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UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

PALLADIUM-CATALYZED CARBOXYLATIVE COUPLING REACTIONS OF ALLYLTRIBUTYLSTANNANES AND ALLYL CHLORIDE

A Dissertation

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

degree of

Doctor of Philosophy

By

RUSSELL JAMES FRANKS

Norman, Oklahoma

2002

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PALLADIUM-CATALYZED CARBOXYLATIVE COUPLING REACTIONS
OF ALLYLTRIBUTYLSTANNANES AND ALLYL CHLORIDE

A Dissertation APPROVED FOR THE
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

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A project as difficult as the pursuit of an advanced degree is very seldom, if ever, a task that one is able to complete alone. I certainly was no exception to this idea. There are so many people who have helped me during my life as a student. I can hardly repay the debt I owe to them, but I would like to acknowledge their help and offer them my sincere gratitude for their kindness. I would first like to begin by offering glory to God and thanking him for the many blessings he has bestowed upon me; for the blessings of family, friends, health, intelligence, and for strengthening my will to persist and persevere during the hard times.

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Chapter 1

AN APPROACH TO CARBOXYLATIVE COUPLING REACTIONS

1.1 INTRODUCTION

1.1.1 CO_2 as an environmental problem

There has been a great deal of concern over the past few decades about the continually increasing amounts of "greenhouse gases" in the atmosphere. The most abundant of these greenhouse gases is carbon dioxide (CO_2). The increase in levels of atmospheric CO_2 has been correlated with the Industrial Revolution. Studies of air samples trapped in pockets of ice from Antarctica showed that CO_2 levels were constant at 280-290 ppm prior to 1800. The concentration of CO_2 in the atmosphere has increased steadily ever since. CO_2 levels were 315 ppm in 1958, 340 ppm in 1980, and 360 ppm in 1995.[1] It has been estimated that the amount of CO_2 in the atmosphere increases at a rate of 7 billion tons per year. This increase in atmospheric CO_2 levels has been blamed on a combination of factors including losses of tropical rain forest areas, increased industrialization, and increased usage of fossil fuels.

It is feared that an increase in the amounts of atmospheric greenhouse gases could alter global weather patterns. Such changes can cause drought in one region and flooding in a neighboring region. There can also be serious economic and political ramifications if agriculture and commerce are disrupted. Some climatologists have even proposed a nightmarish scenario in which the increase in global temperatures causes partial or complete melting of the polar ice caps. This would be a worldwide catastrophe that would flood coastal cities

like New York, Shanghai, New Orleans, Houston, etc. It is amazing that such a small and seemingly innocuous molecule like CO_2 could be the cause of such problems, but the global warming debate is certain to continue in the foreseeable future.[2]

1.1.2 CO_2 as an environmental remedy

Ironically, although CO_2 has been implicated as one of the main causes of one environmental problem, it is also being investigated as a possible solution to another one.[3] Many industrial chemical processes use large amounts of organic solvents, which are often expensive and hazardous. While much effort is made to reuse these solvents, sometimes it is not possible. The large-scale disposal of industrial solvent waste is very expensive as it must either be incinerated or buried in a landfill. There is currently a tremendous amount of research work underway to investigate the possibility of using CO_2 as an alternative solvent. The use of CO_2 as a solvent has economic and environmental benefits. The primary advantage to using CO_2 is that it is cheap and abundant.[4] The atmosphere is perhaps the most familiar source of CO_2. The actual percentage of CO_2 in the atmosphere is 0.03%, but this "small" number is misleading. The mass of CO_2 in the atmosphere has been estimated to be *100 trillion tons.* In the United States alone, the amount of CO_2 emissions from combustion of fossil fuels was estimated (in 1990) to be more than 1.4 billion tons annually. The former USSR is estimated to have produced around 1 billion tons of CO_2 annually.

1.2 CARBON DIOXIDE UTILIZATION

1.2.1 Introduction

The idea of CO_2 utilization is not a new one; CO_2 is already an important industrial chemical. Some of the more familiar applications of CO_2 are in the carbonation of beverages and in fire extinguishers. Supercritical CO_2 is used as a chromatographic solvent and for extracting caffeine from coffee beans.[5] Other less familiar, but important applications of CO_2 are in the industrial production of urea, methanol, secondary oil recovery, and plastics production.[6]

The largest-scale CO_2 utilization process, however, is not of human origin. Nature has been using CO_2 as a chemical building block for billions of years. Photosynthesis could well be described as the single most important chemical process on Earth; as all organisms are either directly or indirectly dependent on it. Approximately 200 billion tons of biomass are produced yearly from photosynthesis. While humans will probably never be able to duplicate the breadth and beauty of photosynthesis, they already use CO_2 for a variety of applications, and the list continues to grow.[7]

1.2.2 CO_2 as a C_1 source

One potential area of application for CO_2 that has not been developed enough, however, is the use of CO_2 as a C_1 source for fine chemical synthesis.[8] The primary benefit of using CO_2 as a C_1 source in chemical production is a reduction in the use of sources derived from fossil fuels. CO_2 is attractive as a C_1 source since it is inexpensive and abundant. There are serious, fundamental

chemical problems with using CO_2 as a C_1 source, however. There is a significant thermodynamic barrier to the conversion of CO_2 to many organic chemicals since CO_2 is a very stable molecule (ΔH_f° = -94.0 kcal mol^{-1}, ΔG_f° = -94.3 kcal mol^{-1}). In addition to the thermodynamic barriers, there are also kinetic problems involved in CO_2 activation. One of the main problems is a mass-transfer problem. Many organic reactions are carried out in solution, but CO_2 is a gas under ambient temperature and pressure conditions. This makes is difficult to attain a CO_2 concentration that is comparable to that of the other reactants in solution. This can reduce the overall rate of reaction. This problem can be minimized by performing the reaction using elevated CO_2 pressures in order to maximize the effective concentration of CO_2. This also poses practical problems, as special equipment capable of withstanding high pressures is needed.

1.2.3 Applications of supercritical fluid technology to CO_2 utilization/activation

A recent approach to the mass transfer problems of CO_2 activation has been to use supercritical CO_2 ($scCO_2$) as a solvent for the reaction.[9] This idea is attractive economically and environmentally. It eliminates the need for large amounts of organic solvents, and simplifies product separation and catalyst recovery. The $scCO_2$ can be collected, purified, and recycled. The primary attractiveness of using $scCO_2$ in CO_2 activation, however, is improved kinetics. Noyori *et al.* were able to achieve catalytic hydrogenation of formic acid in $scCO_2$ eighteen times faster than when the same reaction was done using THF as the solvent.[10] The use of $scCO_2$ does present some unique difficulties. The primary

obstacle to working in $scCO_2$, ironically, is one of solubility. Many catalysts and reagents are insoluble in $scCO_2$; therefore, care must be taken to insure that the reaction is truly homogeneous. This often necessitates modification of catalysts and reagents in order to preserve solubility properties. Additionally, there is a considerable amount of specialized and expensive equipment that must be used for $scCO_2$ work. The study of catalysis in $scCO_2$ is a rapidly growing area and appears to have a great deal of potential for the future.

1.3 TRANSITION METAL-BASED APPROACHES TO CO_2 ACTIVATION

1.3.1 Transition metal catalysis in organic synthesis

A considerable amount of research work over the past several decades has been devoted to the use of transition metal complexes to catalyze organic reactions. Researchers have used homogeneous catalysis to achieve remarkable control of organic reactions. This was recognized in 2001 when the Nobel Prize in Chemistry was awarded to William Knowles, Ryoji Noyori, and K. Barry Sharpless for their contributions in the field of homogeneous catalysis. This intense work on organometallic catalysis has also had an impact on the field of CO_2 activation.

1.3.2 Main group organometal approaches to CO_2 activation

Chemists have been able to overcome the reactivity problems of CO_2 by using organometallic reagents. The most well known reaction of organometallic

reagents and CO_2 is the carboxylation of Group 1 and 2 organometallics used in the synthesis of carboxylic acids (eq 1-1).[11]

$$\text{R-M (M = Li, MgX)} \xrightarrow[\text{2) } H^+]{\text{1) } CO_2} \text{R-CO}_2\text{H} \qquad \text{(1-1)}$$

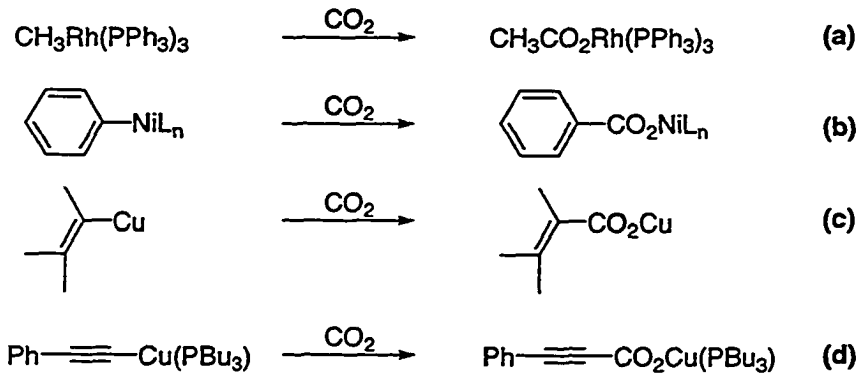
The resulting carboxylic acids can be easily converted into a variety of different, synthetically useful functional groups. The primary disadvantages of this process are the same ones normally encountered in synthetic applications of Group 1 and 2 organometals, i.e. low functional group compatibility and low selectivity. The combination of strong basicity and strong nucleophilicity of these organometals makes them react with most synthetically useful functional groups. This necessitates either using a number of protection/de-protection steps or devising a more complex synthetic route if one wishes to carboxylate a polyfunctional substrate. Either approach is likely to make the synthesis less efficient and more expensive. One way that this problem might be avoided is to use less-reactive main group organometallics (Groups 12-14). These compounds have been shown to be synthetically useful, as they are less reactive, more functional group tolerant, and more selective than Group 1 and 2 organometals. However, many Group 12-14 organometals do not react directly with CO_2, or they react very slowly. The problem is not thermodynamic, as a reaction in which a M-C σ-bond and a C=O π-bond are broken and a C-C σ and a M-O σ-bond are formed should be thermodynamically favorable. The problem is a kinetic one. Group 12-14 organometals are not sufficiently nucleophilic to attack CO_2; and, in addition, the carbon center of CO_2 is not sufficiently electrophilic as to induce attack by the

organometal. This type of problem is not unknown in Group 12-14 organometallics. There are many known C-C bond-forming reactions involving the direct reaction of Group 1 & 2 organometals and electrophiles (e.g. Würtz coupling), but the same types of reactions between Group 12-14 organometallics and electrophiles are not nearly so common. The problem of low reactivity of main group organometals and electrophiles can be overcome using homogeneous transition metal catalysis. This has given rise to a large, synthetically useful family of catalytic C-C bond-forming reactions. These so-called "metal-catalyzed cross-coupling reactions" will be discussed in more detail later. The key step in these coupling reactions is the transmetalation of the organic group from the main group metal to the transition metal. Although the main group organometals are not reactive enough to attack CO_2, it is possible that an analogous transition metal organometal might be reactive enough to attack CO_2.

1.3.3 Stoichiometric reaction of organotransition metal complexes with CO_2

A large variety of transition metal organometallic compounds is known to react stoichiometrically with CO_2. These have been reviewed extensively in the literature.[12] The simplest reaction of this type is the direct reaction between CO_2 and alkyl, aryl, alkenyl, and alkynyl derivatives of organometals (Scheme 1-1).[13]

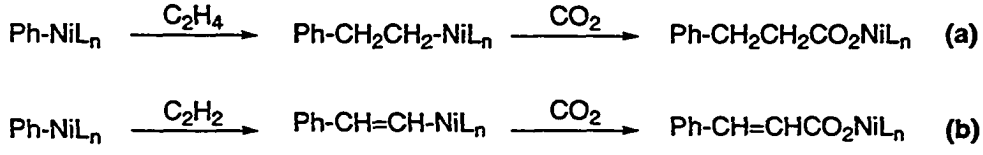
Scheme 1-1
Illustrative reactions of CO_2 with transition metal organometallic reagents



Although these type of reactions appear to be simple, the organometallic substrates can be formed in many different ways, e.g. by nucleophilic substitution, oxidative addition, transmetallation, migratory insertion, or hydrometallation.

A second type of CO_2 insertion reaction is a tandem insertion reaction in which an unsaturated hydrocarbon undergoes a migratory insertion reaction with a metal alkyl. The resulting metal organyl then attacks CO_2. This type of reaction is illustrated in Scheme 1-2.[14]

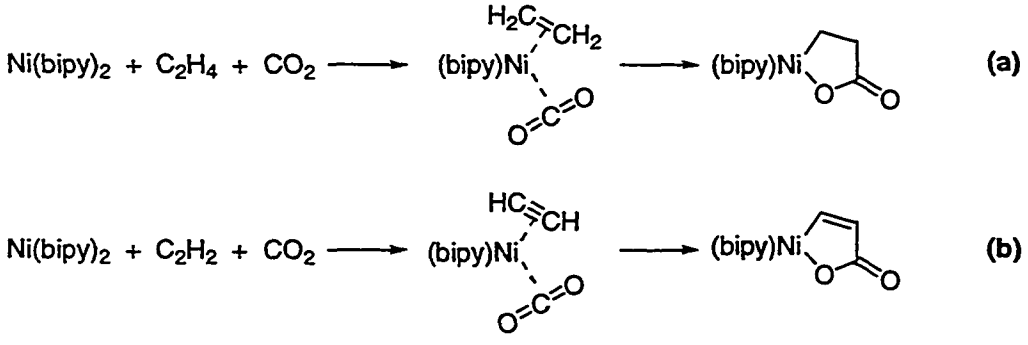
Scheme 1-2
Tandem insertion reactions with CO_2



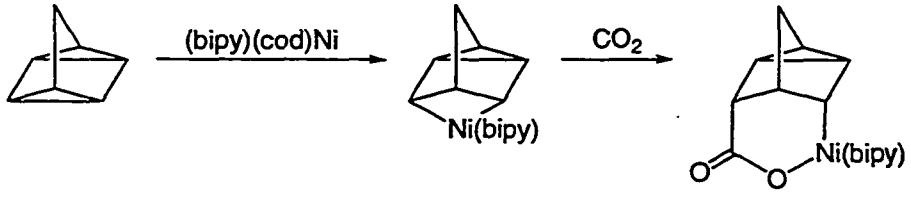
This type of reaction has the net effect of adding three carbon atoms to the substrate. The product of this reaction sub-type is a metal carboxylate.

A third type of CO_2 insertion reaction does not begin with an organometallic, but rather engages the metal complex, an alkene/alkyne, and CO_2 in an electrocyclic process, as shown in Scheme 1-3.[15] The product of this type of reaction is a five-membered metallalactone.

Scheme 1-3
Electrocyclic CO_2 insertion



A fourth type of CO_2 insertion reaction involves generation of a reactive metallacyclobutane intermediate by cleaving one of the highly strained C-C bonds of a polycyclic cyclopropyl ring. The metallacyclobutane produced then undergoes CO_2 insertion and yields a six-membered oxametallacycle. An example of this type of reaction is illustrated in eq. 1-2.[16]



(1-2)

These examples illustrate the variety of different types of stoichiometric reactions that can occur between transition metal organometals and CO_2. Studies of such stoichiometric reactions are important since the development of catalytic reactions often begins with modification of known stoichiometric reactions. The ultimate goal of CO_2 activation chemistry is often to discover and develop a system that reacts with CO_2 catalytically.

1.3.4 Catalytic reactions of organotransition metal complexes with CO_2

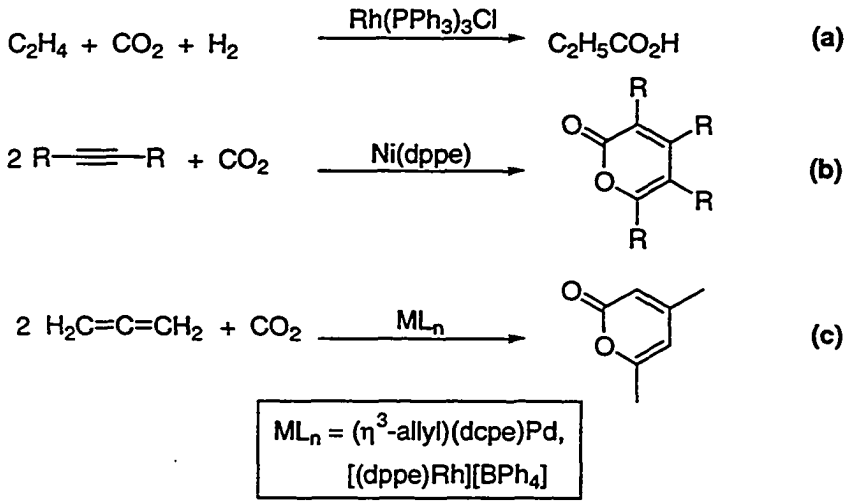
There are a number of catalytic CO_2 activation reactions.[17] The discussion in this work will be limited to homogeneous systems. The simplest catalytic CO_2 reaction is the hydrogenation of CO_2 to formic acid and its derivatives. The most interesting example of this is the work of Noyori *et al.*, shown in eq. 1-3.[10]

$$CO_2 + H_2 \xrightarrow[sc\ CO_2\ /\ Et_3N]{Ru(PMe_3)_4H_2} HCO_2H \qquad (1\text{-}3)$$

Noyori's work is an impressive example of the kinetic benefits of doing reactions in $scCO_2$. The turnover frequency for this reaction was 1400 h^{-1}, which was *eighteen* times faster than when the same reaction was performed in THF. *In situ* observation of the reaction confirmed that the system was indeed homogeneous. Dimethylformamide or methyl formate could also be produced if dimethylamine or methanol were added to the reaction. Although hydrogenation of CO_2 is a simple reaction, this first example of the use of $scCO_2$ as solvent *and* reactant might be an indication of future trends in CO_2 activation work.

A more conventional, catalytic CO_2 activation reaction is that of unsaturated organic molecules with CO_2. Alkenes and alkynes can react with CO_2 in the presence of a transition metal giving the respective carboxylic acids and α-pyrones (Scheme 1-4).

Scheme 1-4
Catalytic reactions of CO_2 and unsaturated hydrocarbons

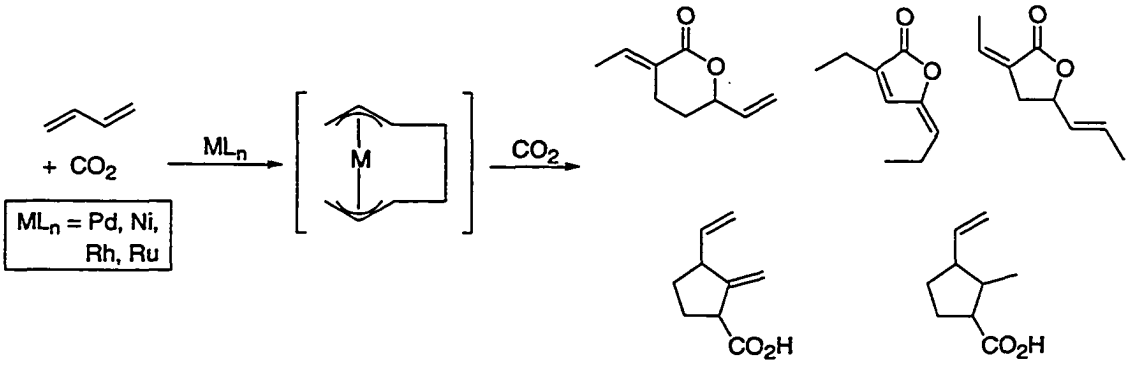


There are not very many catalytic alkene-CO_2 reactions known. Even the type shown above in Scheme 1-4(a) is controversial.[18] There is doubt as to whether or not the carboxylate moiety in the product actually comes from CO_2. More work has been done with the alkyne-CO_2 co-oligomerization (Scheme 1-4 (b)).[19] This reaction is quite sensitive to the nature of the ligand used. The conversion of alkyne to α-pyrones is not clean. Yield of the α-pyrones was only 60 % with almost complete consumption of the alkyne. Another problem in this type of system is poor regiocontrol. Allenes react with CO_2 in the presence of catalyst in a manner similar to that of the alkynes (Scheme 1-4(c)) yielding the substituted

α-pyrone, but also a mixture of esters and other oligomeric materials.[20] The metal-catalyzed reactions of unsaturated hydrocarbons with CO_2 do yield some interesting products; however, the catalytic reactions of 1,3-butadiene with CO_2 have been studied much more extensively.

The reaction of 1,3-butadiene and CO_2 in the presence of a metal catalyst produces a mixture of lactones, esters, and carboxylic acids. Scheme 1-5 illustrates some of the products that can be formed in these reactions; it must be noted that not every reaction yields all of the products shown.

Scheme 1-5
Co-oligomerization products of 1,3-butadiene and CO_2

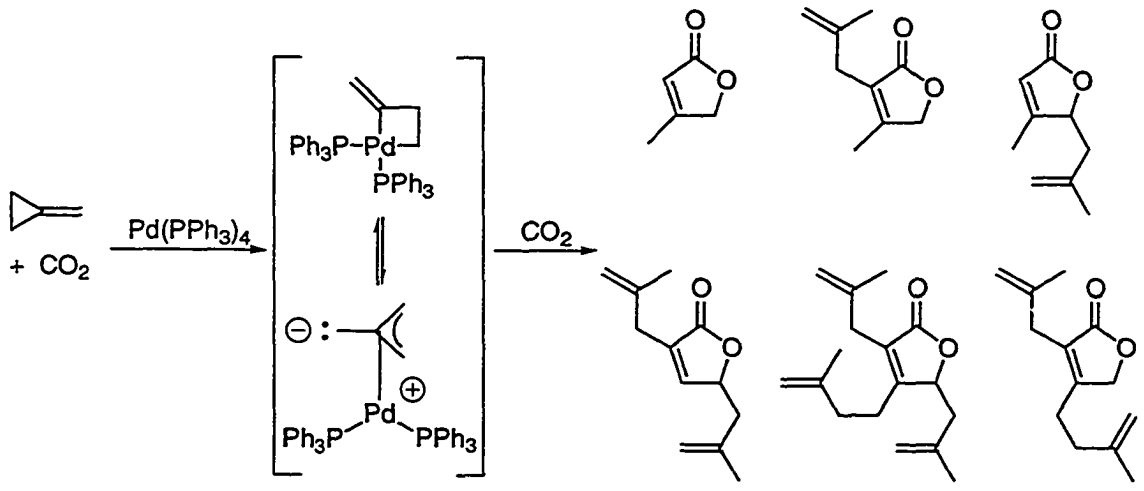


Behr has studied these systems extensively, and has proposed a number of catalytic mechanisms to account for the mixture of products. These mechanisms are quite interesting as they all invoke one or more (η^3-allyl) complexes or bis(η^3-allyl) complexes as intermediates in the reactions. The product distribution can be influenced by choice of metal complex, ligands, and reaction conditions (e.g. temperature, pressure, solvent). In some cases, it is

possible to get selective formation of only one product, but not for each of the possible products.[21]

A reaction that is quite similar to the butadiene-CO_2 reaction is the one between methylenecyclopropane and CO_2. Methylenecyclopropane and CO_2 react in the presence of a palladium(0) catalyst to yield α,β-unsaturated γ-butyrolactones. This is illustrated in Scheme 1-6.

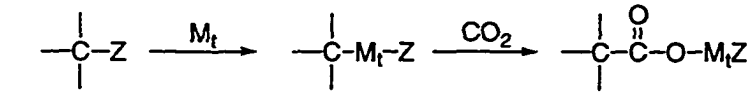
Scheme 1-6
Reactions of methylenecyclopropane and CO_2



This reaction is believed to proceed via a methylenepalladacyclobutane/(η^3-allyl)Pd intermediate. As is the case in the butadiene reactions, the product distribution in this system depends on the nature of the palladium complex, ligand, metal-ligand ratio, and other reaction conditions. Unfortunately, the major negative aspect of this type of reaction is that it is difficult to achieve selective formation for each of the possible products.[22]

1.4 RECENT WORK IN CO_2 ACTIVATION AT THE UNIVERSITY OF OKLAHOMA

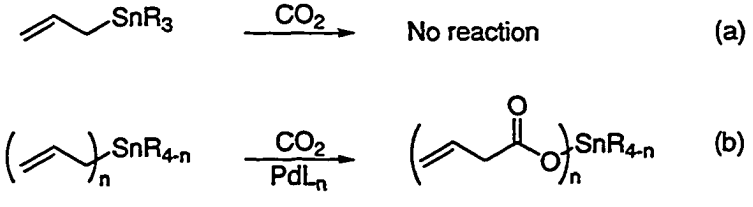
The chemistry of transition metal complexes and CO_2 has long been an interest of the research groups of Prof. Kenneth Nicholas at Boston College and the University of Oklahoma. Recent work in the group has focused on the use of transition metals to activate strained carbon-carbon or labile carbon-main group metal (M_m) bonds (eq. 1-4).



(1-4)

The objective of this work has been to produce reactive intermediates that can activate CO_2. Shi and Nicholas found that allyltin reagents did react with CO_2 at elevated pressure in the presence of a palladium (Pd(0) or Pd(II)) catalyst to give a tin carboxylate.[23] These results are summarized in Scheme 1-7.

Scheme 1-7
Reactions of allyltins and CO_2



This Pd-catalyzed CO_2 insertion even occurred with di- and tetraallyltin substrates; however, non-allylic substrates were not carboxylated under the same conditions. Although this limitation in the scope of the reaction was

disappointing, the discovery of a means of carboxylating organotin reagents was encouraging as main group organometallic reagents now occupy an important niche in synthetic organic chemistry.

