme 1.30



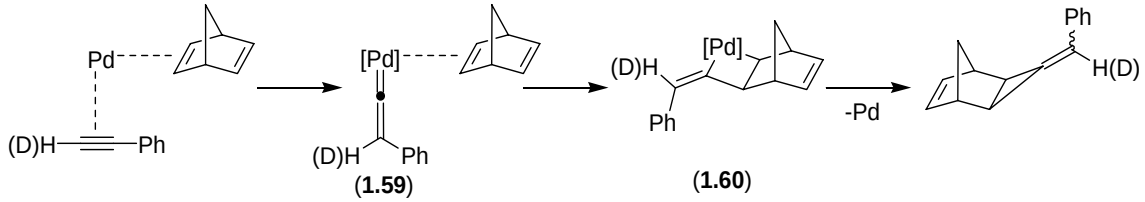
In order to gain insight into the mechanism, Buono and co-workers prepared a deuterated version of phenylethyne and isolated product **1.58** in 88% yield with 80% deuterium incorporation (Scheme 1.31).

Scheme 1.31



They proposed that the reaction may involve a palladium vinylidene species as a key intermediate (Scheme 1.32). This intermediate (**1.59**) could be generated from the alkyne via a 1,2-proton/deuterium shift. This palladium vinylidene could then undergo a [2+2] cycloaddition with norbornadiene forming palladacyclobutane (**1.60**), which would then reductively eliminate to afford the cyclopropane and regenerate the catalyst.

Scheme 1.32



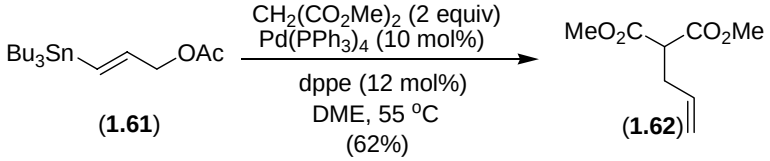
The formation of allenylidenecyclopropane products (**1.57a** and **1.57b**) can be envisioned to arise from a palladium allenylidene intermediate ($Pd=C=C=CR_2$) which would form upon the loss of acetic acid.

1.3.7 Reactions of (α-(tributylstannyl)-π-allyl)palladium(II) Species

Earlier this year, Fillion and Trépanier illustrated the ambiphilic vinylcarbenoid reactivity of (α-(tributylstannyl)-π-allyl)palladium(II) intermediate species. When the acetoxystannane precursor was treated with $Pd(dba)_2$, electrophilic metal-carbene reactions such as dimerization and cyclopropanation of strained alkenes were observed. However, in the presence of $Pd(PPh_3)_4$

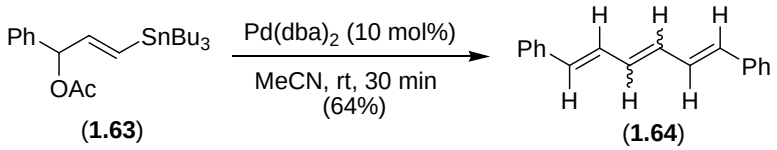
and dppe, **1.61** revealed the basicity of dimetallic intermediates via sequential reactions of the carbon-metal bonds with dimethyl malonate. Using conditions outlined by Trost and co-workers,[31] Fillion and Trépanier reacted propenyl acetate with excess dimethyl malonate, catalytic $Pd(PPh_3)_4$ and dppe in DME at 55 ºC (Scheme 1.33), malonate adduct (**1.62**) was obtained in 62% yield.

Scheme 1.33



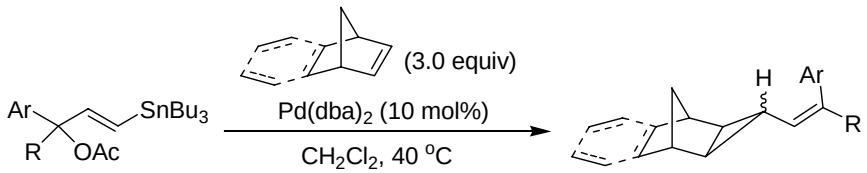
Palladium-catalyzed dimerization using acetoxystannane **1.63** was then analyzed. Under the conditions outlined in Scheme 1.33 the reaction was slow. However, using $Pd(dba)_2$ (10 mol%) in MeCN afforded the dimer product in 64% yield at room temperature (Scheme 1.34).

Scheme 1.34



Attempts at the cyclopropanation of norbornylene and norbornylene derivatives was found to proceed best when CH_2Cl_2 was used as solvent at 40 ºC (Scheme 1.35).

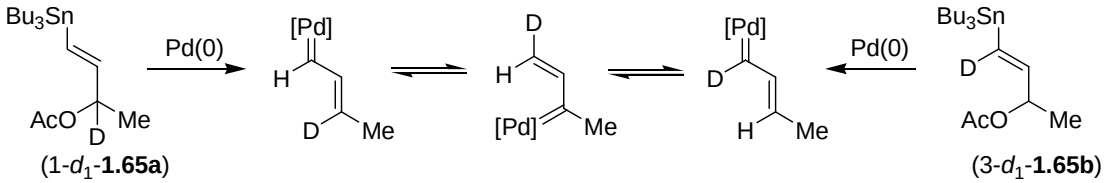
Scheme 1.35



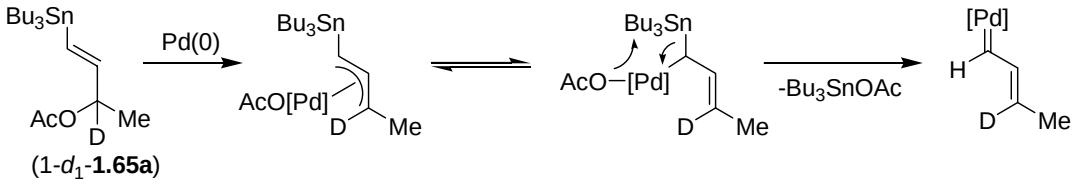
Initially it was thought that both mechanisms proceeded through a palladium-carbene intermediate that underwent C-H insertion of the malonate, dimerization when no malonate or

olefin was present, or cyclopropanation when excess alkene was added. In order to gain insight into the mechanism deuterated compounds 1-d_1-**1.65a** and 3-d_1-**1.65b** were prepared. It was expected that upon formation of the palladium-carbene, via formation of the π-allyl and loss of Bu_3SnOAc, a [1,3]-carbene shift would occur, and C-H insertion into the malonate would lead to common deuterated products (Scheme 1.36).

Scheme 1.36

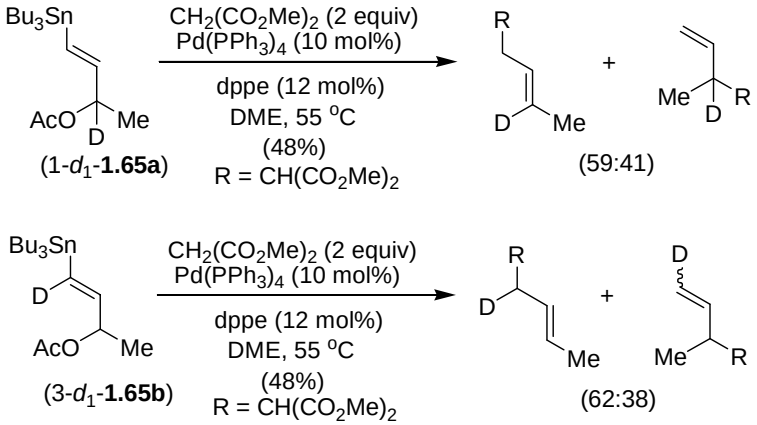


Formation of palladium-carbene:



However, the formation of common deuterated products was not observed and it was concluded that a [1,3]-carbene shift was not occurring (Scheme 1.37).

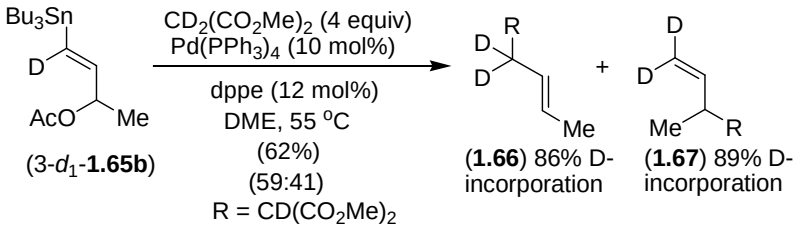
Scheme 1.37



It was then proposed that a protodestannylation of the carbon-tin bond could occur after slippage of the π-allyl intermediate from η_3 to η_1. To test this potential pathway they treated 3-d_1-**1.65b**

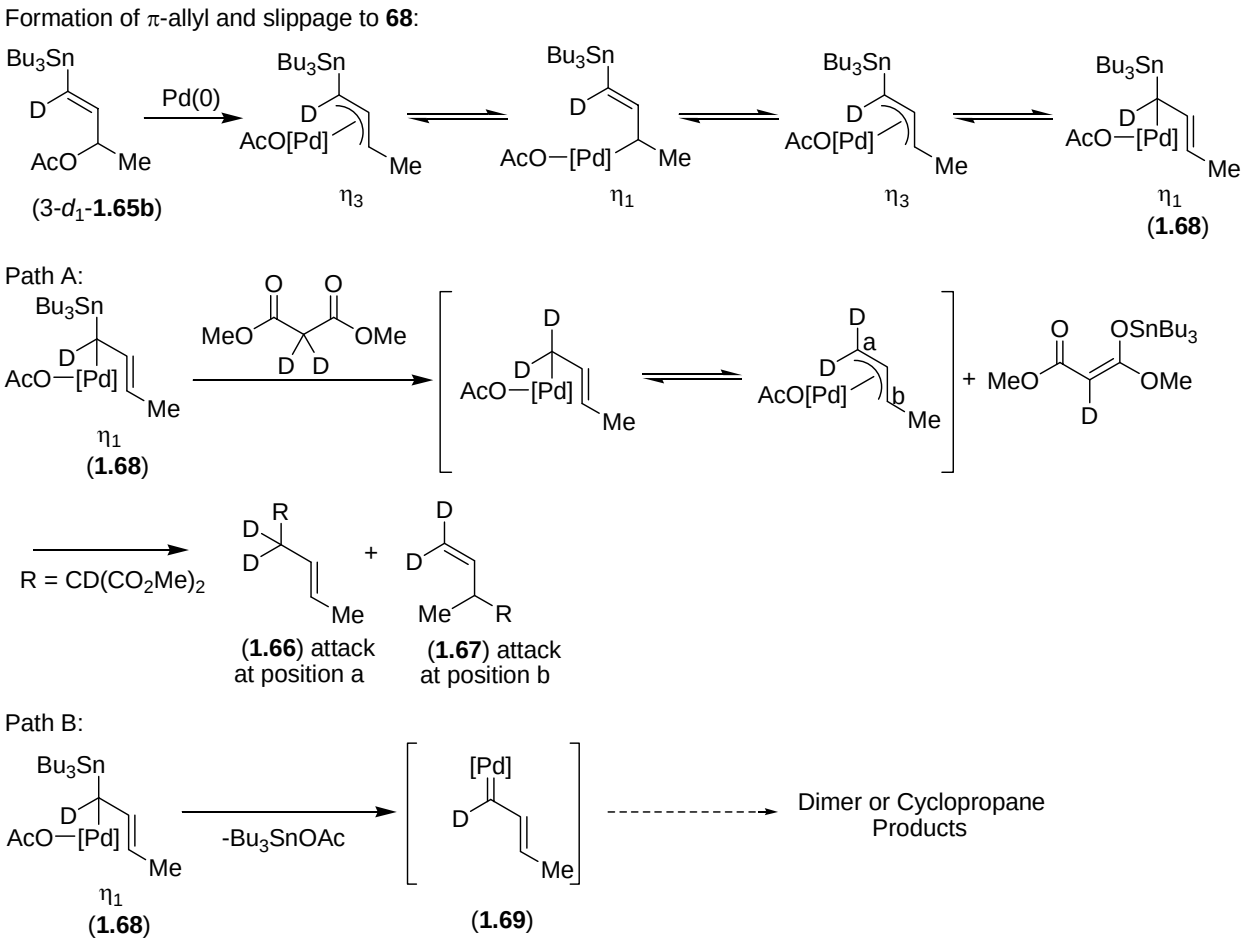
with d_2-dimethyl malonate to see if a second deuterium was incorporated into the final products (Scheme 1.38).

Scheme 1.38



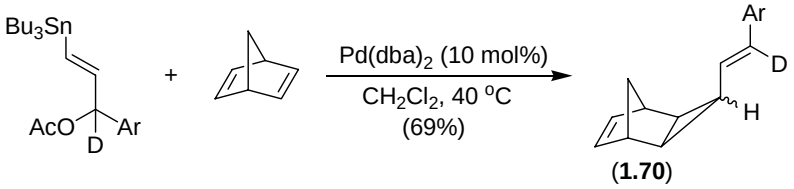
The *gem*-dideuterio compounds (**1.66**, **1.67**) were formed exclusively, establishing the protodestannylation mechanism. The deprotonation of dimethyl malonate illustrated the Brønsted base character of the dimetallic intermediate (**1.68**) (Scheme 1.39, Path A). It was postulated that the electron-rich ligands $Pd(PPh_3)_4$ and dppe promoted this behaviour. On the other hand, when $Pd(dba)_2$ was used as the catalyst, the more electron-deficient ligands contribute to the electrophilic reactivity observed. They still proposed that the formation of the dimer and cyclopropane products was the result of palladium-carbene intermediate (**1.69**), which could be formed in the absence of acidic protons (Scheme 1.39, Path B) and that the [1,3]-carbene shift pathway must be slower then the dimerization and/or cyclopropanation reactions.

Scheme 1.39



Cyclopropanation of norbornadiene using a deuterated alkoxystannane generated the expected cyclopropane (**1.70**) in 69% yield (Scheme 1.40).

Scheme 1.40

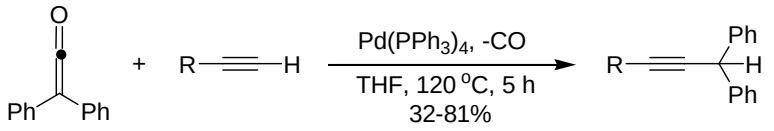


This result supports Path B, illustrated in Scheme 1.39, and further suggests that the cyclopropanation pathway must be faster then a [1,3]-carbene shift.

1.3.8 C-H Insertion Reactions

The insertion of carbenes and metal carbenes into a C-H bond is as characteristic reaction of these chemical species. The use of palladium carbenes for these reactions has only been used in the last twenty-odd years. In 1985, Watanabe and co-workers illustrated that palladium carbenes can insert into the C-H bond of terminal alkynes. The reaction of diphenylketene (**1.71**) with terminal acetylenes in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(0) afforded disubstituted acetylenes (**1.72**) after 5 hours (Scheme 1.41).

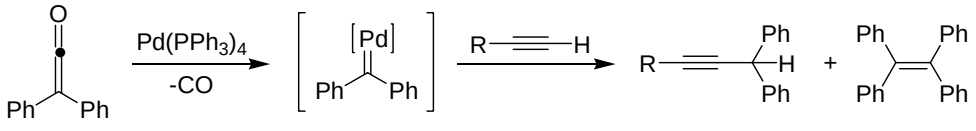
Scheme 1.41



(**1.71**) (**1.72**)

When these conditions were applied to internal alkynes, no reaction was observed. Also, when the reaction was conducted in the presence of carbon monoxide, diphenylketene was not consumed. In all cases, trace amounts of the dimer, tetraphenylethylene (**1.74**), were observed. These results illustrate that diphenylketene is catalytically decarbonylated by the palladium complex and the formation of a palladium carbene (**1.73**) species is supported (Scheme 1.42).

Scheme 1.42



(**1.73**) (**1.74**)

Other transformations involving C-H insertion via palladium catalysis have been reported in the literature, however, to our knowledge none of these have proposed a palladium carbene intermediate or made efforts to trap such an intermediate.

1.3.9 Summary

In summary, there is experimental evidence for the formation and reactivity of palladium carbene species. In the last decade the literature precedent for the existence and use of these reactive intermediates has increased greatly. A key factor in these transformations is the oxidation state of the palladium catalyst used and the ligands it bears. It is anticipated that insight will be gained into the fundamental reactivity of palladium carbenes and the effects of oxidation state on its behaviour in an effort to exploit the reactivity of these intermediates, such that palladium carbenes can be brought to their full synthetic potential.

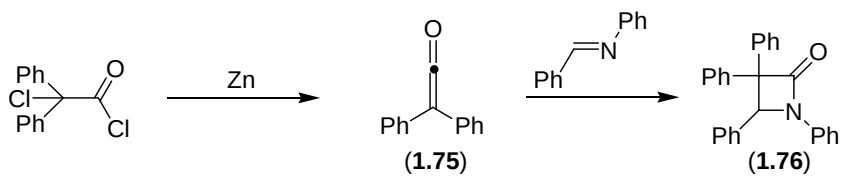
1.4 KETENES

It was illustrated by Watanabe and co-workers that diphenylketene is decomposed by tetrakis(triphenylphosphine)palladium(0) to generate a palladium stabilized carbene intermediate that further dimerizes or inserts into the C-H bond of a terminal alkyne. The use of ketenes to access palladium carbenes will be the basis of their preparation in this research.

1.4.1 History and Discovery

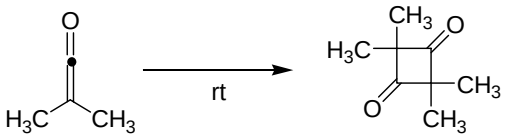
In 1905 Hermann Staudinger reported the discovery of a new group of reactive intermediates called ketenes.[32] He first isolated diphenylketene (**1.75**) by the addition of zinc to α-chlorodiphenylacetyl chloride, which was obtained as a low melting solid (Scheme 1.43).[33] It was found to readily add to imines forming β-lactam products (**1.76**) (Scheme 1.43).

Scheme 1.43



Dimethylketene (**1.77**) was also prepared and found to undergo [2+2] dimerization at room temperature affording the symmetrical cyclobutanedione (**1.78**) (Scheme 1.44).[34]

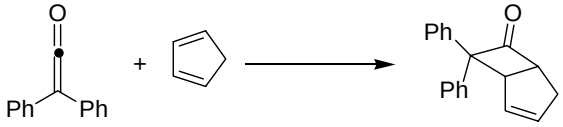
Scheme 1.44



(**1.77**) (**1.78**)

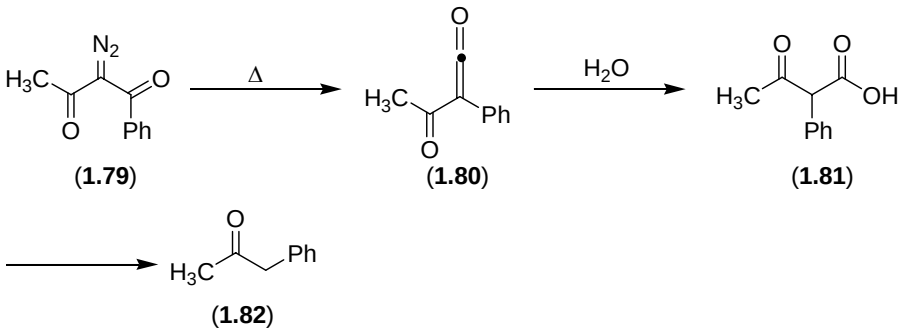
Ketenes were also shown to readily undergo [2+2] cycloaddition reactions with cyclopentadiene (Scheme 1.45).

Scheme 1.45



Ludwig Wolff generated ketenes by a different route in a reaction that became known as the Wolff rearrangement.[35] This reaction involved heating a diazo ketone (**1.79**) at reflux in water forming the ketene intermediate (**1.80)** (Scheme 1.46). This intermediate then formed an acid (**1.81**) which underwent decarboxylation to afford the ketone product (**1.82**) (Scheme 1.46).

Scheme 1.46

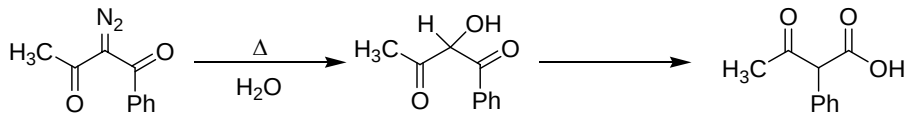


(**1.79**) (**1.80**) (**1.81**) (**1.82**)

Although Wolff recognized the acid intermediate (**1.81**), he proposed that it was the result of a double migration of intermediate **1.83** (Scheme 1.47). He anticipated that intermediate **1.83** was formed by the addition of water onto the starting material **1.79** (Scheme 1.47). Thus, Wolff

failed to recognize the formation of a ketene intermediate and thus Staudinger remains the official founder of ketenes.

Scheme 1.47



(**1.79**) (**1.83**) (**1.81**)

1.4.2 Structure and Substitutent Effects

The most distinguishing feature of the electronic structure of ketenes is the spatial orientation of the HOMO and LUMO.[36] The HOMO lies perpendicular to the ketene plane while the LUMO is in the plane of the ketene (Figure 1.10).

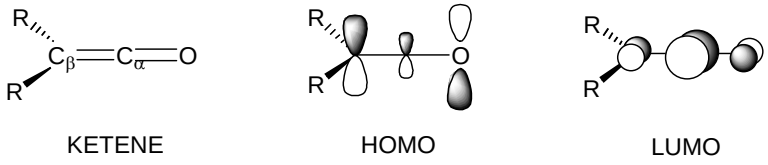


Figure 1.10: Ketene HOMO and LUMO diagrams.

This results in a substantial amount of negative charge on oxygen and the β-carbon and positive charge on the α-carbon. This also predicts the reactivity of ketenes such that electrophiles are expected to attack the ketene perpendicular to the molecular plane at the β-carbon or the oxygen, while nucleophiles are anticipated to attack in the plane at the α-carbon.

As a result of the negative charge buildup on the β-carbon, ketenes are stabilized by electron withdrawing substituents and destabilized by electron-donating groups. In fact, ketenes substituted with *n*-π-donor groups such NH_2 adopt nonplanar conformations in order to minimize the π-donation (Figure 1.11).

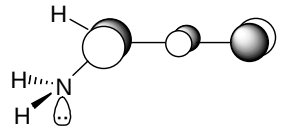


Figure 1.11: Non-planar conformation of ketenes with *n*-π-donor groups.

On the other hand, extra stabilization is observed with π-acceptor substituents such as BH_2 and carbonyl groups, as shown in Figure 1.12, due to resonance.[37]

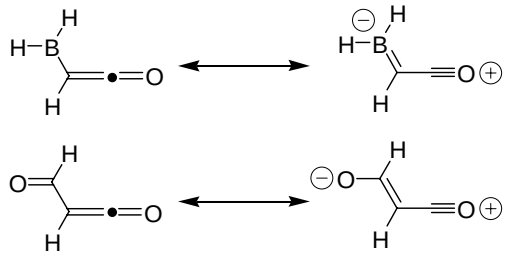
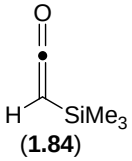


Figure 1.12: Conjugative stabilization of ketenes via π-acceptor substituents.

Another remarkably stable ketene is (trimethylsilyl)ketene (**1.84**) (Figure 1.13).[36]

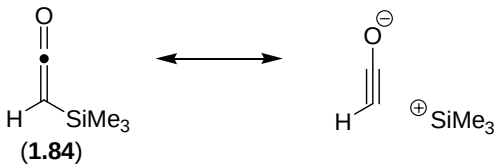


(**1.84**)

Figure 1.13: (trimethylsilyl)ketene.

This ketene is unique because of its resistance to dimerization, and thus, its ability to be stored for long periods of time.[36] It has been suggested that the extraordinary resilience of this ketene towards dimerization is due to ground state stabilization through hyperconjugative electron donation from the C-Si bond (Scheme 1.48).[38]

Scheme 1.48



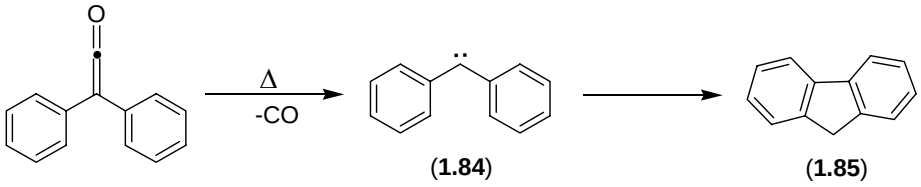
(**1.84**)

This explanation is reasonable since the C-Si bond and the carbonyl π bond are in the same plane, and the power of the C-Si bond as a hyperconjugative electron donor has been documented.[39]

1.4.3 Reactivity

Of the many reactions that ketenes can undergo, thermolysis to carbenes and cycloaddition reactions are the two most studied. In general, ketenes are thermodynamically stable relative to the formation of a carbene and carbon monoxide. The notable exception is difluoroketene, which spontaneously forms CF_2 carbene at room temperature. However, at higher temperatures carbene formation from many ketenes becomes significant. It was observed by Staudinger that pyrolysis of diphenylketene at 600-700 ºC affords diphenylcarbene (**1.84**), which then forms fluorene (**1.85**) (Scheme 1.49).[40]

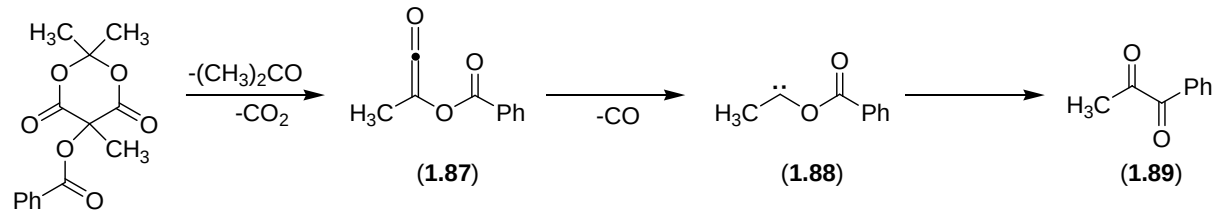
Scheme 1.49



The formation of carbenes by thermal decomposition of ketenes is a reversible process. This is clearly illustrated by the reaction of diazoalkanes in the presence of carbon monoxide whereby ketenes are generated from carbene intermediates.

Other ketene precursors have also demonstrated this reactivity. For example, the Meldrum's acid derivative (**1.86**) shown in Scheme 1.50 undergoes a retro[4+2] cycloaddition at 400-500 ºC to generate a ketene intermediate (**1.87**), which then decarbonylates to form a carbene species (**1.88**) that undergoes a 1,2-acyl shift, affording the diketone product (**1.89**).[41]

Scheme 1.50



(**1.86**) (**1.87**) (**1.88**) (**1.89**)

As mentioned, cycloaddition reactions of ketenes also have a lot of literature precedent. They are unique in their propensity to undergo facile [2+2] cycloadditions with alkenes, alkynes and allenes, even when other reaction pathways are available. The Woodward-Hoffman analysis of these cycloadditions suggested that ketenes reacted with alkenes, termed ketenophiles in these reactions, by the perpendicular arrangement of the two moieties or via an antarafacial [$_{\pi}2_{a}$ + $_{\pi}2_{s}$] process (Figure 1.14).[42] Although this process does not occur thermally between two alkenes, it is an allowed process for a ketene and alkene because of the lesser steric demands of the ketene, as well as the favourable bonding interactions between both carbons on the alkene and the electron-deficient p orbital of the carbonyl carbon.[366]

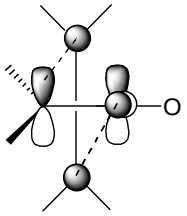
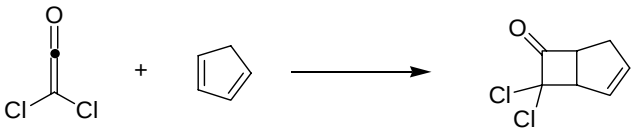


Figure 1.14: Overlap in the [2+2] cycloaddition of a ketene and an alkene.

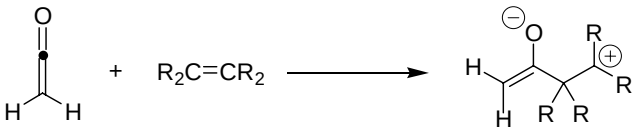
This reaction is facile when a ketene with electron-withdrawing groups is reacted with an electron-rich ketenophile, such as dichloroketene and cyclopentadiene, respectively (Scheme 1.51). The electron-withdrawing chlorines lower the energy of the ketene's LUMO, creating better overlap with the ketenophile's HOMO.[43]

Scheme 1.51



There is some debate over the mechanism of this process. Initially, the Woodward-Hoffman concerted mechanism was accepted as a $[_{\pi}2_a + _{\pi}2_s]$ cycloaddition reaction that was thermally allowed. However, in 1970 a counter proposal was made that the mechanism was a two-step process that involved a dipolar intermediate (Scheme 1.52).[44,45]

Scheme 1.52



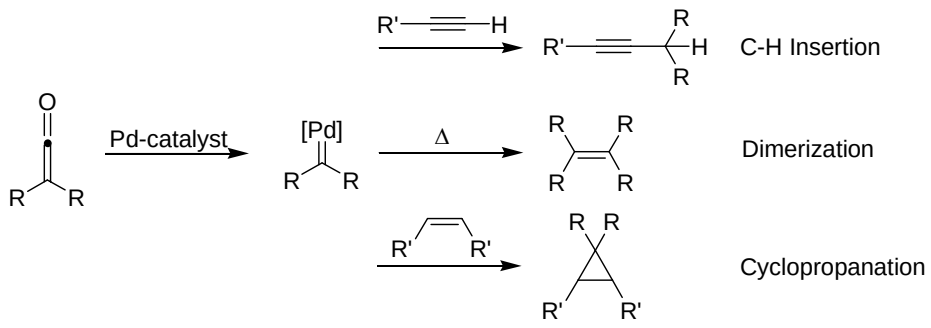
Many attempts have been made at determining whether or not this transformation proceeds by a concerted pathway or a step-wise one. However, in most cases the tests are ambiguous, as unsymmetrical concerted processes mimic the characteristics of a stepwise one.

The use of ketenes to generate metal-stabilized carbenes has very little literature precedent. This research proposal intends to further exploit the use of ketenes as palladium carbene precursors.

1.5 RESEARCH PLAN

Based on the literature precedent for the existence of palladium carbenes, methods to prepare these compounds and analyze their reactivity is proposed. The anticipated strategy for the preparation of palladium carbenes is the decomposition of diphenylketene according to the work done by Watanabe and co-workers (Section 1.3.8). Upon the formation of the proposed palladium carbene intermediate, it is expected to react in a fashion typical of metal carbenes and the reaction conditions will be tuned such that one reaction will be preferred (Scheme 1.53).

Scheme 1.53



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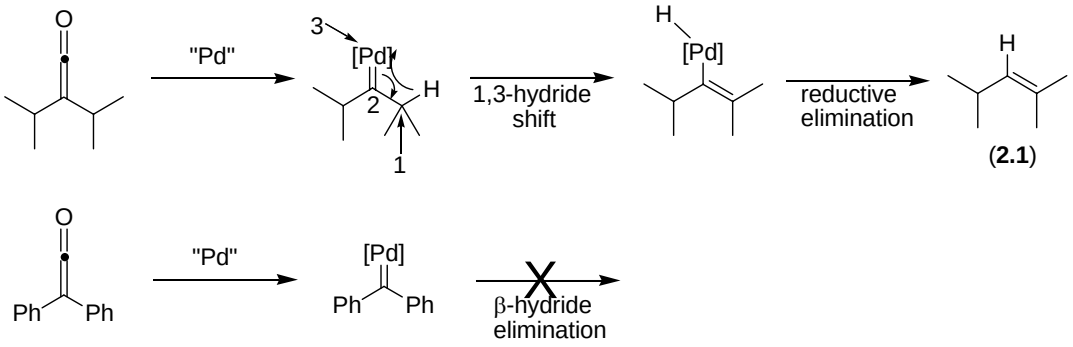
CHAPTER TWO

2.0 RESULTS AND DISCUSSION

2.1 PREPARATION OF PALLADIUM CARBENES

The crucial factor that needs to be considered for successful trapping of the palladium carbene is to ensure that cyclopropanation occurs preferentially over other, nonproductive pathways. The main competing pathway would likely be a 1,3-hydride shift with subsequent reductive elimination leading to olefin products (**2.1**) (Scheme 2.1).

Scheme 2.1



The use of diphenylketene prevents this reaction pathway as it does not contain any β-hydrogens. Using the method proposed by Watanabe and co-workers as a guideline for the formation of palladium carbenes, initial studies were done using their conditions: 1.0 equivalent of diphenylketene, 5 mol % tetrakis(triphenylphosphine)palladium(0), 0.2 M THF stirred at 120 ºC for 5 hours.[1] Trapping reagents (strained alkenes) for cyclopropanation will be present in a ten-fold excess in the reaction mixture.

2.2 REACTIVITY OF PALLADIUM CARBENES VIA DIPHENYLKETENE

As illustrated by Watanabe and co-workers, diphenylketene (**2.2**) is a precursor of palladium carbene ligands.[1] In order to examine specific reactivities such as

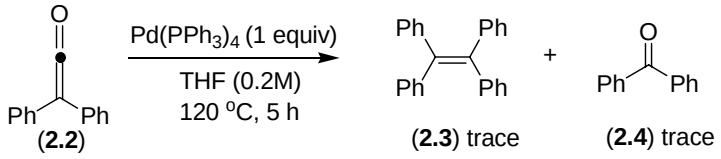
dimerization, C-H insertion and cyclopropanation, reaction conditions were such that one reaction should be favoured. Trimethylsilylacetylene (**2.5**) was used as the terminal alkyne because Watanabe and co-workers had previously shown this substrate to yield a C-H insertion (**2.6**) product in 78% yield. For cyclopropanation reactions the highly reactive norbornylene (**2.7**) was used. Initially, examination of the reactivity of these palladium carbenes was done using tetrakis(triphenylphosphine)palladium(0).

2.2.1 Reactivity Using Palladium(0)

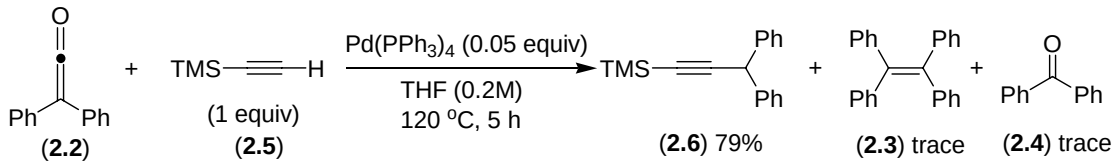
The following reactions were performed favouring dimerization, C-H insertion and cyclopropanation respectively (Scheme 2.2).

Scheme 2.2

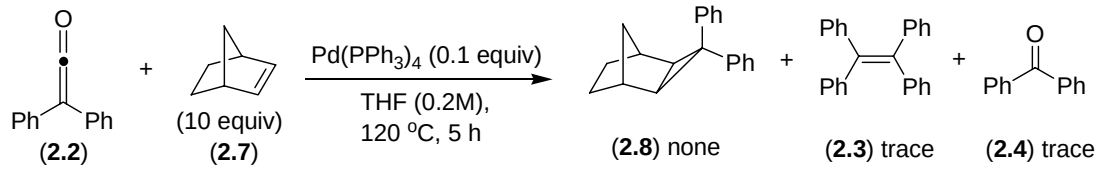
a) Dimerization:



b) C-H Insertion:

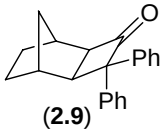


c) Cyclopropanation:



In the first reaction (Scheme 2.2a) the two products observed by GC-MS were the dimer (**2.3**) and benzophenone (**2.4**). They were not isolated as they formed in very small

amounts. This may indicate that the active palladium species requires coordination to either an olefin or an alkyne before forming the palladium carbene in sufficient amounts. Therefore, under dimerization or oxidation conditions, the reaction is sluggish since it does not occur in the presence of an alkene or an alkyne. When the reaction is quenched with oxygen product **2.4** is generated. The second reaction using conditions outlined by Watanabe and co-workers worked well for the C-H insertion of terminal alkynes and product **2.6** was isolated in a 79% yield (Scheme 2.2b). Again the formation of the dimer (**2.3**) and benzophenone (**2.4**) were present by GC-MS but not isolated as they were formed in small amounts. These conditions did not lead to the cyclopropanation of norbornylene (**2.7**) (Scheme 2.2c). In addition to products **2.3** and **2.4**, the [2+2] cycloadduct of diphenylketene and norbornylene (**2.9**) was also formed in the cyclopropanation reaction, as evident by GC-MS, ^{1}H NMR and ^{13}C NMR, however, the yield of its formation was not determined (Figure 2.1). Although cyclopropanation did not occur, the formation of dimer (**2.3**) and benzophenone (**2.4**) were observed by GC-MS and it was concluded that the palladium-carbene was being formed, however, its reactivity needed to be tuned.



(**2.9**)

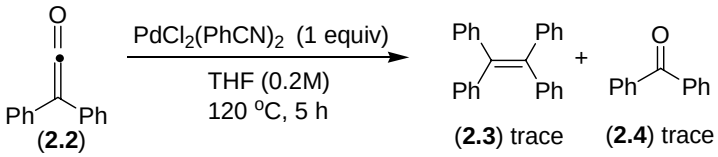
Figure 2.1 [2+2] cycloadduct of diphenylketene and norbornylene.

2.2.2 Reactivity Using Palladium(II)

The same set of reactions were run using a palladium(II) catalyst, $PdCl_2(PhCN)_2$ (Scheme 2.3).

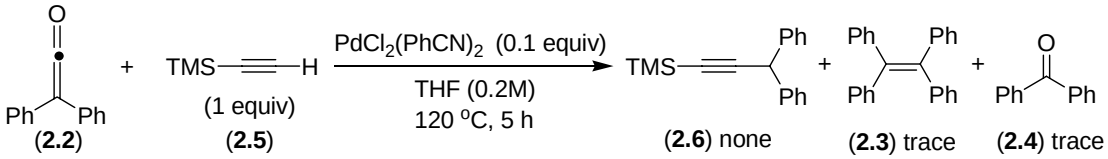
Scheme 2.3

a) Dimerization:



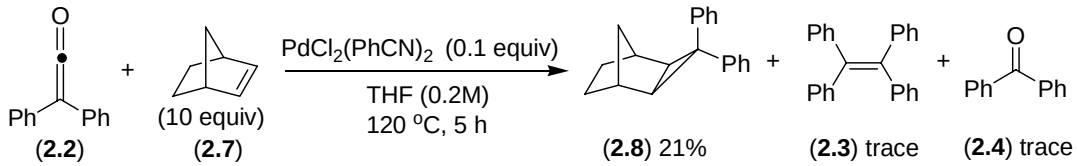
(**2.2**) (**2.3**) trace (**2.4**) trace

b) C-H Insertion:



(**2.2**) (**2.5**) (**2.6**) none (**2.3**) trace (**2.4**) trace

c) Cyclopropanation:



(**2.2**) (**2.7**) (**2.8**) 21% (**2.3**) trace (**2.4**) trace

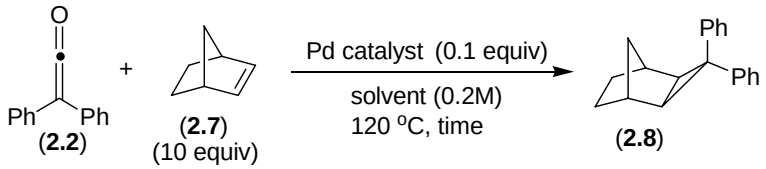
As with the previous conditions (Scheme 2.2), formation of the dimer (**2.3**) and benzophenone (**2.4**) was detected by GC-MS; however, these products were not isolated as they were formed in very small amounts (Scheme 2.3a). The palladium(II) catalyst did not promote C-H insertion and product **2.6** was not formed (Scheme 2.3b). However, evidence that the palladium carbene formed is illustrated by the formation of products **2.3** and **2.4** (Scheme 2.3b)). Finally, the cyclopropanation of norbornylene (**2.7**) afforded **2.8** in a 21% yield. This illustrated that the reactivity of this palladium carbene was strongly dependent on the oxidation state of the palladium catalyst used. In light of these results, the next step was to optimize the cyclopropanation reaction.

2.3 OPTIMIZATION OF CYCLOPROPANATION REACTION

2.3.1 Palladium Catalyst

In order to optimize the cyclopropanation reaction further other catalysts were investigated for this transformation as shown in Table 2.1. The solvent was changed to dichloroethane for complete solubility of the palladium catalysts. After the five hour reaction time, starting material was still observed, therefore the reaction time was increased to twenty-four hours.

Table 2.1: Optimization of Cyclopropanation: Palladium Catalysts.



Entry	Catalyst (10 mol%)	Solvent (0.2 M)	Reaction Time (h)	Yield of 2.8 (%)[a]
1	$Pd(PPh_3)_4$	THF	5	0
2	$Pd_2(dba)_3{\cdot}CHCl_3$	THF	5	0
3	$Pd(PPh_3)_4$	$(CH_2Cl)_2$	24	0
4	$Pd_2(dba)_3{\cdot}CHCl_3$	$(CH_2Cl)_2$	24	0
5	$PdCl_2(PPh_3)_2$	THF	5	9
6	$PdCl_2(PhCN)_2$	THF	5	21
7	$PdCl_2(PhCN)_2$	THF	24	22
8	$PdCl_2(PPh_3)_2$	$(CH_2Cl)_2$	5	Trace
9	$PdCl_2(PPh_3)_2$	$(CH_2Cl)_2$	24	6
10	$PdCl_2(PhCN)_2$	$(CH_2Cl)_2$	5	25
11	$PdCl_2(PhCN)_2$	$(CH_2Cl)_2$	24	50
12	$PdCl_2(CH_3CN)_2$	$(CH_2Cl)_2$	24	54
13	$Pd(OAc)_2$	$(CH_2Cl)_2$	24	17
14	$PdCl_2$(dppe)	$(CH_2Cl)_2$	24	Trace
15	$PdCl_2$(dppf)	$(CH_2Cl)_2$	24	0
16	$PdCl_2$	$(CH_2Cl)_2$	24	Trace
17	PdI_2	$(CH_2Cl)_2$	24	7
18	$PdBr_2$	$(CH_2Cl)_2$	24	17
19	$Pd(OTf)_2$	$(CH_2Cl)_2$	24	0
20	$Pd(OCOCF_3)_2$	$(CH_2Cl)_2$	24	26

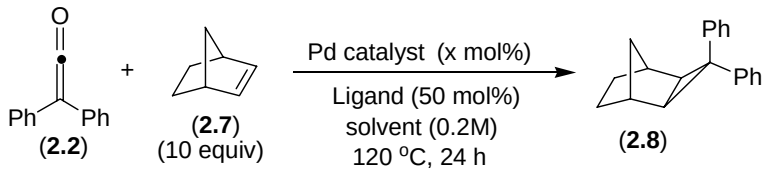
[a]Trace amounts indicates it was present by GC-MS but not isolated during purification.

In all cases, trace amounts of tetraphenylethylene (**2.3**) and benzophenone (**2.4**) were observed by GC-MS, supporting the formation of a palladium carbene intermediate, in addition to the [2+2] cycloadduct between the ketene and norbornylene (**2.9**) as determined by GC-MS, ^{1}H NMR, and ^{13}C NMR. From these results, it can be concluded that the oxidation state of the palladium catalyst was the most important determinant of carbene reactivity. In either THF or $(CH_2Cl)_2$, palladium(0) sources gave no trace of cyclopropane (**2.8**) (Entries 1-4). On the other hand, most palladium(II) catalysts gave at least small amounts of the cyclopropane, with the exception of the very bulky $PdCl_2$(dppf) (Entry 15). Nearly complete inhibition of the reaction by phosphine was observed (Entries 5, 8, 9, 14), while other palladium(II) sources such as palladium-halides, palladium-carboxylates and palladium-triflates were moderately more competent catalysts (Entries 13, 15-20). The best results were obtained using palladium(II) catalysts bearing nitrile ligands (Entries 6, 7, 10-12).

2.3.2 Reaction Conditions

Palladium(II) catalysts containing nitrile ligands were used in further optimization studies in terms of solvent, catalyst loading, and the addition of ligand (Table 2.2). In addition to the cyclopropane (**2.8**), all crude reaction mixtures contained the [2+2] cycloadduct (**2.9**) and trace amounts of benzophenone (**2.4**) and tetraphenylethylene (**2.3**) as determined by GC-MS and ^{1}H NMR, however, these products were not isolated and their yields were not determined.

Table 2.2: Optimization of Cyclopropanation: Reaction Conditions.



Entry	Catalyst	Catalyst Loading (mol%)	Ligand (50 mol%)	Solvent (0.2 M)	Yield of 2.8 (%)
1	$PdCl_2(PhCN)_2$	20	N/A	$(CH_2Cl)_2$	49
2	$PdCl_2(PhCN)_2$	5	N/A	$(CH_2Cl)_2$	34
3	$PdCl_2(PhCN)_2$	10	N/A	PhCl	31
4	$PdCl_2(PhCN)_2$	10	N/A	$PhCH_3$	30
5	$PdCl_2(CH_3CN)_2$	10	N/A	CH_3CN	14
6	$PdCl_2(PhCN)_2$	10	PhCN	DMF	14
7	$PdCl_2(CH_3CN)_2$	10	CH_3CN	DMF	12
8	$PdCl_2(PhCN)_2$	10	PhCN	$(CH_2Cl)_2$	62
9	$PdCl_2(MeCN)_2$	10	CH_3CN	$(CH_2Cl)_2$	43

Increasing the catalyst loading had essentially no effect on the reaction, while lowering it to 5 mol% was detrimental to the yield (Entries 1, 2); changing to aromatic solvents also caused a yield decrease (Entries 3, 4). In an effort to exploit the advantageous chelating effects of nitrile ligands CH_3CN was used as solvent, unfortunately, a drop in yield was observed (Entry 5). Highly polar DMF was not suitable for this reaction (Entries 6, 7). However, returning to the optimal solvent, $(CH_2Cl)_2$, and adding further ligand, the beneficial effect of added benzonitrile over acetonitrile was exemplified (Entries 8 and 9).

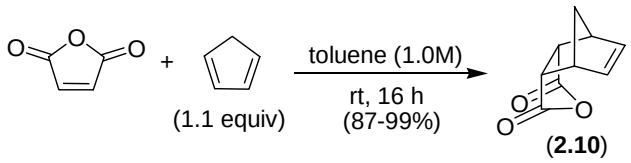
2.4 SCOPE OF CYCLOPROPANATION

In order to assess the chemical compatibility of palladium(II) carbenes in cyclopropanation reactions for further development, models containing a wide variety of functional groups were prepared.

2.4.1 Preparation of Olefins

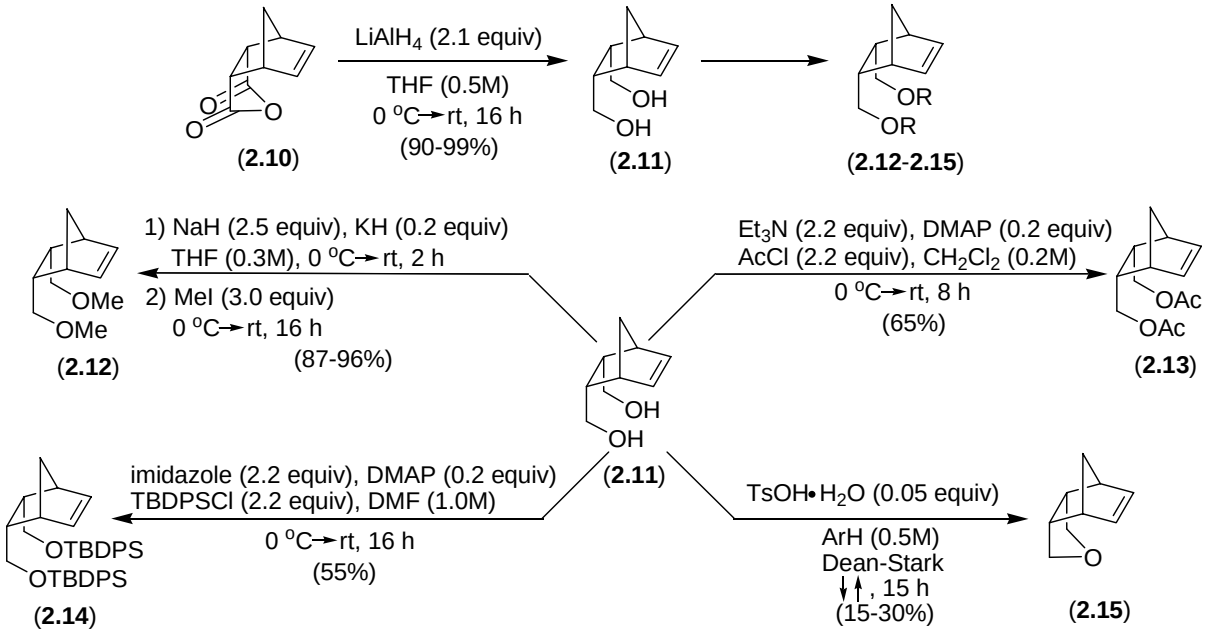
When considering other models for this reaction norbornylene derivatives were used due to the success of cyclopropanating norbornylene during preliminary and optimization experiments. The functional groups examined were various ethers, methyl ester, an anhydride, and different aryl groups. The first set of substrates could all be derived from anhydride **2.10**, which is easily attained by the [4+2] cycloaddition between maleic anhydride and cyclopentadiene (Scheme 2.4).[2]

Scheme 2.4



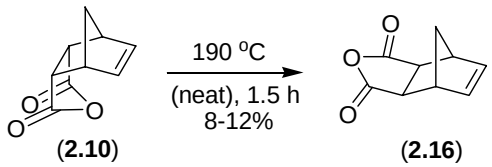
Reduction of **2.10** with $LiAlH_4$ generated the diol (**2.11**) could then be further functionalized to afford methyl ether (**2.12**)[3], acetate (**2.13**)[4], silyl ether (**2.14**)[5], and cyclic ether (**2.15**) (Scheme 2.5).