1.5 METAL-CATALYZED CROSS-COUPLING REACTIONS

1.5.1 Introduction

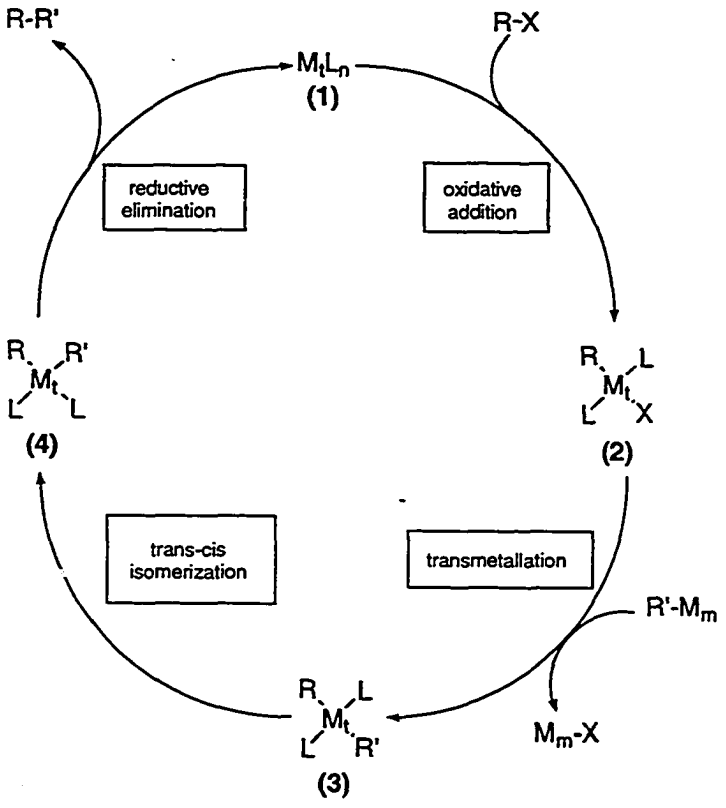
The discovery of metal-catalyzed cross-coupling reactions (MCCCRs) has had a significant impact on organic synthesis over the past twenty years.[24] There is now an entire family of MCCCRs used in organic synthesis. All MCCCRs share a few common elements (eq. 1-5).

$$R\text{-}X + R'\text{-}M_m \xrightarrow{cat.} R\text{-}R' + M_m\text{-}X \qquad (1\text{-}5)$$

MCCCRs use an organic electrophile (R-X) reacting with a main group organometal (R'-M_m) in the presence of a transition metal catalyst. The organic product (R-R') is formed along with the main group by-product (M_m-X). The MCCCR family of reactions shares a common mechanism, which is shown in Scheme 1-8.

The catalytic cycle begins with the catalyst M_tL_n **(1)** undergoing an oxidative addition reaction with the electrophilic species R-X. The organometallic complex formed by oxidative addition **(2)** then undergoes a transmetallation reaction with the main group metal R'-M_m. This transmetallation step is central to all MCCCRs. This gives the *trans* complex **(3)**, which then isomerizes to the *cis* complex **(4)**. The *cis* complex then undergoes a reductive elimination reaction and gives the organic product R-R' and regenerates the catalytic species M_tL_n.

Scheme 1-8
Catalytic mechanism of metal-catalyzed cross-coupling reactions



1.5.2 The advantages of metal-catalyzed cross-coupling reactions

MCCCRs are among the most popular catalytic reactions in current use. One of the primary benefits of using MCCCRs is that they allow C-C bond formation between a broad variety of substrates. MCCCRs can be done with vinyl, aryl, alkynyl, allyl, propargyl, benzyl, allenyl, and even some alkyl substrates. Furthermore, the MCCCRs tolerate a variety of functional groups including ester, nitrile, nitro, halogen, and hydroxyl groups. The reactions give good yields, are normally reasonably fast, and are carried out under mild conditions. The reaction conditions (e.g. temperature, solvent, catalyst, or

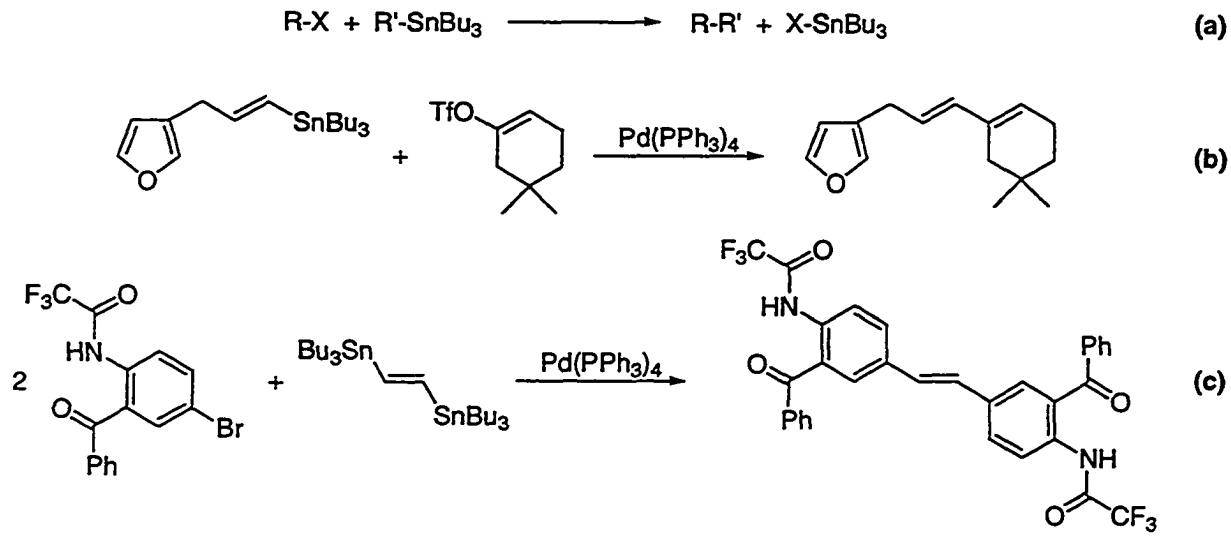
ligands) can also be manipulated to control selectivity. A variety of metal complexes can be used to catalyze MCCCRs including complexes of nickel, palladium, platinum, rhodium, and copper; with palladium being the most popular. A number of main group metals have been used including zinc, boron, silicon, and tin.

The diversity of substrates is what gives MCCCRs their power. The electrophilic substrate R-X can be an organic chloride, bromide, iodide, tosylate, triflate, or acid chloride. The triflates are notable, as they enable vinylic substrates to be generated using enolate chemistry. The chemistry of MCCCRs is now quite mature and they are considered a common synthetic tool. Such versatility has made MCCCRs the subject of considerable study, and they have been reviewed extensively in the literature.

1.5.3 The Stille coupling reaction

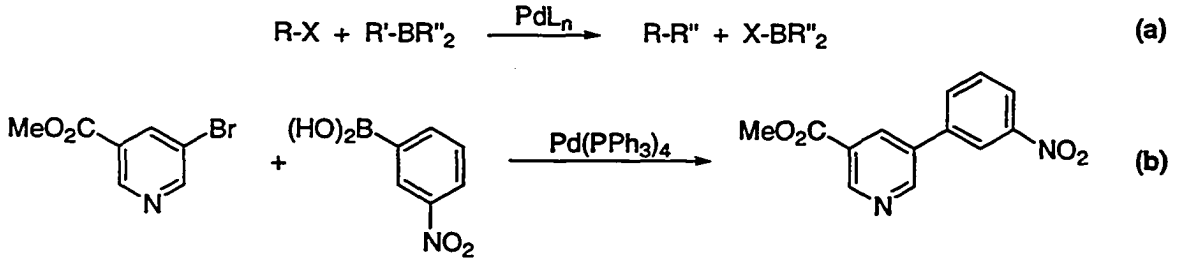
The late Prof. John K. Stille of Colorado State University was one of the pioneers in the field of metal-catalyzed cross-coupling reactions. His work on palladium-catalyzed reactions of organotins remains the most useful and the most thoroughly studied of all the MCCCRs. The term metal-catalyzed cross-coupling reaction, however, refers to a family of reactions. To refer to a specific reaction in the family, the surname of the scientist associated with studying the system is often used colloquially. For example, for example MCCCRs with M_t = Pd and M_m = Sn are referred to as Stille reactions or Stille couplings (Scheme 1-9).

Scheme 1-9
Examples of Stille coupling reactions



If, however, M_t = Pd and M_m = B, then the reaction is commonly referred to as a Suzuki reaction, after Prof. Akira Suzuki of the Okayama University of Science in Japan (Scheme 1-10).[25]

Scheme 1-10
Examples of Suzuki coupling reactions



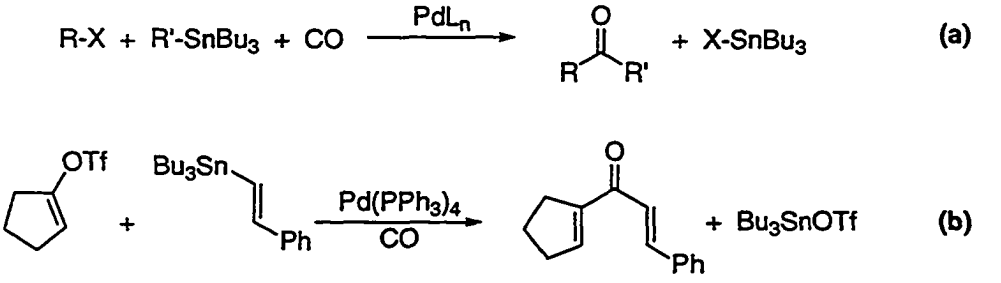
The Stille reaction is the most widely used of all the MCCCRs, and has been reviewed extensively.[26] Stille reactions have been used in the synthesis of an extremely wide array of compounds including natural products, pharmaceutical products, biomimetic compounds, and many others. The utility of

the Stille reaction does not end with simple carbon-carbon bond formation; it also offers another interesting synthetic possibility.

1.5.4 The Stille carbonylative coupling reaction

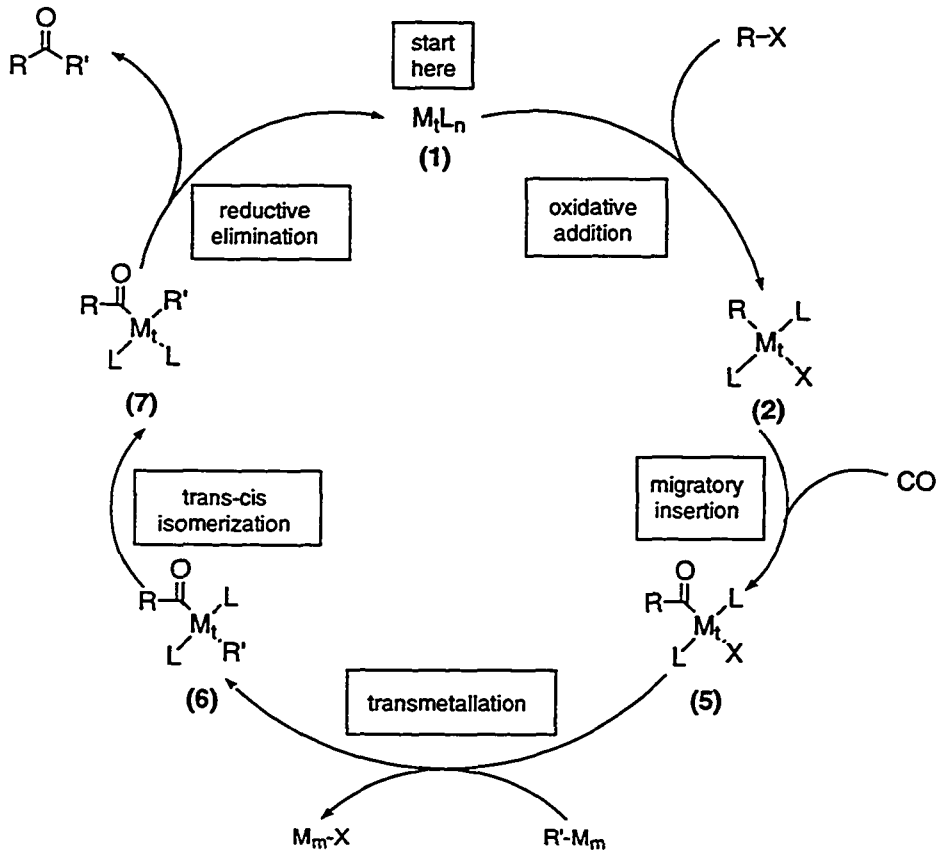
The Stille reaction can also be used to form ketones if it is done in the presence of carbon monoxide, as indicated in Scheme 1-11. This not only forms two new carbon-carbon bonds, but it also adds a carbon atom to the product molecule. The resulting ketone can undergo the normal range of carbonyl chemistry. Hence, this method offers a means of coupling molecular sub-units together with the possibility of subsequent functionalization. These are very attractive qualities for the synthetic chemist.

Scheme 1-11
Examples of Stille carbonylative coupling reactions



The carbonylation occurs through a mechanism that is very similar to the normal MCCCR mechanism with an additional migratory insertion step with CO. The generally accepted mechanism for the carbonylative coupling is shown in Scheme 1-12. It should be noted that the Suzuki coupling can also be done under CO to give carbonylatively coupled products.

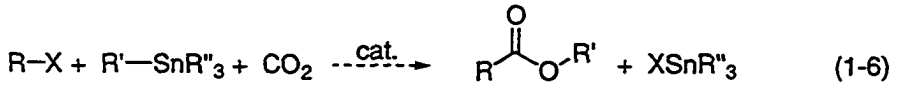
Scheme 1-12
Mechanism for Pd-catalyzed carbonylative coupling reactions



The Suzuki carbonylative coupling also is believed to react via a mechanism that is very similar to the one shown in Scheme 1-12. In most cases, the carbonylation proceeds under mild pressure conditions (1-3 atm) and in good yields. Thus, the carbonylative coupling further amplifies the synthetic usefulness of the Stille reaction.

1.6 CAN A *CARBOXYLATIVE* METAL-CATALYZED CROSS-COUPLING REACTION BE DEVELOPED?

The synthetic potential of the Stille carbonylative coupling reaction provokes some interesting ideas when it is considered in the light of the Nicholas group's discovery of the Pd-catalyzed carboxylation of allyltin reagents. The overall focus of this work is to investigate the use of CO_2 as a C_1 source for the synthesis of esters or lactones. Specifically, this study began with the goal of discovering a metal-catalyzed *carboxylative* coupling reaction, i.e.



(1-6)

If the initial goal were achieved, then the reaction would be explored more fully. Such research would address the following questions:

- Can the reaction be made to work with a variety of substrates?
- Can the system be manipulated to suit synthetic needs?
- Can the mechanism of the reaction be studied?
- Can the reaction be done under ambient conditions?

These questions will be addressed in subsequent chapters.

1.7 BIBLIOGRAPHY

1) Greenwood, N.N.; Earnshaw, A. *Chemistry of the Elements*, 1st ed.; Pergamon: New York, NY, 1984; pp 329-333.

2) (a) Barer, S.J.; Stern, K.M. In *Catalytic Activation of Carbon Dioxide*; Ayers, W.M., Ed.; American Chemical Society: Washington, DC, 1988; pp 1-7. (b) Butler, J.N. In *Catalytic Activation of Carbon Dioxide*; Ayers, W.M., Ed.; American Chemical Society: Washington, DC, 1988; pp 8-15.

3) Halmann, M.M. *Chemical Fixation of Carbon Dioxide: Methods for Recycling CO_2 into Useful Products*; CRC: Boca Raton, FL, 1993; pp 1-29.

4) (a)*Green Engineering*; Anastas, P.T.; Heine, L.G.; Wiliamson, T.C., Eds.; ACS Symposium Series 766; American Chemical Society: Washington, DC, 2001. (b) *Green Chemical Syntheses and Processes*; Anastas, P.T.; Heine, L.G.; Wiliamson, T.C., Eds.; ACS Symposium Series 767; American Chemical Society: Washington, DC, 2000.

5) (a) Taylor, L.T. *Supercritical Fluid Extraction*; Wiley: New York, NY, pp 1–27. (b) Phelps, C.L.; Smart, N.G.; Wai, C.M. *J. Chem. Educ.* **1996**, *73*, 1163.

6) Ballou, W.R. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 4; Wiley-Interscience: New York, NY, 1978, pp 725-742.

7) (a) Asada, K. In *Organic and Bio-organic Chemistry of Carbon Dioxide*; Inoue, S.; Yamazaki, N., Eds.; Wiley: New York, NY, 1982; pp 185-251.

(b) Gregory, R.P.F. *Biochemistry of Photosynthesis*; Wiley Interscience: New York, NY, 1989.

(c) Hall, D.O.; Rao, K.K. *Photosynthesis*, 6th ed.; Cambridge: New York, NY, 1999. (d) *Photosynthesis: A Comprehensive Treatise*; Raghavendra, A.S., Ed.; Cambridge: New York, NY, 1998.

8) (a) Behr, A. *Angew. Chem. Intl. Ed. Engl.* **1988**, *27*, 661. (b) Behr, A. *Nato ASI Ser., Ser. C* **1987**, *206 (Carbon Dioxide Source Carbon: Biochem. Chem. Uses)*, 295. (c) Arakawa, H.; Aresta, M.; Armor, J.N.; Barteau, M.A.; Beckman, E.J.; Bell, A.J.; Bercaw, J.E.; Creutz, C.; Dinjus, E.; Dixon, D.A.; Domen, K.; DuBois, D.L.; Eckert, J.; Fujita, E.; Gibson, D.H.; Goddard, W.A.; Goodman, D.W.; Keller, J.; Kubas, G.J.; Kung, H.H.; Lyons, J.E.; Manzer, L.E.; Marks, T.J.; Morokuma, K.; Nicholas, K.M.; Periana, R.; Que, L.; Rostrup-Nielson, J.; Sachtler, W.M.H.; Schmidt, L.D.; Sen, A.; Somorjai, G.A.; Stair, P.C.; Stults, B.R.; Tumas, W. *Chem. Rev.* **2001**, *101*, 953.

9) (a) Wu, B.C.; Paspek, S.C.; Klein, M.T.; LaMarca, C. In *Supercritical Fluid Technology: Reviews in Modern Theory and Applications*; Bruno, J.J.; Ely, J.F., Eds.; CRC Press: Boca Raton, FL, 1991, pp 511-524. (b) Hutchenson, K.W.; Foster, N.R. In *Innovations in Supercritical Fluids: Science and Technology*; Hutchenson, K.W.; Foster, N.R., Eds.; ACS Symposium Series 608; American Chemical Society: Washington, DC, 1995, pp 1-31.

10) (a) Jessop, P.G.; Ikariya, T.; Noyori, R. *Nature* **1994**, *368*, 231. (b) Jessop, P.G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1994**, *116*, 8851. (c) Jessop, P.G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1995**, 707. (d) Jessop, P.G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1995**, *95*, 259. (e) Jessop, P.G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 344. (f) Jessop, P.G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475.

11) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, NY, 1992, pp 933-934 and references therein.

12) (a) Volpin, M.E.; Kolmnikov, I.S. *Organomet. React.* **1975**, *5*, 313. (b) Lapidus, A.L.; Ping, Y.Y. *Russ. Chem. Rev.* **1981**, *50*, 63. (c) Tanaka, K. *Adv. Inorg. Chem.* **1995**, *43*, 409. (d) Gibson, D.H. *Chem. Rev.* **1996**, *96*, 2063. (e) Leitner, W. *Coord. Chem. Rev.* **1996**, *153*, 257.

13) (a) Keim, W. *J. Organomet. Chem.* **1968**, *14*, 179. (b) Cahiez, G.; Normant, J.F.; Bernard, D. *J. Organomet. Chem.* **1975**, *94*, 463. (c) Miyashita, A.; Yamamoto, A. *J. Organomet. Chem.* **1973**, *49*, C57. (d) Ikariya, T.; Yamamoto, A. *J. Organomet. Chem.* **1974**, *72*, 145. (e) Miyashita, A.; Yamamoto, A. *J. Organomet. Chem.* **1976**, *113*, 187. (f) Marisch, N.; Camus, A.; Nardin, G. *J. Organomet. Chem.* **1982**, *239*, 429.

14) (a) Behr, A.; Keim, W.; Thelen, G. *J. Organomet. Chem.* **1983**, 249, C38. (b) Keim, W.; Behr, A.; Gruber, B.; Hoffmann, B.; Kowaldt, F.H.; Kürschner, U.; Limbäcker, B.; Sistig, F.P. *Organometallics* **1986**, *5*, 2356.

15) Ito, T.; Kindaichi, V.; Takami, Y. *Chem. Ind.* **1980**, *1*, 83.

16) Behr, A.; Thelen, G. *C_1 Mol. Chem.* **1984**, *1*, 137.

17) (a) Ito, T.; Yamamoto, A. In *Organic and Bio-organic Chemistry of Carbon Dioxide*; Inoue, S.; Yamazaki, N., Eds.; Wiley: New York, NY, 1982; pp 79-151. (b) Allen, L.C. In *Catalytic Activation of Carbon Dioxide*; Ayers, W.M., Ed.; American Chemical Society: Washington, DC, 1988; pp 91-101. (c) Baiker, A. *Appl. Organomet. Chem.* **2000**, *14*, 751. (d) Behr, A. *Aspects Homogeneous Catal.* **1988**, *6*, 59. (e) Behr, A. *Carbon Dioxide Activation by Metal Complexes*; Wiley-VCH: New York, NY, 1988. (f) Braunstein, P.; Matt, D.; Nobel, D. *Chem. Rev.* **1988**, *88*, 747.

18) Alvarez, R.; Carmona, E.; Cole-Hamilton, D.; Galindo, A.; Gutiérrez-Puebla, E.G.; Monge, A.; Poveda, M.L.; Ruíz, C. *J. Am. Chem. Soc.* **1985**, *107*, 5529.

19) (a) Inoue, Y.; Itoh, Y.; Hashimoto, H.; *Chem. Lett.* **1977**, 855. (b) Inoue, Y.; Itoh, Y.; Hashimoto, H.; *Chem. Lett.* **1978**, 633. (c) Inoue, Y.; Itoh, Y.; Kazama, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3329. (d) Tsuda, T.; Sumiya, R.; Saegusa, T. *Synth. Commun.* **1987**, *17*, 147. (e) Walther, D.; Schönberg, H.; Dinjus, E.; Sieler, J. *J. Organomet. Chem.* **1987**, *334*, 377.

20) (a) Döhring, A.; Jolly, P.W. *Tetrahedron Lett.* **1980**, *21*, 3021. (b) Aresta, M.; Quranta, E.; Ciccarese, A. *C_1 Mol. Chem.* **1985**, *1*, 283.

21) (a) Dzhemilev, U.M.; Kunakova, R.V.; Sidorova, V.V. *Izv. Akad. Nauk SSSR Ser. Khim.* **1985**, *10*, 2273. (b) Musco, A.; Perego, C.; Tartiari, V. *Inorg. Chim. Acta* **1978**, *28*, L147. (c) Musco, A. *J. Chem. Soc., Perkin*

Trans. 1 **1980**, 693. (d) Behr, A.; Juszak, K.-D.; Keim, W. *Synthesis* **1983**, 574. (e) Behr, A.; Juszak, K.-D. *J. Organomet. Chem.* **1983**, *255*, 263. (f) Behr, A.; v. Ilsemann, G. *J. Organomet. Chem.* **1984**, *276*, C77. (g) Behr, A.; He, R.; Juszak, K.-D.; Krüger, C.; Tsay, Y.-H. *Chem. Ber.* **1986**, *119*, 991. (h) Hoberg, H.; Gross, S.; Milchereit, A. *Angew. Chem. Intl. Ed. Engl.* **1987**, *26*, 571. (i) Behr, A.; Juszak, K.-D.; He, R. *8th International Congress on Catalysis*, West Berlin, 2-6 July 1984, Proceedings, V-565. (j) Behr, A.; He, R. *J. Organomet. Chem.* **1984**, *276*, C69.

22) (a) Inoue, Y.; Hibi, T.; Satake, M.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 982. (b) Binger, P.; Weintz, H.-J. *Chem. Ber.* **1984**, *117*, 654.

23) (a) Shi, M.; Nicholas, K.M. *J. Am. Chem. Soc.* **1997**, *119*, 5057. (b) Shi, M.; Franks, R.; Nicholas, K.M. In *Advances in Chemical Conversions for Mitigating Carbon Dioxide*; Inui, T.; Anpo, M.; Izui, K.; Yanaguida, S.; Yamaguchi, T., Eds.; Elsevier: New York, NY, 1998; pp 165-170. (c) Franks, R.J.; Nicholas, K.M. *Organometallics* **2000**, *8*, 1458.

24) (a) Heck, R.F. *Palladium Reagents in Organic Synthesis*; Academic: Orlando, FL, 1985. (b) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley: New York, NY, 1995. (c) Malleron, J.-L.; Fiaud, J.-C.; J.-Y. *Handbook of Palladium-Catalyzed Organic Reactions: Synthetic Aspects and Catalytic Cycles*; Academic: New York, NY, 1997. (d) *Metal-catalyzed Cross-coupling Reactions*; Diedrich, F.; Stang, P.J., Eds.; Wiley-VCH: New York, NY, 1998. (e) Tsuji,

J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley: New York, NY, 2000.

25) Miyaura, N. Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

26) (a) Stille, J.K. *Pure Appl. Chem.* **1985**, *57*, 1771. (b) Stille, J.K. *Angew. Chem. Intl. Ed. Engl.* **1986**, *25*, 508. (c) Farina, V.; Krishnamurthy, V.; Scott, W.J. *Org. React.* **1997**, *50*, 1-652. (d) Farina, V.; Krishnamurthy, V.; Scott, W.J. *The Stille Reaction*; Wlley: New York, NY, 1998. (e) Mitchell, T.N. In *Metal-catalyzed Cross-coupling Reactions*; Diedrich, F.; Stang, P.J., Eds.; Wiley-VCH: New York, NY, 1998; pp 167-202.

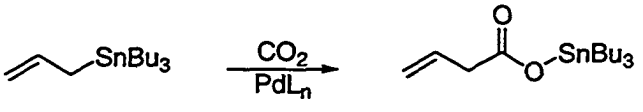
Chapter 2

PALLADIUM-CATALYZED CARBOXYLATIVE COUPLING OF ALLYLTRIBUTYLTIN AND ALLYL CHLORIDE

2.1 INTRODUCTION & BACKGROUND

2.1.1 Carboxylation of allyltin reagents

The research group of Prof. Kenneth Nicholas at the University of Oklahoma has long been interested in the area of metal-catalyzed or metal-mediated CO_2 conversion.[1] One topic of recent interest has been in the study of organic and organometallic compounds that contain reactive C-C or C-M bonds. Allyltin compounds are known to be quite reactive, given their ability to add to carbonyl groups. Dr. Min Shi, a postdoctoral fellow in the Nicholas group, was studying reactive organometallic compounds, including allyltins, in 1996 when he discovered that palladium complexes catalyzed the insertion of CO_2 into various allylic tin compounds (eq 2-1).[2]

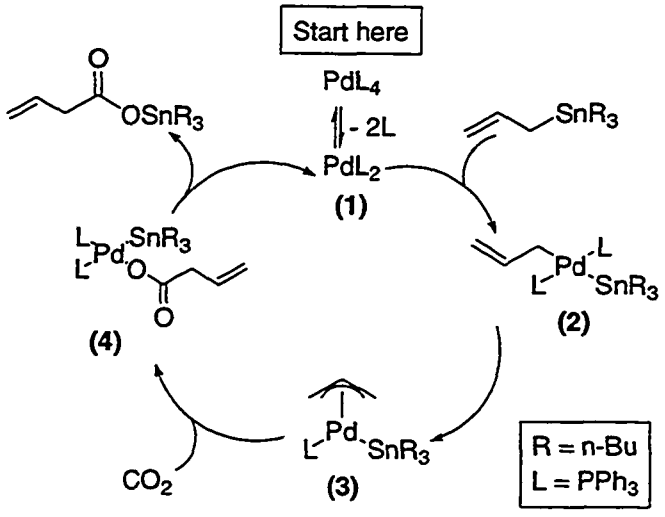


(2-1)

Shi and Nicholas also proposed a catalytic cycle for the reaction (Scheme 2-1). Their cycle began with allyltin undergoing oxidative addition with PdL_2 **(1)** forming an η^1-allyl-Pd intermediate **(2)**. This intermediate could either react with CO_2 directly or could isomerize to the η^3-allyl-Pd intermediate **(3)**, which could then react with CO_2. Either route would give palladium carboxylate **(4)**, which could then undergo reductive elimination forming the tin carboxylate. This reaction was

exciting, because not only did it uncover some heretofore unknown chemistry of allyltin compounds, but also because of the synthetic potential that it held.