Scheme 2.5



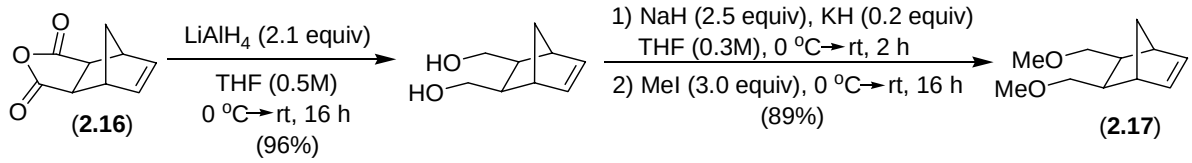
In addition to the *endo* version of these models, the *exo* version of these substrates was also examined (Scheme 2.6).[6]

Scheme 2.6



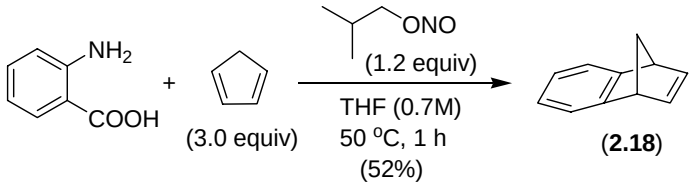
Since purification of **2.16** was quite tedious, it was decided to prepare only one *exo* model, the high yielding methyl ether (**2.17**) (Scheme 2.7).[3]

Scheme 2.7



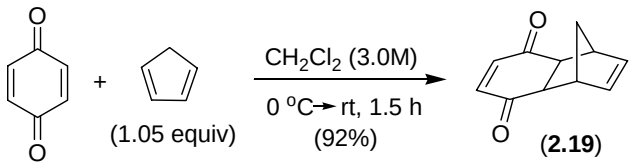
Benzannulated norbornylene derivatives were also prepared. The unfunctionalized aryl norbornylene dervivative (**2.18**), was prepared *via* the [4+2] cycloaddition of cyclopentadiene and benzyne, which was generated *in situ* (Scheme 2.8).[7]

Scheme 2.8



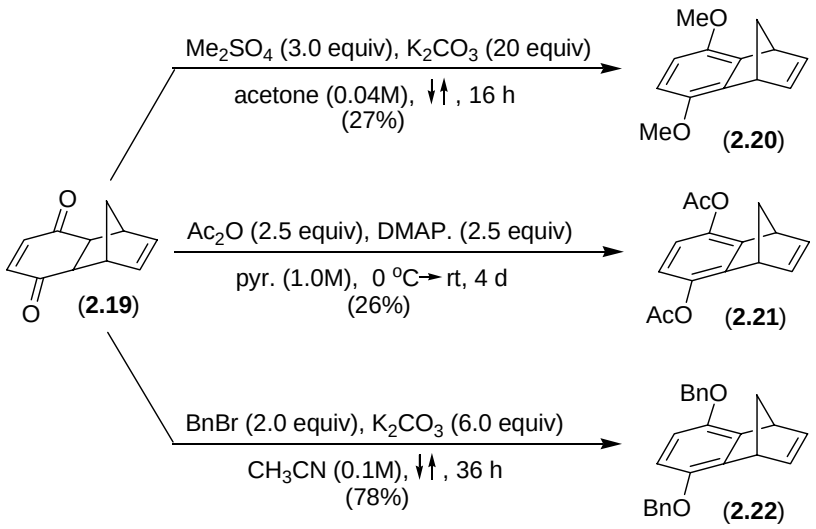
Functionalized aryl norbornylene derivatives were all prepared from a common intermediate (**2.19**) derived from the [4+2] cycloaddtion between benzoquinone and cyclopentadiene (Scheme 2.9).[8]

Scheme 2.9



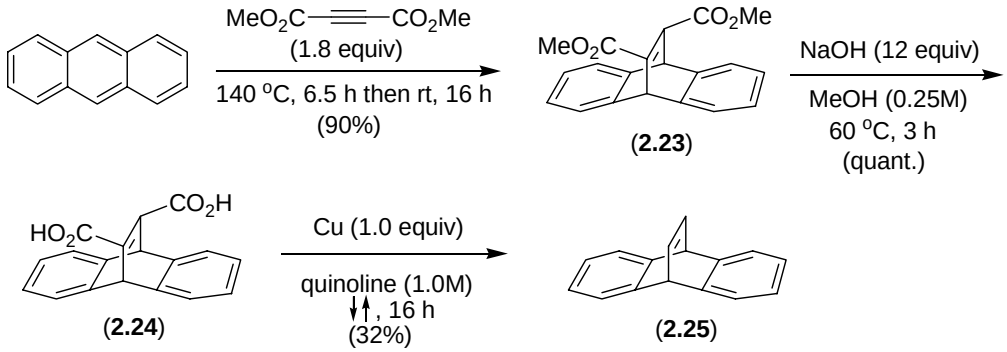
The functionalization of **2.19** generated three different aryl olefins: aryl methyl ether (**2.20**)[9], aryl acetate (**2.21**)[10] and aryl benzyl ether (**2.22**)[11] (Scheme 2.10).

Scheme 2.10



The less strained [2.2.2]bicyclo system was also examined. Derived from anthracene, olefin **2.25**, was prepared in three steps (Scheme 2.11). Anthracene underwent a [4+2] cycloaddition reaction with dimethyl acetylenedicarboxylate to afford the diester (**2.23**). Quantitative conversion to the diacid (**2.24**) was achieved via saponification. Finally, decarboxylation to the olefin (**2.25**) was achieved in the presence of activated copper and freshly distilled quinoline.[12]

Scheme 2.11

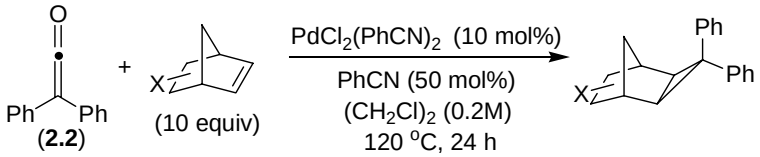


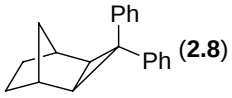
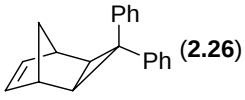
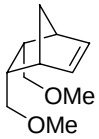
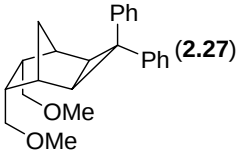
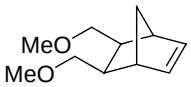
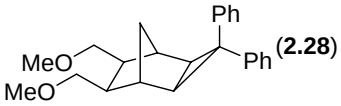
In addition to these prepared olefins (**2.10**, **2.12**-**2.15**, **2.17**, **2.18**, **2.20**-**2.22**, **2.25**) we also examined commercially available norbornadiene.

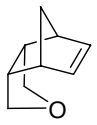
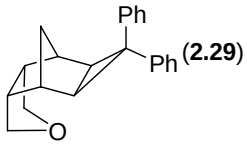
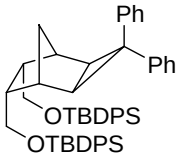
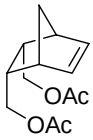
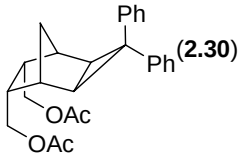
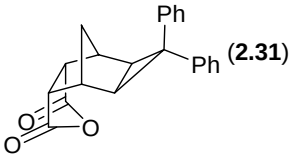
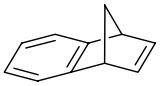
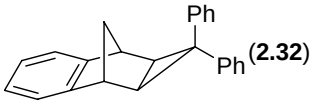
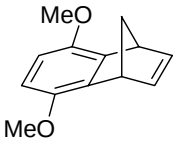
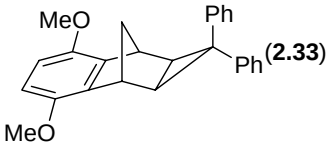
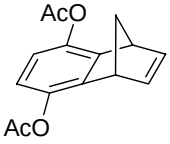
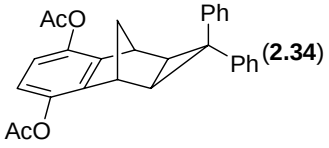
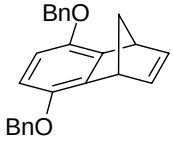
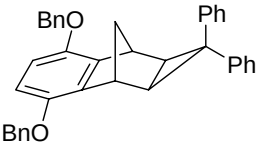
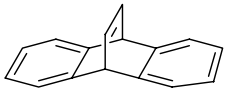
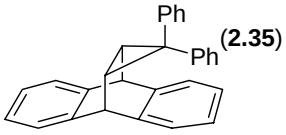
2.4.2 Cyclopropanation of Olefins

With these olefins in hand, trapping of the palladium carbene under optimized conditions was attempted. The results are summarized in Table 2.3.

Table 2.3: Cyclopropanation of Other Olefins: Reaction Scope.



Entry	Substrate	Product	Yield (%)
1		 (**2.8**)	62
2		 (**2.26**)	69
3		 (**2.27**)	52
4		 (**2.28**)	49

5		 (**2.29**)	50
6			0
7		 (**2.30**)	53
8		 (**2.31**)	53
9		 (**2.32**)	51
10		 (**2.33**)	38
11		 (**2.34**)	44
12			0
13		 (**2.35**)	42

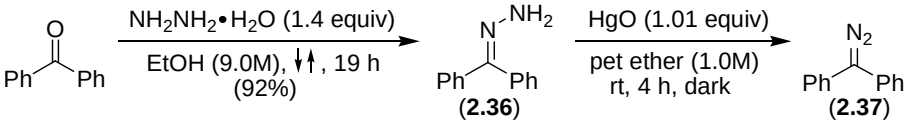
The reaction proceeded in the presence of alkenes, alkyl ethers, esters, and anhydrides (Entries 2-5, 7, 8). The desired product was not obtained in the presence of silyl ethers (Entry 6). This could be the result of an interaction between the palladium and the silyl group, inhibiting the desired reaction. Benzannulated norbornyl derivatives were competent cyclopropanation substrates (Entries 9-11), with the exception of the benzyl

ether (Entry 12). It could be envisioned that palladium may interact with the benzyl ether preventing the formation of the palladium carbene or hindering the carbene from further reacting. This is plausible since palladium is used in the deprotection of benzyl ethers. In addition, the reaction of less strained and more sterically hindered [2.2.2]-bicyclooctene system, although in moderate yield, illustrated the high reactivity of this palladium carbene.

2.4.3 Independent Preparation of Cyclopropanes

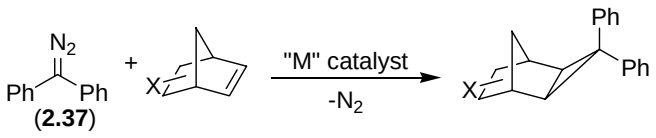
For characterization purposes it was necessary to prepare these cyclopropane products independently by another method. Using this methodology, the formation of various side-products and left-over olefin made purification tedious. Although product yields were attainable based on impurity identification and ^{1}H NMR, the purity of the compounds was not sufficient for publication. The most apparent method of preparation was via the diazo precursor (**2.37**), which could easily be generated from benzophenone via the hydrazone (**2.36**) (Scheme 2.12).[13]

Scheme 2.12

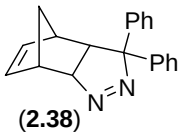


In the presence of a metal catalyst and olefin, it was presumed that the diazo compound (**2.37**) would undergo cyclopropanation via the loss of nitrogen (Scheme 2.13).

Scheme 2.13



Initially, the reaction was performed using catalytic Cu(acac). When the olefin was a liquid or an oil it was used as solvent in a 10-fold excess. When the olefin was solid, it was dissolved in a minimal amount of benzene. The reaction was run using norbornadiene as solvent, in a 10-fold excess. Instead of the expected cyclopropane, compound **2.38** was isolated instead (Figure 2.2).

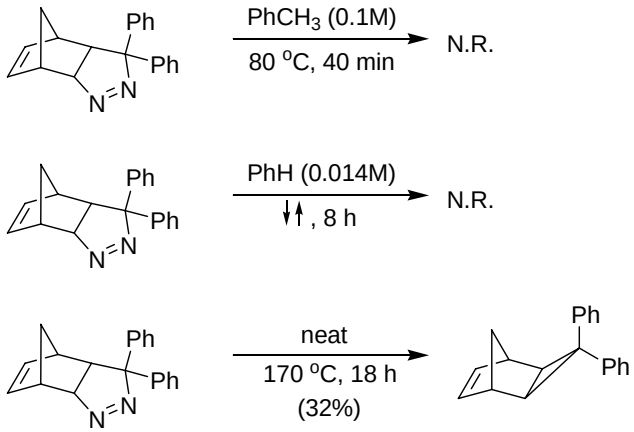


(**2.38**)

Figure 2.2 Product formed from reaction of norbornadiene and diphenyldiazomethane.

Therefore, instead of the expected [2+1] cycloaddition of the metal carbene and the olefin, the [3+2] cycloadduct (**2.38**) was attained. Thus, the diazo compound was undergoing a 1,3-dipolar cycloaddition rather then decomposing to a metal carbene. In an attempt to circumvent product **2.38**, other metal catalysts, including $Rh_2(OAc)_4$, $Pd(OAc)_2$ and $CuSO_4$, were tried. All efforts yielded the same outcome, thus, the cyclopropane was generated from **2.38** via the loss of nitrogen. Attempts to expel nitrogen from **2.38** are shown in Scheme 2.14.

Scheme 2.14

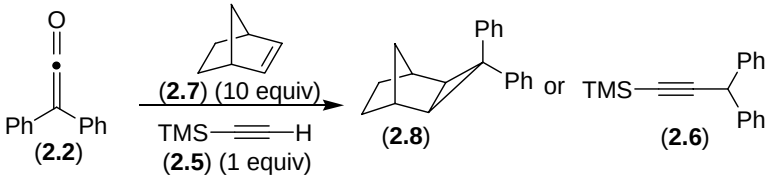


Heating **2.38** neat at 170 ºC for 18 h[14] afforded the desired product with 55% conversion and 32% isolated yield. This method was used to prepare cyclopropanes **2.8**, and **2.26-2.35**, the yields were not calculated as only acquiring the material was necessary. This allowed their identity to be confirmed and comparison to the impure material from the palladium catalyzed reaction was done to ensure proper peak assignment.

2.5 COMPETITION STUDIES

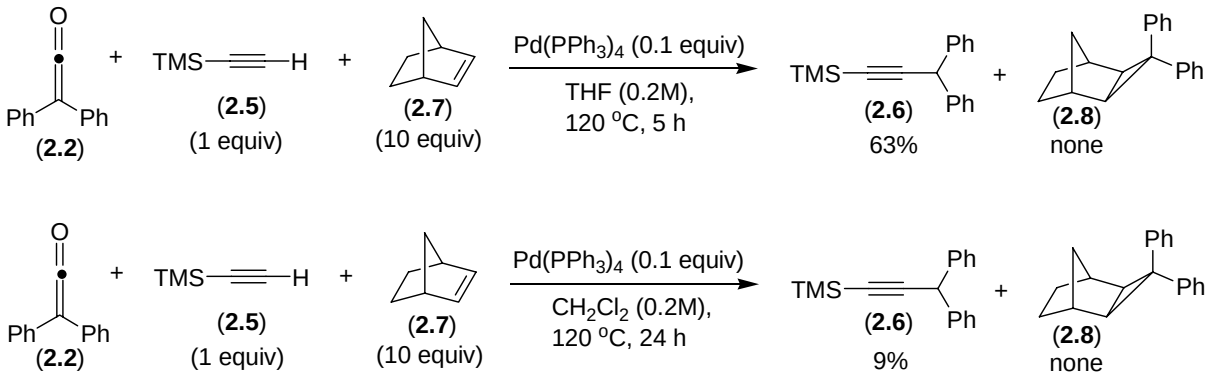
During the optimization studies it became apparent that the oxidation state of the metal carbene was the greatest determinant of its reactivity. The difference between palladium(0) and palladium(II) carbenes was further emphasized in the competition studies outlined in Scheme 2.15

Scheme 2.15



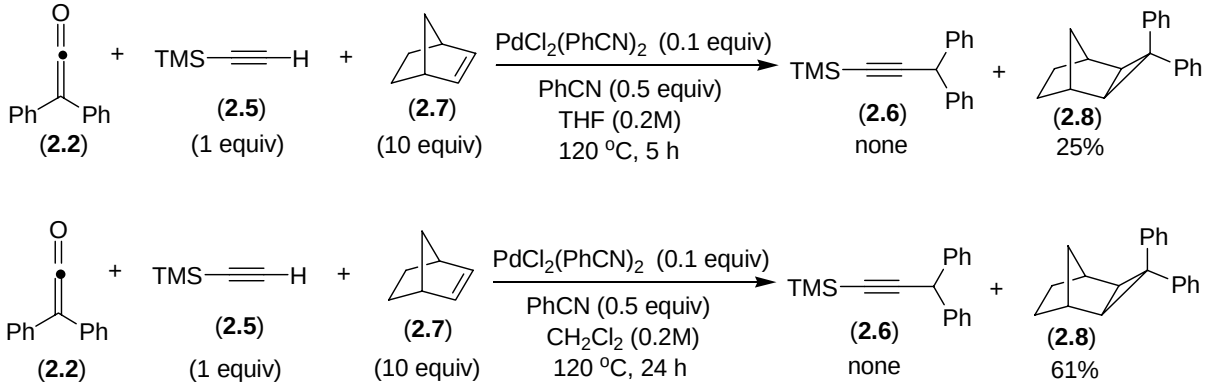
In these, an equimolar amount of trimethylsilylacetylene and a 10-fold excess of norbornylene was reacted with diphenylketene under either Watanabe's C-H insertion conditions (Scheme 2.16) or the cyclopropanation conditions developed (2.17).

Scheme 2.16



Under both sets of conditions, Pd(0) gave exclusively the product of C-H insertion. The yield of the acetylenic material using Watanabe's optimized reaction conditions was near that achieved in the original publication, with a slight drop attributed to the competitive formation of **2.9**.

Scheme 2.17



The replacement of the palladium(0) with a palladium(II) catalyst and addition of ligand afforded the cyclopropane exclusively.

The decrease in yield when the solvent is changed from the optimal reaction conditions highlights the interplay between catalyst, ligand, solvent, and reaction time to achieving maximum yield from the same reactant. These results emphasize the high

chemoselectivity of both processes and the different reactivity achievable by changing the oxidation state of the palladium-carbene.

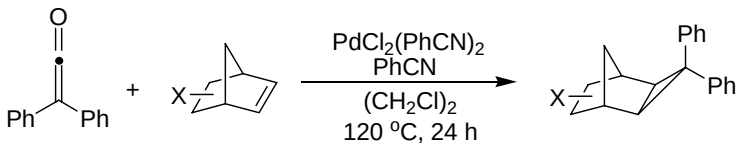
The observed selectivity can be explained by the notion that palladium(II) carbenes act as electrophiles, while palladium(0) carbenes exhibit nucleophilic behaviour. It has been proposed that cyclopropanation occurs by the nucleophilic attack of the olefin onto the metal-carbene in diazo-based cyclopropanations. This could translate to the diphenylketene system and account for why palladium(0) carbenes do not cyclopropanate under these reaction conditions. However, this is not a general statement of palladium carbene cyclopropanation reactions and may be specific to diazo-based and ketene-based precursors.

2.5 EXPERIMENTAL SECTION

General Methods

All reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere. All reaction solvents were obtained from a solvent system or freshly distilled. Dichloroethane, benzonitrile and norbornadiene were distilled over CaH_2 and degassed by freeze-pump-thaw method (three cycles).[15] All commercially available reagents were from Sigma-Aldrich and used without further purification. The palladium catalysts were purchased from Strem and also used without further purification. ^{1}H NMR spectra were referenced to residual ^{1}H shift in $CDCl_3$ (7.24 ppm). ^{13}C NMR spectra were referenced to residual ^{13}C shift in $CDCl_3$ (77.0 ppm). Carbons were assigned based on Dept 90 and Dept 135 experiments. Flash chromatography was performed using 230-400 mesh silica gel. Melting points are uncorrected. High resolution mass spectra were run by Dr. R. Smith at the University of Waterloo with a source temperature of 200 ºC, mass resolution of 9000, and electron energy of 70 eV.

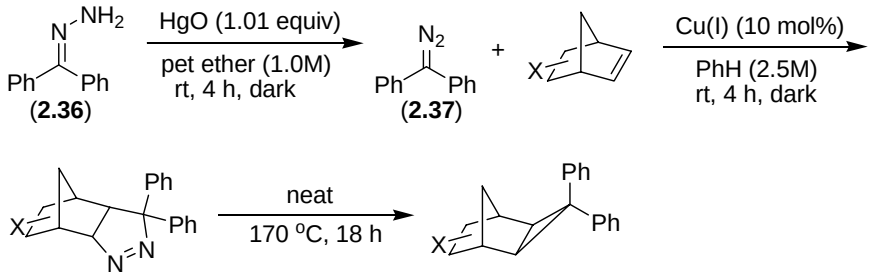
Preparation of Cyclopropanes – General Procedure A



A flame-dried resealable Schlenk tube was charged with diphenylketene (**2.2**) (1.0 equiv), followed by palladium catalyst (0.1 equiv), benzonitrile (0.5 equiv), olefin (10 equiv) and solvent (0.2 M) in a glove box. The tube was sealed and allowed to react in a temperature controlled oil bath at 120 ºC for 24 h. After 24 h, the crude material was

cooled to room temperature and filtered through a pad of silica using dichloromethane as the eluent. Purification was achieved using flash chromatography.

Preparation of Cyclopropanes – General Procedure B[13,14]

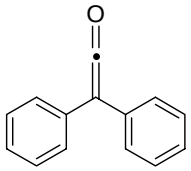


Using flame-dried glassware, benzophenone (25 g, 139.9 mmol, 1.0 equiv) was diluted in absolute EtOH (16 mL, 9.0M) and heated to reflux. Hydrazine monohydrate (9.7 mL, 199.8 mmol, 1.4 equiv) was added drop-wise to the mixture and the reaction was allowed to reflux for 19 h. It was then cooled to 0 ºC and filtered; the crude solid (**2.36**) was used without further purification. The hydrazone (**2.36**) (2.0 g, 10.19 mmol, 1.0 equiv) was treated with yellow HgO (2.24 g, 10.34 mmol, 1.01 equiv) and diluted with petroleum ether (10.2 mL, 1.0M). The reaction mixture was covered with aluminum foil and stirred at rt for 4 h. After 4 h the crude diazo compound (**2.37**) was filtered and concentrated to afford purple needles which were used immediately (Note: storage of this compound is potentially dangerous and decomposition occurs quickly). Intermediate **2.37** was diluted in either the olefin (10 equiv) or benzene (5 mL, 2.0M) and the olefin (10 equiv), followed by the Cu(I) catalyst (0.1 equiv). The reaction was covered in aluminum foil and stirred at rt for 16-20 h. The reaction was complete when the solution had changed from a purple colour to green. The reaction was diluted in EtOAc (4X volume) and H_2O (4X volume) and extracted with EtOAc (3X). The combined organic layers were washed

once with H_2O and brine, then dried over $MgSO_4$, filtered and concentrated. The crude residue was loaded onto silica and purified by flash chromatography. The purified compound was then heated neat, in a flask equipped with an air condenser, to 170 ºC. The reaction was cooled to rt and loaded onto silica and purified by flash chromatography.

Substrate Preparation – Specific Procedures

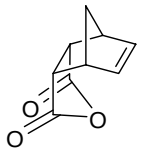
Diphenylketene[16] (2.2)



Diphenylacetic acid (20.0 g, 94.2 mmol, 1.0 equiv) was dissolved in freshly distilled benzene (60 mL, 1.6 M) and heated to reflux. Oxalyl chloride (41.1 mL, 471 mmol, 5.0 equiv) was added dropwise over 30 min and the reaction was refluxed for 8 h. The volatiles were evaporated and the crude material was redissolved in benzene and the volatiles were again evaporated (to ensure removal of oxalyl chloride and HCl). The residue was dissolved in hot hexanes, activated charcoal and refluxed for 5 min. The hot mixture was filtered and cooled to 0 ºC. After 2 h the white solid was filtered and rinsed with cold hexanes (16.3 g, 75%). The acid chloride was generally used immediately or could be stored at 0 ºC under a nitrogen atmosphere. Diphenylacetyl chloride (16.3 g, 79.7 mmol, 1.0 equiv) was dissolved in diethyl ether (140 mL, 0.5 M) and cooled to 0 ºC. Freshly distilled triethylamine (11.1 mL, 79.9, 1.0 equiv) was added dropwise over 30

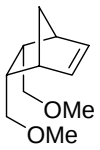
min. When addition was complete the flask was stoppered and stored at 0 ºC for 16 h. The reaction mixture was warmed to rt and the salts were filtered and washed with diethyl ether until washings were colourless. The mother liquor was concentrated and the oil was distilled via Kugelrhor distillation to afford an orange-yellow oil at b.p. 118-120 ºC (1 mm) (11.6 g, 75%). The product could be stored up to 30 days at -10 ºC in the glove box before substantial decomposition or trimerization occurred. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (5H, t, *J* = 7.7 Hz), 7.28 (5H, d, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.1 (C), 130.759 (C), 129.2 (CH), 127.7 (CH), 126.2 (CH), 46.8 (C); HRMS (EI) expected for $C_{14}H_{10}O$: 194.0732. Found for $C_{14}H_{10}O$: 194.0731.

endo-4-oxa-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (2.10)



Maleic anhydride (23.0 g, 234.6 mmol, 1.0 equiv) was diluted in toluene (235 mL, 1.0 M). Freshly cracked cyclopentadiene (21.1 mL, 258.0 mmol, 1.1 equiv) was added dropwise at rt and the reaction was stirred for 15 h. The volatiles were evaporated and the white solid required no further purification (36.9 g, 96%). M. p. 164.5-165.5 ºC ($CDCl_3$) (164-166 ºC)[17]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.30 (2H, s), 3.56 (2H, t, *J* = 12.1 Hz), 3.49 (2H, s), 1.77 (1H, d, *J* = 9.0 Hz), 1.55 (1H, d, *J* = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2 (C), 135.5 (CH), 52.7 (CH_2), 47.1 (CH), 46.1 (CH); HRMS (EI) expected for $C_9H_8O_3$: 164.0473. Found for $C_9H_8O_3$: 164.0468.

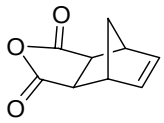
***endo,endo*-5,6-bis-Methoxymethyl-bicyclo[2.2.1]hept-2-ene (2.12)**



A flame-dried flask was charged with $LiAlH_4$ (9.6 g, 252.0 mmol, 2.1 equiv) and cooled to 0 ºC. THF (240 mL, 0.5 M) was added dropwise and the suspension was stirred at 0 ºC for 5 min. Olefin **2.10** (19.7 g, 120.0 mmol, 1.0 equiv) was added portion-wise over 10 min and the reaction mixture was allowed to warm to rt and stirred an additional 15 h. The crude mixture was cooled to 0 ºC and 9.6 mL deionized H_2O was added dropwise, followed by 9.6 mL 15% NaOH and then 28.7 mL deionized H_2O. The mixture was filtered and the mother liquor concentrated to yield a white solid (36.9 g, 95%). The crude diol (**2.11**) was used without any further purification. A flame-dried flask was charged with NaH (7.8 g, 194.5 mmol, 2.5 equiv) and KH (1.8 g, 15.6 mmol, 0.2 equiv) and the mineral oil was removed by washing with hexanes three times. The flask was cooled to 0 ºC and THF (200 mL) was added slowly. In a separate flask **2.11** (12.0 g, 77.8 mmol, 1.0 equiv) was diluted in THF (60 mL) and cannulated over the suspension at 0 ºC. The reaction mixture was warmed to rt and stirred for 2 h. The reaction was cooled to 0 ºC and MeI (14.6 mL, 233.5 mmol, 3.0 equiv) was added dropwise. The reaction was warmed to rt and stirred for 18 h. The reaction mixture was cooled to 0 ºC and quenched with MeOH (added dropwise until solution became transparent) after which the volatiles were evaporated. The crude mixture was diluted with H_2O and extracted three times with Et_2O. The combined organic layers were washed once with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography using hexanes:ethyl acetate (95:5) as eluent to give **2.12** as a clear oil (14.2 g, 89%); ^1H

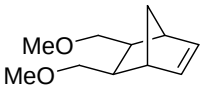
NMR ($CDCl_3$, 300 MHz) δ 6.10 (2H, s), 3.27 (6H, s), 3.15 (2H, dd, *J* = 9.1, 5.9 Hz), 2.97 (2H, t, *J* = 8.9 Hz), 2.88 (2H, s), 2.43 (2H, br t, *J* = 5.5 Hz), 1.44 (1H, d, *J* = 8.3 Hz), 1.28 (1H, d, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.2 (CH), 72.8 (CH_2), 58.7 (CH_3), 49.0 (CH_2), 45.5 (CH), 41.4 (CH); HRMS (EI) expected for $C_{11}H_{18}O_2$: 182.1307. Found for $C_{11}H_{18}O_2$: 182.1300.

exo-4-oxa-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (2.16)



A flame-dried flask equipped with condenser was charged with the *endo*-anhydride (**2.10**) (9.5 g, 57.9 mmol) and heated to 190 ºC neat for 1.5 h. The crude residue was cooled to rt and purified by flash chromatography using a gradient of hexanes:ethyl acetate (90:10 → 60:40) as eluent to afford **2.16** as a white solid (1.0 g, 10.3%). M. p. 140.5-141.5 ºC ($CDCl_3$) (140-142 ºC); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.31 (2H, s), 3.44 (2H, s), 2.98 (2H, s), 1.65 (1H, d, *J* = 10.3 Hz), 1.43 (1H, d, *J* = 10.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6 (C), 137.9 (CH), 48.7 (CH), 46.8 (CH), 44.1 (CH_2); HRMS (EI) expected for $C_9H_8O_3$: 164.0473. Found for $C_9H_8O_3$: 164.0472.

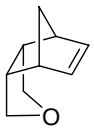
exo,exo-5,6-bis-Methoxymethyl-bicyclo[2.2.1]hept-2-ene (2.17)



A flame-dried flask was charged with $LiAlH_4$ (2.7 g, 70.4 mmol, 2.1 equiv) and cooled to 0 ºC. THF (67 mL, 0.5 M) was added dropwise and the suspension was stirred at 0 ºC for 5 min. Olefin (**2.16**) (5.5 g, 33.5 mmol, 1.0 equiv) was added portion-wise over 10 min

and the reaction mixture was allowed to warm to rt and stirred for an additional 15 h. The crude mixture was cooled to 0 ºC and 2.7 mL of deionized H_2O was added dropwise, followed by 2.7 mL of 15% NaOH and then 8.1 mL of deionized H_2O. The mixture was filtered and the mother liquor concentrated to yield a white solid (36.9g, 95%). The crude diol was used without any further purification. A flame-dried flask was charged with NaH (3.4 g, 84.3 mmol, 2.5 equiv) and KH (0.77 g, 6.74 mmol, 0.2 equiv) and the mineral oil was removed via washing three times with hexanes. The flask was cooled to 0 ºC and THF (100 mL) was added slowly. In a separate flask the crude diol (5.2 g, 33.7 mmol, 1.0 equiv) was diluted in THF (12 mL) and cannulated over the suspension at 0 ºC. The reaction mixture was warmed to rt and stirred for 2 h. The reaction was cooled to 0 ºC and MeI (6.3 mL, 101.2 mmol, 3.0 equiv) was added dropwise. The reaction was warmed to rt and stirred for 18 h. The reaction mixture was cooled to 0 ºC and quenched with MeOH (until reaction mixture turned transparent) after which the volatiles were evaporated. The crude mixture was diluted with H_2O and extracted three times with Et_2O. The combined organic layers were washed once with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography using hexanes:ethyl acetate (95:5) as eluent to give **2.17** as a clear oil (5.5 g, 89%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.12 (2H, s), 3.50 (2H, dd, J = 9.1, 5.1 Hz), 3.32 (6H, s), 3.21 (2H, t, J = 8.8 Hz), 2.72 (2H, s), 1.75 (2H, br t, J = 4.1 Hz), 1.44 (1H, d, J = 8.9 Hz), 1.27 (1H, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3 (CH), 74.0 (CH_2), 58.7 (CH_3), 44.7 (CH), 42.6 (CH_2), 40.4 (CH); HRMS (EI) expected for $C_{11}H_{18}O_2$: 182.1307, $C_{11}H_{18}O_2$ - C_4H_3O: 150.1045. Found for $C_{11}H_{18}O_2$ - C_4H_3O: 150.1042.

***Endo*-4-Oxa-tricyclo[5.2.1.0^{2,6}]dec-8-ene (2.15)**



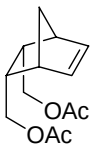
A flame-dried flask was charged with diol (**2.11**) (5.0 g, 32.4 mmol, 1.0 equiv), TsOH·H_2O (0.31 g, 1.62 mmol, 0.05 equiv) and benzene (65 mL, 0.5 M). The reaction mixture was equipped with a Dean-Stark trap and heated to reflux for 20 h. The water was removed and the reaction mixture was cooled to rt. After removing the volatiles the residue was diluted with Et_2O and saturated $NaHCO_3$. The crude mixture was extracted three times with Et_2O and the combined organic layers were washed once with saturated $NaHCO_3$, H_2O, brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography using hexanes:ethyl acetate (95:5) as eluent to give **2.15** as a white solid (0.97 g, 22%). M. p. 57-58 ºC ($CDCl_3$) (58-60 ºC)[18]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.18 (2H, s), 3.57-3.52 (2H, m), 3.40 (2H, dd, *J* = 9.4, 2.0 Hz), 2.87-2.83 (4H, m), 1.50 (1H, d, *J* = 8.1 Hz), 1.41 (1H, d, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.0 (CH), 70.0 (CH_2), 52.6 (CH_2), 47.9 (CH), 45.8 (CH); HRMS (EI) expected for $C_9H_{12}O$: 136.0888. Found for $C_9H_{12}O$: 136.0883.

***Endo,endo*-5,6-bis-*tert*-Butyldiphenylsiloxymethyl-bicyclo[2.2.1]hept-2-ene (2.14)**

A flame-dried flask was charged with diol (**2.11**) (2.0 g, 13.0 mmol, 1.0 equiv), imidazole (2.1 g, 31.1 mmol, 2.4 equiv), DMAP (0.32 g, 2.59 mmol, 0.2 equiv), and DMF (13 mL, 1.0 M) and cooled to 0 ºC. TBDPSCl (6.6 mL, 25.9 mmol, 2.0 equiv) was added

dropwise and slowly brought to r.t. where it was stirred an additional 16 h. The reaction mixture was diluted in H_2O and extracted with CH_2Cl_2:hexanes (1:9) twice. The combined organic layers were washed once with H_2O and brine then dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography using hexanes:ethyl acetate (95:5) as eluent to give **2.14** as a clear oil (3.0 g, 37%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (8H, td, *J* = 7.9, 1.4 Hz), 7.43-7.28 (12H, m), 5.91 (2H, s), 3.58 (2H, dd, *J* = 9.9, 5.9 Hz), 3.24 (2H, t, *J* = 9.2 Hz), 2.97 (2H, s), 2.49 (2H, br s), 1.46 (1H, d, *J* = 8.1 Hz), 1.34 (1H, d, *J* = 8.1 Hz), 1.01 (18H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.5 (CH), 135.5 (CH), 135.2 (CH), 134.0 (C), 129.4 (CH), 129.4 (CH), 127.5 (CH), 64.0 (CH_2), 48.9 (CH_2), 45.5 (CH), 44.3 (CH), 26.8 (CH_3), 19.2 (C); HRMS (EI) expected for $C_{41}H_{50}O_2Si_2$ – (C_4H_9): 573.2645. Found for $C_{41}H_{50}O_2Si_2$ – (C_4H_9): 573.2645.

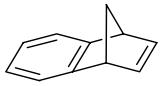
***endo,endo*-5,6-bis-Acetoxymethyl-bicyclo[2.2.1]hept-2-ene (2.13)**



A flame-dried flask was charged with diol **2.11** (10.0 g, 64.9 mmol, 1.0 equiv) and diluted with CH_2Cl_2 (324 mL, 0.2 M). The flask was cooled to 0 ºC and Et_3N (19.9 mL, 142.7 mmol, 2.2 equiv), DMAP (18.2 g, 149.2 mmol, 2.3 equiv) and acetyl chloride (10.1 mL, 142.7 mmol, 2.2 equiv) were added. The reaction was allowed to warm to rt and stirred for 8 h. After the 8 h the mixture was quenched with 10% HCl. The crude mixture was extracted three times with CH_2Cl_2 and the combined organic layers were washed once with 10% HCl, H_2O, brine, dried over $MgSO_4$, filtered and concentrated.

The solid crude product was recrystallized from Et_2O to afford **2.13** as a white solid (10.5 g, 68%). M. p. 66.5-67.5 ºC ($CDCl_3$) (65.8-67.2 ºC)[19]; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.14 (2H, s), 3.87 (2H, dd, *J* = 11.0, 6.2 Hz), 3.74 (2H, dd, *J* = 10.8, 8.8 Hz), 2.89 (2H, s), 2.50 (2H, br t, *J* = 6.5 Hz), 2.04 (6H, s), 1.50 (1H, d, *J* = 8.5 Hz), 1.32 (1H, d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9 (C), 135.4 (CH), 64.5 (CH_2), 49.0 (CH_2), 45.5 (CH), 40.5 (CH), 21.0 (CH_3); HRMS (EI) expected for $C_{13}H_{18}O_4$: 238.1205. Found for $C_{13}H_{18}O_4$: 238.1232.

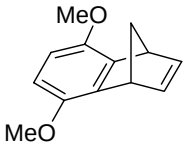
1,4-Dihydro-1,4-methano-naphthalene 2.18



In a flame-dried three-necked flask equipped with two addition funnels and a condenser was charged with freshly cracked cyclopentadiene (25 mL, 305.2 mmol, 3.0 equiv) was diluted in THF (35 mL) and refluxed gently at about 50 ºC. In one addition funnel was anthranilic acid (14.0 g, 101.7 mmol, 1.0 equiv) dissolved in THF (85 mL), the other addition funnel was charged with isobutyl nitrite (14.5 mL, 122.1 mmol, 1.2 equiv) diluted in THF (25 mL) and both were added dropwise, simultaneously, over 45 min. After the addition of acid and nitrite was complete the reaction was stirred at reflux for another 30 min. The solution was cooled to rt and the volatiles were evaporated. The crude residue was diluted in saturated $NaHCO_3$ and Et_2O and extracted twice with Et_2O. The combined organic layers were washed once with H_2O and brine, dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography using hexanes:ethyl acetate (99:1) as eluent to afford **2.18** as a clear oil (7.5 g, 52%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (2H, dd, *J* = 5.1, 3.1 Hz), 6.99 (2H, dd, *J* = 5.1, 3.1 Hz), 6.85

(2H, t, *J* = 1.6 Hz), 3.94 (2H, t, *J* = 1.6 Hz), 2.37 (1H, dt, *J* = 7.1, 1.5 Hz), 2.30 (1H, d, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.8 (C), 143.0 (CH), 124.2 (CH), 121.5 (CH), 70.1 (CH_2), 50.3 (CH); HRMS (EI) expected for $C_{11}H_{10}$: 142.0783. Found for $C_{11}H_{10}$: 142.0777.

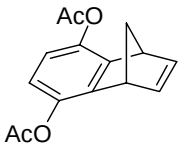
5,8-Dimethoxy-1,4-dihydro-1,4-methano-naphthalene[8,9] (2.20)



Benzoquinone (10.0 g, 92.5 mmol, 1.0 equiv) was diluted in CH_2Cl_2 (31 mL, 3.0 M) and cooled to 0 ºC. Freshly cracked cyclopentadiene (8.0 mL, 97.1 mmol, 1.0 equiv) was added dropwise and then was stirred for 1 h at 0 ºC then 30 min at rt. The volatiles were removed and the solid was triturated in hexanes at 0 ºC. The reaction mixture was filtered and the solid obtained was used without further purification (14.81 g, 92%). The olefin **2.19** (10.0 g, 57.4 mmol, 1.0 equiv) was diluted in acetone (574 mL, 0.1 M) and K_2CO_3 (79.3 g, 574.1 mmol, 10 equiv) was added and the reaction mixture was stirred for at rt for 10 min. After this time Me_2SO_4 (17.4 mL, 183.8 mmol, 3.2 equiv) was added and the suspension was heated to reflux for 16 h. The reaction mixture was cooled to rt and the volatiles were evaporated. The crude residue was diluted in H_2O and extracted three times with EtOAc. The combined organic layers were washed once with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography using toluene:ethyl acetate (99:1) as eluent to afford **2.20** as an off-white solid (3.13 g, 27%). M. p. 76-77 ºC ($CDCl_3$) (76.5-77.5 ºC)[20]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (2H, t, *J* = 1.7 Hz), 6.49 (2H, s), 4.15 (2H, t, *J* = 1.4 Hz), 3.78 (6H, s),

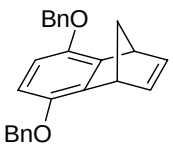
2.20 (2H, q, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.7 (C), 143.0 (CH), 140.5 (C), 109.5 (CH), 70.1 (CH_2), 56.3 (CH_3), 47.0 (CH); HRMS (EI) expected for $C_{13}H_{14}O_2$: 202.0994. Found for $C_{13}H_{14}O_2$: 202.0995.

5,8-Diacetoxy-1,4-dihydro-1,4-methano-naphthalene (2.21)



Olefin **2.19** (15.0 g, 86.1 mmol, 1.0 equiv) was diluted in acetic acid (15 mL, 5.74 M) then treated with acetic anhydride (24.4 mL, 258.3 mmol, 3.0 equiv) and a few drops of HCl. The reaction was stirred for 15 h at rt. The crude mixture was cooled to 0 ºC and the flask was scratched with a glass pipette to induce crystallization. The crystals were filtered off and recrystallized from Et_2O to afford **2.21** as a white solid (16.9 g, 87%). M. p. 104.5-105.5 ºC ($CDCl_3$) (105-106 ºC)[21]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79 (2H, t, J = 1.8 Hz), 6.63 (2H, s), 3.87 (2H, t, J = 1.6 Hz), 2.30 (6H, s), 2.21-2.20 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2 (C), 144.9 (C), 142.4 (CH), 142.1 (C), 119.2 (CH), 68.3 (CH_2), 48.0 (CH), 20.9 (CH_3); HRMS (EI) expected for $C_{15}H_{14}O_4$: 258.0892. Found for $C_{15}H_{14}O_4$: 258.0897.

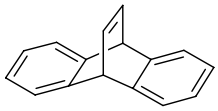
5,8-Dibenzyloxy-1,4-dihdro-1,4-methano-naphthalene (2.22)



Olefin **2.19** (1.74 g, 10 mmol, 1.0 equiv) and K_2CO_3 (8.3 g, 60 mmol, 6 equiv) were diluted with CH_3CN (100 mL, 0.1 M). BnBr (2.4 mL, 20 mmol, 2.0 equiv) was added

and the reaction mixture was heated to reflux for 36 h. After 36 h the crude mixture was cooled to rt and quenched with NH_4Cl (sat'd) then extracted three times with CH_2Cl_2. The combined organic layers were washed once with $NaHCO_3$ (sat'd), H_2O, brine, then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography using hexanes:ethyl acetate (98:2) as eluent to afford **2.22** as a white solid (2.5 g, 71%). M. p. 180-181.5 ºC ($CDCl_3$) (182-183 ºC); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47-7.32 (10H, m), 6.81 (2H, t, *J* = 1.7 Hz), 6.57 (2H, s), 5.05 (4H, s), 4.21 (2H, t, *J* = 1.7 Hz), 2.22 (1H, d, *J* = 11.5 Hz), 2.20 (1H, d, *J* = 11.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.2 (C), 142.9 (CH), 141.4 (CH), 137.7 (CH), 128.4 (CH), 127.8 (CH), 127.4 (CH), 112.0 (CH), 71.6 (CH_2), 69.9 (CH_2), 47.2 (CH); HRMS (EI) expected for $C_{25}H_{22}O_2$: 354.1612. Found for $C_{25}H_{22}O_2$: 354.1613.

Dibenzo-bicyclo[2.2.2]octatriene (2.25)

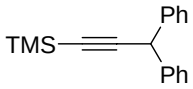


A flame-dried flask was charged with anthracene (20.0 g, 112.2 mmol, 1.0 equiv) and dimethyl acetylenedicarboxylate (24.8 mL, 222.0 mmol, 1.8 equiv) and heated to 140 ºC for 6.5 h then cooled to rt and stirred for an additional 15 h. The crude residue was used without further purification (31.6 g, 90%). The diester (**2.23**) (20.0 g, 62.4 mmol, 1.0 equiv) was diluted in MeOH (250 mL, 0.25 M) and treated with 4 N NaOH (200 mL, 800 mmol, 12.6 equiv). The reaction mixture was heated to 60 ºC for 3 h. After 3 h the reaction mixture was cooled to 0 ºC and acidified with 4 N HCl to pH 3-4 which was monitored by pH paper. The solid product was filtered off and used without further

purification. The diacid (**2.24**) (5.0 g, 17.1 mmol, 1.0 equiv) was diluted in freshly distilled quinoline (17 mL, 1.0 M) and treated with activated Cu powder (1.1 g, 17.1 mmol, 1.0 equiv). The reaction mixture was heated to reflux for 16 h. After cooling to rt the crude mixture was diluted in CH_2Cl_2 and washed with 10% HCl (7-10 times), the first few washes were extracted three times with CH_2Cl_2. The combined organic layers were washed once with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography using 100% hexanes as eluent to afford **2.25** as a white solid (1.1 g, 35%); M. p. 118-119 ºC ($CDCl_3$) (119.5-120.5 ºC)[22]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (4H, dd, *J* = 5.2, 3.2 Hz), 7.01 (2H, t, *J* = 3.7 Hz), 6.95 (4H, dd, *J* = 5.3, 3.1 Hz), 5.15 (2H, t, *J* = 3.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.1 (C), 139.4 (CH), 124.4 (CH), 123.0 (CH), 51.2 (CH); HRMS (EI) expected for $C_{16}H_{12}$: 204.0939. Found for $C_{16}H_{12}$: 204.0938.

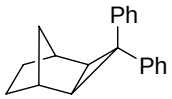
C-H Insertion and Cyclopropane Products

(3,3-Diphenyl-prop-1-ynyl)trimethylsilane (2.6)



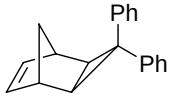
Prepared by the method outlined by Watanabe and co-workers. The crude residue was purified by flash chromatography using 100% hexanes as eluent to afford **2.6** as a clear oil (0.21 g, 79%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (4H, d, *J* = 7.5 Hz), 7.29 (4H, t, *J* = 7.4 Hz), 7.24-7.18 (2H, m), 5.01 (1H, s), 0.20 (9H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.5 (C), 128.5 (CH), 127.8 (CH), 126.8 (CH), 106.6 (C), 89.1 (C), 44.1 (CH), 0.1 (CH_3); HRMS (EI) expected for $C_{18}H_{20}Si$: 216.1334. Found for $C_{18}H_{20}Si$: 264.1333.