Scheme 2-1
Tentative catalytic cycle for Pd-catalyzed carboxylation of allyltin



2.1.2 Metal-catalyzed cross-coupling reactions

Shi's findings held potential because tin and palladium form the cornerstone of one of the most synthetically useful applications of transition metal catalyzed reactions, metal-catalyzed cross-coupling reactions (MCCCRs). The impressive versatility of MCCCRs has made them an important tool in organic synthesis.[3] The variety of main group and transition metals that do MCCCRs is now quite large. These reactions go by different names, depending on the specific metals used, but they have many things in common. The general form of MCCCRs is given in eq. 2-2, and a general catalytic cycle for MCCCRs is given in Scheme 1-8.

$$R\text{-}X + R'\text{-}M_m \xrightarrow{cat.} R\text{-}R' + M_m\text{-}X \qquad (2\text{-}2)$$

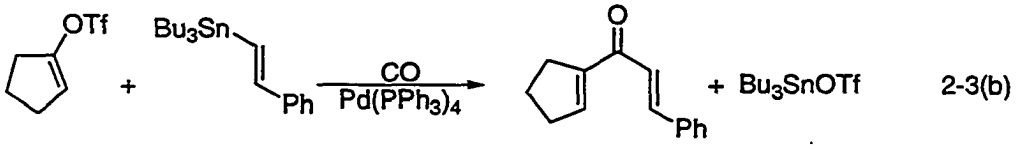
An amazing variety of C-C bonds can be formed using MCCCRs. The most popular of the MCCCRs uses an organotin reagent and palladium catalyst, and is known as the Stille reaction, after the late John K. Stille, who was a pioneer in the development of MCCCRs. Stille reactions have been reviewed extensively, and have now reached the point of ubiquity in organic synthesis.[4] One interesting modification of the Stille coupling reaction is that it can be used for the synthesis of ketones and aldehydes.

2.1.3 Carbonylative coupling reactions

If the Stille reaction is conducted under an atmosphere of CO, the resulting product will have a carbonyl group inserted between the fragment originating from the organotin reagent and the fragment originating from the electrophile (eq 2-3(a)).



2-3(a)

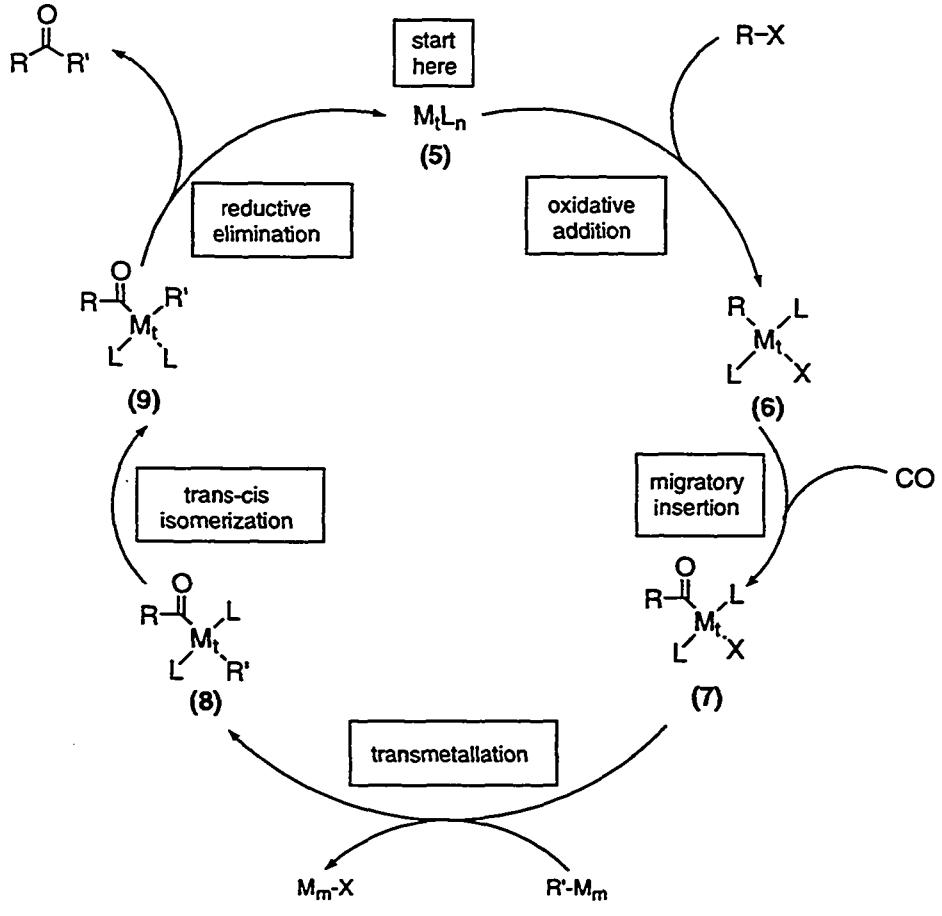


2-3(b)

Such carbonylative coupling reactions have been used in natural product synthesis for the formation of important carbonyl linkages (eq. 2-3(b)). The catalytic mechanism proposed for the Stille carbonylative coupling (Scheme 2-2) is similar to that of the normal Stille coupling (Scheme 1-8). The first step of the cycle is the electrophile undergoing oxidative addition with the metal **(5)** to give **(6)**. The key difference between the carbonylative Stille coupling mechanism and

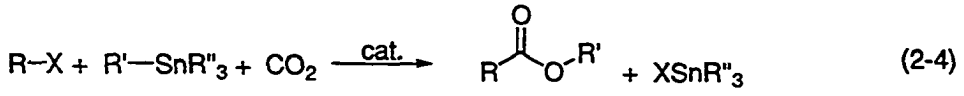
the normal Stille coupling mechanism is that, in the carbonylative mechanism, insertion of CO occurs after oxidative addition, producing carbonylated intermediate **(7)**. The carbonylated complex **(7)** then receives the other organic fragment by transmetallation. The bis-organyl intermediate **(8)** isomerizes and forms the products of the reaction, a ketone and the catalytic species M_tL_n **(5)** by reductive elimination.

Scheme 2-2
Mechanism for Pd-catalyzed carbonylative coupling reactions



2.1.4 Carboxylative coupling reactions

Shi's results and the literature precedent of carbonylative coupling reactions led to our idea of creating an analogous carboxylative coupling reaction. The reaction would be performed under an atmosphere of CO_2 instead of CO (eq 2-4), and, if successful, would yield an ester.



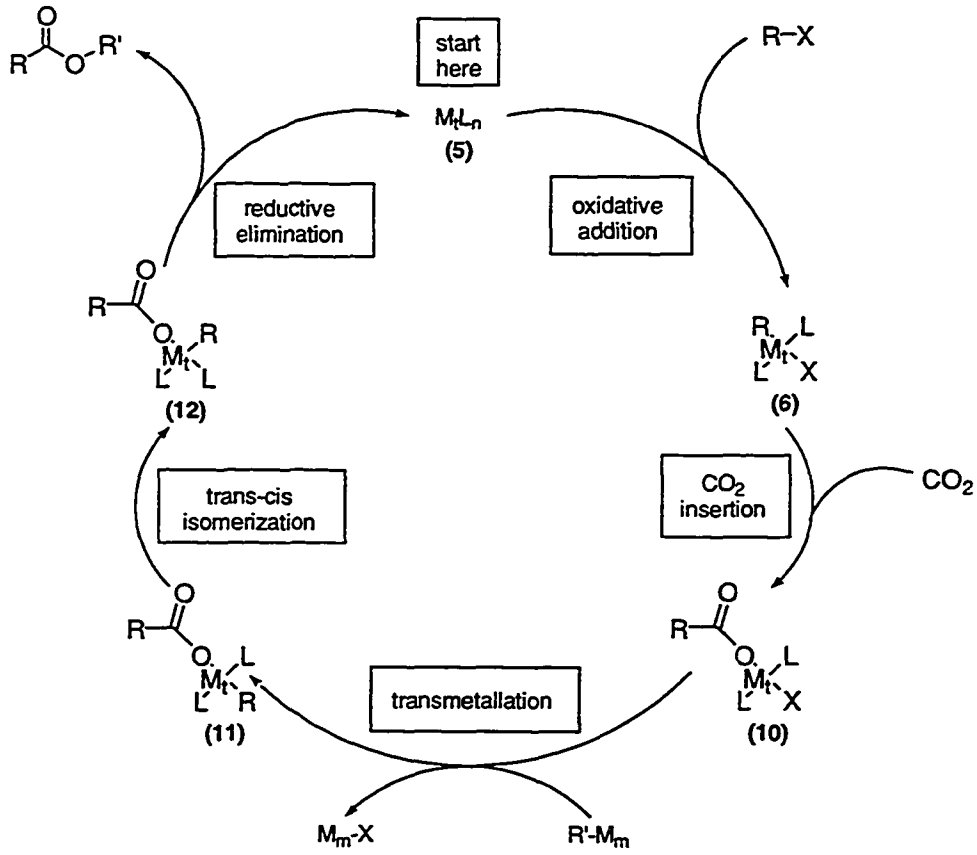
(2-4)

It is possible that such a carboxylation reaction could proceed in a manner analogous to the carbonylative coupling reaction. We envisioned a reaction that would proceed via a mechanism analogous to the carbonylative coupling mechanism (Scheme 2-3). In the hypothetical scheme, a transition metal complex M_tL_n **(5)** first undergoes an oxidative addition reaction with an organic electrophile R-X forming intermediate **(6)**. Species **(6)** reacts with CO_2 to form the carboxylato complex **(10)**. Intermediate **(10)** undergoes a transmetallation reaction, in which an organic fragment is transferred to the carboxylato complex **(10)** from a main group organometal R'-M_m. The resulting *trans*-carboxylato complex **(11)** can then isomerize to the *cis*-carboxylato complex **(12)**, which can then undergo reductive elimination to form the ester product R-CO_2R' and the metal complex M_tL_n **(5)**.

Kinetic issues were one of our main concerns in contemplating such a scheme. We were especially concerned with the relative rates of the transmetallation step and the carboxylation step. If the rate of transmetallation were significantly faster than that of carboxylation, then the reaction would presumably proceed via the normal Stille coupling pathway, and carboxylation

would not occur to any great extent. We hoped that, if this happened, we would be able to overcome such a problem by modification of ligands or other changes in the reaction conditions.

Scheme 2-3
Hypothetical mechanism for Pd-catalyzed carboxylative coupling reactions

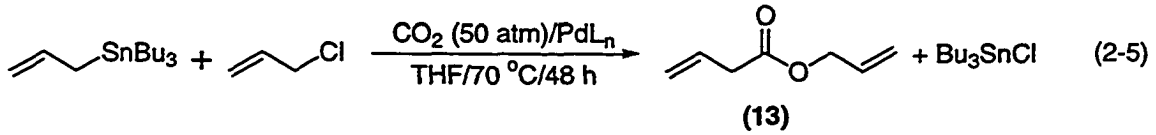


The successful development of such methodology was interesting, not only on its own scientific merits, but also because it stood to make an important contribution to organic synthesis.

2.2 CARBOXYLATIVE COUPLING OF ALLYLTIN AND ALLYL CHLORIDE

2.2.1 Initial results

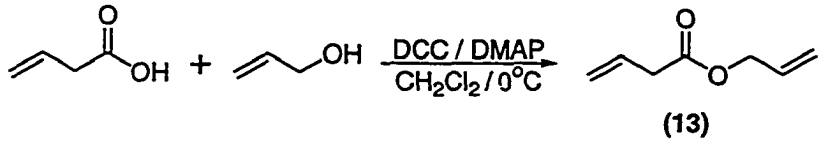
We used Shi's experimental work as a model and attempted a carboxylative coupling reaction of allyltributyltin and allyl chloride. The reaction was performed in a stainless steel autoclave by heating allyltributyltin, allyl chloride, and a palladium complex (10 mol %) in THF at a temperature of 70 °C under a CO_2 pressure of 50 atm for 48 h. The autoclave was vented, opened, and the solvent was removed from the reaction mixture by rotary evaporation. GC analysis of the residual material showed two peaks, which had retention times of 7.8 and 22.0 min. The mass spectrum of the 7.8 min peak gave a base peak at m/z 69, which is consistent with a vinylacylium ion ($[H_2C{=}CH\text{-}CH_2\text{-}C{\equiv}O]^+$). The mass spectrum of the second peak contained several clustered, high mass peaks, which are characteristic of a tin-containing moiety. The ^{1}H-NMR spectrum of the residue showed peaks at δ 3.10 (d, 2H), 4.60 (d, 2H), and 5.15-5.35 (overlapping d, 2H), which were characteristic of an allyl ester product. The NMR spectrum also showed three complex multiplets from δ 0.80-1.90, which were presumably due to the n-butyl groups bonded to tin. These data led us to conclude that allyl 3-butenoate **(13)** was formed in the reaction (eq. 2-5).



(13) (2-5)

Further confirmation of the production of ester in this reaction was provided by comparison of spectral data from the reaction mixture with that

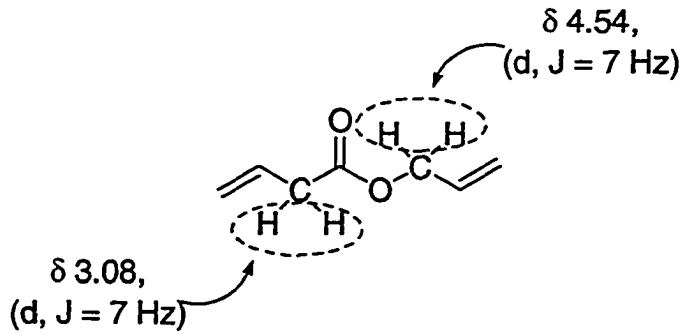
recorded from authentic samples of **(13)**. Authentic samples of **(13)** were synthesized using a DCC/DMAP coupling of the 3-butenoic acid and allyl alcohol (eq. 2-6).[5]



(13) (2-6)

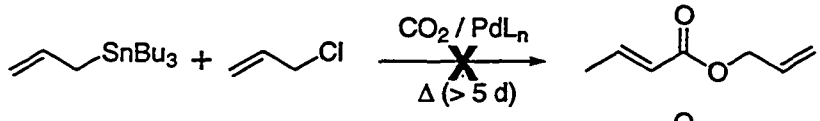
The data obtained from the authentic ester were compared to those from reaction mixtures. The two most useful diagnostic pieces of ^{1}H-NMR spectral data for assigning the structure of **(13)** are the signals for the two sets of α-protons (figure 2-1). The H_2C=CH-CH_2CO_2- protons give a characteristic doublet (J = 7 Hz) at δ 3.08. The H_2C=CH-CH_2-O-(CO)- protons also give a doublet (J = 6 Hz) at δ 4.54.

Figure 2-1
^{1}H-NMR chemical shifts for allylic ester protons of (13)

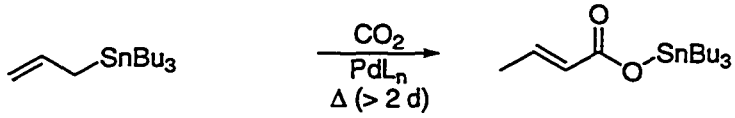


These two signals proved themselves quite useful in later studies. The signal at 3.1 ppm indicated the presence of the 3-butenoyl moiety. The signal at 4.5 ppm, however, was unique for the allyl ester. These signals were useful in identifying more complex mixtures of carboxylated products (*vide infra*) and in studying the mechanism of the carboxylation reaction, which will be discussed in the next chapter. One interesting thing to note from these initial results was that at no

time was evidence ever found for isomerization of the β,γ-unsaturated ester to the α,β-unsaturated ester (eq. 2-7(a)), even after heating for over five days under the reaction conditions.



(2-7(a))



(2-7(b))

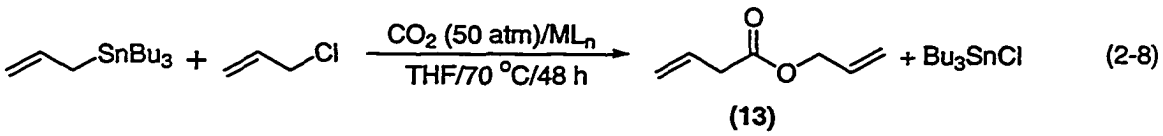
This is in contrast to Shi's findings for the allyltin carboxylation, in which significant isomerization to the α,β-unsaturated tin ester occurred after heating for more than two days (eq. 2-7(b)).

These initial results were encouraging; we had indeed managed to perform a carboxylative coupling reaction. This initial success also left us with many questions and many ideas that we wanted to explore. We wanted to study this new allyl-allyl coupling reaction before moving on to other areas.

2.2.2 Catalyst and ligand variations

One possibility that intrigued us was the idea of being able to control the reaction by varying the catalyst system. Our initial results had indicated that the reaction was catalyzed by Pd(0) and Pd(II) complexes, the best catalysts being $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2/2PPh_3$. We decided to investigate the effects of changing the metal complex and/or the ligand on the yield of the reaction.

The carboxylative coupling reaction was performed using a representative set of zero- and divalent Group 10 complexes and a variety of phosphine ligands (eq. 2-8).



(13) (2-8)

All of these experiments were performed under identical conditions, i.e. in THF, T = 70 °C, t = 48 h, $P(CO_2)$ = 50 atm. The results of these catalyst and ligand variation studies are summarized in Table 2-1.

Table 2-1
Yield and catalyst turnover for allyl-allyl coupling

Entry	Catalyst	Ligand	% yield of ester[§]	TON[‡]
1	none	none	0	0
2	$Pd(PPh_3)_4$	none	46	4.0
3	$PdCl_2(PPh_3)_2$	none	55	3.5
4	$PdCl_2(PPh_3)_2$	PPh_3 (2 equiv)	96	8.1
5	$PdCl_2(PhCN)_2$	PBu_3 (2 equiv)	97	10.3
6	$PdCl_2(PhCN)_2$	dppe[#] (2 equiv)	0	0.0
7	$Pt(PPh_3)_4$	none	87	6.6
8	$PtCl_2(PPh_3)_2$	none	71	6.7
9	$PtCl_2(PPh_3)_2$	PPh_3 (2 equiv)	8	0.8
10	$Ni(1,5\text{-}COD)_2$	PPh_3 (4 equiv)	0	0
11	$NiCl_2(PPh_3)_2$	none	0	0
12	$NiCl_2(PPh_3)_2$	PPh_3 (2 equiv)	0	0

[§]% yield was determined by GC analysis of the reaction mixture and was based on allyltributyltin
[#] dppe = 1,2-bis(diphenylphosphino)ethane
[‡] TON = mmol ester / mmol catalyst

The first of these experiments was a control reaction, which proved that the catalyst is indeed necessary for the reaction to occur (entry 1). Interestingly the reaction appears to proceed better with Pd(II) catalysts than with Pd(0) catalysts (compare entries 2 & 3). The reaction itself does not appear to be very sensitive

to the electronic effects as good turnovers were obtained with PPh_3 and with $P(n\text{-}Bu)_3$ as ligands (entries 4 & 5). Interestingly, the reaction did not occur when the bidentate phosphine 1,2-bis(diphenylphosphino)ethane (dppe) was used (entry 6).

Much more surprising and interesting, however, were the results that were obtained with nickel and platinum complexes. Interestingly, no reaction occurs when $Pt(PPh_3)_4$ was used as the catalyst (entry 7). The results from reactions done with Pt(II) complexes were opposite those obtained from Pd(II) complexes. A yield of 71 % (TON = 6.7) was obtained when $PtCl_2(PPh_3)_2$ was used as the catalyst (entry 8). However, the yield was only 8% (TON = 0.8) when $PtCl_2(PPh_3)_2$ plus 2 additional equivalents of PPh_3 were used as the catalyst (entry 9).

In contrast to the seemingly cooperative, but antithetical catalytic behavior of platinum, nickel was quite recalcitrant; neither Ni(0) nor Ni(II) complexes catalyzed any ester formation at all (entries 10-12). The GC analysis of the reaction mixture showed only unreacted starting materials. The unreactivity of the nickel complexes was surprising, as they have been known to react catalytically with a variety of organic substrates, and they have even been used to catalyze Stille-coupling reactions.[6] The main question that arose from these studies was why were there such striking differences in the reactivities of the nickel and platinum complexes compared to those of the palladium complexes? This is a difficult question to answer specifically without addressing the particular nuances of the reaction mechanism, which will be discussed in the next chapter.

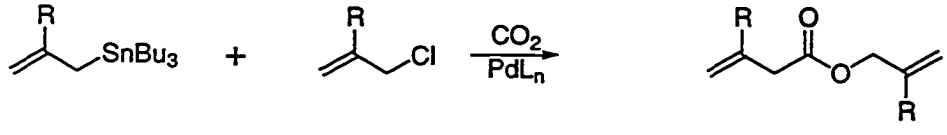
Most likely, the reason for the reactivity differences between the three group 10 metals is that platinum and nickel are unable to form the same catalytic intermediates as palladium under the reaction conditions.

Since the overall objective of this project was to develop a general carboxylative coupling reaction, the next step taken was to investigate the effects of structural variation on the reaction. The study of structural variations on the reaction was carried out in three phases: (1) modification of the allyl substrates (2) variation of the tin substrate and (3) variation of the electrophile.

2.2.3 Allyl substrate variations

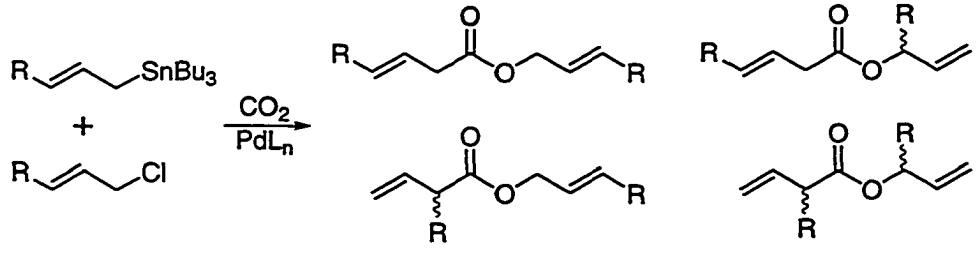
2.2.3.1 Homocoupling of 2-methallyl substrates

The first of these experiments involved using 2-methyl substituted allylic reagents.



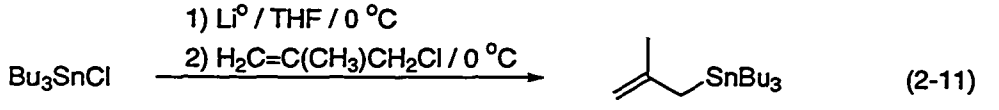
(2-9)

The 2-methyl substituted substrates (eq. 2-9) were selected in order to avoid the possible formation of a complex mixture of regio- and stereoisomeric products (eq 2-10), which would complicate product identification.



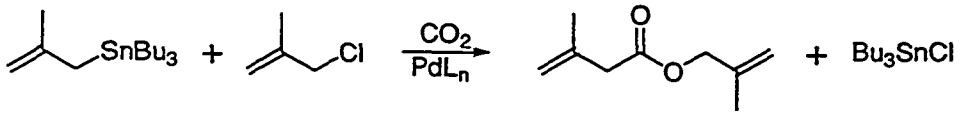
(2-10)

Tri(n-butyl)(2-methallyl)tin was synthesized from 2-methallyl chloride and tributyltin chloride. Tributyltin chloride was first lithiated and subsequently reacted with 2-methallyl chloride using a simple substitution reaction (eq. 2-11).[7]



(2-11)

The product was easily isolated in pure form by vacuum distillation. The resulting tri(n-butyl)(2-methallyl)tin was used in further reactions. The reaction was carried out under the standard reaction conditions (in THF, T = 70 °C, $P(CO_2)$ = 50 atm) using tributyl(2-methallyl)tin and 2-methallyl chloride (eq. 2-12).



(2-12)

(14)

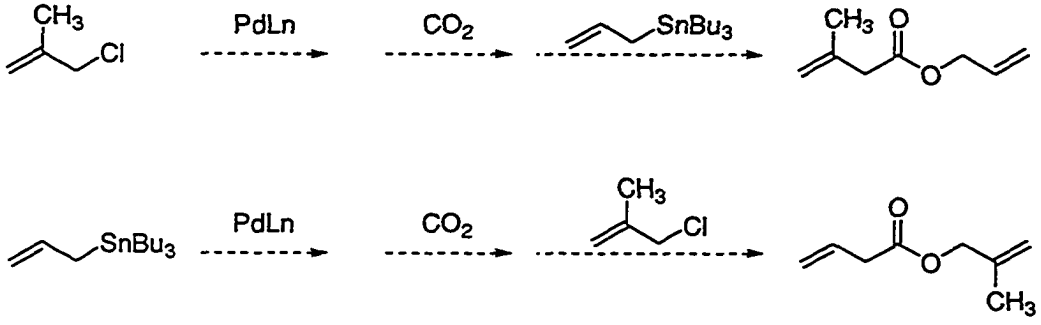
None of the 2-methallyl 3-methyl-3-butenoate product **(14)** was observed by GC or by NMR analysis of the reaction mixture when $Pd(PPh_3)_4$ was used as the catalyst. When $PdCl_2(PPh_3)_2/2PPh_3$ was used as the catalyst, ester **(14)** was formed in 25% yield (by GC) only after the system was heated at 100 °C for five days. These results indicated that the reaction is quite sensitive to steric effects, especially when the allyl substrate is substituted at the 2-position.

2.2.3.2 Heterocoupling of allyl/2-methallyl substrates

These initial results were very encouraging and we were especially interested in determining at which point in the reaction the CO_2 insertion was occurring, especially the order of substrate activation, i.e. does allyltin or allyl chloride react first? We thought that a simple probe that could be used to test

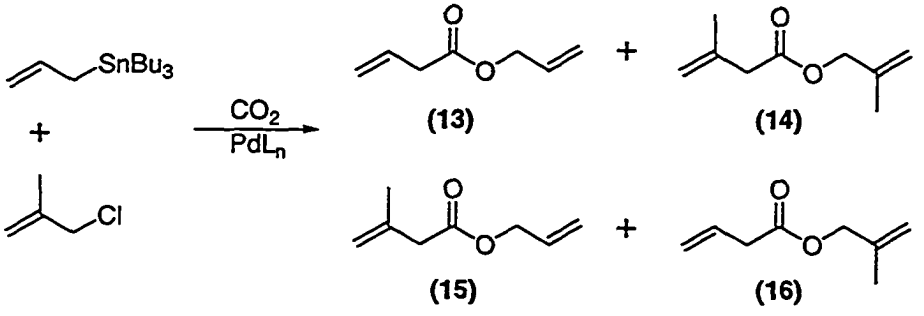
this was a mixed allyl/methallyl substrate combination. Such a system has the potential of producing two different regioisomeric esters during the reaction. If one particular regioisomer were to predominate, this could give us insight into the nature of the CO_2 insertion (Scheme 2-4). We would soon find out that this idea would lead to some very interesting results.