***exo*-3,3-Diphenyl-tricyclo[3.2.1.0^{2,4}]octane (2.8)**



Prepared by general procedure A. The crude residue was purified by flash chromatography using 100% hexanes as eluent and then flash chromatography using reverse phase silica[23] using 100% CH_3CN as eluent to afford **2.8** as a white solid (62%); M. p. 79.5-80.5 ºC ($CDCl_3$) (79.5-81.5 ºC); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (2H, d, *J* = 7.5 Hz), 7.28-7.21 (4H, m), 7.16 (3H, t, *J* = 7.1 Hz), 7.04 (1H, t, *J* = 7.1 Hz), 2.50 (2H, s), 1.47 (2H, s), 1.46 (2H, d, *J* = 7.5), 1.27 (2H, d, *J* = 6.6 Hz), 0.50 (1H, d, *J* = 10.9 Hz), 0.40 (1H, d, *J* = 10.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.3 (C), 142.7 (C), 129.2 (CH), 128.8 (CH), 128.1 (CH), 127.9 (CH), 125.8 (CH), 125.5 (CH), 36.6 (CH), 36.6 (C), 31.9 (CH), 31.3 (CH_2), 30.2 (CH_2); HRMS (EI) expected for $C_{20}H_{20}$: 260.1565. Found for $C_{20}H_{20}$: 260.1565.

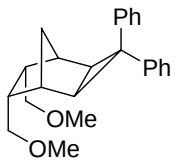
***exo*-3,3-Diphenyl-tricyclo[3.2.1.0^{2,4}]oct-6-ene (2.26)**



Prepared by general procedure A. The crude residue was purified by flash chromatography using hexanes:ethyl acetate (99:1) as eluent then preparative TLC using a gradient of 100% hexanes (2 elutions) then hexanes:ethyl acetate (98:2) to afford **2.26** as an off-white solid (69%); M. p. 79-80 ºC ($CDCl_3$) (82-83.5 ºC); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (2H, d, *J* = 7.7 Hz), 7.36 (2H, t, *J* = 7.5), 7.29-7.11 (6H, m), 6.59 (2H, s), 3.12 (2H, s), 1.78 (2H, s), 0.86 (1H, d, *J* = 9.6 Hz), 0.73 (1H, d, *J* = 9.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.2 (C), 142.8 (C), 142.0 (CH), 129.0 (CH), 128.7 (CH), 128.2

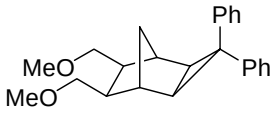
(CH), 128.2 (CH), 127.4 (CH), 126.0 (CH), 125.6 (CH), 57.6 (C), 42.9 (CH), 41.6 (CH_2), 37.6 (CH); HRMS (EI) expected for $C_{20}H_{18}$: 258.1409. Found for $C_{20}H_{18}$: 258.1399.

endo,endo-6,7-bis(methoxymethyl)-3,3-diphenyl-tricyclo[3.2.1.0^{2,4}]octane (2.27)



Prepared by general procedure A. The crude residue was purified by flash chromatography using a gradient of hexanes:ethyl acetate (98:2 → 95:5) as eluent then preparative TLC using hexanes:ethyl acetate (99:1) to afford **2.27** as a white solid (49%); M. p. 98.5-99.5 ºC ($CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.33 (4H, m), 7.24 (4H, dt, *J* = 11.1, 7.6 Hz), 7.18-7.09 (2H, m), 3.55 (2H, dd, *J* = 8.9, 8.9 Hz), 3.44 (2H, dd, *J* = 9.2, 6.1 Hz), 3.34 (6H, s), 2.66 (2H, s), 2.27 (2H, t, *J* = 6.3 Hz), 1.68 (2H, s), 0.73 (1H, d, *J* = 11.2 Hz), 0.55 (1H, d, *J* = 11.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.4 (C), 143.5 (C), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 125.9 (CH), 125.8 (CH), 70.5 (CH_2), 58.8 (CH_3), 42.7 (CH), 39.2 (CH), 36.7 (C), 31.7 (CH_2), 25.7 (CH); HRMS (EI) expected for $C_{24}H_{28}O_2$: 348.2089. Found for $C_{24}H_{28}O_2$: 348.2086.

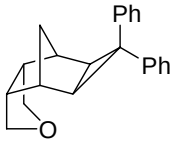
exo,exo-6,7-bis(methoxymethyl)-3,3-diphenyl-tricyclo[3.2.1.0^{2,4}]octane (2.28)



Prepared by general procedure A. The crude residue was purified by flash chromatography using a gradient of hexanes:ethyl acetate (98:2 → 95:5) as eluent then preparative TLC using hexanes:ethyl acetate (99:1) to afford **2.28** as a white solid (49%);

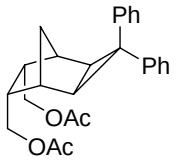
M. p. 86-87 ºC ($CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.02 (10H, m), 3.33-3.29 (2H, m), 3.29 (6H, s), 3.12 (2H, t, *J* = 8.7 Hz), 2.51 (2H, s), 2.05 (2H, br s), 1.57 (2H, s), 0.78 (1H, d, *J* = 11.7 Hz), 0.43 (1H, d, *J* = 11.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.0 (C), 142.9 (C), 128.8 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 125.9 (CH), 125.7 (CH), 72.2 (CH_2), 58.7 (CH_3), 45.9 (CH), 39.9 (CH), 38.8 (C), 31.8 (CH), 26.1 (CH_2); HRMS (EI) expected for $C_{24}H_{28}O_2$: 348.2089. Found for $C_{24}H_{28}O_2$: 348.2084.

endo-4-Oxa-9,9-diphenyl-tetracyclo[5.5.1.0$^{2,6:8,10}$]undecane (2.29)



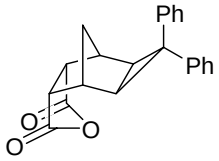
Prepared by general procedure A. The crude residue was purified by flash chromatography using a gradient of hexanes:ethyl acetate (98:2 → 95:5) as eluent then preparative TLC hexanes:ethyl acetate (99:1) (2 elutions) to afford **2.29** as a white solid (50%); M. p. 156.5-158 ºC ($CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.23 (4H, m), 7.18-7.12 (5H, m), 7.06-7.03 (1H, m), 4.05 (2H, d, *J* = 9.8 Hz), 3.45 (2H, dd, *J* = 9.6, 6.3 Hz) 2.60 (2H, br s), 2.54 (2H, s), 1.69 (2H, s), 0.74 (1H, d, *J* = 11.0 Hz), 0.64 (1H, d, *J* = 11.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.3 (C), 143.4 (C), 129.1 (CH), 128.9 (CH), 128.1 (CH), 127.7 (CH), 125.9 (CH), 125.4 (CH), 68.2 (CH_2), 48.4 (CH), 39.8 (CH), 35.7 (C), 35.1 (CH_2), 27.4 (CH); HRMS (EI) expected for $C_{22}H_{22}O$: 302.1671. Found for $C_{22}H_{22}O$: 302.1662.

***endo,endo*-6,7-bis(acetoxymethyl)-3,3-diphenyl-tricyclo[3.2.1.0^{2,4}]octane (2.30)**



Prepared by general procedure A. The crude residue was separated from the olefin via crystallization in hexanes:ethyl acetate (95:5) the filtrate was then concentrated and subjected to flash chromatography using a gradient of hexanes:ethyl acetate (98:2 → 95:5) as eluent to afford **2.30** as a white solid (53%); M. p. 129-130 ºC ($CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (2H, d, *J* = 7.7 Hz), 7.28-7.24 (4H, m), 7.21-7.15 (3H, m), 7.09 (1H, q, *J* = 7.2 Hz), 4.23 (4H, d, *J* = 5.4 Hz), 2.66 (2H, s), 2.31 (2H, br s), 2.08 (6H, s), 1.71 (2H, s), 0.78 (1H, d, *J* = 11.2 Hz), 0.57 (1H, d, *J* = 11.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0 (C), 147.6 (C), 142.9 (C), 129.0 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 126.1 (CH), 125.9 (CH), 62.4 (CH_2), 41.8 (CH), 39.4 (CH), 36.4 (C), 31.7 (CH_2), 25.9 (CH), 21.1 (CH_3); HRMS (EI) expected for $C_{26}H_{30}O_4$: 404.1988. Found for $C_{26}H_{30}O_4$: 404.1986.

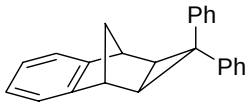
***endo*-4-Oxa-9,9-diphenyl-tetracyclo[5.5.1.0$^{2,6:8,10}$]undecane-3,5-dione (2.31)**



Prepared by general procedure A. The crude residue was separated from the olefin via crystallization in hexanes:ethyl acetate (90:10), the filtrate was then concentrated and subjected to flash chromatography using neutral silica with a gradient of hexanes:ethyl acetate (90:10 → 50:50) as eluent to afford **2.31** as a white solid (53%); M. p. 219.5-

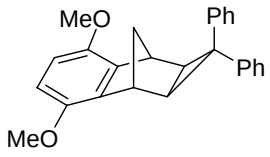
220.5 ºC ($CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.10 (10H, m), 3.42 (2H, br t, *J* = 2.0 Hz), 3.22 (2H, s), 1.83 (2H, s), 1.04 (1H, d, *J* = 11.8 Hz), 0.80 (1H, d, *J* = 11.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6 (C), 145.8 (C), 141.2 (C), 129.4 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 126.7 (CH), 126.6 (CH), 50.9 (CH), 40.4 (CH), 36.9 (C), 34.5 (CH_2), 26.0 (CH); HRMS (EI) expected for $C_{22}H_{18}O_3$: 330.1256. Found for $C_{22}H_{18}O_3$: 330.1253.

1,5-Dihydro-1,5-methano-naphthalene-3,3-diphenyl-cyclopropane (2.32)



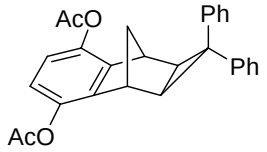
Prepared by general procedure A. The crude residue was purified by flash chromatography using 100% hexanes as eluent followed by Kugelrohr distillation to afford **2.32** as a white solid (51%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44 (2H, d, *J* = 7.3 Hz), 7.33 (2H, t, *J* =7.6 Hz), 7.24-7.11 (7H, m), 6.99-6.97 (3H, m), 3.53 (2H, s), 1.72 (2H, s), 1.11 (1H, d, *J* = 10.4 Hz), 0.98 (1H, d, *J* = 10.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.6 (C), 147.6 (C), 142.8 (C), 129.2 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 126.2 (CH), 125.8 (CH), 124.7 (CH), 120.6 (CH), 53.4 (C), 44.1 (CH), 41.6 (CH_2), 36.3 (CH); HRMS (EI) expected for $C_{24}H_{20}$: 308.1565. Found for $C_{24}H_{20}$: 308.1567.

6,9-Dimethoxy-1,5-dihydro-1,5-methano-naphthalene-3,3-diphenyl-cyclopropane (2.33)



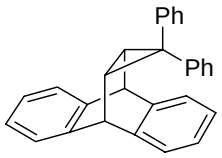
Prepared by general procedure A. The crude residue was purified by flash chromatography using 100% toluene as eluent to afford **2.33** as a white solid (38%); M. p. 140-141 ºC ($CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44 (2H, d, *J* = 7.6 Hz), 7.29 (2H, t, *J* =7.5 Hz), 7.23 (2H, d, *J* = 7.5 Hz), 7.18-7.08 (3H, m), 6.99 (1H, t, *J* = 7.3 Hz), 6.55 (2H, s), 3.80 (8H, s), 1.76 (2H, s), 1.08 (1H, d, *J* = 10.3 Hz), 0.94 (1H, d, *J* = 10.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.0 (C), 147.7 (C), 142.9 (C), 140.5 (C), 129.2 (CH), 128.5 (CH), 128.1 (CH), 127.7 (CH), 126.1 (CH), 125.8 (CH), 109.5 (CH), 56.3 (CH_3), 53.8 (C), 41.3 (CH_2), 40.8 (CH), 35.7 (CH); HRMS (EI) expected for $C_{26}H_{24}O_2$: 368.1776. Found for $C_{26}H_{24}O_2$: 368.1770.

6,9-Diacetoxy-1,5-dihydro-1,5-methano-naphthalene-3,3-diphenyl-cyclopropane (2.34)



Prepared by general procedure A. The crude residue was purified by flash chromatography using toluene:ethyl acetate (99:1) as eluent to afford **2.34** as a white solid (44%); M. p. 198.5-199.5 ºC ($CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (2H, d, *J* = 7.4 Hz), 7.29 (2H, t, *J* =7.6 Hz), 7.19-7.00 (6H, m), 6.70 (2H, s), 3.56 (2H, s), 2.34 (6H, s), 1.89 (2H, s), 1.10 (1H, d, *J* = 10.5 Hz), 1.00 (1H, d, *J* = 10.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3 (C), 147.0 (C), 144.5 (C), 142.5 (C), 141.6 (C), 129.2 (CH), 128.6 (CH), 128.2 (CH), 127.5 (CH), 126.4 (CH), 125.9 (CH), 119.5 (CH), 52.4 (C), 41.8 (CH), 41.3 (CH_2), 34.7 (CH), 21.0 (CH_3); HRMS (EI) expected for $C_{28}H_{24}O_4$: 424.1675. Found for $C_{28}H_{24}O_4$: 424.1672.

Dibenzo-8,8-diphenyl-tricyclo[4.2.1.0^{7,9}]octatriene (2.35)



Prepared by general procedure A. The crude residue was purified by flash chromatography using hexanes:ethyl acetate (99:1) as eluent then preparative TLC using hexanes:ethyl acetate (99:1) to afford **2.35** as a white solid (42%); M. p. 169-170 ºC ($CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (2H, dd, *J* = 5.2, 3.3 Hz), 7.09 (4H, t, *J* = 2.7 Hz), 6.99 (3H, dd, *J* = 5.3, 3.3), 6.92 (2H, d, *J* = 7.1 Hz) 6.81-6.77 (5H, m), 6.53 (2H, dd, *J* = 5.4, 3.3 Hz), 4.73 (2H, br t, *J* = 2.0 Hz), 2.19 (2H, t, *J* = 2.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.0 (C), 147.5 (C), 141.5 (C), 138.4 (C), 130.5 (CH), 128.1 (CH), 127.2 (CH), 127.1 (CH), 125.6 (CH), 125.2 (CH), 125.0 (CH), 124.7 (CH), 123.4 (CH), 51.5 (C), 45.6 (CH), 34.5 (CH); HRMS (EI) expected for $C_{29}H_{22}$: 370.1721. Found for $C_{29}H_{22}$: 370.1730.

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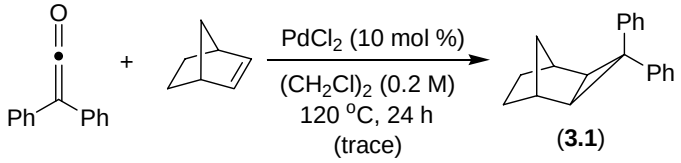
CHAPTER THREE

3.0 ISOMERIZATION OF DIPHENYLCYCLOPROPANE

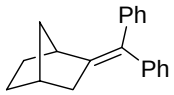
During initial palladium catalyst screening for the cyclopropanation of norbornylene (Section 2.3.1) $PdCl_2$ afforded the diphenylcyclopropane product (**3.1**) in trace amounts (Scheme 3.1).

Scheme 3.1



(**3.1**)

Analysis of the crude material by GC-MS and ^1H NMR revealed the formation of another product that was isolated in 53% yield. The molecular ion observed by mass spectrometry indicated a product with the same molecular weight as product **3.1**; however, the retention time was slightly lower. The ^1H NMR spectrum indicated a compound that was not symmetrical. After further NMR studies, including ^{13}C NMR, COSY, NOSY, and HMQC, the structure (**3.2**) was elucidated, as shown in Figure 3.1.

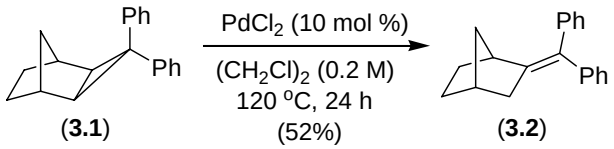


(**3.2**)

Figure 3.1: Isolated product from reaction with $PdCl_2$.

In order to determine whether this product was the result of a direct reaction between diphenylpalladium carbene and norbornylene or a subsequent reaction occurring after the formation of the cyclopropane, cyclopropane (**3.1**) was treated with $PdCl_2$ under the conditions outlined Scheme 3.1 (Scheme 3.2).

Scheme 3.2



(**3.1**) (**3.2**)

Product **3.2** was isolated in a 52% yield. Thus, the cyclopropane was being formed via diphenylpalladium carbene and further reacting with $PdCl_2$ to afford alkene product **3.2**.

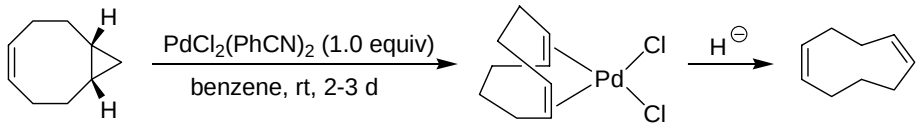
3.1 LITERATURE REVIEW

Generally, palladium(II) cyclopropane ring-openings require a vinyl, allyl, or homoallyl alkene to assist with directing the palladium to the cyclopropane via coordination.[1] Other examples of this reactivity include the oxidation and isomerization of phenylcyclopropane by aqueous $PdCl_2$[2] and most recently, the palladium-catalyzed oxidative activation of arylcyclopropanes.[3]

3.1.1 Palladium Ring Opening of Vinyl, Allyl, and Homoallyl Cyclopropanes

Early work performed by Rettig and co-workers illustrated the palladium(II) ring-openings of allylic and homoallylic cyclopropanes.[1a-c] Bicyclo[6.1.0]non-4-ene (**3.3**) afforded dichloro-*cis*,*cis*-1,5-cyclononadienepalladium(II) (**3.4**), which liberated *cis*,*cis*-1,5-cyclononadiene (**3.5**) when treated with hydride (Scheme 3.3).[1a]

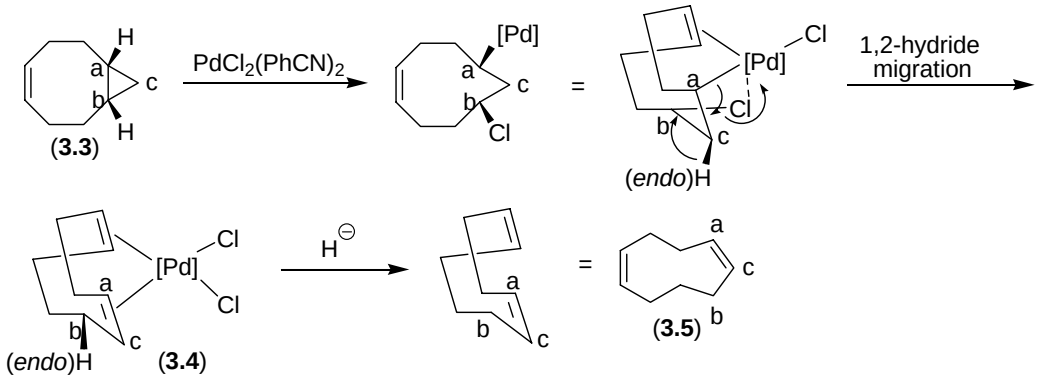
Scheme 3.3



(**3.3**) (**3.4**) (**3.5**)

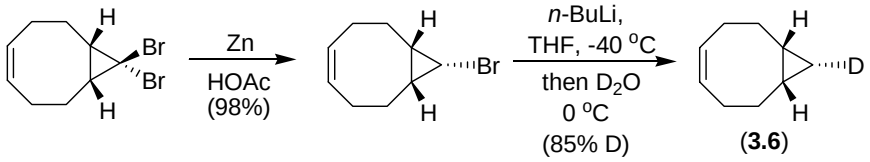
The mechanism they proposed for this reaction is a step-wise process involving the initial *cis*-addition of Pd-Cl to the (*a*-*b*) bond of **3.3** (Scheme 3.4). The next likely step is a 1,2-hydride migration from carbon *c* to carbon *a* or *b*, which assists in the chloride abstraction by palladium(II), resulting in the formation of a new double bond and palladium-coordinated product (**3.4**). Addition of a hydride source liberates **3.5**.[1a]

Scheme 3.4



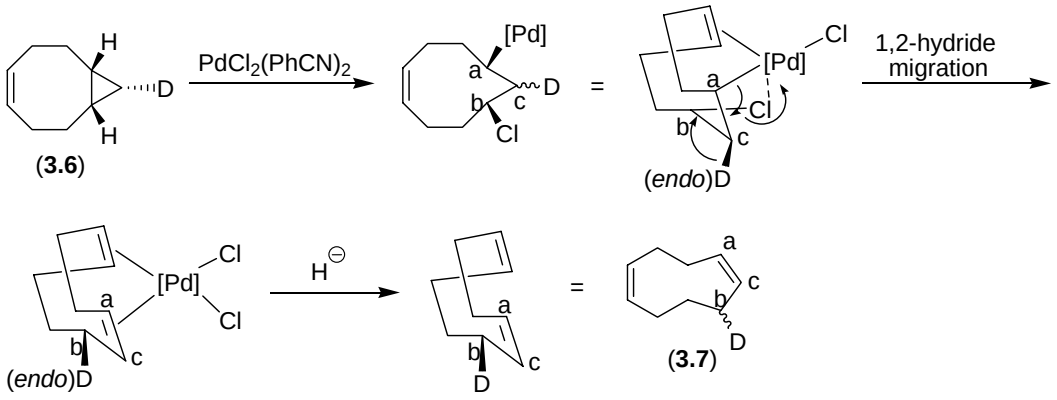
In order to determine whether or not the cyclopropyl hydrogen migrated stereospecifically, they prepared *endo*-9-deuterio-bicyclo[6.1.0]non-4-ene (**3.6**) via the route outlined in Scheme 3.5. They analyzed the final product (**3.6**) and achieved 85% deuterium incorporation at the *endo* position. The remaining 15% was the undeuterated product (**3.3**).[1a]

Scheme 3.5



Reaction of **3.6** with $PdCl_2(PhCN)_2$ gave only one deuterated, rearranged hydrocarbon product, which they determined to be 7-deuterio-*cis*,*cis*-1,5-cyclononadiene (**3.7**) (Scheme 3.6).[1a]

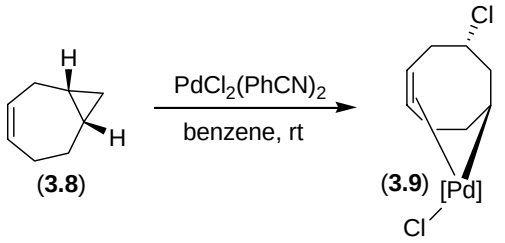
Scheme 3.6



Product **3.7** would arise from the 1,2-*endo*-D migration from **3.6**.

Rettig and co-workers then studied these cyclopropane ring-openings using allylic cyclopropanes, specifically, *cis*-bicyclo[5.1.0]oct-3(*Z*)-ene (**3.8**).[1b] When treated with palladium(II), **3.8** generated the stable di-μ-chloro-(1,4,5-η-7-chlorocyloocetyl)-dipalladium(II) (**3.9**) (Scheme 3.7).