Scheme 2-4
Regiochemical probe of reaction mechanism



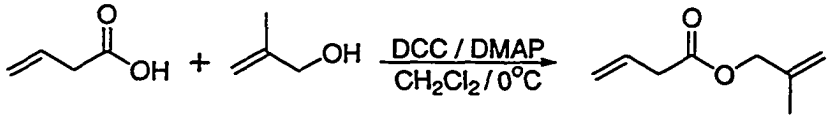
Since allyltributyltin and 2-methallyl chloride were both commercially available we decided to use them to test this idea. Allyltributyltin and 2-methallyl chloride were reacted under the standard reaction conditions using $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2/2PPh_3$ as catalysts (eq. 2-13). The reaction produced some surprising results. An initial GC analysis of the reaction mixture showed that there were four different compounds present at the end of the reaction. Additionally, all four products were present in approximately equal amounts. This nearly statistical distribution of products was observed with either Pd(0) or Pd(II) catalysts. ^{1}H-NMR analysis of the mixture showed a number of suspected ester peaks, but many of these peaks were seen "in pairs", which further led us to suspect that we had a formed a mixture of ester products. We suspected the presence of the two heterocoupled esters **(15)** and **(16)** from the beginning, but

the identity of the other two compounds was quite puzzling. Comparison of data from these experiments to that from earlier allyl-allyl coupling experiments led us to believe that the homocoupled ester **(13)** was also a product in the reaction. The only other permutation of ligands possible was the methallyl-methallyl coupled ester **(14)**. That **(14)** could have been formed in the reaction mixture amazed us. The identities of the four esters were finally confirmed by comparison with authentic samples.



(2-13)

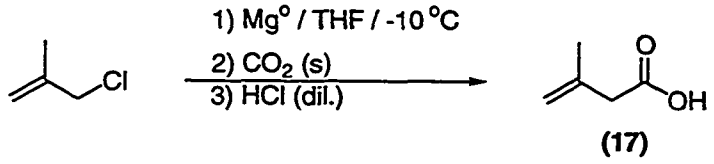
The heterocoupled ester **(16)** was synthesized in 73 % yield from 3-butenoic acid and 2-methallyl alcohol using the standard DCC/DMAP procedure (eq. 2-14).



(16)

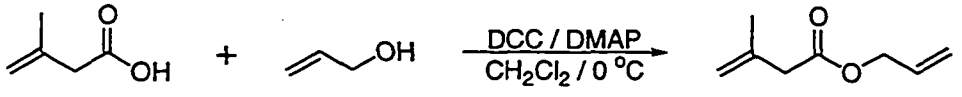
(2-14)

The synthesis of authentic samples of the 3-methyl-3-butenoate esters **(14)** and **(15)**, however, was more challenging. This was primarily because the parent 3-methyl-3-butenoic acid **(17)** was not available commercially. The acid **(17)** was prepared in 52 % yield from 2-methallylmagnesium chloride and CO_2 (eq. 2-15).[8]



(17) (2-15)

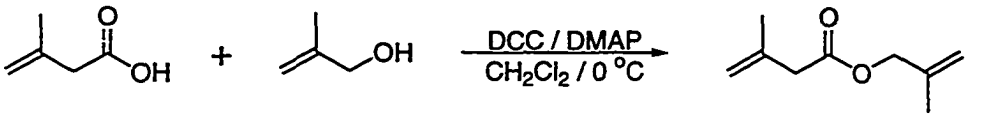
The acid was purified by vacuum distillation. The identity of the acid was confirmed by NMR (^{1}H & ^{13}C), IR, and MS. The 3-methyl-3-butenoate esters were synthesized using DCC/DMAP, **(17)**, and the appropriate alcohol. The heterocoupled ester allyl 3-methyl-3-butenoate **(15)** was prepared as shown in eq. 2-16.



(17) **(15)** (2-16)

The resulting ester **(15)** was extracted, isolated, and purified by vacuum distillation (71% yield based on **(17)**). The most useful spectroscopic traits for confirming the identity of ester **(15)** were the ^{1}H-NMR signals for the α-protons, as was the case for the allyl-allyl coupled ester **(13)** (eq. 2-6). The protons adjacent to the carboxyl group ($H_2C=C(CH_3)-CH_2-CO_2-$) gave a signal at δ 3.07, as was observed for **(13)**, but the signal was a singlet, not a doublet. This gave conclusive evidence that the 3-methyl-3-butenoyl moiety was present in the sample. The identity of the allyl ester was confirmed by the presence of the signal at δ 4.60 for the protons adjacent to the oxygen atom ($H_2C=CH-CH_2-O-(CO)$). The ester product was also analyzed by ^{13}C-NMR, IR, and MS.

The heterocoupled ester 2-methallyl 3-methyl-3-butenoate **(14)** was synthesized from acid **(17)** and 2-methallyl alcohol in 59% yield using the same synthetic method (eq. 2-17).



(2-17)

(17) (14)

Ester **(14)** was isolated, purified, and characterized spectroscopically. A singlet for the protons adjacent to the carboxyl group (H_2C=C(CH_3)-CH_2-CO_2-) was observed at δ 3.07, as had been seen for the other 3-methyl-3-butenoate ester **(15)**. The peak for the methallyl ester, however was different, as had been seen with the other methallyl ester **(16)**. The peak for the protons adjacent to the oxygen atom (H_2C=C(CH_3)-CH_2-O-) was seen as a singlet at δ 4.52. This indicated that the methallyl ester had indeed been formed.

That all four esters **(13)**, **(14)**, **(15)**, and **(16)** were formed when 2-methallyl chloride and allyltributyl tin were carboxylatively coupled was confirmed by comparison of data from GC retention time analysis, GC-MS analysis, and ^{1}H-NMR analysis of the authentic samples and the reaction mixture. The presence of the two heterocoupled esters **(15)** and **(16)** was not surprising as the CO_2 insertion was not expected to be very regioselective given the mixed allyl-methallyl substrates. The presence of the two homocoupled esters **(13)** and **(14)**, however, was quite surprising. The mechanism by which they are believed to have been formed will be discussed in the next chapter. Although the studies that we did on the various allylic substrates produced some interesting and encouraging results, we were ultimately interested in widening the synthetic scope of the reaction to include not only allylic substrates, but also non-allylic substrates. We set out to do this by studying variations in the organotin substrate and in the electrophilic substrate.

2.3 ATTEMPTED CARBOXYLATIVE COUPLING REACTIONS OF NON-ALLYLIC SUBSTRATES

2.3.1 Organotin substrate variations

The normal Stille coupling reaction and the carbonylative Stille coupling reaction both have been performed on a large variety of organotin substrates. We have investigated extensively the effect of varying the organotin substrates on both the carboxylation reaction and the carboxylative coupling reaction. Shi had performed some experiments in this area earlier in the project. He tried, unsuccessfully, to induce carboxylation of a number of organotin compounds (Table 2-2).

Table 2-2
Attempted Pd-catalyzed carboxylation of organotins

$$R\text{-}SnR'_3 \xrightarrow[Pd(PPh_3)_4]{CO_2} \text{No carboxylation}$$
THF / Δ

R	R'	result
n-butyl	n-butyl	no reaction*
vinyl	n-butyl	no reaction*
phenyl	n-butyl	no reaction*
benzyl	n-butyl	no reaction*
propargyl	phenyl	polymerization
phenylethynyl	n-butyl	no reaction*

* = unreacted starting materials observed by GC and/or ^{1}H-NMR

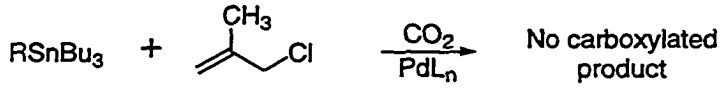
Although these initial results were not very optimistic, we were eager to try performing the reaction with non-allylic tin substrates. Our hope was that the presence of the electrophile, which had not been present in Shi's experiments, would cause the reaction to proceed down a mechanistic pathway more like that

depicted in Scheme 2-4. Such a pathway might produce intermediates that were more likely to react with CO_2. We began with allyltributyltin, tributylvinyltin, tributylphenyltin, and tributyl(phenylethynyl)tin as they could be purchased commercially. It was necessary to synthesize benzyltributyltin **(19)**, however. This was done by reacting commercially purchased benzylmagnesium chloride **(18)** with tributyltin chloride (eq. 2-18).

$$\underset{\textbf{(18)}}{PhCH_2MgCl} + Bu_3SnCl \xrightarrow[0\,^{\circ}C \rightarrow r.t.]{Et_2O} \underset{\textbf{(19)}}{PhCH_2SnBu_3} + MgCl_2 \qquad \textbf{(2-18)}$$

The carboxylative coupling experiments were done under the "standard" carboxylative coupling reaction conditions, i.e. in THF, 70 °C, Pd(0) or Pd(II) catalyst (10 mol %), and $P(CO_2)$ = 50 atm; but using different organotin reagents.

Table 2-3
Attempted carboxylative coupling with variations of tin substrate



entry	R	PdL_n	result
1	vinyl	$PdCl_2(PPh_3)_2$ /2 PPh_3	no carboxylated product*
2	phenyl	$Pd(PPh_3)_4$	no carboxylated product*
3	phenyl	$PdCl_2(PPh_3)_2$/2 PPh_3	no carboxylated product*
4	benzyl	$Pd(PPh_3)_4$	no carboxylated product*
5	benzyl	$PdCl_2(PPh_3)_2$/2 PPh_3	no carboxylated product*
6	phenylethynyl	$PdCl_2(PPh_3)_2$ /2 PPh_3	no carboxylated product*

* = unreacted starting materials observed by GC and/or ^{1}H-NMR

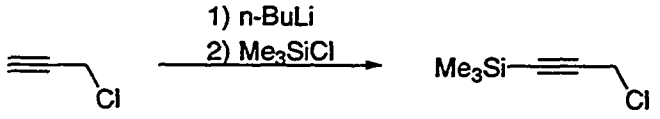
Unfortunately, these experiments produced neither the desired carboxylatively coupled products nor the carboxylated product. Unreacted tributylvinyltin was detected by GC, GC-MS, and ^{1}H-NMR after heating under the reaction conditions (entry 1). The normal Stille coupling product was not detected as it would have been lost during solvent removal after the reaction. Likewise, unreacted starting materials were recovered when tributylphenyltin was heated under the reaction conditions, using either a Pd(0) or a Pd(II) catalyst (entries 2 & 3). No evidence was seen by GC, GC-MS, IR, or NMR of either any carboxylated product or of the normal Stille coupling product (3-phenyl-1-propene). Similar results were observed for benzyltributyltin (entries 4 & 5) and for tributyl(phenylethynyl)tin (entry 6).

The absence of any carboxylated products from these experiments was disappointing, but not altogether surprising given the precedent established in Shi's early experiments. What was surprising, however, was that the normal Stille-coupled products were not observed. Our initial thoughts were that perhaps the presence of a high concentration of CO_2 in the system might have some type of inhibitory effect on the normal Stille coupling mechanism. Later results in our lab and later literature reports have indicated, however, that it is possible for Stille coupling to occur under conditions of high CO_2 pressure, or even in supercritical CO_2. We do not know why the normal Stille coupling was inhibited in these experiments. We were able, however, to perform the Stille couplings of these substrates in the absence of CO_2. A possible reason for this effect, oxidation of the phosphine ligand, will be discussed later in this chapter.

Although these results were somewhat discouraging, the structural variational studies continued.

2.3.2 Electrophilic substrate variations

Since we had unsuccessfully attempted the carboxylative coupling using an allylic electrophile and a variety of non-allylic organotin substrates, we decided to attempt the coupling using different electrophilic substrates, while keeping the organotin substrate allylic. We were especially interested in attempting reactions with substrates that were at least somewhat similar in structure or in reactivity to the allyl group, in the hope that the similarity to the allyl group would translate into reactivity. One such substrate was the propargyl group.[9] We decided to try propargyl chloride **(20)**, which was commercially available, and 3-trimethylsilyl-1-chloro-2-propyne **(21)**, which could easily be prepared from **(20)** (eq. 2-19).[10]

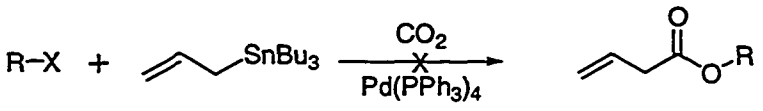


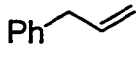
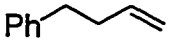
(2-19)

(22) **(23)**

A set of experiments was performed in which the electrophilic species in the reaction was varied, but the organotin reagent was always allyltributyltin. In this phase, as in the other phases, the experiment was carried out under the previously described "standard" conditions, i.e. in THF, 70 °C, $Pd(PPh_3)_4$ (10 mol %), and $P(CO_2)$ = 50 atm; but using aryl, benzyl, and propargyl halides as the electrophile.

Table 2-4
Attempted carboxylative coupling with variations of electrophilic substrate



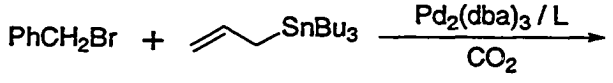
entry	R-X	product
1	PhBr	
2	$PhCH_2Br$	
3	$\equiv\!\!-CH_2Cl$	none
4	$(CH_3)_3Si-\!\!\equiv\!\!-CH_2Cl$	none

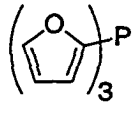
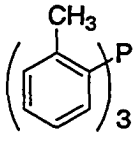
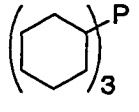
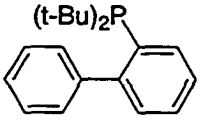
No ester products were observed by GC, GC-MS, or NMR in any of these experiments either. Interestingly the Stille coupling products were detected when bromobenzene (entry 1) or benzyl bromide (entry 2) were used. These were the only experiments, of all of the substrate variation experiments, in which the normal Stille coupled products were observed. The experiments with propargylic substrates produced ambiguous results. NMR and GC-MS analysis of the reaction mixtures indicated that the starting materials were no longer present in the reaction, but the experiment did not produce the Stille-coupled product or the carboxylated product (entries 3 & 4). While the lack of success encountered in these experiments was disappointing, the fact that benzyl bromide and allyltributyltin did react via the normal Stille coupling reaction gave us faint hope that we might be able to achieve carboxylative coupling in a non-allylic substrate.

2.3.3 Benzyl bromide and allyltributyltin: more ligand variations

Normal Stille coupling did occur when benzyl bromide was used as the electrophile (Table 4, entry 2).[11] We were interested to see if we might be able to induce carboxylation by manipulating the ligands in the system. If we could slow either the transmetallation of the allylic fragment from the tin or the isomerization/reductive elimination, we might be able to produce an intermediate that could react with CO_2. This led to an interesting subset of ligand variation experiments. The attempted carboxylative coupling reaction was repeated using a variety of phosphine ligands (Table 2-5). Ligands tested were $P(n\text{-}Bu)_3$, PPh_3, $P(2\text{-furyl})_3$, $P(o\text{-tolyl})_3$, PCy_3, and $P(t\text{-}Bu)_2(o\text{-}Ph\text{-}C_6H_4)$. These ligands were chosen in order to give a reasonably wide range of electronic, steric, and combined electronic-steric properties in the ligand.[12] Unfortunately, none of these experiments produced any ester or carboxylated products. The Stille-coupled product, 4-phenyl-1-butene, was formed when $P(n\text{-}Bu)_3$, PPh_3, $P(2\text{-furyl})_3$, were used as the ligand (entries 1-3 respectively). These are ligands are all fairly basic and are not appreciably sterically bulky. The Stille-coupled product was not formed, however, when $P(o\text{-tolyl})_3$, PCy_3, and $P(t\text{-}Bu)_2(o\text{-}Ph\text{-}C_6H_4)$ were used (entries 4-6 respectively); only starting materials were observed by GC analysis of the reaction mixtures. Furthermore, no GC evidence for the formation of Bu_3SnCl was observed when these ligands were used.

Table 2-5
Attempted carboxylative coupling using benzyl bromide & allyltributyltin with ligand variations



entry	ligand	product
1	$P(n\text{-}Bu)_3$	
2	PPh_3	
3		
4		no reaction
5		no reaction
6		no reaction

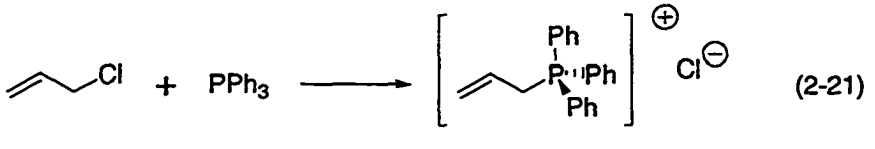
It could be that these ligands were too bulky to allow even the normal Stille-coupling reaction to occur. Although these experiments did not produce the desired carboxylatively coupled products, the results were important because they showed that the normal Stille coupling reaction could occur under carboxylative coupling conditions. This was not the case in some of the earlier experiments using non-allylic substrates (see Scheme 2-3).

2.3.4 Triphenylphosphine oxide as a possible inhibitor of normal Stille coupling

One possible factor that could inhibit the Stille coupling might be a metal-mediated reaction in which PPh_3 is oxidized by CO_2 to $Ph_3P{=}O$ (eq. 2-20).

$$PPh_3 + CO_2 \xrightarrow{ML_n} Ph_3P{=}O + CO \qquad (2\text{-}20)$$

Such atom transfer reactions have been reported in the literature.[13] GC-MS and ^{31}P-NMR experiments, which were performed as part of our study of the mechanism of the allyl-allyl carboxylative coupling, indicated that not only was $Ph_3P{=}O$ formed in the reaction, but also that free PPh_3 was not present at the end of the carboxylative coupling experiments. If this same type of oxidation were common in all of the experiments, the overall concentration of phosphine ligand in the system would be reduced. Such a phenomenon could also have an inhibitory effect on the Stille coupling reaction, which is quite sensitive to ligand effects, by destroying the catalyst. That carboxylation did occur in the case of the allylic systems could be due to a number of reasons. The main reason could be kinetics. The essential catalytic intermediate believed to be formed in the allyl-allyl coupling reactions is likely very reactive toward CO_2 and could react with CO_2 before any atom transfer reaction could occur. Another possible reason could be formation of allyltriphenylphosphonium chloride **(22)** in the system (eq. 2-21).

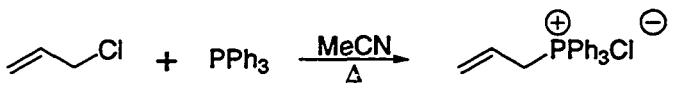


(2-21)

(22)

Although detailed mechanistic discussion of this mechanism will be covered in the next chapter, it is known that allyl chloride and $Pd(PPh_3)_4$ react very rapidly, forming (η^3-allyl)$(PPh_3)PdCl$ **(23)**. Since the Pd-complex is present only in a 1:10 ratio with the allyl chloride, not all of the allyl chloride is converted to **(23)** initially. Some of the remaining allyl chloride could react with PPh_3 to form **(22)**. Such a tetravalent phosphorus species might serve to "protect" the phosphine from oxidation as P(IV) is not as likely as P(III) to participate in any atom transfer reactions. As Pd(0) is regenerated in the catalytic cycle, **(22)** could react with Pd(0) by oxidative addition, form **(23)**, and proceed through the catalytic cycle. It is also possible that benzyl bromide could have reacted in a similar fashion to "protect" the phosphine from oxidation. The other systems that were tested with non-allylic substrates might not have been able to form such a phosphorus (IV) intermediate. This is pure speculation, but could be an explanation for the lack of Stille coupling in these systems.

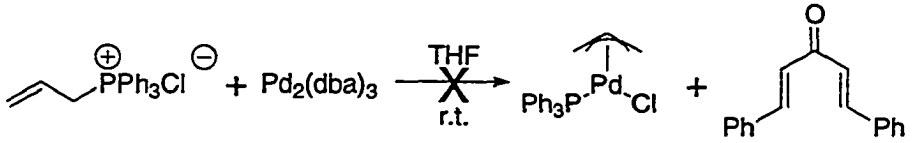
We conducted a set of experiments to test the idea that **(22)** might be a participant in the carboxylative coupling reaction. We first synthesized the phosphonium salt **(22)** by nucleophilic substitution (eq. 2-22). Allyl chloride and triphenylphosphine were refluxed overnight in acetonitrile. Compound **(22)** was isolated as a white solid in 90 % yield. The identity of **(22)** was confirmed using ^1H- and ^{31}P-NMR spectroscopy. After **(22)** had been made, we were able to use it instead of allyl chloride in several of our reactions.



(2-22)

(22)

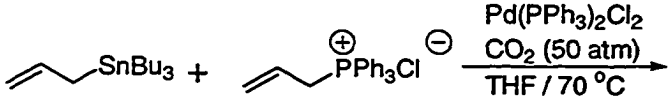
For reasons to be discussed in the next chapter, we were interested in knowing whether or not **(22)** would react with $Pd(PPh_3)_4$ to form (η^3-allyl)$(PPh_3)PdCl$ **(23)**. Normally, **(23)** is formed using $Pd(PPh_3)_4$, but we wanted to avoid introducing external sources of PPh_3 into the system. Thus, we opted to use $Pd_2(dba)_3$ as the Pd(0) source instead. Equimolar amounts of **(22)** and $Pd_2(dba)_3$ were stirred under N_2 overnight at room temperature in THF (eq. 2-23). The following day, however, after the THF had been removed, and CH_2Cl_2 had been added to remove dibenzylideneacetone **(24)**, a black solid remained. Unfortunately, complex **(23)** is yellow, hence evidently some sort of decomposition had occurred, and the procedure was unsuccessful at making **(23)**.



(2-23)

(22) **(23)** **(24)**

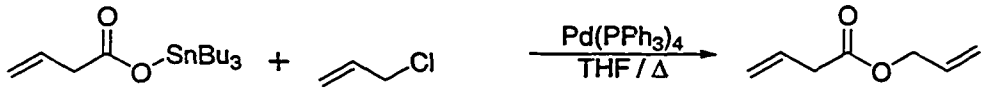
We also wanted to learn if **(22)** would react with allyltributyltin to form ester **(13)** under our standard carboxylative coupling reaction conditions. Allyltributyltin and **(22)** were heated for 48 h in an autoclave in the presence of $Pd(PPh_3)_2Cl_2$ under the standard conditions (eq. 2-24). GC analysis of the reaction mixture after 48 h indicated that ester **(13)** had not been formed in the reaction.



(2-24)

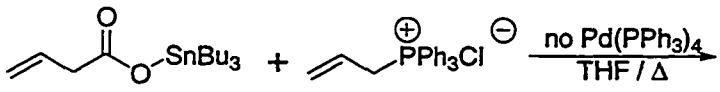
(22)

The last experiments we tried using **(22)** instead of allyl chloride involved an attempted Pd-catalyzed metathesis reaction between tributyltin 3-butenoate and **(22)**. We had discovered that allyl chloride and tributyltin 3-butenoate reacted in refluxing THF in the presence of $Pd(PPh_3)_4$ to form **(13)** (eq. 2-25). Our interest in this reaction was for mechanistic reasons, and will be explained in more detail in the next chapter. We tried a control reaction using **(22)** and tributyltin 3-butenoate, but without Pd-catalyst (eq. 2-26). We also tried the reaction under the same conditions, but using **(22)** instead of allyl chloride (eq. 2-27). In both cases, the system was heated at reflux overnight. GC analysis of the reaction mixture the following day indicated that ester **(13)** had not been formed in either case.



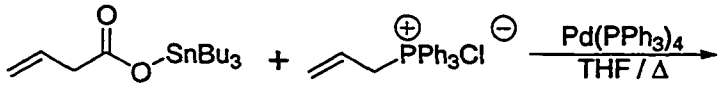
(2-25)

(13)



no ester product formed (2-26)

(22)



no ester product formed (2-27)

(22)

From these results, it became apparent that even if **(22)** is indeed formed during the reaction, it does not appear to transfer its allyl group to the product.

2.4 CONCLUSIONS

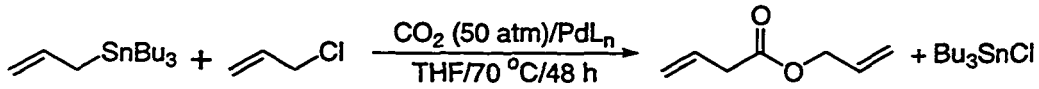
This study met with a good deal of initial success. We did realize our original goal of discovering a palladium-catalyzed carboxylative coupling reaction. We found that allyltributyltin and allyl chloride can be carboxylatively coupled under CO_2 in the presence of a palladium catalyst yielding allyl 3-butenoate. A number of aspects of the original allyl-allyl coupling system were studied including: catalyst, ligand, and numerous substrate variations. Substrate variations included studies of homocoupling of 2-methallyl substrates, heterocoupling of allyl/2-methallyl substrates, organotin/2-methallyl chloride coupling, and electrophile/allyltributyltin coupling. Unfortunately, we were only able to achieve coupling in systems in which both reagents were allylic.
We have concluded that the reaction is unique to allylic substrates based on these results, on our own mechanistic studies (to be discussed later), and on literature reports. We believe that the preference for allyl substrates is because allylic substrates are able to form a highly reactive allyl-palladium intermediate, which is capable of reacting with CO_2. We believe that other, non-allylic substrates are incapable of generating such a reactive intermediate. As we began to study the reaction mechanism, we began to see that there was indeed a nucleophilic palladium complex that was reacting with CO_2.

2.5 EXPERIMENTAL SECTION

All reagents were used as received from the suppliers. All glassware was oven-dried prior to use. THF and diethyl ether were distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from calcium hydride. CO_2 was anaerobic grade (Mattheson). High pressure reactions were carried out in Parr stainless steel autoclaves. GC analysis was carried out on a Hewlett-Packard HP 5790A GC using a 3 m column packed with 10 % OV-101 on Supelcort B, with nitrogen or helium as the carrier gas, and a flame ionization detector. NMR analysis was done using a Varian Unity/Inova 400 or a Varian XL-300. NMR references were tetramethylsilane for ^{1}H and ^{13}C (internal standard), 85 % H_3PO_4 for ^{31}P (external standard), and tetramethyltin for ^{119}Sn (external standard). IR analysis was done using a Bio-Rad model FTS 135 FT-IR spectrometer. GC-MS analysis was carried out on a Hewlett-Packard HP 5985 using a 30 m capillary column packed with 3% SE-54.