Scheme 3.7

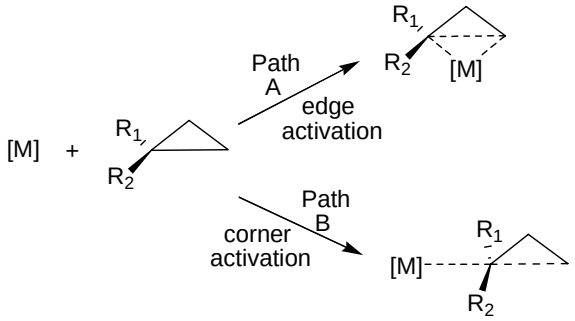


Contrary to the results seen with the homoallylic cyclopropane **3.3** in which the first step of the mechanism appears to be a *cis*-chloropalladation (Scheme 3.4 and 3.6), these allylic cyclopropanes seemed to be undergoing a *trans*-chloropalladation, as observed by ^{1}H NMR.[1b]

It was suggested by Bäckvall and co-workers that there must be two principle mechanisms occurring for the cyclopropane activation, resulting in the opening of the ring.[1f] The reaction could be initiated by an edge activation (or oxidative addition) across

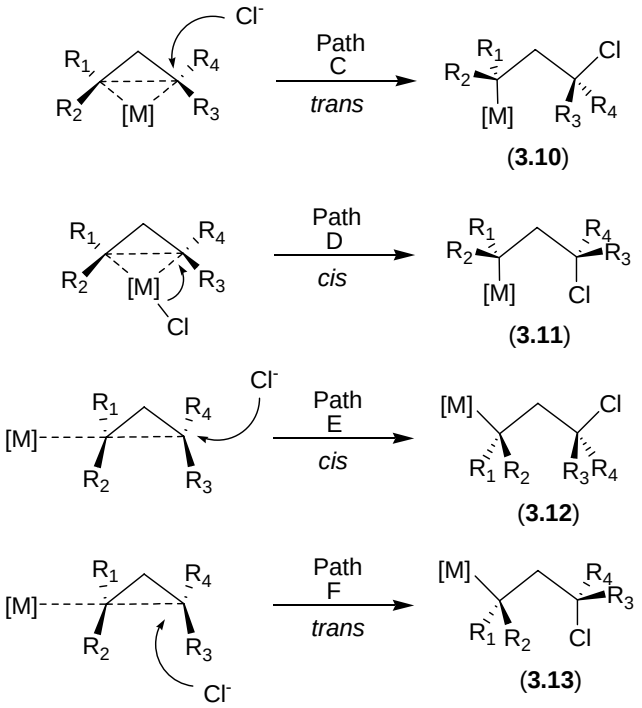
the carbon-carbon bond, generating a metallacyclobutane (Path A, Scheme 3.8). Another possible pathway is via corner activation by the metal (Path B, Scheme 3.8). The stereochemical consequences of these two pathways are different such that Path A would occur with retention of the carbon attached to the metal, whereas, Path B takes place with inversion of the carbon attached to the metal.

Scheme 3.8



Each of these intermediates then has two options for the addition of chloride (Scheme 3.9). Path A can precede either Path C or Path D; Path C representing intermolecular chloride addition generating an overall *trans* stereochemical addition product (**3.10**) and Path D illustrating intramolecular chloride addition affording a *cis* product (**3.11**) (Scheme 3.9). For Path B, the corner-activated intermediate can undergo two intermolecular chloride additions; Path E forming the *cis* product (**3.12**) and Path F affording the *trans* product (**3.13**) (Scheme 3.9).

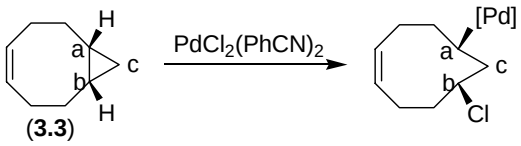
Scheme 3.9



Therefore, in Path C and Path E, the carbons that become attached to the chloride undergo inversion of configuration; while in Path D and Path F, the carbon bearing the chloride retains its configuration. Thus, the ring-openings of cyclopropanes can occur with either retention or inversion at the carbon bearing the metal and/or the chloride. It is quite possible that *cis*-chloropalladation of a cyclopropane is the result of inversion at both carbon atoms, rather then retention at both carbons.

Thus the work shown by Rettig and co-workers can be related to these possible reaction pathways. It was postulated that (**3.3**) was undergoing a *cis*-chloropalladation of the a-b bond (Scheme 3.10).

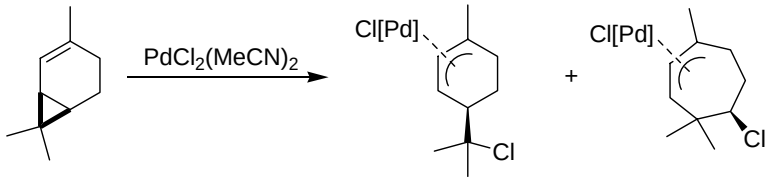
Scheme 3.10



Therefore, it can be presumed that this *cis* addition is the result of either an edge-activation (Path A, Scheme 3.8) followed by intramolecular chloride addition (Path D, Scheme 3.9) or a corner-activation (Path B, Scheme 3.8) followed by inversion at the carbon that becomes attached to chloride (Path E, Scheme 3.9). When allylic cyclopropanes were treated with palladium(II) they afforded products containing the *trans* stereochemistry of the chloride relative to the palladium (Scheme 3.7). Therefore, based on the possible reaction pathways proposed by Bäckvall and co-workers, this *trans* addition is the result of either an edge-activation (Path A, Scheme 3.8) followed by intermolecular chloride addition (Path C, Scheme 3.9) or a corner-activation (Path B, Scheme 3.8) followed by retention at the carbon that becomes attached to chloride (Path F, Scheme 3.9).

In conjunction with the work done by Rettig and co-workers, Bäckvall and co-workers examined the ring-opening of vinyl cyclopropane, (+)-car-2-ene (**3.14**), via $PdCl_2(MeCN)_2$ to further elucidate the mechanism of chloropalladation, in particular, how the metal activates the ring and the overall stereochemistry of the chloropalladation itself.[1e] They observed that treatment of **3.14** with palladium(II) generated two products, **3.15** and **3.16** (Scheme 3.11).

Scheme 3.11



(**3.14**) (**3.15**) (**3.16**)

The formation of product **3.15** led to mechanistic studies. The ^{1}H NMR of **3.15** was consistent with a *trans* configuration of the palladium and chloroisopropyl moieties (Figure 3.2).

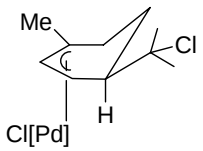
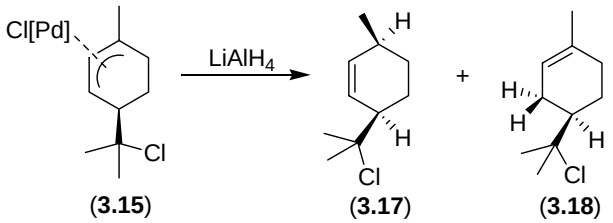


Figure 3.2: Proposed *trans* chloropalladation structure.

To further support the *trans* configuration, **3.15** was reduced with $LiAlH_4$, generating products **3.17** and 3.**18** in a 1:4 mixture, respectively (Scheme 3.12).

Scheme 3.12

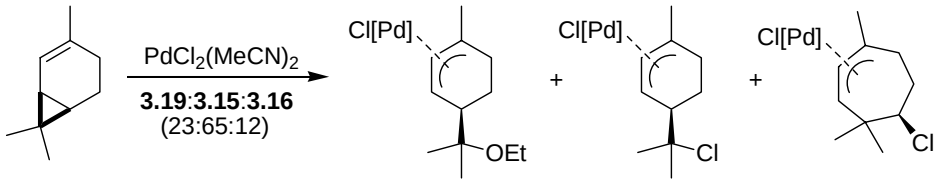


Since it is known that π-allylpalladium bonds are cleaved by $LiAlH_4$ with retention of configuration[4], the results obtained support the notion that the palladium and the chloroisopropyl group in **3.15** are *trans* to each other. In a latter study, they obtained a crystal structure of **3.15**, and indeed, the chloro-group and palladium were *trans* to each other.[1f] These results are consistent with edge-activation (Path A, Scheme 3.8) followed by intermolecular chloride addition (Path C, Scheme 3.9) or corner-activation (Path B, Scheme 3.8) and then intermolecular chloride addition as seen in Path F (Scheme 3.8).

In 1985, Bäckvall and co-workers reported the selective formation of **3.15** or **3.16** when they utilized different solvents.[1g] In addition, reactions that were run in nucleophilic solvents such as methanol or acetic acid were also examined. These reactions resulted in

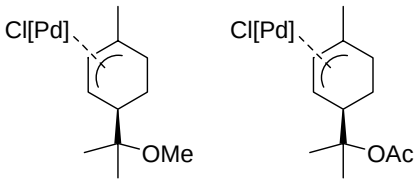
methoxy- or acetoxypalladation, respectively, across the cyclopropane ring. Previously, the palladium(II) cyclopropane ring-opening was done using benzene as solvent and they isolated products **3.15** and **3.16** in a ratio of 1:6.1, respectively.[1e,f] When the same reaction was run in commercial chloroform a product ratio of 6.4:1 was observed (**3.15**:**3.16**). When analytical grade chloroform was used the ratio decreased to 1.4:1 (**3.15**:**3.16**). It became apparent that it was the ethanol stabilizer in the commercial chloroform that increased the yield of **3.15**. Using ethanol as an additive in the solvent, it was realized that amounts exceeding 3% started generating a new product (**3.19**), which was the result of oxypalladation (Scheme 3.13).

Scheme 3.13



(**3.14**) (**3.19**) (**3.15**) (**3.16**)

When the same reaction was run using methanol as solvent, methoxypalladation was observed, affording product **3.20** (Figure 3.3), in addition to **3.15**, in an overall 80% yield with a ratio of 6:1, however, none of the seven-membered ring product (**3.16**) was observed. The same reaction was run in acetic acid, afforded the acetoxypalladation product (**3.21**) (Figure 3.3), in addition to products **3.15** and **3.16** in an overall yield of 40-50% and product ratio of 34:23:43 (**3.21**:**3.15**:**3.16**).

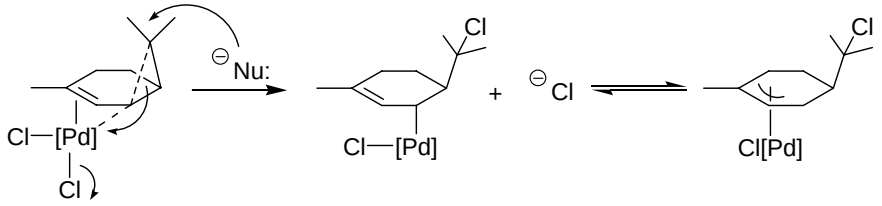


(**3.20**) (**3.21**)

Figure 3.3: Oxypalladation products of (+)-car-2-ene.

Based on ^{1}H NMR studies as well as treatment with $LiAlH_4$, it was confirmed that these oxypalladation reactions were also generating *trans* products (palladium relative to methoxy or acetoxy). Therefore, since the nucleophile was external it had to be delivered intermolecularly. Thus, the ring opening of the cyclopropane affording the six-membered rings (**3.15**, **3.19**-**3.21**) must be occurring with inversion at the carbon that becomes attached to the metal via corner-activation (Path B, Scheme 3.8) followed by intermolecular attack of the nucleophile (i.e. Cl^-,or RO^-) with retention (Path F, Scheme 3.9) to generate the observed *trans* relationship (Scheme 3.14).

Scheme 3.14:



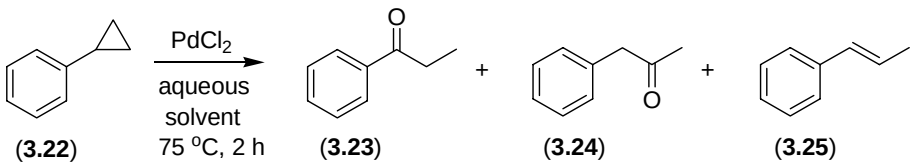
The liberation of chloride ion after nucleophilic attack explains why products **3.15** and **3.16** are still generally observed.

3.1.2 Oxidation and Isomerization of Phenylcyclopropane by Aqueous Palladium(II)

In 1968, Levin and co-workers reported the ring opening and oxidation of phenylcyclopropane by $PdCl_2$ in aqueous solutions. Treatment of phenylcyclopropane (**3.22**) with a stoichiometric amount of $PdCl_2$ in aqueous solution at 75 ºC for 2 hours

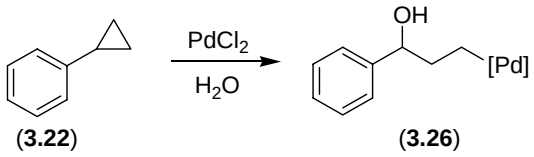
afforded three products, two the result of an oxidation reaction (**3.23** and **3.24**) and the third the result of an isomerization reaction (**3.25**) (Scheme 3.15).[2]

Scheme 3.15



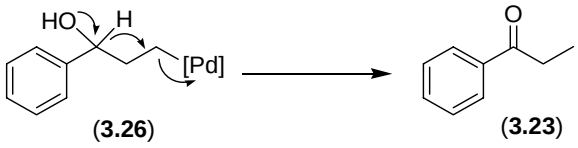
Propiophenone (**3.23**) was the major product and formed in 60% yield. Phenylacetone (**3.24**) was generated in 35% yield and *trans*-propenylbenzene (**3.25**) was afforded in <5% yield. The origin of **3.23** was rationalized to arise from intermediate **3.26**, a Markovnikov-type adduct which is the homolog of the adduct proposed for olefin reactions (Scheme 3.16).[2]

Scheme 3.16



From this intermediate it was postulated that a 1,3-hydride shift was occuring, generating the ketone and expelling palladium (Scheme 3.17).[2]

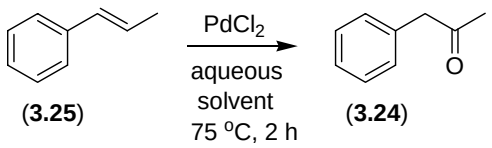
Scheme 3.17



It was also contemplated that the C-Pd bond could be undergoing protonolysis, followed by oxidation of the alcohol generating **3.23**, however, when the reaction was run in D_2O as solvent, there was no deuterium incorporation in the methyl group.[2]

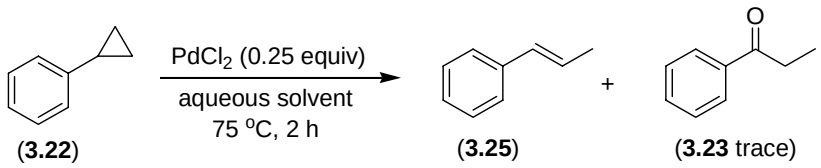
The formation of product **3.24** seemed unlikely to arise directly from phenylcyclopropane but rather from *trans*-propenylbenzene (**3.25**), which could be formed directly from the isomerization of phenylcyclopropane (**3.22**). In order to test this theory **3.25** was treated with palladium(II) in aqueous solution and produced **3.24** exclusively (Scheme 3.18).[2]

Scheme 3.18



Therefore, the rate of isomerization must be comparable to the rate of oxidation (affording **3.23**), hence, the relative reactivities of phenylcyclopropane (**3.22**) and *trans*-propenylbenzene (**3.25**) must be similar. To test this experimentally a reaction in which **3.22**, **3.25** and palladium(II) in a ratio of 1:1:2, were reacted. After 2 hours the quantities of the substrates remaining were nearly 1:1.[2] It was also observed that when the original reaction, as outlined in Scheme 3.15, was run with only 0.25 equivalents of palladium(II), the only significant product formed was **3.25**, with trace amounts of **3.23** (Scheme 3.19).[2]

Scheme 3.19



However, after 26 hours both oxidation products (**3.23** and **3.24**) and **3.25** were formed. Thus, the isomerization reaction was occurring in competition with the oxidation process. It can be envisioned that the slowing of the oxidation reaction with increasing quantities of cyclopropane may be the result of a multi equilibrium system where palladium(II) complexes with either one or two cyclopropane molecules (Figure 3.4).[2]

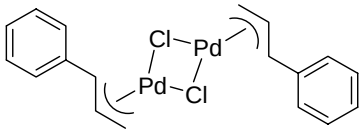
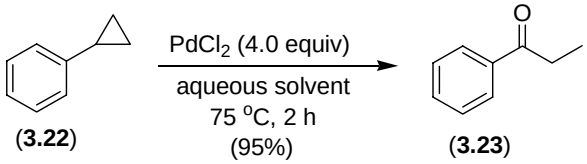


Figure 3.4: Pd(II) complex to two cyclopropane moieties.

Since it is believed that the formation of **3.23** requires coordination of palladium to water, complexation of two cyclopropane molecules prevents this from occurring. In these complexes, a secondary process, namely isomerization to **3.25**, occurs.[2] To further support this hypothesis, a 4-fold excess of palladium(II)chloride was used in the reaction. In this case product **3.23** was formed in 95% yield, with no traces of products **3.24** or **3.25** (Scheme 3.20).[2]

Scheme 3.20

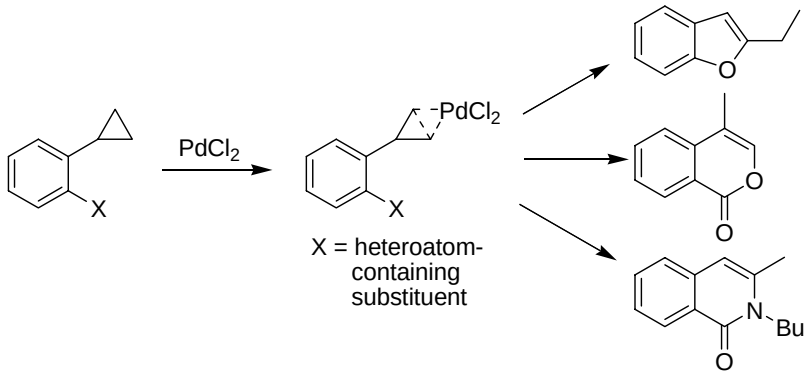


Thus, oxidative cleavage is enhanced, which is consistent with the formation of a complex ion containing one cyclopropane moiety.

3.1.3 Palladium-Catalyzed Oxidative Activation of Arylcyclopropanes

In 2006, Yudin and co-workers illustrated a palladium-catalyzed intramolecular activation of electroneutral cyclopropane derivatives, which resulted in the cleavage of the cyclopropane ring followed by the formation of heterocyclic derivatives (Scheme 3.21).

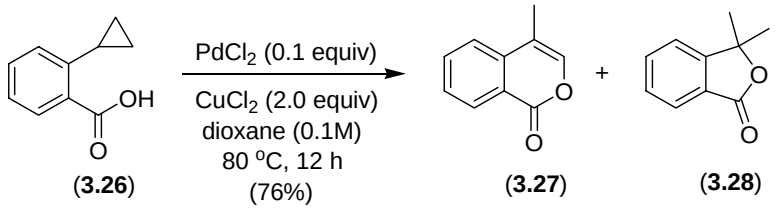
Scheme 3.21



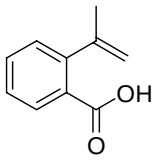
Various phenyl cyclopropanes substituted at the *ortho*-position with either a carboxylic acid, hydroxyl or amide were subjected to the palladium(II) oxidation conditions to generate a variety of cyclic ethers, lactones and lactams.[3] The optimal conditions were generally found to be 0.1 equivalents $PdCl_2(MeCN)_2$, 1.0 equivalents of benzophenone (as oxidant) in 0.1 M dioxane at 80 ºC for 12 hours. Some reactions required $PdCl_2$ in 0.1-0.3 equivalents and an additional 2.0 equivalents of $CuCl_2$. The phenol substrates needed harsher conditions of 100 ºC for 24 hours.

In an attempt to elucidate the mechanism they followed the reaction of substrate **3.26**, which formed products **3.27** and **3.28** in an 86:14 ratio, by ^{1}H NMR (Scheme 3.22).[3]

Scheme 3.22



Intermediate **3.29** was detected by ^{1}H NMR during the cyclization of **3.26** (Figure 3.5).[3]

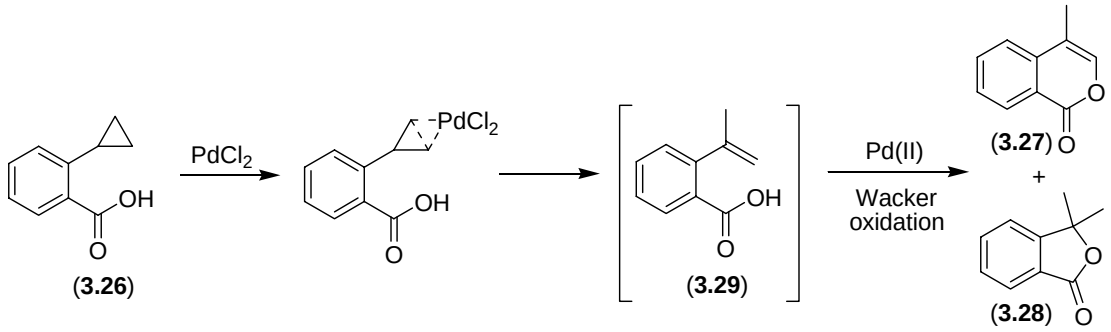


(**3.29**)

Figure 3.5: Intermediate observed by ^{1}H NMR during palladium catalyzed oxidative activation of arylcyclopropanes.

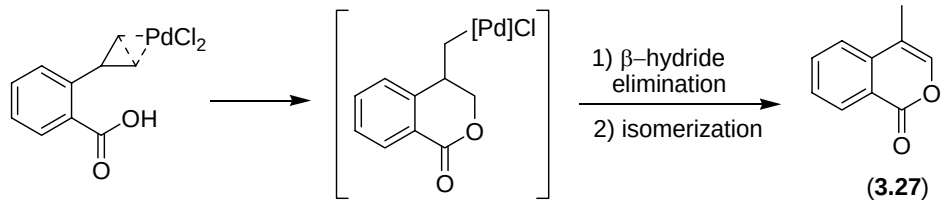
This suggested an initial palladium(II) catalyzed isomerization of the cyclopropane to **3.29**, via coordination of palladium(II) to the distal carbon-carbon bond of the cyclopropane, followed by a Wacker oxidation (Scheme 3.23).[3]

Scheme 3.23



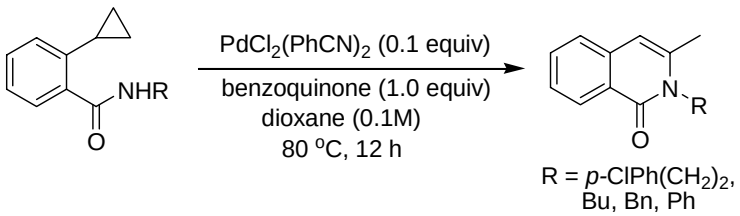
This pathway would also account for the phenol-containing substrates as well as the five-membered ring lactam products derived from the amide-containing substrates. It was also proposed that **3.27** could arise from direct carboxypalladation of the activated species, followed by β-hydride elimination and isomerization (Scheme 3.24).[3]

Scheme 3.24



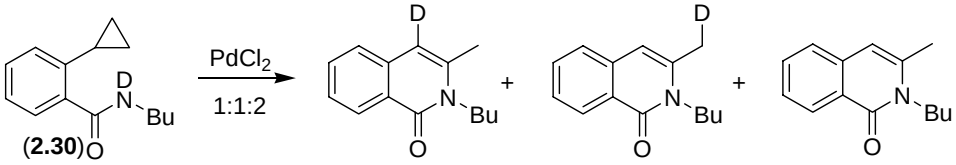
The regioselectivity observed for six-membered ring lactam products was different than that of **3.27** (Scheme 3.25).