General procedure for carboxylative coupling reactions

Reaction:

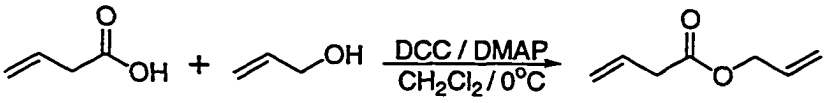


An autoclave was charged with a stir bar and naphthalene (15-25 mg), catalyst (~0.1 mmol, ~10 mol %), allyltributyltin (300 μL, 0.969 mmol), and allyl chloride (100 μL, 1.23 mmol). Distilled THF (20 mL) was added. The autoclave was sealed and purged with CO_2 three times. The system was pressurized to 750 psig with CO_2. After the pressure stabilized, the system was heated at 70 °C

for 48 h. Samples were periodically withdrawn from the autoclave *via* the dip tube and analyzed by GC.

Preparation of allyl 3-butenoate

Rxn:



Reference: Neises, B.; Steiglich, W. *Org. Synth.* **1984**, *63*, 183 (procedure)

Procedure:

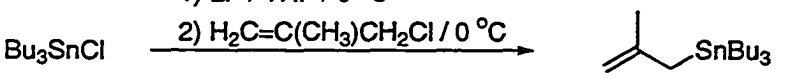
A flask was charged with vinylacetic acid (3.0 mL, 3.0 g, 35 mmol), allyl alcohol (5.0 mL, 4.3 g, 73 mmol), and DMAP (4.94 g, 40.4 mmol). The flask was cooled to 0 °C. A separate flask was charged with DCC (9.31 g, 45.1 mmol). The DCC was dissolved in dry CH_2Cl_2 (20 mL). The DCC/CH_2Cl_2 solution was added to the acid/alcohol/DMAP mixture by syringe over a 5 min period. The mixture was stirred at 0 °C for 5 min and at room temperature for 5 h.

The mixture was filtered and washed with 2 x 20 mL portions of 0.5 N HCl and then with 2 x 50 mL portions of saturated aqueous $NaHCO_3$. The organic solution was filtered, dried with anhydrous Na_2SO_4, and the solvent was removed by rotary evaporation. The product was isolated by vacuum distillation.

^{1}H-NMR: (400 MHz, d_8-THF) δ 3.08 (d, J = 8 Hz, 2 H), 4.54 (d, J = 6 Hz, 2 H), 5.08 (d, J = 12 Hz, 1 H), 5.16 (d, J = 12 Hz, 1 H), 5.28 (d, J = 18 Hz, 1 H), 5.90 (m, 2 H).

Preparation of tributyl(methallyl)tin

Reaction:



Reference: Tamborski, C.; Ford, F.E.; Soloski, E.J. *J. Org. Chem.* **1963**, *28*, 237 (prep. of Bu_3SnLi)

Procedure:

A flask was charged with small pieces of lithium wire (960 mg, 140 mmol). Tributyltin chloride (10.0 mL, 36.9 mmol) was added by syringe. Dry THF (20 mL) was added by cannula. The mixture was stirred under nitrogen at room temperature overnight. A separate flask was charged with methallyl chloride (4.0 mL, 40.6 mmol) and dry THF (20 mL) and cooled to 0°C in an ice bath. The solution of tributylstannyllithium was added to the methallyl chloride solution by cannula. Dry THF (~ 20 mL) was used to rinse any residual material into the flask. The mixture was stirred for 1 h in an ice bath and poured into a solution of saturated potassium fluoride (100 mL). This mixture was vigorously stirred for 90 min. The product was filtered, extracted into hexane, dried over anhydrous $MgSO_4$, and the solvent was removed by rotary evaporation. The product was isolated by vacuum distillation; the product distilled at 107-120°C (1.2 mm Hg). The yield was 7.65 g (60.1 % yield based on tributyltin chloride).

GC: 96.4 % purity

IR: (neat film, NaCl plates) 3075 (m), 2956 (s), 1630 (s), 1418 (m), 1376 (m), 860 (s) cm^{-1}

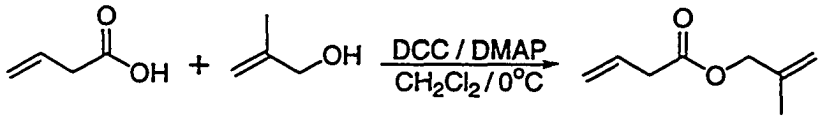
^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.80-1.70 (br, 32 H); 4.42-4.50 (br, 2 H)

^{13}C-NMR: (100 MHz, $CDCl_3$): δ 8.8, 9.4, 13.8, 25.0, 27.4, 29.2, 106, 146

GC-MS: (12 eV) 291 (M^+-C_4H_7), 235 (M^+-C_4H_7-C_4H_9), 179(M^+-C_4H_7-$2C_4H_9$)

Preparation of methallyl 3-butenoate

Rxn:



Reference: Neises, B.; Steiglich, W. *Org. Synth.* **1984**, *63*, 183.

Procedure:

A flask was charged with vinylacetic acid (3.0 mL, 35 mmol), 2-methallyl alcohol (3.0 mL, 44 mmol), and DMAP (3.00 g, 24.6 mmol). These were dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C. A separate flask was charged with DCC (5.6 g, 27 mmol). The DCC was dissolved in dry CH_2Cl_2 (5 mL) and added to the acid/alcohol/DMAP mixture by syringe over a period of 5 min. The system was stirred for 5 min at 0 °C and then at room temperature overnight. The mixture was filtered and the solids were washed with CH_2Cl_2. The solvent was removed by rotary evaporation. The product was isolated by vacuum distillation (bp = 57 °C @ 6.5 mm Hg). Product yield was 3.60 g (72.8 % yield based on vinylacetic acid).

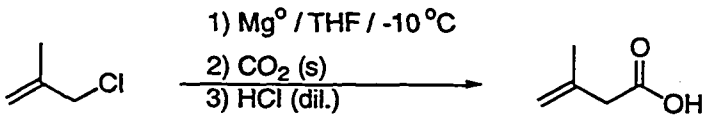
GC: > 99 % purity

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 1.78 (s, 3 H), 3.08 (d, J = 13 Hz, 2 H), 4.51 (s, 2 H), 4.95 (d, J = 20 Hz, 1 H), 5.16 (s, 2 H), 5.19 (d, J = 9 Hz, 1 H), 5.94 (m, 1 H)

^{13}C-NMR: (100 MHz, $CDCl_3$)δ 19, 39, 68, 113, 118, 130, 140, 171

Preparation of 3-methyl-3-butenoic acid

Reaction:



Reference: O' Brien, S.; Fishwick, M.; McDermott, B.; Wallbridge, M.G.H.; Wright, G.A. *Inorg. Synth.* **1971**, *13l*, 74 (procedure)

Procedure:

A flask was charged with granular magnesium (21.7 g, 893 mmol, 1.76 equiv., 20 mesh) and an iodine crystal. Dry THF (300 mL) was added by cannula. The mixture was stirred vigorously. An addition funnel was charged with methallyl chloride (50.0 mL, 508 mmol) and dry THF (250 mL). A small amount of the methallyl chloride solution was added to initiate the reaction. The vessel was cooled to < -10 °C in an ice-salt bath. The methallyl chloride was added over several hours. The mixture was stirred at < -10 °C for 30 min. The mixture was poured over crushed dry ice. Water (200 mL) and 2 M HCl were added until the solution was acidic to pH paper. The product was salted out with sodium chloride, and extracted with 3 x 50 mL portions of diethyl ether. The product was dried with anhydrous $MgSO_4$, and the solvent was removed by rotary evaporation. The product was purified by vacuum distillation. Product distilled at 48-50 °C (0.2 mm Hg). The yield of distilled product was 26.9 g (52.8 % yield based on methallyl chloride).

GC: (EtOAc) 92.6% purity

IR: (NaCl plate, neat film): 3680-2400 (br, s), 1710 (s) cm^{-1}

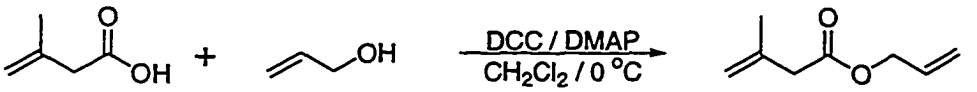
^{1}H-NMR: (400 MHz, d_6-acetone) δ 1.80 (s, 3H), 3.04 (s, 2H), 4.85 (br m, 1H), 4.87 (br m, 1H), 9.20 (br, 1H)

^{13}C-NMR: (100 MHz, d_6-acetone) δ 22, 43, 118, 140, 176

MS (DIP, 70 eV) m/z 100 (84%, M), 85 (12%, M-CH_3), 83 (11%, M-OH), 72 (77%, M-CO), 55 (M-CO_2H)

Preparation of allyl 3-methyl-3-butenoate

Reaction:



Reference: Neises, B.; Steglich, W. *Org. Synth.* **1984**, *63*, 183 (procedure)

Procedure:

A flask was charged with DMAP (10.6 g, 87.1 mmol, 1.56 equiv.), 3-methyl-3-butenoic acid (5.59 g, 55.8 mmol), and allyl alcohol (8.0 mL, 120 mmol, 2.1 equiv.). The flask was cooled to 0 °C. A separate flask was charged with DCC (15.1 g, 55.8 mmol, 1.31 equiv.) and 30 mL of dry CH_2Cl_2. The DCC/CH_2Cl_2 solution was added to the DMAP/acid/alcohol mixture over a period of 5 min. The mixture was stirred at 0 °C for 5 min and then at room temperature for 1 h.

The mixture was filtered to remove solids. The solvent was removed from the filtered liquid by rotary evaporation. The product was isolated in pure form by vacuum distillation. The product distilled at 46-55 °C (6.4 mm Hg). The yield of product was 5.55 g (71.0 % yield based on 3-methyl-3-butenoic acid).

IR: (NaCl plates, neat film) 3084 (m), 2978 (m), 2942 (m), 1739 (s), 1651 (s) cm^{-1}

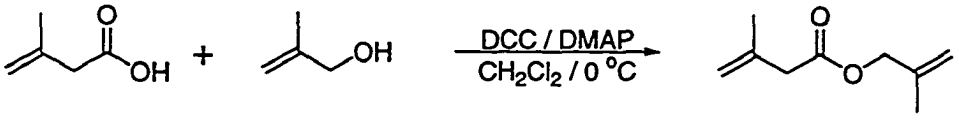
^{1}H-NMR: (400 MHz, $CDCl_3$) δ 1.82 (s, 3H), 3.07 (s, 2H), 4.60 (dt, 2H, J = 6 Hz, 2 Hz), 4.86 (br s, 1H), 4.92 (br s, 1H), 5.24 (dd, 1H, J = 10 Hz, 1 Hz), 5.32 (dd, 1H, J = 17 Hz, 2 Hz), 5.92 (br m, 1H)

^{13}C-NMR: (100 MHz, $CDCl_3$) δ 24, 44, 66, 116, 119, 133, 139, 172

MS: (DIP, 70 eV) m/z 140 (2%, M), 125 (2%, M-CH_3), 99 (8%, M-C_3H_5), 83 (29%, M-C_3H_5O), 55 (100%, M-$C_4H_5O_2$), 41 (7%, M-$C_5H_7O_2$)

Preparation of methallyl 3-methyl-3-butenoate

Reaction:



Reference: Neises, B.; Steglich, W. *Org. Synth.* **1984**, *63*, 183 (procedure)

Procedure:

A flask was charged DMAP (3.72 g, 30.4 mmol, 1.4 equiv.), 3-methyl-3-butenoic acid (2.12 g, 21.2 mmol), and methallyl alcohol (3.0 mL, 36 mmol, 1.7 equiv.). Dry CH_2Cl_2 (10 mL) was added. The flask was cooled to 0 °C. A separate flask was charged with DCC (6.14 g, 29.8 mmol, 1.4 equiv.) and dry CH_2Cl_2 (20 mL). The DCC/CH_2Cl_2 solution to the DMAP/acid/alcohol mixture by syringe over a period of 5 min. The mixture was stirred at 0 °C for 5 min and then at room temperature for 90 min.

The mixture was filtered to remove solids. The solvent was removed by rotary evaporation. The product was isolated by vacuum distillation. The product distilled at 44-48 °C (3.2 mm Hg). Yield of product was 1.94 g (58.6 % yield based on 3-methyl-3-butenoic acid).

GC: (CH_2Cl_2) 94.9 % purity

IR: (NaCl plates, neat film) 3084, 2978, 2937, 1710, 1653 cm^{-1}

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 1.76 (s, 3H), 1.83 (s, 3H), 3.08 (s, 2H), 4.52 (s, 2H), 4.87 (s, 1H), 4.92-4.93 (overlapping singlets, 2H), 4.98 (s, 1H)

^{13}C-NMR: (100 MHz, $CDCl_3$) δ 20, 24, 44, 69, 114, 116, 139, 141, 172

MS: (DIP, 70 eV) 139 (2%, M^+-CH_3), 113 (6%, M^+-C_3H_5), 99 (2%, M^+-C_4H_7), 83 (13%, M^+-C_4H_7O), 57 (100%), 55 (44%, M^+-C_5H_7O)

Preparation of benzyltributyltin

Reaction:

$$PhCH_2MgCl + Bu_3SnCl \xrightarrow[0\,^\circ C \rightarrow r.t.]{Et_2O} PhCH_2SnBu_3 + MgCl_2$$

Reference: Labadie, J.W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129 (compound)

Procedure:

A 50-mL round bottom flask was charged with a stir bar, tributyltin chloride (5.0 mL, 6.0 g, 18.5 mmol), and dry diethyl ether (~25 mL). The flask was sealed with a septum and immersed in an ice bath. Benzylmagnesium chloride (30.0 mL, 30.0 mmol (1.0 M soln. in Et_2O), 1.62 equiv.) was added slowly using a syringe. A syringe pump was used to control the rate of addition (500 μL/min). A white precipitate, presumably $MgCl_2$, formed immediately upon addition of the Grignard reagent. The mixture was stirred overnight at room temperature after all of the Grignard reagent had been added. The reaction was worked up the next day by carefully adding saturated NH_4Cl (aq). The mixture was filtered through Celite. The organic phase was separated, dried with anhyd. $MgSO_4$, and concentrated

by rotary evaporation. The sample was dried under vacuum for 2 h. Yield of product was 6.93 g (98 % yield based on Bu_3SnCl).

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.78-1.44 (br m, 27 H, butyl H), 2.30 (s, 2 H, benzylic H, J_{Sn-H} = 56 Hz), 6.96-7.14 (m, 5 H, aromatic H)

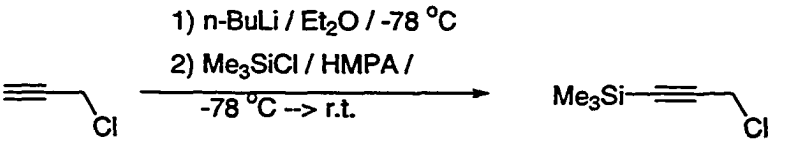
^{13}C-NMR: (100 MHz, $CDCl_3$) δ 9.3, 13.7, 18.2, 27.4, 29.1, 122.9, 127.0, 128.3, 143.7

IR: (neat, NaCl plates) 3022 (m), 3000-2800 (s, br), 1600 (s), 1490 (vs), 1377 (m), 1208 (m), 753 (vs), 696 (vs) cm^{-1}

MS: (FAB, 3-nitrobenzyl alcohol) *m/z*, rel. intensity 325 (81%, M^+-C_4H_9), 291 (100%, M^+-C_7H_7), 267 (7%, M^+-$2C_4H_9$), 235 (28%, M^+-C_7H_7-C_4H_9), 211 (63%, M^+-$3C_4H_9$), 177 (59%, M^+-C_7H_7-$2C_4H_9$), 121 (22%, M^+-C_7H_7-$3C_4H_9$)

Preparation of 3-chloro-1-trimethylsilyl-2-propyne

Reaction:



Reference: Brandsma, L. *Preparative Acetylene Chemistry*, 2nd, ed.; Elsevier: New York, NY, 1988, pp 25, 121-122 (procedure)

Procedure:

A 250-mL round bottom flask was charged with a stir bar and propargyl chloride (8.0 mL, 110 mmol). Dry Et_2O was transferred into the flask via a SS cannula. The flask and contents were cooled to –78 °C in a dry ice-acetone bath. A syringe was used to add n-butyllithium (45.0 mL, 113 mmol (2.5 M in

hexane), 1.0 equiv.). The n-BuLi was added slowly, using a syringe pump, over a 45 min period. The mixture was stirred for 30 min after all of the n-BuLi had been added. A syringe was used to add chlorotrimethylsilane (28.0 mL, 221 mmol, 2.00 equiv.). A separate 50-mL round bottom flask was charged with HMPA (10 mL) and Et_2O (10 mL). This was added dropwise using a syringe over a 30 min period. The mixture turned a milky-white when this was done. The reaction was allowed to warm up slowly to room temperature.

The reaction was quenched by pouring it into icewater (~200 mL). The mixture was transferred to a separatory funnel. The product was extracted using Et_2O (3 x 25 mL) and washed with H_2O (6 x 25 mL) to remove HMPA. The product was dried with anhyd. $MgSO_4$, filtered, and concentrated by rotary evaporation. The NMR of the product showed that it was sufficiently pure such that no further purification was necessary. Yield of product was 15.0 g, 92 % based on propargyl alcohol.

^{1}H-NMR: (300 MHz, $CDCl_3$) δ 0.12 (s, 9 H, $Si(CH_3)_3$), 4.07 (s, 2 H, propargylic H)

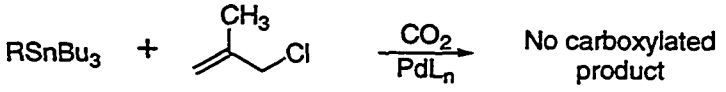
^{13}C-NMR: (75 MHz, $CDCl_3$) δ -0.4, 30.6, 91.6, 99.7

IR: (neat, NaCl plates) 2954, 2900, 2180, 1410, 1254, 1028, 845 cm^{-1}

MS: (DIP, 70 eV) *m/z* 73 (100 %, $(Me_3Si)^+$)

General procedure for attempted carboxylative coupling reactions using allylic electrophilic substrates and non-allylic organotin substrates

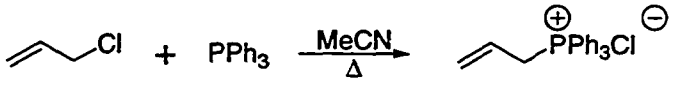
Reaction:



An autoclave was charged with a stir bar and naphthalene (15-25 mg), catalyst (~0.1 mmol, ~10 mol %), organotin reagent (~1 mmol,), and 2-methallyl chloride (100 μL, 1.02 mmol,). Distilled THF (20 mL) was added. The autoclave was sealed and purged with CO_2 three times. The system was pressurized to 750 psig with CO_2. After the pressure stabilized, the system was heated at 70 °C for 48 h. Samples were periodically withdrawn from the autoclave *via* the dip tube and analyzed by GC.

After the reaction period was over, the autoclave was cooled, vented, and opened. The reaction mixture was transferred to a round bottom flask and the solvent was removed under vacuum. The residual material was analyzed by GC, GC-MS, and NMR.

Preparation of allyltriphenylphosphonium chloride
Reaction:



Procedure:

A 50-mL round bottom flask was charged with a stir bar, triphenylphosphine (2.99 g, 11.4 mmol), allyl chloride (2.0 mL, 1.9 g, 25 mmol, 2.2 equiv.), and acetonitrile (30 mL). A condenser was attached and the mixture

was heated overnight at reflux. The following day the solvent was removed under vacuum yielding a white solid. Yield of product was 3.48 g (90 % yield based on triphenylphosphine).

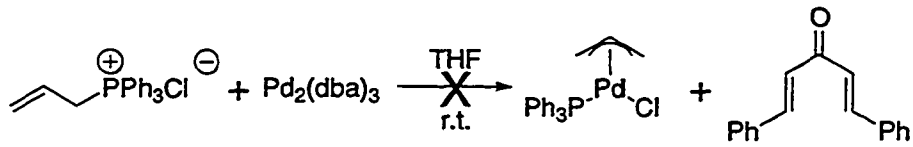
^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.837 (dd, 2 H, J_{H-P} = 15.6 Hz, J_{H-H} = 6.9 Hz, H_2C=CHC**H**$_2$PPh_3), 5.380 (ddd, 1 H, J_{cis} = 9.8 Hz, J_{H-P} = 4.4 Hz, J_{gem} = 1.2 Hz), 5.547 (ddd, 1 H, J_{trans} = 17.0 Hz, J_{H-P} = 5.1 Hz, J_{gem} = 1.2 Hz), 5.683 (m, 1 H, H_2C=C**H**CH_2PPh_3), 7.2-7.9 (br m, 15 H, aromatic H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.6 (d, J_{C-P} = 49.0 Hz, H_2C=CH**C**H_2PPh_3), 117.8 (d, J_{C-P} = 85.4 Hz, ipso C), 123.0 (d, J_{C-P} = 9.7 Hz, H_2**C**=CHCH_2PPh_3), 126.1 (d, J_{C-P} = 13.4 Hz, H_2C=**C**HCH_2PPh_3), 130.1 (d, J_{C-P} = 12.5 Hz, ortho C), 133.7 (d, J = 9.7 Hz, meta C), 134.8 (d, J_{C-P} = 2.9 Hz, para C)

^{31}P-NMR (121 MHz, $CDCl_3$) δ -4.99 (PPh_3), +21.7 (product)

Attempted preparation of (η^3-allyl)(PPh_3)PdCl from $Pd_2(dba)_3$ and allyltriphenylphosphonium chloride

Reaction:



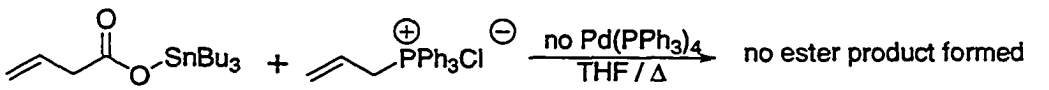
Procedure:

A 100-mL round bottom flask was charged with a stir bar, allyltriphenylphosphonium chloride (689.0 mg, 2.034 mmol, 1.003 equiv.), and dipalladium(0)tris(dibenzylideneacetone) (928.1 mg, 1.014 mmol). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF

(50 mL) was added using a syringe. The system was stirred overnight at room temperature under N_2. The mixture was originally a dark burgundy color, but darkened to brown-black approximately 1 h after the stirring had begun. The following day, the THF was removed under vacuum. Degassed CH_2Cl_2 (50 mL) was added by syringe and the mixture was stirred for 5 min. This was done to dissolve dibenzylideneacetone. The mixture was allowed to settle, and was filtered leaving a black solid. The reaction was discontinued at this point because (η^3-allyl)(PPh_3)PdCl is a yellow solid. Some type of decomposition must have occurred while the mixture was stirred.

Attempted metathesis of allyltriphenylphosphonium chloride and tributyltin 3-butenoate (no catalyst)

Reaction:

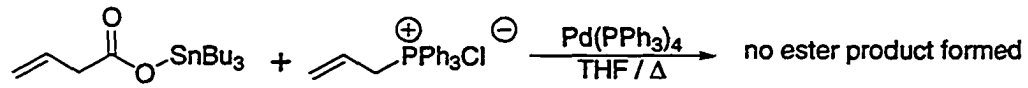


Procedure:

A 100-mL round bottom flask was charged with a stir bar, allyltriphenylphosphonium chloride (339.6 mg, 1.002 mmol), and tributyltin 3-butenoate (387.0 mg, 1.032 mmol). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (50 mL) was added using a syringe. A condenser was attached and the system was heated overnight at reflux under N_2. The following day, the system was allowed to cool to room temperature and an aliquot of the mixture was taken for GC analysis. No traces of allyl 3-butenoate were seen in the chromatogram.

Attempted Pd-catalyzed metathesis of allyltriphenylphosphonium chloride and tributyltin 3-butenoate

Reaction:



Procedure:

A 100-mL round bottom flask was charged with a stir bar, allyltriphenylphosphonium chloride (335.3 mg, 0.9897 mmol), and tributyltin 3-butenoate (380.2 mg, 1.014 mmol), and $Pd(PPh_3)_4$ (125.7 mg, 0.1088 mmol, 11.0 mol %). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (50 mL) was added using a syringe. A condenser was attached and the system was heated overnight at reflux under N_2. The following day, the system was allowed to cool to room temperature and an aliquot of the mixture was taken for GC analysis. No traces of allyl 3-butenoate were seen in the chromatogram.

2.6 Bibliography

1) (a) Fu, P.-F.; Khan, M.A.; Nicholas, K.M. *J. Organomet. Chem.* **1996**, *506*, 49. (b) Fu, P.-F.; Rahman, A.K.F.; Nicholas, K.M. *Organometallics* **1994**, *13*, 413. (c) Fu, P.-F.; Khan, M.A.; Nicholas, K.M. *J. Am. Chem. Soc.* **1992**, *114*, 6579. (d) Fu, P.F.; Khan, M.A.; Nicholas, K.M. *Organometallics* **1992**, *11*, 2607. (e) Tsai, J.-C.; Nicholas, K.M. *J. Am. Chem. Soc.* **1992**, *114*, 5117. (f) Tsai, J.-C.; Wheeler, R.A.; Khan, M.A.; Nicholas, K.M. *Organometallics* **1991**, *10*, 1344. (g) Tsai, J.-C.; Khan, M.A.; Nicholas, K.M. *Organometallics* **1991**, *10*, 29. (h) Tsai, J.-C.; Khan, M.A.; Nicholas, K.M. *Organometallics* **1989**, *8*, 2967. (i) Belmore, K.A.; Vanderpool, R.A.; Tsai, J.-C.; Khan, M.A.; Nicholas, K.M. *J. Am. Chem. Soc.* **1988**, *110*, 2004.

2) Shi, M.; Nicholas, K.M. *J. Am. Chem. Soc.* **1997**, *119*, 5057.

3) (a) Heck, R.F. *Palladium Reagents in Organic Synthesis*; Academic: Orlando, FL, 1985. (b) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley: New York, NY, 1995. (c) Malleron, J.-L.; Fiaud, J.-C.; J.-Y. *Handbook of Palladium-Catalyzed Organic Reactions: Synthetic Aspects and Catalytic Cycles*; Academic: New York, NY, 1997. (d) *Metal-catalyzed Cross-coupling Reactions*; Diedrich, F.; Stang, P.J., Eds.; Wiley-VCH: New York, NY, 1998. (e) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley: New York, NY, 2000.

4) (a) Stille, J.K. *Pure Appl. Chem.* **1985**, *57*, 1771. (b) Stille, J.K. *Angew. Chem. Intl. Ed. Engl.* **1986**, *25*, 508. (c) Farina, V.; Krishnamurthy, V.; Scott, W.J. *Org. React.* **1997**, *50*, 1-652. (d) Farina, V.; Krishnamurthy, V.; Scott, W.J. *The Stille Reaction*; Wlley: New York, NY, 1998. (e) Mitchell, T.N. In *Metal-catalyzed Cross-coupling Reactions*; Diedrich, F.; Stang, P.J., Eds.; Wiley-VCH: New York, NY, 1998; pp 167-202.

5) Neises, B.; Steiglich, W. *Org. Synth.* **1984**, *63*, 183.

6) See References 4c and 4d for examples

7) Tamborski, C.; Ford, F.E.; Soloski, E.J. *J.Org. Chem.* **1963**, *28*, 237.

8) O' Brien, S.; Fishwick, M.; McDermott, B.; Wallbridge, M.G.H.; Wright, G.A. *Inorg. Synth.* **1971**, *13l*, 74.

9) (a) Tsuji, J.; Mandai, T. *Angew. Chem. Intl. Ed. Engl.* **1995**, *34*, 2589. (b) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *120*, 1938. (c) Tsutsumi, K.; Ogoshi, S.; Kakiuchi, K.; Nishiguchi, S.; Kurosawa, H. *Inorg. Chim. Acta* **1999**, *296*, 37. (d) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687.

10) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: New York:NY, 1988, pp 25, 121-122.

11) (a) Lau, K.S.Y.; Wong, P.K.; Stille, J.K. *J. Am. Chem. Soc.* **1976**, *98*, 5832. (b) Becker, Y.; Stille, J.K. *J. Am. Chem. Soc.* **1978**, *100*, 838. (c) Becker, Y.; Stille, J.K. *J. Am. Chem. Soc.* **1978**, *100*, 845. (d) Milstein, D.;

Stille, J.K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. (e) Sustmann, R.; Lau, J.; Zipp, M. *Tetrahedron Lett.* **1986**, *27*, 5207.

12) (a) Tolman, C.A. *Chem. Rev.* **1977**, *77*, 313. (b) Driver, M.S.; Hartwig, J.F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (c) Wolfe, J.P.; Wagaw, S.; Buchwald, S.L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (d) Marcoux, J.-F.; Wagaw, S.; Buchwald, S.L. *J. Org. Chem.* **1997**, *62*, 1568. (e) Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1997**, *119*, 6054. (f) Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* **1997**, *62*, 6066. (g) Hamann, B.C.; Hartwig, J.F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (h) Wolfe, J.P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S.L. *Acc. Chem. Res.* **1998**, *31*, 805. (i) Mann, G.; Baranano, D.; Hartwig, J.F.; Rheingold, A.L.; Guzei, I.A. *J. Am. Chem. Soc.* **1998**, *120*, 9205. (j) Old, D.W.; Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (k) Mann, G.; Incarvito, C.; Rheingold, A.L., Hartwig, J.F. **1999**, *121*, 3224. (l) Aranyos, A.; Old, D.W.; Kiyomori, A.; Wolfe, J.P.; Sadighi, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (m) Wolfe, J.P; Singer, R.A.; Yang, B.H.; Buchwald, S.L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (n) Fox, J.M.; Huang, X.; Chieffi, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

13) (a) Nicholas, K.M. *J. Organomet. Chem.* **1980**, *188*, C10. (b) Dickson, M.K.; Dixit, N.S.; Roundhill, D.M. *Inorg. Chem.* **1983**, *22*, 3130. (c) Lawson, H.J.; Atwood, J.D. *J. Am. Chem. Soc.* **1989**, *111*, 6223. (d) Ziegler, W.; Nicholas, K.M. *J. Organomet. Chem.* **1992**, *423*, C35.

(e) Yin, C.; Xu, Z.; Yang, S.-Y.; Ng, S. M.; Wong, K. Y.; Lin, Z.; Lau, C. P. *Organometallics* **2001**, *20*, 1216.

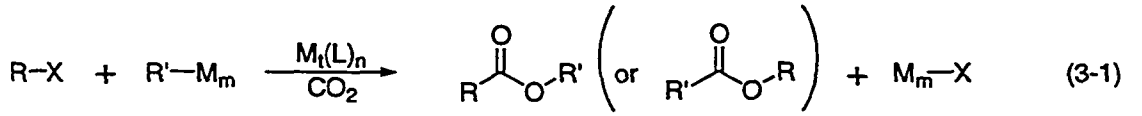
Chapter 3

MECHANISTIC STUDIES OF THE Pd-CATALYZED ALLYLTIN-ALLYL CHLORIDE CARBOXYLATIVE COUPLING REACTION

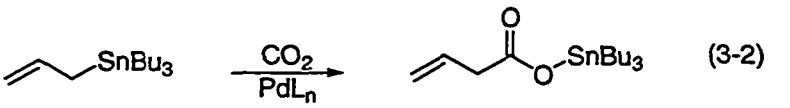
3.1 INTRODUCTION AND BACKGROUND

3.1.1 Summary of previous results

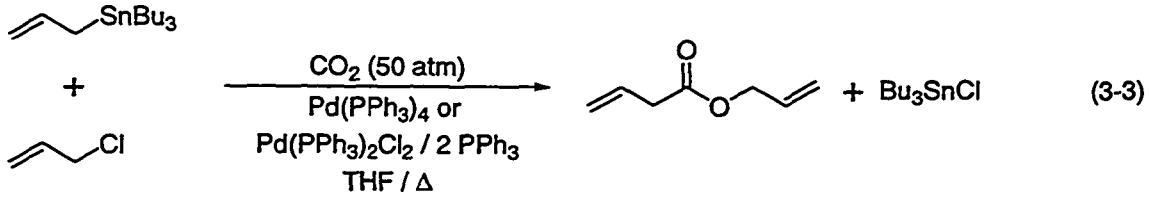
We began this project with the goal of developing a catalytic carboxylative coupling reaction (eq. 3-1) based on Dr. Min Shi's initial discovery of the Pd-catalyzed carboxylation of allyltributyltin (eq 3-2).[1] Indeed, we found that allyltributyltin and allyl chloride can be carboxylatively coupled at high CO_2 pressures in the presence of either a Pd(0) or Pd(II) catalyst to form allyl 3-butenoate **(1)** (eq. 3-3). After this initial success, we then investigated the effects on the reaction of using other group 10 metals, ligands, and substrates. We found that optimal coupling occurred using $Pd(PPh_3)_2Cl_2$ and two additional equivalents of PPh_3. The coupling did not occur when nickel complexes were used, and results were not as good when platinum complexes were used. Additionally, we investigated the effects of varying the organic substrates on the reaction. Unfortunately, we found that the reaction only worked when both the organotin substrate *and* the electrophile contained the allylic moiety.[2]



(3-1)



(3-2)



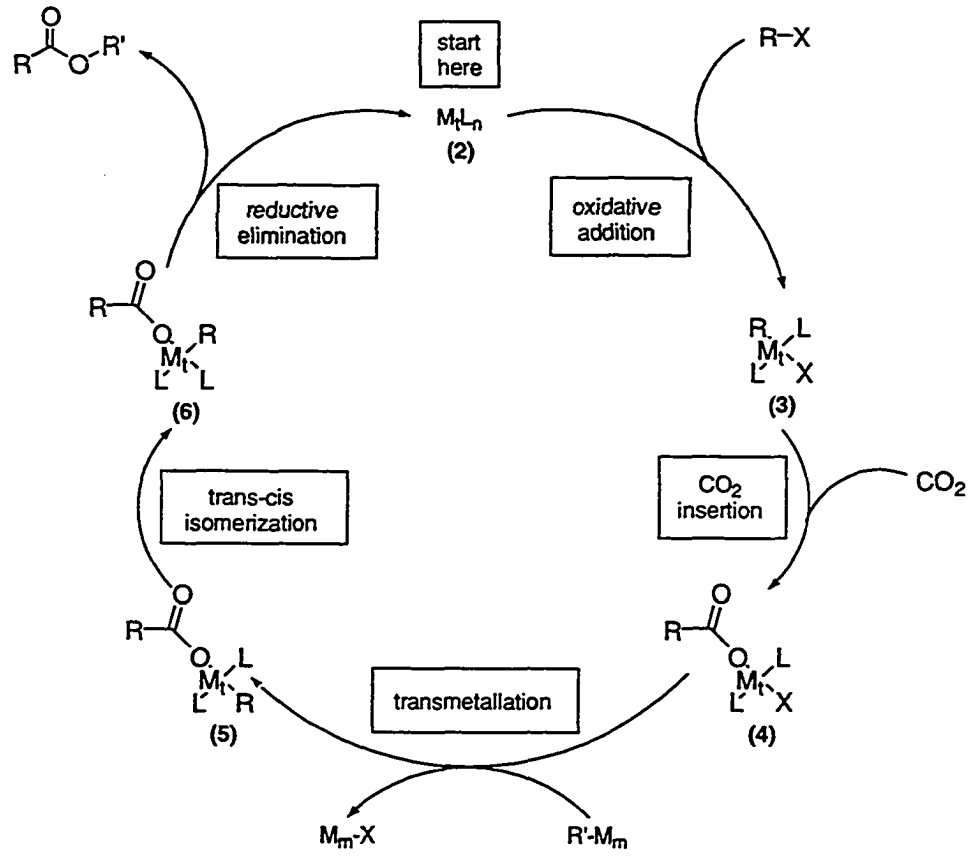
(3-3)

3.1.2 An initial mechanistic hypothesis

Despite this apparent limitation in the scope of the reaction, we still found the allyl-allyl carboxylative coupling to be quite interesting, so we began to investigate it in detail. We were especially interested in the mechanism of the coupling. In addition to learning about how the allylic coupling reaction worked, we also hoped that a greater understanding of the reaction mechanism would enable us to modify our system, and broaden the synthetic scope of the reaction. At the beginning of this project, we envisioned a possible catalytic mechanism for carboxylative coupling that was analogous to that which had been postulated for the Stille carbonylative coupling reaction (Scheme 3-1).[3] In this scheme, a transition metal complex M_tL_n **(2)** first undergoes an oxidative addition reaction with an organic electrophile R-X forming intermediate **(3)**. This intermediate can then react with CO_2 to form the carboxylato complex **(4)**. This intermediate can then undergo a transmetallation reaction, in which an organic fragment R' is transferred to the carboxylato complex **(4)** from a main group organometal R'-M_m. The resulting *trans*-carboxylato complex **(5)** can then isomerize to the *cis*-carboxylato complex **(6)**, which can then undergo reductive elimination to form the ester product R-CO_2R' and the metal complex M_tL_n **(2)** With this hypothetical

mechanistic scheme in mind, we set out to learn more about how the reaction works.

Scheme 3-1
Hypothetical mechanism for Pd-catalyzed carboxylative coupling reactions

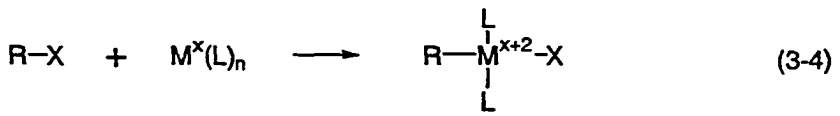


Before beginning an in-depth discussion of our mechanistic work, it would be appropriate at this point to discuss some basic principles of organometallic reaction mechanisms that are especially relevant to organometallic catalysis.

3.1.3 Organometallic reaction mechanisms

3.1.3.1 Oxidative addition

The first step in many organometallic catalytic processes involves an organic substrate undergoing oxidative addition with a low-valent metal complex. In an oxidative addition reaction, the substrate R-X reacts with a transition metal complex $M^{x}(L)_n$ to yield a product $R\text{-}M^{x+2}\text{-}X(L)_n$, which contains both the organic fragment R and also the X group (eq. 3-4). Interestingly, unless the metal complex is constrained by either the ligands or the substrate, oxidative addition usually gives a product that has trans geometry at the metal. Additionally, the oxidation number of the metal is increased from *x* to *x+2*. As a component of catalytic reaction mechanisms, oxidative addition occurs most frequently with low-valent oxidation states of metals, especially 16-electron complexes, e.g. Ir(I), Rh(I), Ni(0), Pd(0). The rate of oxidative addition is enhanced by the use of ligands with greater σ-donating character.



(3-4)

Oxidative addition has been studied extensively for many catalytic reactions, including the Stille coupling reaction.[4] Recently, Espinet and co-workers studied the oxidative addition step in the Stille reaction and discovered that the mechanism is much more complex than had been thought previously.[5] They found that the reaction could proceed through both dissociative and associative pathways, with the associative pathway being preferred. They also

found that the solvent (usually THF) is also directly involved in the mechanism. Interestingly, they accounted for the trans geometry of the product by proposing that the electrophile initially adds to the complex in cis fashion, but subsequently undergoes a series of Berry pseudorotations to give the trans product.

A variety of organic substrates can participate in oxidative addition reactions. Organic electrophiles with diverse groups such as aryl, alkenyl, allyl, benzyl, and, even in some cases, alkyl groups have all been shown to be able to undergo oxidative addition. The substrates that do oxidative addition in catalytic reactions are typically electrophilic, e.g. X = Cl, Br, I, OAc, OTs, OTf. The resulting intermediate can then undergo a variety of subsequent reactions, including transmetallation.

3.1.3.2 Transmetallation

Transmetallation is an important step in all metal-catalyzed coupling reactions. Transmetallation is basically a metathesis reaction, in which an organic fragment is transferred from typically a main-group organometal R'-M_m to an organotransition metal complex, R-$M_t(L)_nX$, to give a bis(organyl)transition metal complex, R-$M_t(L)_nR'$ (eq. 3-5). A variety of main-group organometals has been shown to participate in transmetallation reactions.

$$R\text{–}M_m + R\text{-}M_t(L)_nX \longrightarrow R\text{-}M_t(L)_nR' + M_mX \qquad (3\text{-}5)$$

The most common metals used are Mg, B, Al, Si, Zn, Hg, and Sn for the main group metals and Pd, Ni, and Cu for the transition metals. The particular combination of main group metal and transition metal compounds used in

transmetallation is important. Ideally, the transition metal should be more electronegative than the main group metal in order for the transmetallation to be thermodynamically favorable. In the Stille coupling, in which M_m = Sn (Pauling electronegativity = 1.96) and M_t= Pd (Pauling electronegativity = 2.20), the thermodynamic driving force for the reaction is the formation of the more stable Pd-C and Sn-X bonds. Along with thermodynamic considerations, the kinetics of transmetallation are also important. Transmetallation has been determined to be the rate-limiting step for the Stille coupling reaction. The organotin compounds used in the Stille coupling are often organotrialkyl ($RSnR'_3$), compounds, e.g. R = alkynyl, aryl, alkenyl, allyl, benzyl, etc., R' = n-Bu or Me. One question that arises is, "Why do the butyl groups not undergo transmetallation in addition to the desired organyl group, which would yield a mixture of coupled products?" Stille studied the transmetallation portion of the coupling reaction, and demonstrated that the reason for this apparent preference for transfer of non-alkyl groups is that the rate of transmetallation for *non-alkyl* groups is much faster than that for *alkyl* groups. The relative rates of organic group transfer in the Stille reaction are alkynyl > alkenyl ~ aryl > allyl ~ benzyl >> alkyl.[6]

The bis(organyl)metal complexes resulting from transmetallation have been isolated only in a few special cases, since subsequent reaction steps are usually faster than transmetallation. Echavarren has managed to isolate and characterize some transmetallation products from *intra*molecular transmetallations, but these complexes are constrained from undergoing reductive elimination.[7] In addition to Stille's earlier studies of the transmetallation

of organic groups from tin to palladium, Espinet and Casado more recently have conducted detailed kinetic studies of the transmetallation mechanism as well.[8] Their studies focused on transmetallation of the vinyl and aryl groups from tributyl(organyl)tin to an (aryl)bis(triphenylarsine)palladium(II) iodide complex. In contrast to earlier reports, which proposed that the transmetallation occurred via a dissociative pathway, Espinet's group proposed that the transmetallation proceeds through an associative mechanism. Additionally, in the case of the aryl group transmetallation, they proposed a transition state structure that contained the iodide and the aryl group bridging between the tin and palladium centers. Their model also accounts for the rate enhancement that is observed in the reaction when weaker-donating ligands (e.g. $AsPh_3$) are used.[9] The rationale behind this was that weaker-donating ligands will increase the electrophilic character of the metal center and, thus, would favor an associative process. The traditional model for the Stille mechanism postulates that the transmetallation product has the two organyl groups in trans geometry. In order for reductive elimination to occur, the complex must isomerize to the cis complex. Espinet, on the other hand, asserted that the intermediate resulting from such an associative, nucleophilic attack on the palladium complex by the tin compound would also be amenable to rapid reductive elimination. The two organyl groups would be cis to one another after the transmetallation, thus negating the need for subsequent isomerization.

3.1.3.3 Reductive elimination

As was alluded to in the previous section, reductive elimination is often the final step in catalytic cycles. In reductive elimination, a bis(organyl)metal R-$M_t^{x+2}(L)_nR'$ forms the coupled product, R-R', and the oxidation state of the transition metal is decreased from *x+2* to *x* (eq. 3-6). The primary geometric requirement for reductive elimination to occur is that the two organic groups need to be cis to each other. In addition to the overall geometry of the metal complex, the nature of the ligands used can influence the rate of reductive elimination also. Just as the use of stronger-donating ligands can increase the nucleophilicity of the metal complex, enhancing oxidative addition rates, conversely, the use of weaker-donating ligands can increase the electrophilicity of the metal complex and enhance the rates of reductive elimination. A number of mechanistic studies of reductive elimination have been made by Stille and others.[10] Study of the reductive elimination process is more difficult than for oxidative addition or transmetallation because of the unstable nature of the precursor complexes. The reductive elimination reaction is important, however, not only because it is the step that forms the organic product, but also because it regenerates the metal complex so that it can begin the catalytic cycle anew.

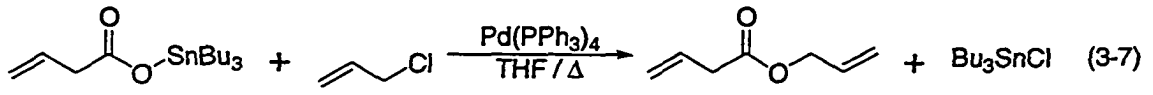
$$R\text{-}M_t^{x+2}(L)_nR' \longrightarrow R\text{–}R' + M_t^{x}(L)_n \qquad (3\text{-}6)$$

3.2 RESULTS AND DISCUSSION

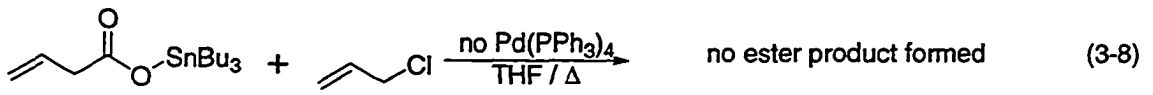
3.2.1 Tin carboxylate/allyl chloride metathesis

After our initial successes with the high-pressure carboxylative coupling reaction, we were interested in trying other experimental variations. At this point, we believed that our system was reacting in a manner very similar to the carbonylative Stille couplings, i.e. the reaction proceeded first through oxidative addition, followed by transmetallation, CO_2 insertion, and reductive elimination. We were also interested in studying the mechanism of the reaction to see if it could give us any insights into how the reaction could be made to react with a greater variety of organic substrates. Since the Stille coupling had been achieved with a variety of tin substrates, we decided to try an experiment to see if the tin carboxylate that had been formed in Shi's work could be converted to the ester in an analogous fashion. This experiment produced some interesting results. Tributyltin 3-butenoate **(7)** and allyl chloride were refluxed overnight in THF in the presence of $Pd(PPh_3)_4$ (eq. 3-7). The reaction was performed under a nitrogen atmosphere at ambient pressure. The reaction mixture was analyzed by GC, GC-MS, and ^{1}H-NMR. The major product of the reaction was allyl 3-butenoate **(1)**. The presence of **(1)** was confirmed by comparison of GC-MS and NMR data from the reaction mixture with data from authentic samples. A tributyltin-containing by-product, presumably tributyltin chloride, was also formed in the reaction. No other carboxylated species, e.g. crotonate esters, were observed in the GC, GC-MS, or NMR of the reaction mixture. A subsequent quantitative GC study of the reaction mixture showed that the ester **(1)** was

formed in almost quantitative yield. A control reaction, conducted under identical conditions, but in the absence of $Pd(PPh_3)_4$, did not yield any of the ester product, thus demonstrating that the catalyst was indeed necessary for the reaction to occur (eq. 3-8). To date, there has only been one other similar Pd-catalyzed metathesis reaction involving a tin carboxylate and an electrophile reported in the literature.[11]



(7) (1) (3-7)



(7) (3-8)

Thus, the reaction appeared to be a type of double metathesis reaction. Additionally, these results provided us with an important link between Shi's results from his work on the Pd-catalyzed carboxylation of allyltins and the results from our work on the Pd-catalyzed carboxylative coupling of allyltins and allyl halides. We decided to conduct a series of mechanistic studies to learn more about the carboxylative coupling reaction.

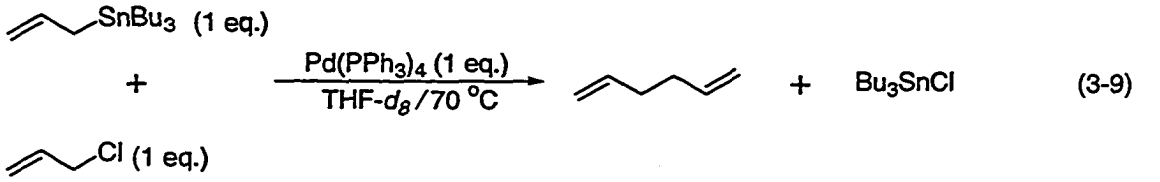
3.2.2 High-pressure NMR studies

We were especially interested in observing the formation of carboxylated intermediates in the reaction. We conducted a series of high-pressure ^{1}H-NMR reactions using a special thick-walled 5-mm diameter NMR tube, which was capable of withstanding pressures up to 8-10 atm. Although we would be able to

use higher CO_2 pressures with the tube, the tube itself presented some serious experimental challenges. Since the tube had an inner diameter of only ~1 mm, the amount of reagents that could be loaded into the tube was severely limited. The active volume of the tube was only 25-50 μL. This only further exacerbated the usual detection limit problems that are encountered when trying to use NMR techniques to observe reaction intermediates, as the intermediates would likely be present in low concentrations. Long scan times of up to 1 h and signal averaging were used in order to achieve a better signal-to-noise ratio. The experiments were all conducted using THF-d_8 as the solvent. We also decided to conduct the reaction using a stoichiometric amount of the palladium complex. This was done in order to try to increase the concentration of any intermediate species that might form, and hopefully reduce the expected detection problems. This, however, also presented another problem: low solubility of the palladium complexes in the deuterated THF solvent. The deuterated THF was available in 1 g ampules, thus the available amount of THF was ~ 800 μL. Given this amount of solvent, it was found that ~ 25 mg (21 μmol) of $Pd(PPh_3)_4$ would dissolve in the 1 g aliquot of THF-d_8. Although a higher concentration of the palladium complex would have been better, we decided to try the NMR experiments under these conditions and hope to be able to observe the formation of intermediates.

The first experiment was a control experiment to test the viability of the experimental methods. Only allyltributyltin, allyl chloride and $Pd(PPh_3)_4$ (~ 1 equiv. of each) were dissolved in THF-d_8 and loaded into the NMR tube. The loading procedure was performed in the glove box. No CO_2 was used in this

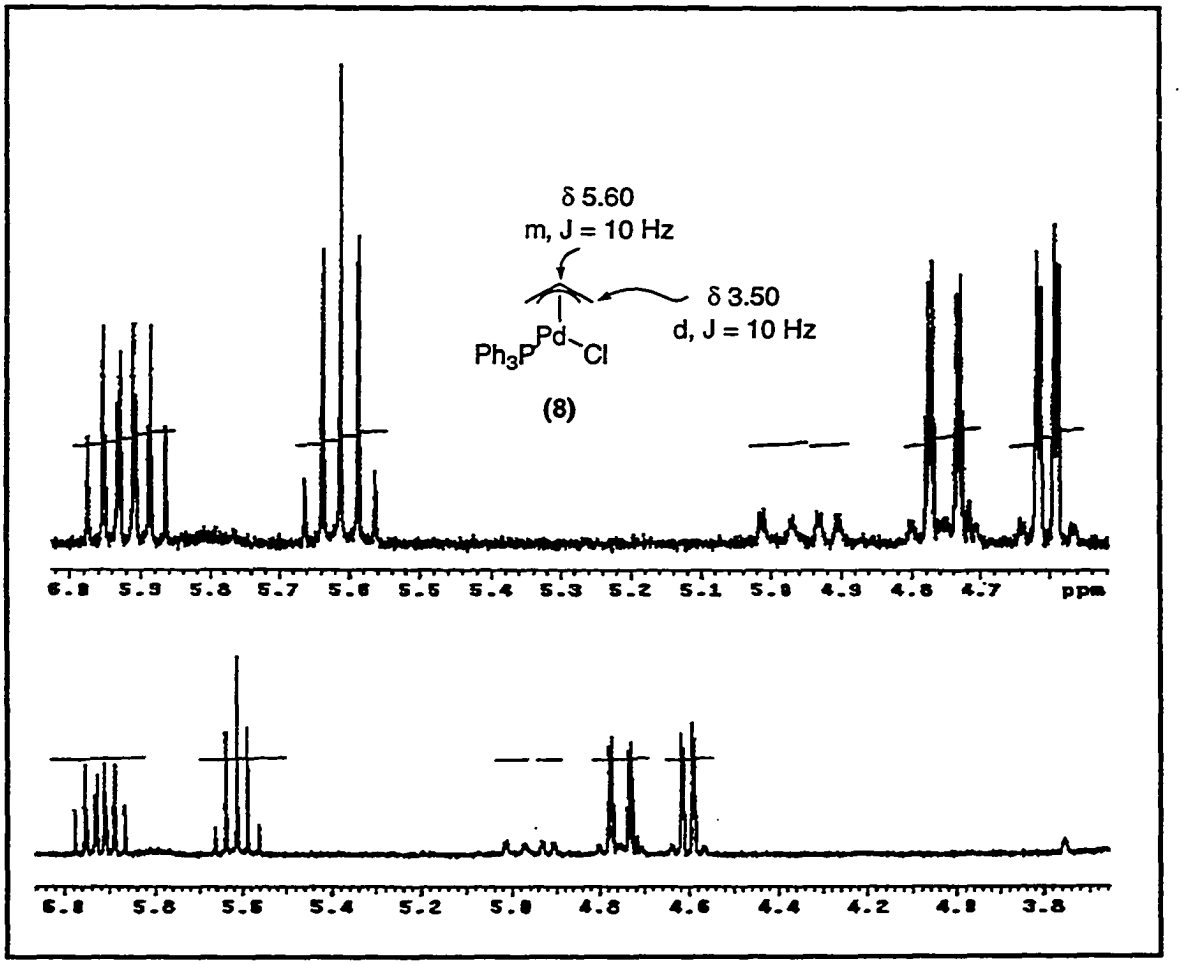
initial experiment. A preliminary NMR spectrum (Figure 3-1) of the system clearly showed peaks for olefinic protons of the allyltin reagent at δ 4.60 and 4.75. Additionally, a new peak, a multiplet (J = 10 Hz) at δ 5.60 was also present. Literature reports (*vide infra*) led us to believe that this peak was likely to be due to (η^3-allyl)(PPh_3)PdCl **(8)**, which resulted from the allyl chloride undergoing oxidative addition with the palladium complex. The signal at δ 5.60 arises from the "internal" proton on the η^3-allyl ligand. In some cases, we were also able to observe a signal at ~δ 3.5, which was believed to arise from the terminal protons on the η^3-allyl ligand. Analysis of this signal was unreliable, however, as the signal partially overlapped with the residual proton impurity peak from the THF-d_8 solvent (δ 3.60). The signal sometimes appeared as a doublet (J = 10 Hz), but sometimes appeared as a broad singlet, depending on the quality of the lock and shims that were available on the NMR spectrometer used for a given experiment. The signal at δ 5.60, on the other hand, showed no such fluctuations. The tube was then heated at 70 °C for several hours. An NMR spectrum of the sample at this point showed the presence of several new peaks in the olefinic region of the spectrum. Additionally, the multiplet at δ 5.60 from the complex **(8)** had disappeared. Comparison with ^{1}H-NMR data from an authentic sample showed that these new olefinic peaks were due to the formation of 1,5-hexadiene in the system (eq. 3-9). This indicated that the "normal" Stille coupling reaction had occurred in the absence of CO_2.