Scheme 3.25



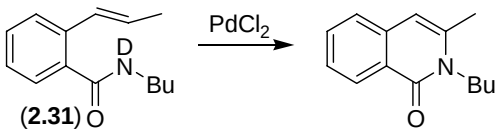
To try and understand this difference in regioselectivity deuterium-labeling studies of the R = butyl model (**2.30**) were conducted. Treating **2.30** under the reaction conditions outlined in Scheme 3.25 generated three products (Scheme 3.26).[3]

Scheme 3.26



The formation of these three products illustrated that this reaction likely proceeded by a pathway other then simple cyclopropane isomerization followed by a Wacker oxidation. To ensure this was the case, substrate **2.31** was prepared and reacted under Wacker oxidation conditions (Scheme 3.27).[3]

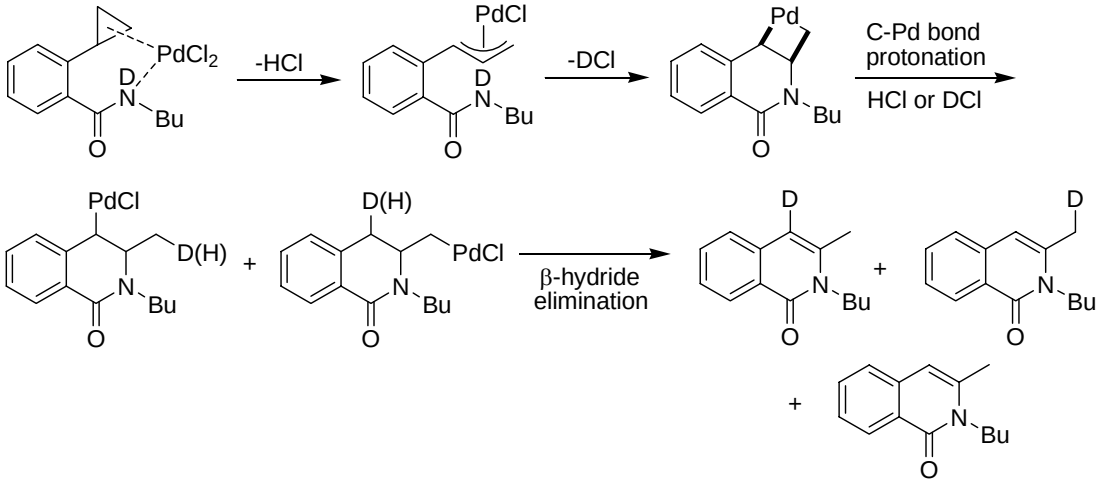
Scheme 3.27



No deuterium incorporation was observed and this reaction pathway was confidently ruled out. It was proposed that nitrogen could coordinate the palladium as well as the cyclopropane (Scheme 3.28).[3] Loss of HCl would generate the π-allyl complex, which

could then undergo nucleophilic attack by nitrogen to lose DCl (Scheme 3.28).[3] Addition of either HCl or DCl across the carbon-palladium bond followed by β-hydride elimination would account for the products observed, as well as the relative product distribution (Scheme 3.28).[3]

Scheme 3.28



Thus, the palladium-nitrogen coordination is a key factor in the different products observed during the activation of acids and amides.

3.1.4 SUMMARY

In summary, the use of $PdCl_2$, with and without additional ligands, for the activation and ring-opening of cyclopropanes has been illustrated in the literature. Most examples require a neighbouring olefin to direct the palladium to the cyclopropane via coordination.[1] Other cases that do not require an olefin have also been presented, however, they require stoichiometric amounts of palladium catalyst or an additional oxidant for the re-oxidation of palladium.[2,3] Also, reactions not containing a coordinating group generally need a higher reaction temperature.[2,3] The final products isolated after

these transformations generally incorporate a nucleophile such as water[2] or a heteroatom[3]. In addition, many of these products contain a chlorine derived from $PdCl_2$. It appears then that the isomerization of (**3.1**) to (**3.2**) is unique in many respects: it is catalytic and does not require a re-oxidant; it does not need an olefin to direct the palladium; and it reacts in a catalytic cycle that does not require an external nucleophile for ring-opening.

3.2 RESULTS AND DISCUSSION

3.2.1 OPTIMIZATION OF REACTION CONDITIONS

In an attempt to run this reaction under milder reactions, lower temperatures and shorter reaction times were examined.

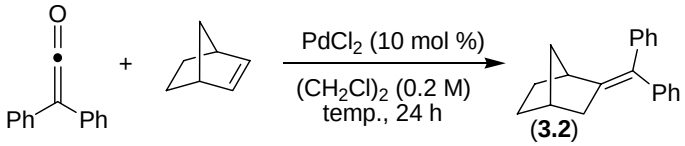


Table 3.1: Optimization of Temperature for Isomerization Reaction.

Entry	Temperature (ºC)	Yield of **3.2** (%)[a]	Conversion (% from cyclopropane)[b]
1	100	53	81
2	60	No rxn	N/A
3	rt	No rxn	N/A

[a]Combined yield of cyclopropane and isomerization product. [b]Conversions are based on amount of cyclopropane observed in the reaction mixture by ^{1}H NMR if applicable.

Given the above results, it was concluded that the optimal temperature was still 120 ºC. To ensure that these observations were not the result of the inhibition of the intial cyclopropanation reaction, temperature studies were also conducted starting from the cyclopropane. The results obtained were essentially the same. The requirement for the

higher temperature may be due to the lack of a coordinating group that can direct the palladium.

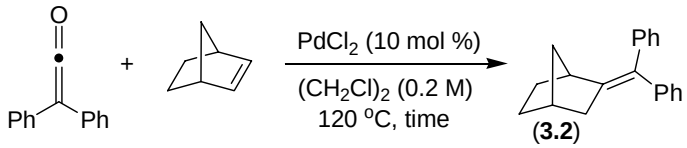


Table 3.2: Optimization of Time for Isomerization Reaction.

Entry	Time (h)	Yield of **3.2**(%)[a]	Conversion (% from cyclopropane)[b]
1	6	50	16
2	12	51	50
3	24	53	97
4	36	54	97

[a]Combined yield of cyclopropane and isomerization product. [b]Conversions are based on amount of cyclopropane observed in the reaction mixture by ^{1}H NMR.

3.2.2 ISOMERIZATION OF OTHER DIPHENYLCYCLOPROPANES

With the success of the norbornylene model these reaction conditions were applied to other olefins The reaction using olefins shown in Table 3.3 generated similar tetrasubstituted olefins (**3.32** and **3.33**) to that observed with norbornylene.

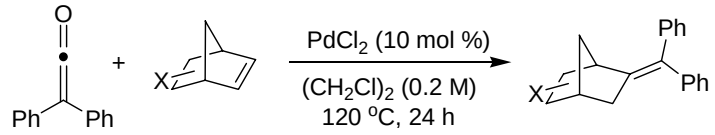
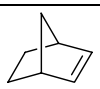
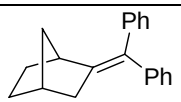
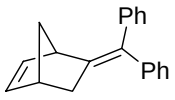
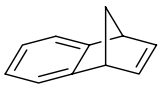
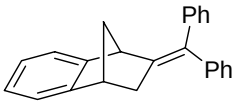


Table 3.3: Isomerization of Other Olefins Generating Tetrasubstituted Products.

Entry	Olefin	Product	Yield (%)
1		 (**3.2**)	53
2		 (**3.32**)	61

3		 (**3.33**)	48[a]

[a]Mixture with cyclopropane in a ratio of 88:12 (product:cyclopropane) as determined by ^{1}H NMR.

When these conditions were applied to olefins shown in Table 3.4, trisubstituted olefin products (**3.34** and **3.35**) were formed, rather then the previously observed tetrasubstituted olefins.

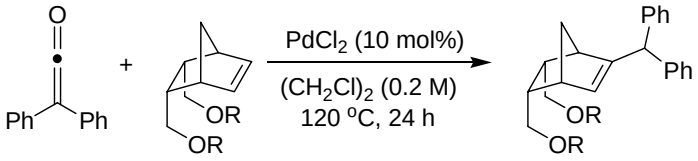
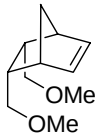
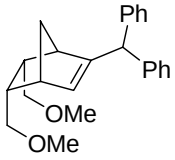
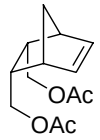
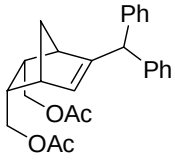


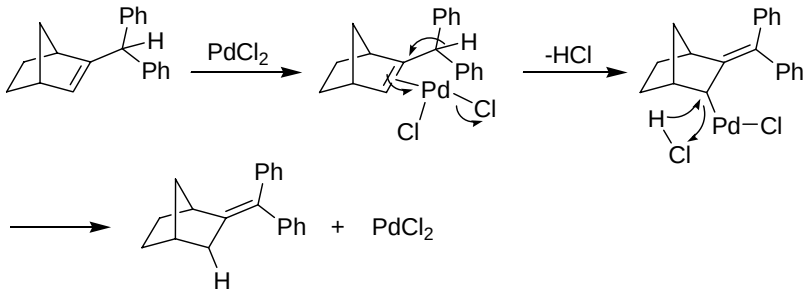
Table 3.4: Isomerization of Other Olefins Generating Trisubstituted Products.

Entry	Olefin	Product	Yield (%)
1		 (**3.34**)	57[a]
2		 (**3.35**)	56

[a]Mixture with cyclopropane in a ratio of 74:26 (product:cyclopropane) as determined by ^{1}H NMR.

From these results it was proposed that the trisubstituted olefin is formed first and in the presence of $PdCl_2$ it isomerizes to the more stable tetrasubstituted double bond for products **3.2**, **3.32**, and **3.33**. Therefore, there must be some aspect of **3.34** and **3.35** that does not permit the isomerization of the trisubstituted olefin to occur. The proposed mechanism of olefin isomerization in the presence of palladium(II) is shown in Scheme 3.29.

Scheme 3.29



Thus, the palladium(II) catalyst acts as a Lewis acid, coordinating to the double bond and inducing a formal 1,3-hydride shift. Therefore, the trisubstituted alkenes (**3.34** and **3.35**) could be undergoing some electronic effect causing them to be less Lewis basic. One possible explanation is the overlap of the σ* of the C-O bond with the π electrons of the double bond (Figure 3.8).

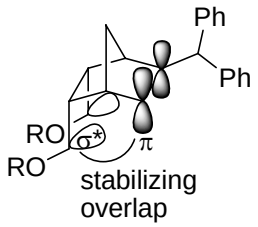


Figure 3.6: Possible stabilizing effect for trisubstituted olefin products

This would reduce the Lewis basicity of the olefin and may inhibit coordination to the Lewis acid.

3.2.3 Proposed Mechanisms for Isomerization

From the results obtained some key factors can be deduced about the potential reaction mechanism. First, it is not a direct reaction between the alkene and diphenylpalladium carbene, but rather a reaction that takes place after cyclopropanation occurs. Second, the reaction undergoes a catalytic cycle that does not require a re-oxidant and therefore the active palladium(II) catalyst must be regenerated. Finally, it is suspected that a

trisubstituted olefin is formed and then isomerizes (in some cases) to the more stable tetrasubstituted olefin. Based on the literature precedent for cyclopropane ring-opening by $PdCl_2$ it is proposed that this reaction is initiated by a chloropalladation of the cyclopropane.[1-3] It is thought that this occurs in a *cis* fashion by either edge activation (Path A, Scheme 3.8) followed by intramolecular chloride delivery (Path D, Scheme 3.9) or via corner activation (Path B, Scheme 3.8) followed by intermolecular chloride delivery with inversion at the carbon (Path E, Scheme 3.9) to afford intermediate **3.36** (Figure 3.7).

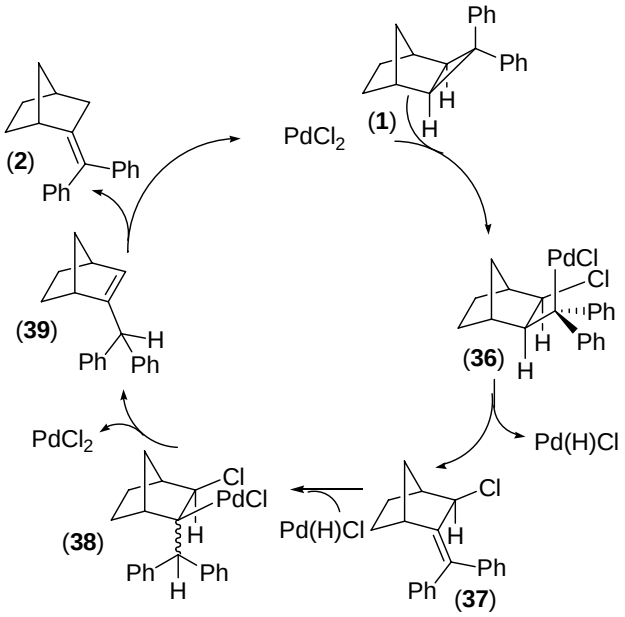
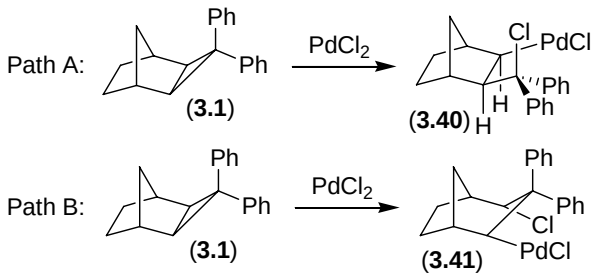


Figure 3.7: Proposed catalytic cycle for cyclopropane isomerization.

This proposed carbopalladation would allow for the alignment necessary in the subsequent β-hydride elimination, after rotation, to generate intermediate **3.37**. The formation of Pd(H)Cl could then re-add to the newly formed double bond via hydropalladation affording **3.38**. The regeneration of the palladium(II) catalyst via β-chloro elimination and formation of **3.39** would account for the observed trisubstituted products (**3.34** and **3.35**). To afford the tetrasubstituted olefin products, olefin

isomerization of **3.39** by palladium(II) to give **3.2** is suggested. The regioselectivity of the cyclopropane ring-opening is proposed to occur in the above fashion. There are two other possible ring-openings shown in Scheme 3.30.

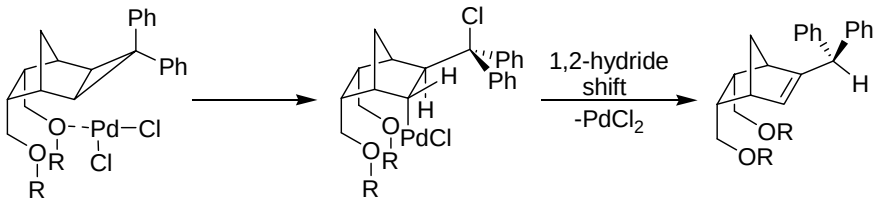
Scheme 3.30



Path A would not likely be able to undergo β-hydride elimination due to the anti relationship of the palladium and the proton in product **3.40**. Path B can be ruled out as the formation of intermediate **3.41** would not lead to the desired product.

An alternative mechanism for the formation of **3.34**, and **3.35** could be derived from a [1,2]-hydride shift, which could occur following chloropalladation via coordination to the *endo* substituents (Scheme 3.31).

Scheme 3.31

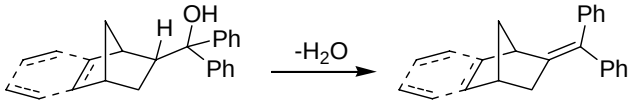


In order to elucidate the mechanism further, deuterium labeling studies need to be performed (see Section 4.2.2).

3.2.4 Independent Preparation of Isomers

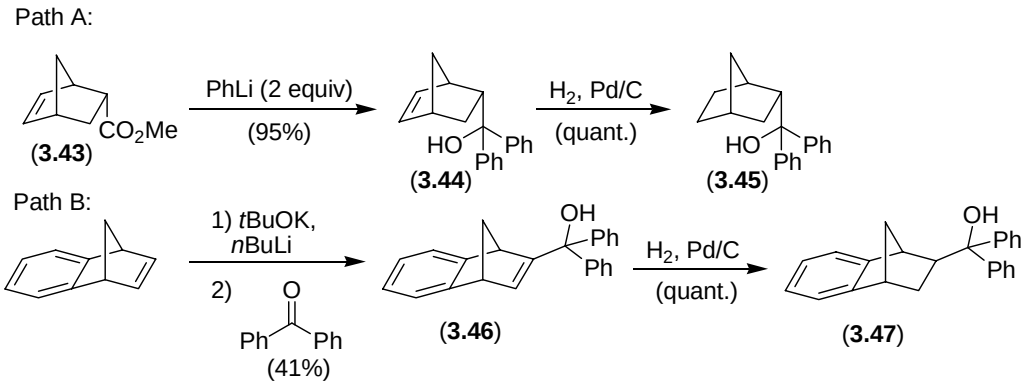
As with the cyclopropanes, these products needed to be prepared independently for characterization purposes since there was usually inseparable cyclopropane still present after purification. It should be noted that product **3.35** was purified from the crude reaction mixture and did not require independent preparation. Product **3.34** isomerized to the tetrasubstituted olefin (**3.42**) during purification and the tetrasubstituted product (**3.42**) was prepared independently. In addition, all attempts to prepare **3.34** independently also isomerized to the tetrasubstituted product (**3.42**) during the reaction, purification, or analysis. The preparation of **3.2**, **3.32** and **3.33** was envisioned to arise from a dehydration reaction (Scheme 3.32).

Scheme 3.32



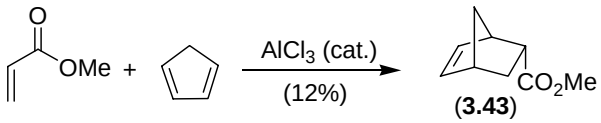
This tertiary alcohol could be derived by two different paths, one path for the formation of products **3.2** and **3.32** (Path A)[5] and another path for the formation of product **3.33** (Path B)[6] (Scheme 3.33).

Scheme 3.33



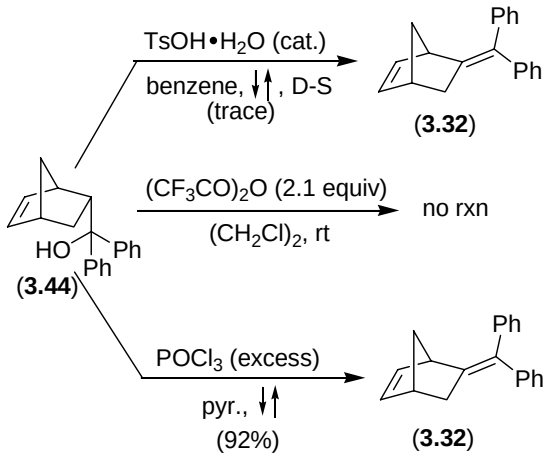
Compound **3.43** was obtained from the Lewis-acid catalyzed Diels-Alder reaction of cyclopentadiene and methyl acrylate (Scheme 3.34).[7]

Scheme 3.34



The dehydration precursors, **3.44**, **3.45** and **3.47** were prepared and various dehydration methods[8] were attempted using **3.44** (Scheme 3.35).

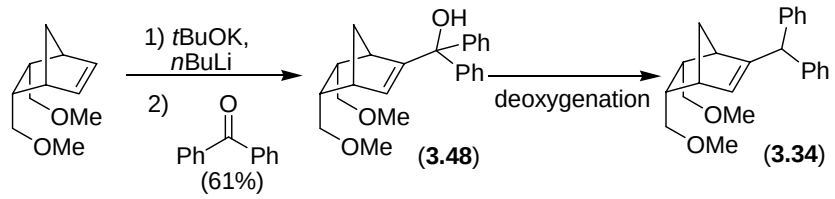
Scheme 3.35



The third method affording 92% of **3.32** was also used to prepare products **3.2** and **3.33** in 90% and 88% yield, respectively.

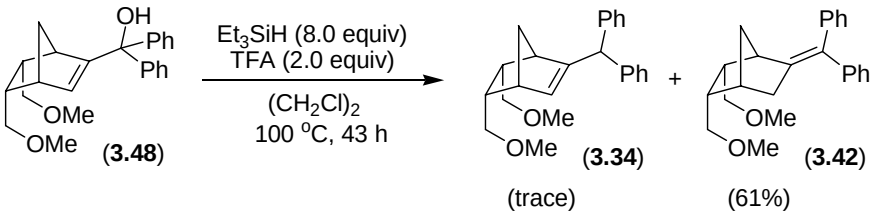
The preparation of product **3.34** was envisioned to arise from the deprotonation of the alkene using *t*BuOK and *n*BuLi and trapping the anion with benzophenone (Scheme 3.36). Following the formation of the tertiary alcohol **3.48**, it was thought that deoxygenation would give **3.34** (Scheme 3.36).

Scheme 3.36



Deoxygenation via triethylsilane and trifluoroacetic acid was attempted as shown in Scheme 3.37.[9]

Scheme 3.37



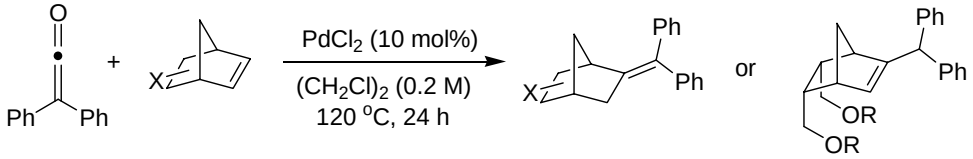
The desired product **3.34** was generated in trace amounts, however, the major product **3.42** was the isomerized, tetrasubstituted product. The reaction was attempted under milder reaction conditions (50 ºC for 24 h and rt for 24 h), however; either product **3.34** was formed in trace amounts or no reaction occurred at all. Since product **3.34** isomerizes on silica gel during purification, product **3.42** was characterized.

3.3 EXPERIMENTAL SECTION

General Methods

All reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere. All reaction solvents were obtained from a solvent system or freshly distilled. Dichloroethane and norbornadiene were distilled over CaH_2 and degassed by freeze-pump-thaw method (three cycles).[10] All commercially available reagents were from Sigma-Aldrich and used without further purification. $PdCl_2$ was purchased from Strem and also used without further purification. ^1H NMR spectra were referenced to residual ^1H shift in $CDCl_3$ (7.24 ppm). ^{13}C NMR spectra were referenced to residual ^{13}C shift in $CDCl_3$ (77.0 ppm). Flash chromatography was performed using 230-400 mesh silica gel. Melting points are uncorrected. High resolution mass spectra were run by Dr. R. Smith at the University of Waterloo with a source temperature of 200 ºC, mass resolution of 9000, and electron energy of 70 eV.

Preparation of Isomerization Products – General Procedure A

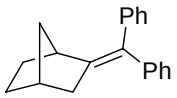


A flame-dried resealable Schlenk tube was charged with diphenylketene (1.0 equiv), followed by palladium(II)chloride (0.1 equiv), olefin (10 equiv) and solvent (0.2 M) in a glove box. The tube was sealed and allowed to react in a temperature controlled oil bath at 120 ºC for 24 h. After 24 h, the crude material was cooled to rt and filtered through a silica pad using dichloromethane as the eluent. Purification was achieved using flash chromatography.

Substate Preparation – Specific Procedures (see Chapter 2, Section 2.5)

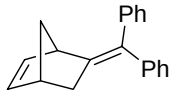
Isomerization Products

2-Benzhydrylidene-bicyclo[2.2.1]heptane 3.2



Prepared by general procedure A. The crude residue was purified by flash chromatography using 100% hexanes as eluent then flash chromatography using reverse phase silica with an eluent of 100% CH_3CN to afford product as white solid (53%); M. p. 69-70 ºC ($CDCl_3$) (68-69 ºC); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.16 (10H, m), 2.96 (1H, d, *J* = 3.3 Hz), 2.44 (1H, d, *J* = 16.4), 2.40 (1H, s), 1.89 (1H, dd, *J* = 16.0, 3.0 Hz) 1.76-1.72 (1H, m), 1.64-1.59 (2H, m), 1.48 (1H, d, *J* = 11.2 Hz), 1.33 (2H, t, *J* = 9.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.9 (C), 143.1 (C), 143.0 (C), 130.6 (C), 129.3 (CH), 128.0 (CH), 127.8 (CH), 125.9 (CH), 43.1 (CH), 39.7 (CH_2), 39.3 (CH_2), 36.6 (CH), 29.7 (CH_2), 28.3 (CH_2); HRMS (EI) expected for $C_{20}H_{20}$: 260.1565. Found for $C_{20}H_{20}$: 260.1564.

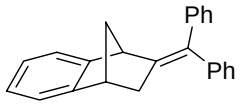
5-Benzhydrylidene-bicyclo[2.2.1]hept-2-ene 3.32



Prepared by general procedure A. The crude residue was purified by flash chromatography using a gradient of hexanes:ethyl acetate (99:1 → 97:3) as eluent then preparative TLC using hexanes:ethyl acetate (99:1) to afford the product as a white solid (61%); M. p. 74-75 ºC ($CDCl_3$) (73-75 ºC)[11]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.18

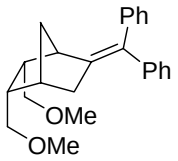
(10H, m), 6.23 (2H, dd, *J* = 7.2, 2.7 Hz), 3.43 (1H, s), 3.05 (1H, s), 2.59 (1H, dd, *J* = 15.2, 3.5 Hz), 1.80 (1H, dd, *J* = 15.3, 3.2 Hz), 1.65 (1H, dt, *J* = 8.2, 1.5 Hz), 1.55 (1H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.4 (C), 143.2 (C), 142.2 (C), 136.7 (CH), 134.4 (CH), 132.4 (C), 129.4 (CH), 129.2 (CH), 127.9 (CH), 127.9 (CH), 126.2 (CH), 126.0 (CH) 50.6 (CH_2), 48.7 (CH), 41.8 (CH), 34.0 (CH_2); HRMS (EI) expected for $C_{20}H_{18}$: 258.1409. Found for $C_{20}H_{18}$: 258.1408.