(3-9)

These results were encouraging, as they showed that we could indeed observe the formation of reaction intermediates despite the limitations imposed by the special NMR tube.

Figure 3-1
400 MHz ^{1}H-NMR spectrum of (η^3-allyl)(PPh_3)PdCl intermediate (8)

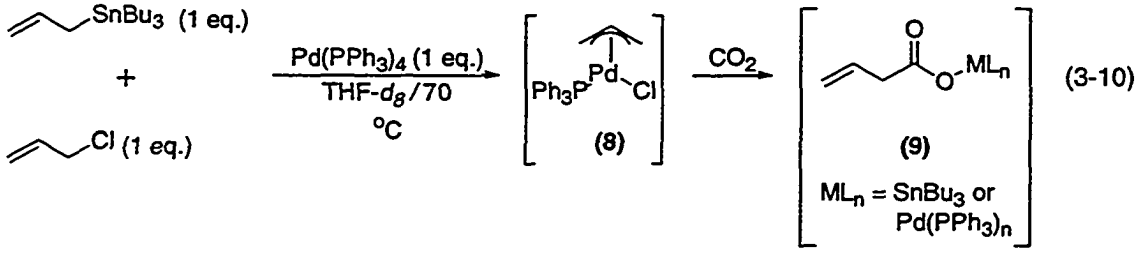


We now planned to carry out the same experiment in the presence of CO_2. After the reagents and solvent were loaded into the NMR tube in the glove box, the tube was sealed and removed from the glove box. The tube was then connected to a high-pressure CO_2 line and pressurized with CO_2 (60 psig). Several additions of CO_2 were done in order to try to maximize the concentration of CO_2 in the solvent.

As was the case in the previous experiment, an initial ^{1}H-NMR spectrum of the reaction mixture showed the olefinic peaks for allyltributyltin and allyl chloride, and also for complex **(8)** at δ 5.60. The tube was heated for 22 h at 70 °C and another NMR spectrum was recorded (Figure 3-2). This spectrum showed three significant changes from the initial spectrum: (a) the intensity of the olefinic signals from the reagents was reduced, (b) the intensity of the signal at δ 5.60 from **(8)** was also greatly reduced, and most importantly (c) a new peak, a double triplet (J = 7.2, 1.2 Hz) at δ 2.97 had appeared.

The appearance of this new peak was quite exciting, as the chemical shift value and the coupling constant were consistent with that which would be expected for allylic protons that are adjacent to a carbonyl or carboxyl group (H_2C=CHCH_2C(=O)O-). We had observed such signals before from allyl 3-butenoate (δ 3.08, d, J = 8 Hz) and tributyltin 3-butenoate (δ 3.10, d, J = 7 Hz). The tube was heated for an additional 24 h. The spectrum recorded after 48 h was not appreciably different from the one recorded at 24 h. The peak at δ 2.97 was still present along with a number of peaks in the olefinic region of the spectrum. We concluded from these results that we had indeed formed some

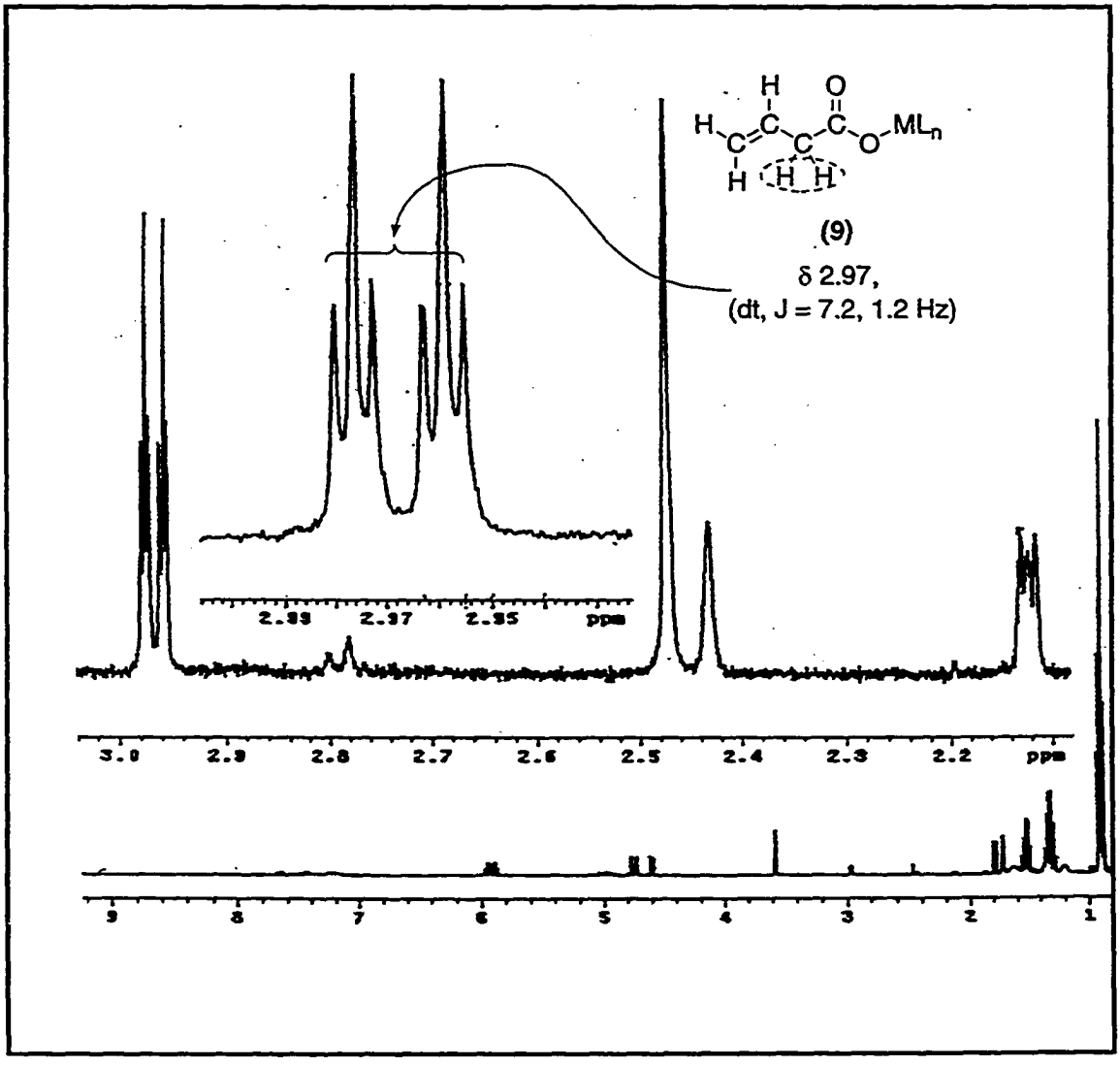
sort of carboxylated intermediate **(9)** in the reaction. The exact identity of this intermediate was still unclear, however. The two most likely possibilities were: (a) the intermediate was a palladium carboxylate or (b) the intermediate was a tin carboxylate.



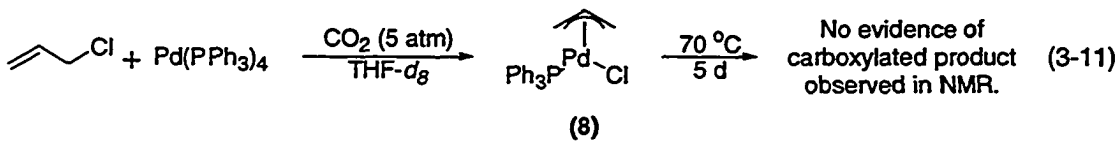
(3-10)

Additionally, we also failed to observe conversion of the carboxylated intermediate to the ester product. No NMR signals characteristic of the ester (e.g. a doublet at δ 4.60 for the allylic protons of the allyloxy H_2C=CH-CH_2-O-C(=O)-CH_2-CH=CH_2) were ever observed in the high-pressure NMR experiments. Thus the reaction proceeded to the formation of the carboxylated intermediate and then stopped. The failure of the system to turn over to produce the ester was not terribly surprising, however, given that the reaction was conducted using a stoichiometric amount of the palladium complex (*vide infra*).

Figure 3-2
400 MHz ^{1}H-NMR spectrum of carboxylate intermediate (9)



We also considered the fact that CO_2 could be reacting with (η^3-allyl)-(PPh_3)PdCl **(8)**. We conducted a control experiment in the high-pressure NMR tube to investigate this possibility. The tube was loaded with equimolar amounts of allyl chloride and $Pd(PPh_3)_4$ dissolved in THF-d_8. The tube was then pressurized with CO_2 (75 psig) and sealed. An initial ^{1}H-NMR spectrum of the mixture showed a multiplet at δ 5.60, consistent with the formation of **(8)**. The tube was then heated at 70 °C for 24 h, and another spectrum was recorded. The ^{1}H-NMR spectrum of the mixture after being heated for 24 h showed no great change from the initial spectrum. There was no evidence that carboxylation had occurred, as no peaks characteristic of the 3-butenoyl moiety were seen in the δ 3.0 region of the spectrum (eq. 3-11). The system was then heated for an additional 96 h. At this point the ^{1}H-NMR spectrum indicated that complex **(8)** had decomposed. The signal at δ 5.60 had disappeared. No evidence of carboxylation after five days of heating was seen in the spectrum. This experiment showed clearly that CO_2 did not react with complex **(8)**.



(3-11)

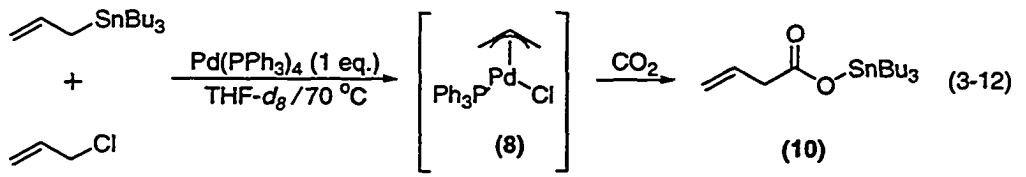
(8)

The high-pressure NMR experiments gave us four interesting points of insight into the reaction mechanism: the first important intermediate species formed in the reaction is likely to be (η^3-allyl)(PPh_3)PdCl **(8)**, which is formed rapidly and is subsequently consumed in later steps. Additionally, complex **(8)** alone does not react with CO_2. In the absence of CO_2, the "normal" Stille

coupling occurs, to produce 1,5-hexadiene. In the presence of CO_2, however, the Stille coupling does not occur, but rather a carboxylated intermediate **(9)** is formed. Our work now turned to identification of **(9)**.

3.2.3 Preparative-scale stoichiometric reactions

We decided that a preparative-scale synthesis would be the best approach to identifying the carboxylated intermediate. The preparative experiment was conducted stoichiometrically as were the high-pressure NMR experiments. A stainless-steel autoclave was charged with $Pd(PPh_3)_4$, allyltributyltin, and allyl chloride (1 mmol of each). The reagents were dissolved in THF and the autoclave was sealed and pressurized with CO_2 (850 psig). The autoclave was heated for 68 h. After the solvent was removed, NMR spectra (^1H, ^{13}C, and ^{31}P) were recorded from the residual material (eq. 3-12).



(1 equiv. each) (8) (10) (3-12)

The ^1H-NMR spectrum (Figure 3-3) of the residue showed the characteristic doublet for the 3-butenoate group at ~δ 3.0. Although the characteristic peaks for the n-butyl groups bonded to tin were seen in the ^1H- and ^{13}C-NMR (Figure 3-4) spectra of the residue, it was not possible to discriminate between different tin-containing species using only the ^1H- or ^{13}C-NMR spectra.

We were uncertain whether the tin species was present as tributyltin chloride, bis(tributyltin) oxide, tributyltin 3-butenoate, unreacted allyltributyltin, or some other tin-containing species. The ^{31}P-NMR spectrum (Fig. 3-5) of the material had a number of peaks in the δ 20-30 region, among these was a peak at δ 29.6, which indicated that a large portion of the phosphorus-containing material was triphenylphosphine oxide. This was not surprising, as it is not uncommon for triphenylphosphine to be oxidized under this type of reaction conditions.[12]

In an effort to identify the tin-containing species conclusively, we decided to use ^{119}Sn-NMR. The ^{119}Sn-NMR spectrum of the residue gave a single resonance at δ 116.3 (Figure 3-6). Comparison of the ^{119}Sn chemical shift value from the residue with that recorded for an authentic sample (Figure 3-7), showed that the unknown tin-containing species was, in fact, tributyltin 3-butenoate **(7)**. A spectrum of the residual material spiked with a sample of authentic tributyltin 3-butenoate gave only one peak at δ 116.4 (Figure 3-8). The ^{119}Sn-NMR experiments showed that the intermediate produced in the stoichiometric experiments was, most likely, tributyltin 3-butenoate **(7)**.

Figure 3-3
400 MHz ^{1}H-NMR spectrum of product mixture from preparative-scale experiment

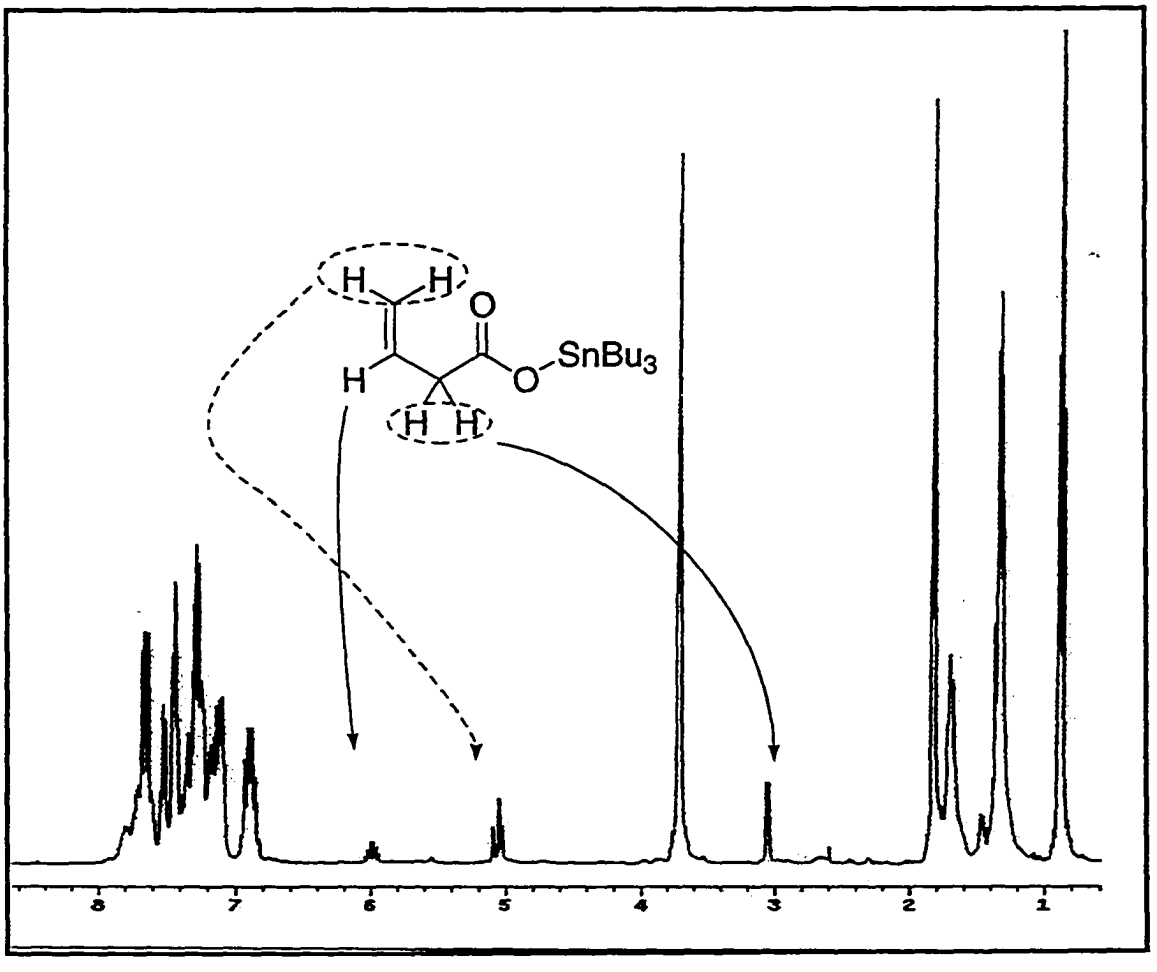


Figure 3-4
100 MHz ^{13}C-NMR spectrum of product mixture from preparative-scale experiment

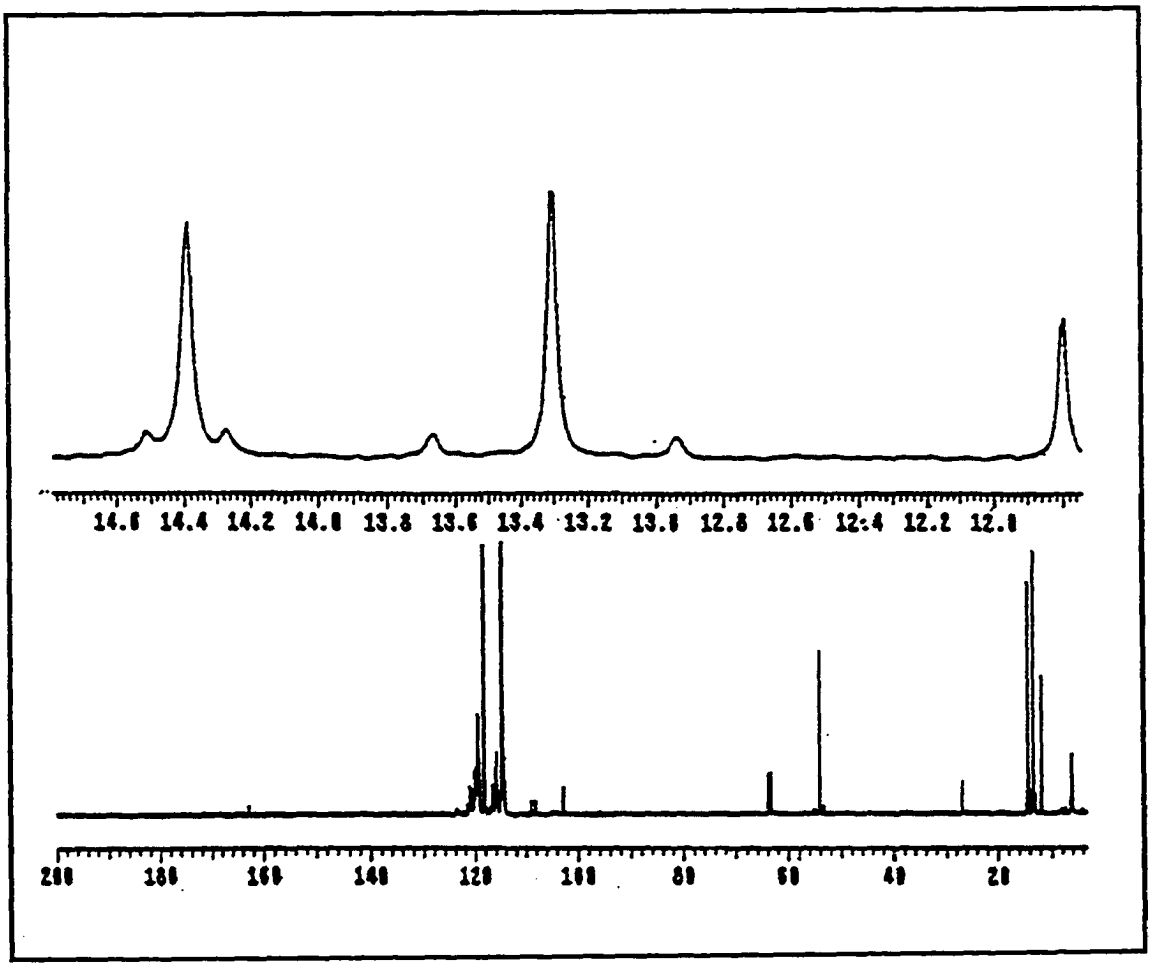


Figure 3-5
162 MHz ^{31}P-NMR spectrum of product mixture from preparative-scale experiment

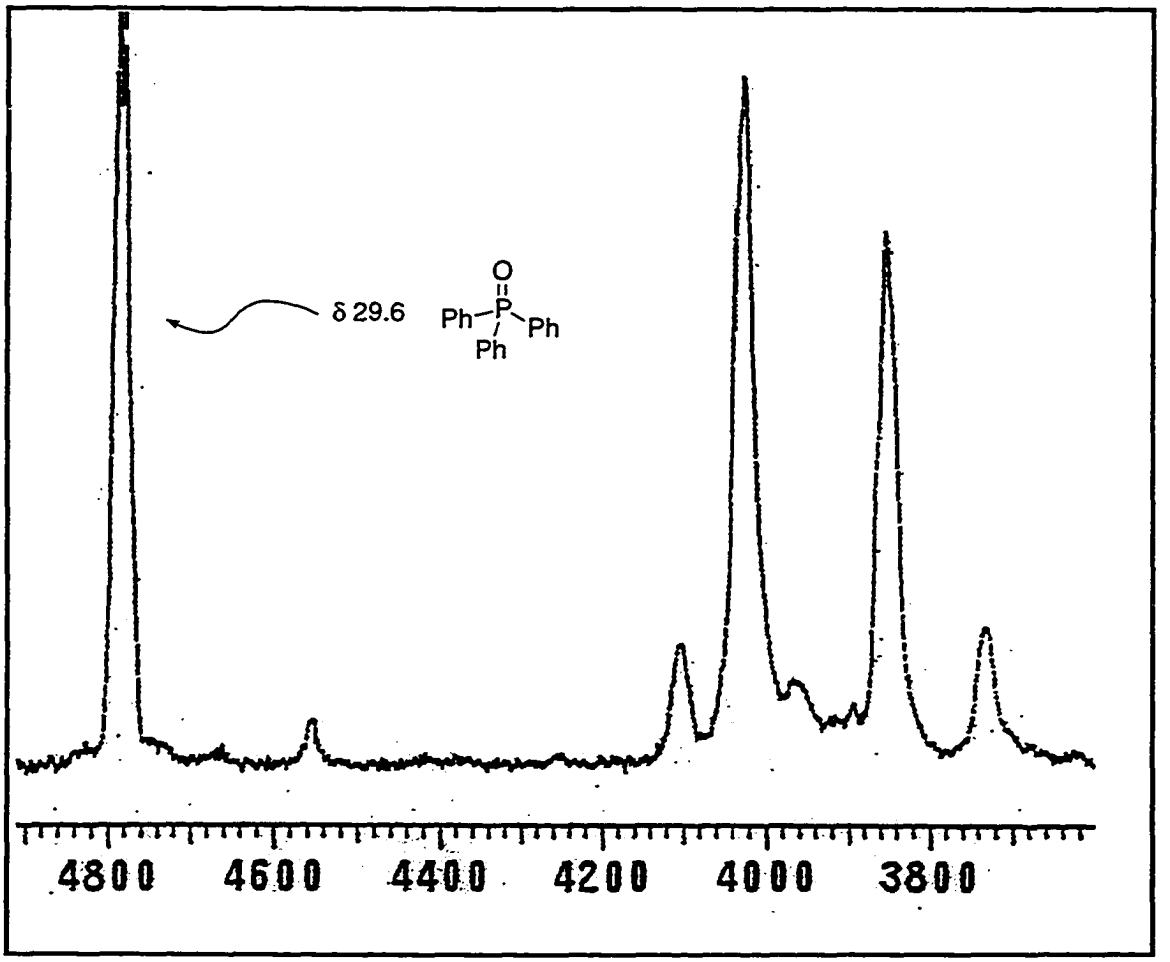


Figure 3-6
184 MHz ^{119}Sn-NMR spectrum of product mixture from preparative-scale experiment