2-Benzhydrylidene-1,3,4-trihydro-1,4-methano-naphthalene 3.33



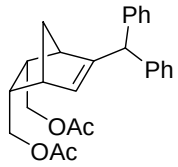
Prepared by general procedure A. The crude residue was purified by flash chromatography using a hexanes as eluent then Kugelrohr distillation twice to afford the product as a white solid (42%); M. p. 119-120.5 ºC ($CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (2H, t, *J* = 7.3 Hz), 7.30-7.19 (7H, m), 7.15-7.05 (5H, m), 3.87 (1H, s), 3.46 (1H, d, *J* = 2.2 Hz), 2.86 (1H, dd, *J* = 16.1, 4.0 Hz), 1.98-1.93 (2H, m), 1.87 (1H, d, *J* = 8.4 Hz),; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.2 (C), 146.0 (C), 143.2 (C), 142.7 (C), 141.3 (C), 133.1 (C), 129.5 (CH), 129.0 (CH), 128.0 (CH), 127.9 (CH), 126.4 (CH), 126.2 (CH), 125.7 (CH), 125.6 (CH), 121.1 (CH), 121.1 (CH) 51.6 (CH_2), 50.4 (CH), 43.5 (CH), 36.0 (CH_2); HRMS (EI) expected for $C_{24}H_{20}$: 308.1565. Found for $C_{24}H_{20}$: 308.1559.

2-Benzhydrylidene-*endo,endo*-5,6-bis-methoxymethyl-bicyclo[2.2.1]heptane 3.42



Prepared by general method A. The crude residue was purified by flash chromatography using a gradient of hexanes:ethyl acetate (92:2 → 95:5) then preparative TLC using hexanes:ethyl acetate (95:5) to afford the product as a clear oil (42%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.24 (4H, m), 7.21-7.16 (6H, m), 3.53 (1H, dd, *J* = 9.4, 6.3 Hz), 3.44-3.33 (2H, m), 3.35 (3H, s), 3.24 (1H, d, *J* = 3.1 Hz), 3.19-3.12 (1H, m), 3.12 (3H, s), 2.45 (1H, s), 2.38 (2H, dd, *J* = 17.4, 2.5 Hz), 2.26-2.16 (1H, m), 1.95 (1H, dd, *J* = 17.2, 3.7 Hz), 1.54 (2H, q, *J* = 9.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.8 (C), 142.7 (C), 141.0 (C), 134.3 (C), 129.5 (CH), 129.0 (CH), 128.0 (CH), 127.8 (CH), 126.1 (CH), 126.0 (CH), 71.9 (CH_2), 70.8 (CH_2), 58.8 (CH_3), 58.4 (CH_3), 45.8 (CH), 41.3 (CH), 39.7 (CH), 39.2 (CH_2), 39.2 (CH), 31.1 (CH_2); HRMS (EI) expected for $C_{24}H_{28}O_2$: 348.2089. Found for $C_{24}H_{28}O_2$: 348.2087.

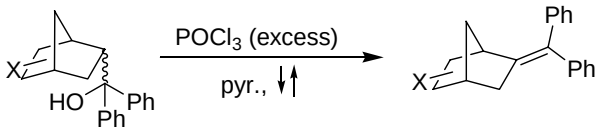
2-Benzhydryl-*endo,endo*-5,6-bis-methoxymethyl-bicyclo[2.2.1]heptane 3.35



Prepared by general method A. The crude residue was purified by flash chromatography using hexanes:ethyl acetate (95:5) as eluent then preparative TLC using hexanes:ethyl acetate (90:10) (2 elutions) then flash chromatography using a gradient of pentane:diethyl ether (100:0 → 90:10) as eluent to afford a white solid (56%); M. p. 125.5-126.5

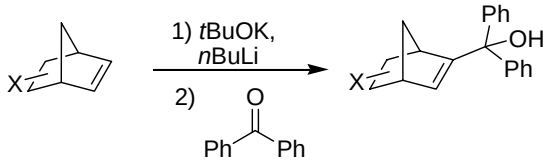
($CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.11 (8H, m), 7.05 (2H, d, *J* = 7.6 Hz), 5.34 (1H, s), 4.55 (1H, d, *J* = 1.7 Hz), 4.13 (1H, dd, *J* = 10.9, 5.9 Hz), 3.94-3.80 (2H, m), 3.66 (1H, dd, *J* = 10.9, 6.0 Hz), 2.87 (1H, s), 2.73 (1H, s), 2.56-2.55 (2H, m), 2.04 (3H, s), 1.98 (3H, s), 1.78 (1H, d, *J* = 8.5 Hz), 1.38 (1H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9 (C), 152.9 (C), 142.4 (C), 142.1 (C), 130.6 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 126.7 (CH), 126.4 (CH), 64.4 (CH_2), 64.2 (CH_2), 54.2 (CH), 49.3 (CH_2), 48.5 (CH), 45.7 (CH), 41.6 (CH), 40.2 (CH), 21.1 (CH_3), 21.1 (CH_3); HRMS (EI) expected for $C_{26}H_{28}O_4$: 404.1988. Found for $C_{26}H_{28}O_4$: 404.1991.

Independent Preparation of Isomerization Products – General Procedure B[8c]



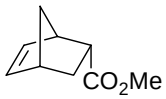
The tertiary alcohol (1.0 equiv) was dissolved with pyridine (0.1 M) and cooled to 0 ºC. $POCl_3$ (15 equiv) was added dropwise and upon completion of addition the reaction was heated to reflux for 20 h. After the allotted reaction time the crude mixture was cooled to -78 ºC and quenched with H_2O (2.5X vol. of $POCl_3$). The mixture was then allowed to warm to rt and diluted in 5% HCl (half volume). The mixture was extracted three times with $(CH_2Cl)_2$ and the combined organic layers were washed once with H_2O and brine, dried over $MgSO_4$, filtered and concentrated.

Independent Preparation of Isomerization Products – General Procedure C



The olefin (1.0 equiv) was diluted with THF (1.5 M) and cooled to -78 ºC. *t*-BuOK (1.0 M, 1.0 equiv) was added drop-wise followed by the drop-wise addition of *n*-BuLi (2.5 M, 1.0 equiv). Warmed reaction up to -65 ºC and stirred for 30 min and then warmed to -40 ºC and stirred for 30 mins. The mixture was then cooled back down to -78 ºC and benzophenone (1.1 equiv) diluted in a minimal amount of THF was added dropwise. The reaction mixture was then warmed to -40 ºC and stirred for 1.5 h before being warmed to rt and stirring an additional 4 h. The crude reaction mixture was quenched with aq. NH_4Cl (sat'd) and extracted 3X with Et_2O. The combined organic layers were washed once with H_2O and brine, dried over $MgSO_4$, filtered and concentrated.

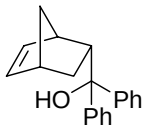
Bicyclo[2.2.1]hept-5-ene-2 carboxylic acid methyl ester 3.43[7]



A flame-dried flask was charged with $AlCl_3$ (0.75 g, 5.55 mmol, 0.1 equiv), which was diluted with dichloromethane (550 mL, 0.1 M) and cooled to -78 ºC. Freshly cracked cyclopentadiene (5.0 mL, 55.5 mmol, 1.0 equiv) was added and the reaction was stirred for 5 min. Methyl acrylate (9.1 mL, 111.0 mmol, 2.0 equiv) was then added drop-wise and the reaction was stirred at -78 ºC for 2 h. The reaction was then quenched with H_2O (20 mL) and warmed to rt. The organic layer was washed once with H_2O and brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography using hexanes:ethyl acetate (99:1) as eluent to afford a clear oil (1.0 g, 12%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.15 (1H, dd, J = 5.3, 3.0 Hz), 5.89 (1H, dd, J = 5.4, 2.7 Hz), 3.59 (3H, s), 3.16 (1H, s), 2.94-2.87 (2H, m), 1.87 (1H, ddd, J = 10.6, 9.2, 3.3 Hz), 1.41-1.36 (2H, m), 1.24 (1H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2

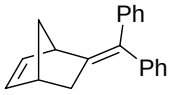
(C), 137.7 (CH), 132.3 (CH), 51.4 (CH_3), 49.5 (CH_2), 45.6 (CH), 43.1 (CH), 42.4 (CH), 29.2 (CH_2); HRMS (EI) expected for $C_9H_{12}O_2$: 152.0837. Found for $C_9H_{12}O_2$: 152.0827.

Bicyclo[2.2.1]hept-5-en-2-yldiphenylmethanol 3.44[5]



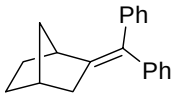
Ester **3.43** (1.0 g, 6.75 mmol, 1.0 equiv) was diluted with THF (22.5 mL, 0.3 M) and cooled to -78 ºC. Phenyllithium (18.8 mL, 33.8 mmol, 5.0 equiv) was added dropwise and the reaction was stirred for 2 h at -78 ºC. The remaining phenyllithium was quenched with 5% HCl at -78 ºC and the reaction warmed to rt. The crude mixture was extracted three times with Et_2O and the combined organic layers were washed once with H_2O and brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography using hexanes:ethyl acetate (95:5) as eluent to afford a clear oil (1.8 g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (4H, d, *J* = 7.9 Hz), 7.31-7.23 (4H, m), 7.16 (2H, t, *J* = 7.9 Hz), 6.33 (1H, d, *J* = 5.1 Hz), 6.14 (1H, d, *J* = 5.3 Hz), 3.42-3.36 (1H, m), 2.85 (1H, s), 2.58 (1H, s), 2.51 (1H, brs), 1.95 (1H, ddd, *J* = 10.6, 9.2, 3.3 Hz), 1.52-1.38 (1H, m), 1.15 (1H, d, *J* = 12.1 Hz), 1.14 (1H, d, *J* = 12.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.4 (C), 148.1 (C), 139.2 (CH), 132.7 (CH), 128.0 (CH), 128.0 (CH), 126.4 (CH), 126.2 (CH), 125.9 (CH), 125.6 (CH), 79.0 (C), 51.2 (CH_2), 48.3 (CH), 45.0 (CH), 43.0 (CH), 29.3 (CH_2); HRMS (EI) expected for $C_{20}H_{20}O$: 276.1514. Found for $C_{20}H_{20}O$: 276.1509.

5-Benzhydrylidene-bicyclo[2.2.1]hept-2-ene 3.32[8]



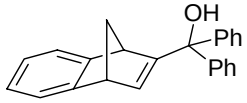
Prepared by general procedure B using alcohol **3.44**. The crude residue was purified by flash chromatography using hexanes as eluent to afford a white solid (0.43 g, 92%). The M. p. and NMR data matched the previous data reported.

2-Benzhydrylidene-bicyclo[2.2.1]heptane 3.2[8]



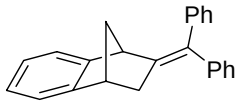
Olefin **3.44** (0.66 g, 2.39 mmol, 1.0 equiv) was dissolved in EtOAc (3.4 mL, 0.7 M) and degassed 3X using a water aspirator and backfilled with argon. The degassed solution was treated with Pd/C (0.07 g, 10 wt%) and degassed again using water aspirator 3X and backfilled once with argon and then with H_2. The reaction was equipped with an H_2 balloon at ambient pressure and stirred at rt for 16 h. After 16 h the crude mixture was filtered through a pad of celite and concentrated. The crude residue was used without further purification as it went to 100% conversion. Prepared by general procedure B. The crude residue was purified by flash chromatography using hexanes as eluent to afford a white solid (0.56 g, 90%). The M. p. and NMR data matched the previous data reported.

1,4-Dihydro-1,4-methano-naphthalene-2-yldiphenylmethanol 3.46[6]



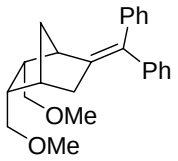
Prepared by general method C. The crude residue was purified by flash chromatography using a gradient of hexanes:ethyl acetate (99:1) → (97:3) as eluent to afford a clear oil (0.47 g, 41%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.17 (11H, m), 6.94-6.85 (3H, m), 6.29 (1H, d, J = 2.8 Hz), 3.93 (1H, s), 3.83 (1H, s), 2.59 (1H, d, J = 7.2 Hz), 2.29 (1H, s), (1H, d, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.0 (C), 151.4 (C), 151.0 (C), 144.5 (C), 144.5 (C), 139.1 (CH), 127.9 (CH), 127.8 (CH), 127.1 (CH), 127.0 (CH), 127.0 (CH), 127.0 (CH), 124.2 (CH), 124.0 (CH), 121.8 (CH), 121.0 (CH), 80.2 (C), 68.6 (CH_2), 52.0 (CH), 50.3 (CH); HRMS (EI) expected for $C_{24}H_{20}O$: 324.1514. Found for $C_{24}H_{20}O$: 324.1522.

2-Benzhydrylidene-1,3,4-trihydro-1,4-methano-naphthalene 3.33[8]



Olefin **3.46** (0.87 g, 2.69 mmol, 1.0 equiv) was dissolved in EtOAc (3.8 mL, 0.7 M) and degassed 3X using a water aspirator and backfilled with argon. The degassed solution was treated with Pd/C (0.09 g, 10 wt%) and degassed again using water aspirator 3X and backfilled once with argon and then with H_2. The reaction was equipped with an H_2 balloon at ambient pressure and run at rt for 16 h. After 16 h the crude mixture was filtered through a pad of celite and concentrated. The crude residue was used without further purification as it went to 100% conversion. Prepared by general procedure B. The crude residue was purified by flash chromatography using hexanes as eluent to afford a clear oil (0.73 g, 88%). The NMR data matched the previous data reported.

2-Benzhydrylidene-*endo,endo*-5,6-bis-methoxymethyl-bicyclo[2.2.1]heptane 3.40[6,9]



Prepared by general procedure C. The crude residue was run through a pad of silica using CH_2Cl_2 as eluent to provide a clear oil that required no further purification (0.87 g, 87%). A flame-dried Schlenk tube was charged with alcohol **3.53** (0.27 g, 0.74 mmol, 1.0 equiv), trifluoroacetic acid (0.11 mL, 1.48 mmol, 2.0 equiv) and $(CH_2Cl)_2$ (1.6 mL, 0.5 M) under an argon atmosphere. Triethylsilane (0.95 mL, 5.93 mmol, 8.0 equiv) was added and the tube was sealed and heated to 100 ºC for 43 h. The crude reaction was cooled to rt and neutralized with aq. $NaHCO_3$ (sat'd) then extracted three times with CH_2Cl_2. The combined organic layers were washed once with H_2O and brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography using hexanes:ethyl acetate (97:3) as eluent to afford a clear oil (0.16 g, 61%). The NMR data matched the previous data reported.

3.4 REFERENCES

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CHAPTER FOUR

4.0 CONCLUSIONS AND FUTURE WORK

4.1 CONCLUSIONS

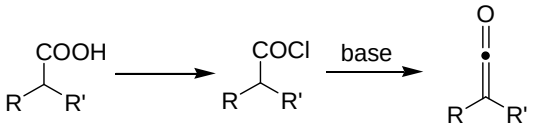
In conclusion these studies have illustrated the ability to tune the reactivity of diphenylketene by changing the oxidation state of the palladium carbene it forms. Previous conditions have allowed for C-H insertion of terminal alkynes.[1] A system in which cyclopropanation is achieved has been established (Section 2.2-2.3). This cyclopropanation reaction has been shown to be compatible with various functional groups, including; alkenes, ethers, esters, anhydrides, and alkynes as well as benzannulated norbornyl derivatives (Section 2.4). The high reactivity of palladium carbenes, derived from diphenylketene, has also been demonstrated by its reaction with the less strained and more sterically hindered [2.2.2]bicyclooctene system (Section 2.4.2). An unusual palladium(II)-catalyzed cyclopropane isomerization reaction has been shown (Section 3.2). This unique transformation does not require a directing group, such as an olefin or an amide, and it runs under catalytic conditions without the addition of an oxidant. In the presence of $PdCl_2$, diphenylcyclopropane generates the corresponding trisubstituted or tetrasubstituted olefin (Section 3.2.2). The norbornylene, norbornadiene and benzannulated norbornyl systems afford tetrasubstituted olefin products; while methyl ether and acetate *bis*-*endo*-substituted systems initially generated the trisubstituted product, however, after purification the methyl ether system isomerized to the more substituted alkene (Section 3.2.2). A catalytic cycle has been proposed which is based on an initial chloropalladation of the cyclopropane (Section 3.2.3).

4.2 FUTURE WORK

4.2.1 Ketenes as Metal Carbene Precursors

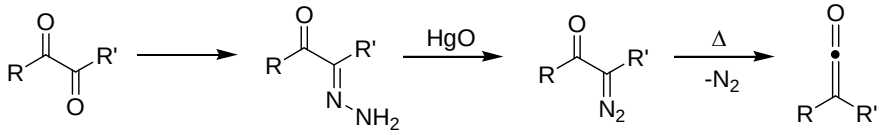
The utilization of ketenes as precursors to metal carbenes is relatively unprecedented. Expanding the use of these substrates would be beneficial, as it will provide an alternative to diazo-based precursors. While diazo compounds are fairly reliable in metal carbene chemistry, they are potentially dangerous due to their highly explosive nature. Ketenes can be easily prepared from the corresponding acid chloride via the carboxylic acid (Scheme 4.1).

Scheme 4.1



An alternative method to ketene preparation is from the hydrazone, which generates the diazo compound *in situ*, upon treatment with HgO, and undergoes a Wolff rearrangment with heating (Scheme 4.2).[2]

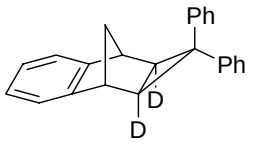
Scheme 4.2



Stable ketenes, such as aryl, acyl and silyl ketenes can be prepared, isolated, and stored for extended periods of time.[3] These ketenes also do not contain β-hydrogens, therefore, the 1,3-hydride shift pathway is not available (Section 2.1). Unstable ketenes can be prepared *in situ* in the presence of a metal to generate the metal carbene.

4.2.2 Mechanistic Studies of Cyclopropane Isomerization

Studies into the mechanism of the palladium(II)-catalyzed diphenylcyclopropane isomerization is necessary. Given the unique reactivity of these species, investigations into how it occurs will provide further insight into palladium(II) cyclopropane ring-openings, in general. The use of deuterium-labelling experiments would provide clues into the mechanism of this process. Preparation of a deuterated cyclopropane (**4.1**) would illustrate whether or not the hydrogens of the cyclopropane are being conserved in the final product (Figure 4.1).

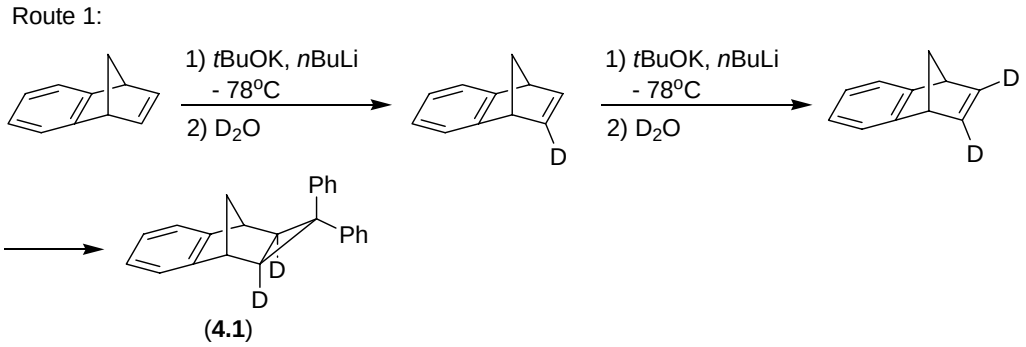


(**4.1**)

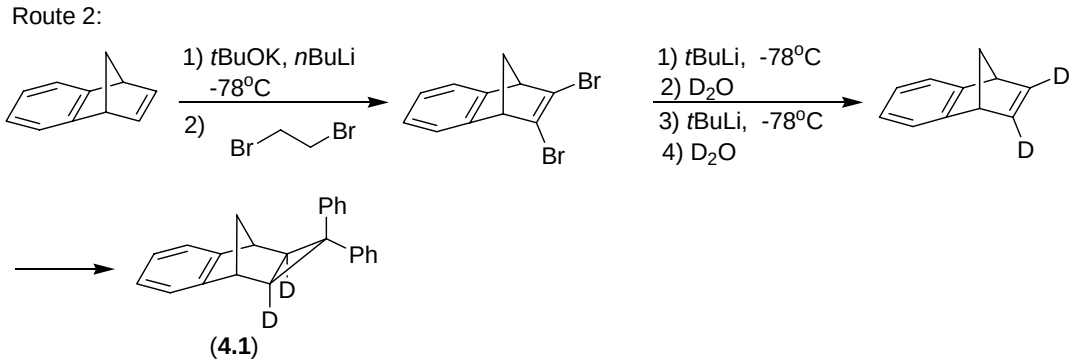
Figure 4.1: Deuterated cyclopropane for mechanistic studies.

Two potential routes for the preparation of **4.1** are outlined in Scheme 4.3.[4]

Scheme 4.3



(**4.1**)



Treating compound **4.1** with catalytic $PdCl_2$, in 0.2 M $(CH_2Cl)_2$ for 24 h at 120 ºC should afford the following product (Figure 4.2).

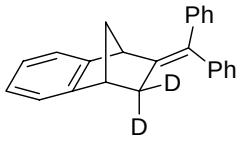


Figure 4.2: Proposed product of isomerization using deuterated cyclopropane.

The formation of this product would indicate that there is no external proton source and that the reaction forms the product within the reaction mixture. However, if an external proton source is playing a role in the reaction then the product shown in Figure 4.3 is expected.

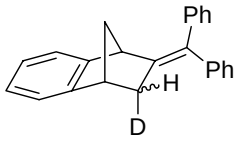


Figure 4.3: Product of external proton source.

In order to gain insight into the formation of the trisubstituted products, other cyclopropanes need to be prepared and reacted under the isomerization conditions. It was proposed that the formation of these products was the result of either a stabilizing overlap between the σ* of the C-O bond and the π electrons of the double bond (Figure 4.4a) or via chelation to the palladium before chloropalladation of the cyclopropane (Figure 4.4b).

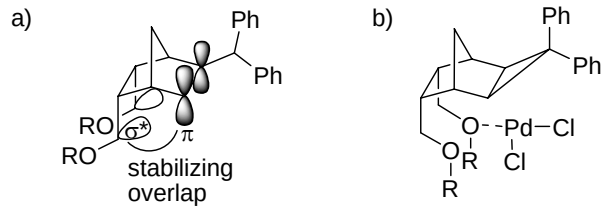


Figure 4.4: Proposals for the formation of the trisubstituted products.

Therefore, preparation of the *exo*-version of these cyclopropanes (**4.2**) would help elucidate the mechanism further (Figure 4.5).

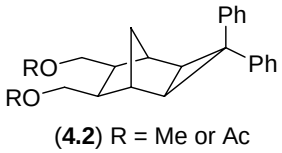
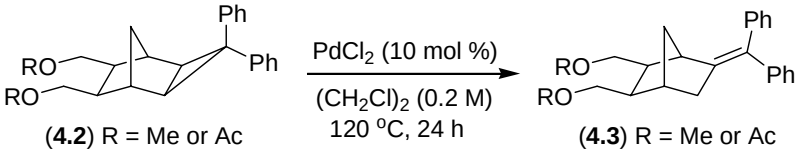


Figure 4.5: *exo*-cyclopropane substrate.

If the formation of the trisubstituted products is the result of a stabilizing overlap (Figure 4.4a) or chelation to palladium (Figure 4.4b) then **4.2** should afford the tetrasubstituted olefin **4.3** (Scheme 4.4).

Scheme 4.4:



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[2]Smith, L. I.; Hoehn, H. H. *Org. Synth.* **1940**, *20*, 47.
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[4]a) Stäble, M.; Lehmann, R.; Schlosser, M. *Chimica* **1985**, *39*, 229, b) Verkruijsse, H. D.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas*. **1986**, *105*, 66, c) Tranmer, G. K.; Yip, C.; Handerson, S.; Jordan, R. W.; Tam, W. *Can. J. Chem.* **2000**, *78*, 527.