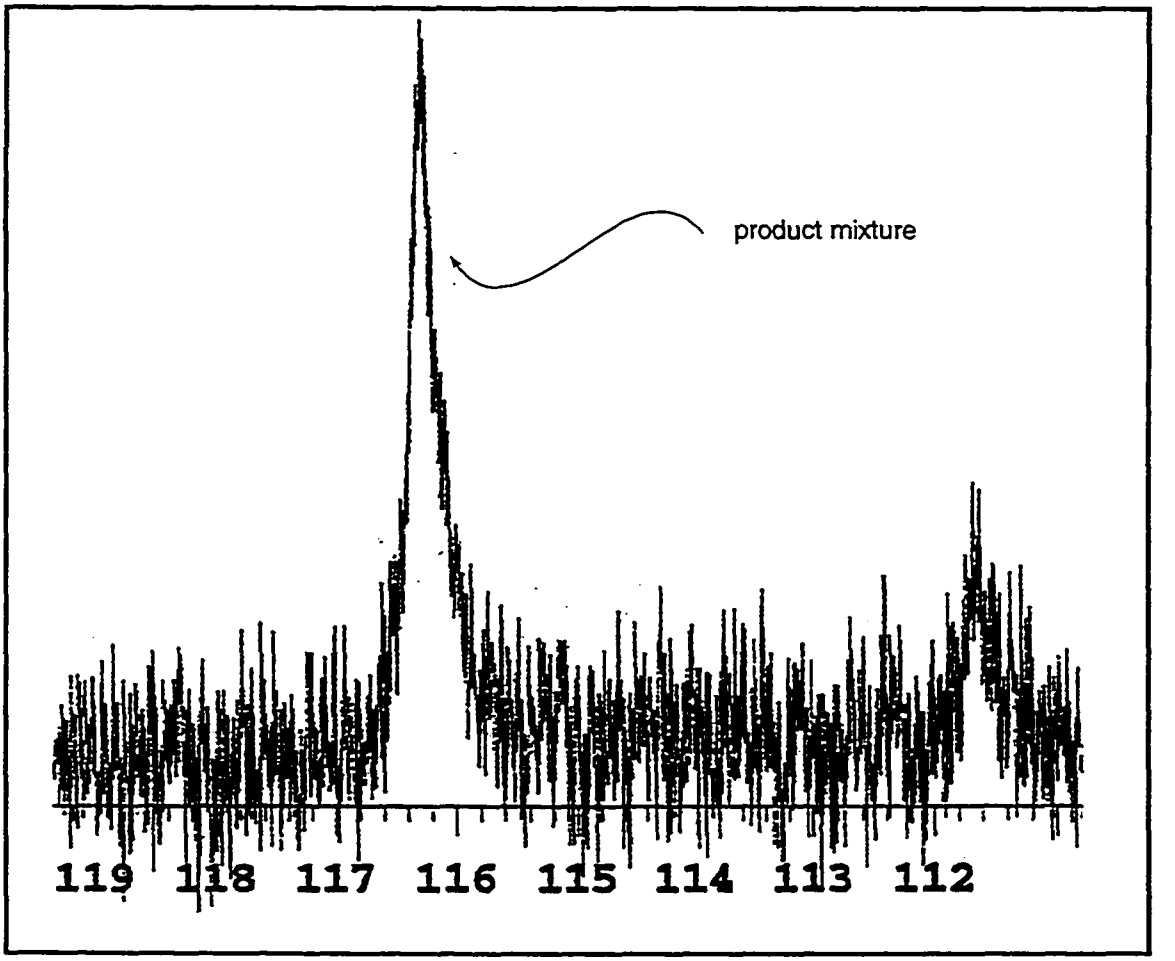


Figure 3-7
184 MHz ^{119}Sn-NMR spectrum of authentic tributyltin 3-butenoate (7)

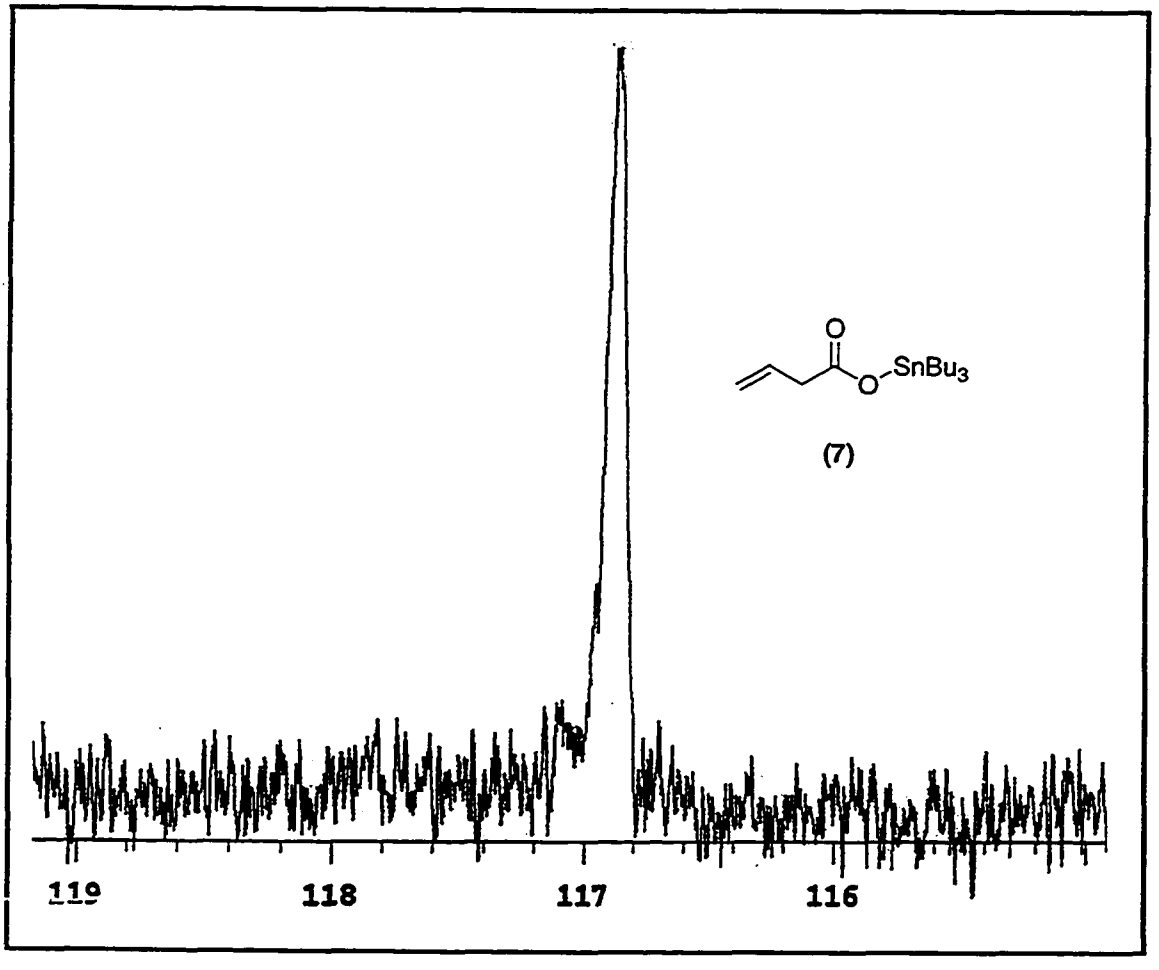
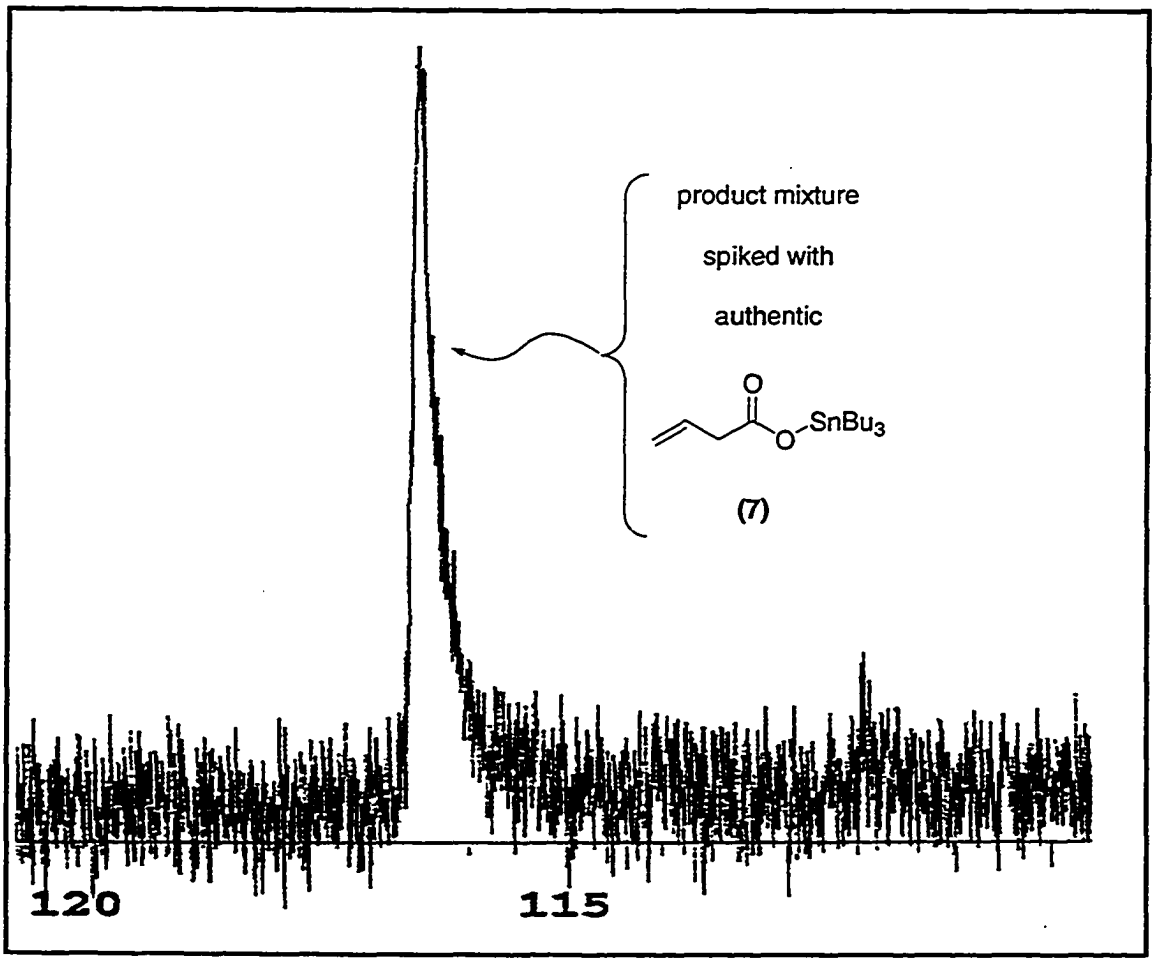


Figure 3-8
184 MHz ^{119}Sn-NMR of mixture of product mixture and authentic tributyltin 3-butenoate (7)



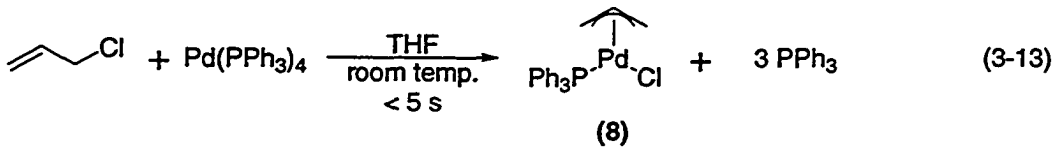
3.2.4 Conclusions from our mechanistic studies

The metathesis reactions, the stoichiometric high-pressure NMR experiments, and the preparative-scale experiments gave us some important insights into the reaction mechanism. The NMR experiments showed that the reaction most likely proceeds via the initial formation of (η^3-allyl)(PPh_3)PdCl **(8)**, which most likely results from oxidative addition between allyl chloride and $Pd(PPh_3)_4$. In addition, the NMR and preparative experiments showed that it is indeed possible for **(8)** to be converted to a tin carboxylate intermediate **(9)**. Finally, the tributyltin 3-butenoate/allyl chloride metathesis results provide an important mechanistic connection between the formation of the aforementioned tin carboxylate and its subsequent conversion to the ester product. In order to develop a more complete mechanistic model for the reaction, we turned to the literature.

3.2.5 Literature studies of relevant Pd-allyl reactions

3.2.5.1 Yamamoto's studies of Pd-catalyzed allyltin addition reactions

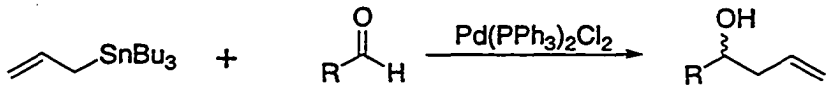
Of particular interest was the exact nature of the formation of the (η^3-allyl)(PPh_3)PdCl intermediate **(8)** and its subsequent conversion to the tin carboxylate intermediate **(9)**. There are a number of literature accounts that report the formation of **(8)** from allyl chloride and $Pd(PPh_3)_4$ (eq. 3-13).[13] The reaction is a simple oxidative addition reaction, and is quite facile, proceeding quickly at room temperature.



(8) (3-13)

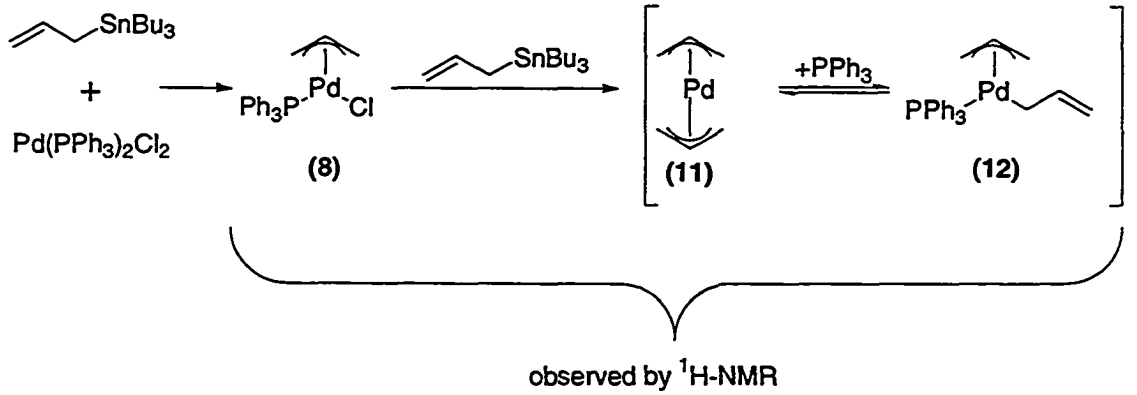
More interesting, and more relevant to our system, was the work of the group of Prof. Yoshinori Yamamoto at Tohoku University in Japan. Yamamoto and co-workers reported the formation of **(8)** via a transmetallation reaction between allyltributyltin and $Pd(PPh_3)_3Cl_2$.[14] Their findings grew out of investigations of new synthetic methodologies for the stereospecific allyl additions to carbonyl compounds (Scheme 3-2).[15]

Scheme 3-2
Pd-catalyzed addition of allyltin to aldehydes



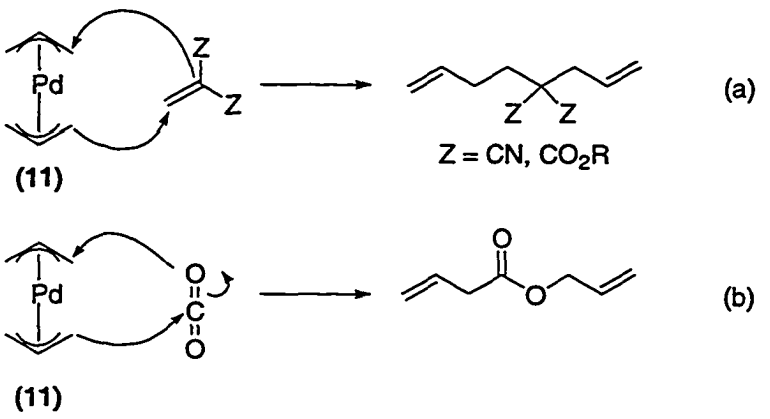
They studied the mechanism of the reaction using ^{1}H-NMR, and were able to observe the formation and subsequent consumption of complex **(8)** spectroscopically. Furthermore, they showed that **(8)** could undergo a second transmetallation with another equivalent of allyltin and be converted to bis(η^3-allyl)Pd **(11)**. They observed that complex **(11)** actually exists in an equilibrium between bis(η^3-allyl)Pd **(11)** and bis(η^1,η^3-allyl)(PPh_3)Pd **(12)** (Scheme 3-3). They were also able to show that **(12)** could subsequently react with aldehydes to form the corresponding homoallyl alcohol products.

Scheme 3-3
Formation of complexes (8), (11), and (12) from allyltin and Pd(II)



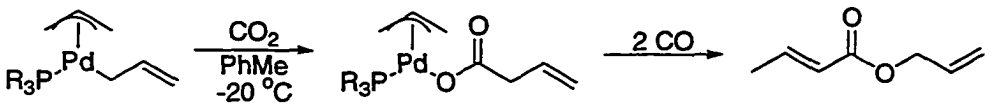
Although Yamamoto and co-workers were primarily interested in using these reactions for stereospecific allyl additions to aldehydes and ketones, they also showed that the bis(η^3-allyl)Pd **(11)** complex can act amphiphilically and effect α,β-bisallylation of Michael acceptors (Scheme 3-4(a)).[16] This mode of reactivity, wherein one allyl fragment adds nucleophilically and the other allyl fragment adds electrophilically, resembles, at least conceptually, that which had been previously observed by Wilke and co-workers (*vide infra*), and our own carboxylative coupling reaction with CO_2 (Scheme 3-4(b)).

Scheme 3-4
Amphiphilic addition reactions of bis(η^3-allyl)Pd (11)



3.2.5.2 Literature reports of reactions of Pd-allyls with CO_2

The majority of studies of the structure and chemistry of bis(allyl) complexes of Group 10 metals has come first from the group of Prof. Günther Wilke, and later from the group of Prof. Peter Jolly of the Max-Planck-Institut für Kohlenforschung in Germany.[17] They were able to synthesize a large number of bis(η^3-allyl)Pd and bis(η^1,η^3-allyl)(PR_3)Pd complexes and studied their structures using NMR and X-ray crystallographic methods.[18] In addition to their extensive structural work, Wilke's group also studied the reactivity of these complexes. They showed that bis(η^1,η^3-allyl)(PR_3)Pd (R = Me, Cy) **(13)** reacts very rapidly with CO_2 at -30 °C. The resulting carboxylato complexes are quite stable, forming the crotonate ester **(15)** only in the presence of excess CO (eq. 3-14).[19]

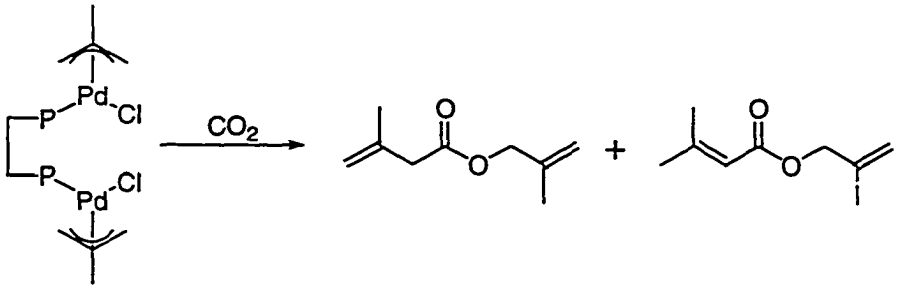


(3-14)

(13) (14) (15)

R = Me, Cy

The results of Wilke and co-workers showed that bis(allyl)Pd complexes can indeed react with CO_2. Other groups have also reported the reactivity of Pd-allyl complexes toward CO_2. Santi and Marchi reported that a bis[(η^3-2-methallyl)(μ-dppe)]Pd_2Cl_2 complex **(16)** reacted with CO_2 yielding a mixture of ester products (eq. 3-15).[20]

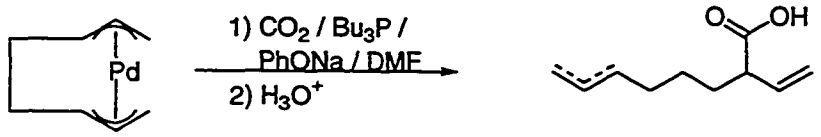


(3-15)

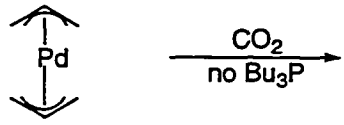
(16)

P
P = $Ph_2PCH_2CH_2PPh_2$

Ito and co-workers found that a bis(allylic)Pd complex **(17)** reacted with CO_2 (eq. 3-16). Interestingly, they also found that bis(η^3-allyl)Pd **(11)** does not insert CO_2 in the absence of additional phosphine ligand (eq. 3-17).[21]



(17) (3-16)



no CO_2 insertion product (3-17)

(11)

The results of Wilke and Yamamoto gave us some valuable mechanistic insights into our system. Their work demonstrated that:

a. It is possible for palladium(II) phosphine complexes and allyltin to react to form a Pd-allyl complex

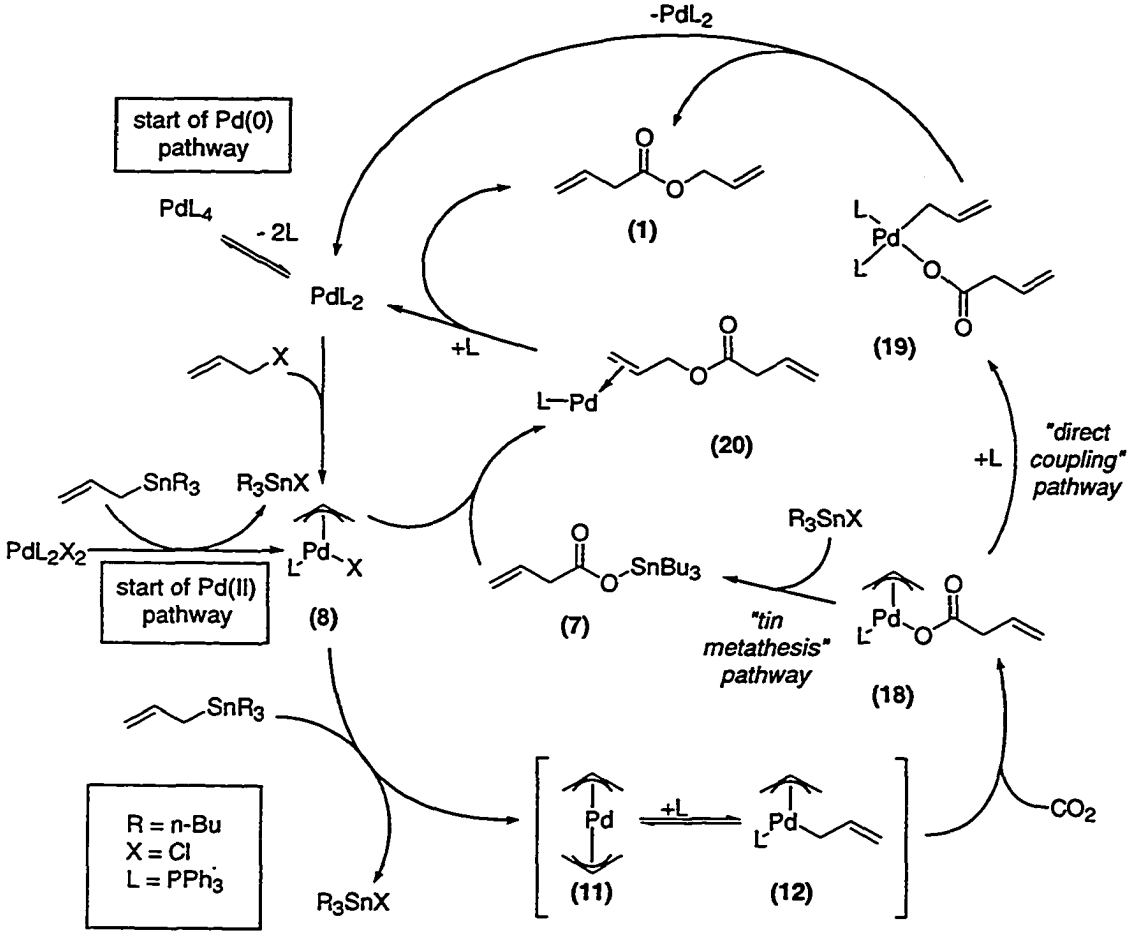
b. A Pd-allyl complex resulting from such a reaction might be reactive toward CO_2

3.3 A REVISED MECHANISTIC MODEL

After considering the literature reports and our own experimental work, we were then able to postulate a more complete mechanistic model for our carboxylative coupling reaction. The necessity of incorporating the formation of tributyltin 3-butenoate and its subsequent conversion tc the ester product makes for a model that is much more complex than our initial hypothetical mechanistic model (Scheme 3-1). The key intermediate in the mechanistic model is (η^3-allyl)(PPh_3)PdCl **(8)**. This intermediate can be formed starting from either Pd(0) or Pd(II). If Pd(0) is used, it must first lose two phosphine ligands in order to become coordinatively unsaturated. The resulting bis(phosphine)Pd complex, PdL_2, then undergoes oxidative addition with allyl chloride forming **(8)**.

Alternatively, intermediate **(8)** can be formed starting from Pd(II) by undergoing a transmetallation reaction with allyltributyltin, as was described by Yamamoto, *et al.*[14] Complex **(8)** then undergoes a transmetallation reaction with allyltributyltin to form the bis(η^3-allyl)Pd complex **(11)**, which can also exist as bis(η^1,η^3-allyl)(PPh_3)Pd **(12)**. The bis-allylic intermediate can then insert CO_2 forming (η^3-allyl)(3-butenoato)(PPh_3)Pd **(18)** in a manner analogous to that which was described by Wilke and co-workers. This intermediate could then conceivably follow two different pathways. The simplest pathway, the "direct coupling" pathway, consists of two steps. The first step in the "direct coupling" pathway involves addition of another phosphine ligand to form the *cis*-(η^1-allyl)(3-butenoato)(PPh_3)$_2$Pd complex **(19)**. In the second step, the *cis*-complex **(19)** could then form the ester **(1)** and regenerate the zerovalent PdL_2 by reductive elimination. This pathway, however, accounts for neither the formation of tributyltin 3-butenoate, nor its conversion to the ester. These things could be accounted for, however, if complex **(18)** were to follow a different pathway, the "tin metathesis" pathway. In this scheme, complex **(18)** undergoes a double metathesis reaction with tributyltin chloride to yield tributyltin 3-butenoate **(7)** and regenerate the important catalytic intermediate (η^3-allyl)(PPh_3)PdCl **(8)**. The tin carboxylate **(7)** could then attack the terminus of the η^3-allylic ligand of **(8)**, which would be expected to be quite electrophilic. This would yield a labile η^2-allyl complex **(20)**, which could then add an equivalent of phosphine ligand, liberating the ester **(1)**, and regenerating PdL_2, thus turning over the catalytic cycle. This new mechanistic model is shown in Scheme 3-2.

Scheme 3-5
Revised catalytic model for carboxylative coupling



3.3.1 Discussion of the revised model

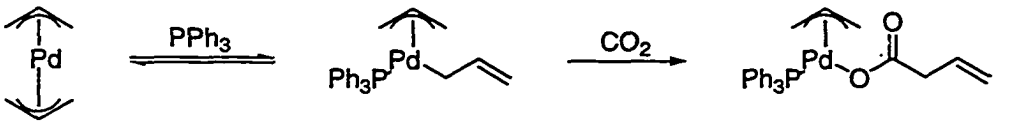
This revised mechanistic scheme is admittedly more complex than had been previously thought. Although we do not have any experimental evidence that can conclusively rule out the "direct coupling" pathway, we believe that it is not the preferred pathway. The "direct coupling" pathway certainly consists of mechanistic steps that have been observed for other coupling reactions. However, given the NMR evidence that tributyltin 3-butenoate **(7)** is formed under

the reaction conditions, and given that we have shown that **(7)** reacts with allyl chloride to form the ester (eq. 3-7), we believe the "tin metathesis" pathway to be predominant.

3.3.2 Attempted synthesis of mechanistic intermediates

The putative butenoato complex **(18)** plays an important role in our revised mechanistic model, as it is at this point where we believe the mechanism diverges into the "direct coupling" and "tin metathesis" pathways. We were interested in trying to synthesize this complex, characterize it spectroscopically, and study its reactivity. Our model would certainly have much more viability if we were able to show that indeed bis(η^1,η^3-allyl)(PPh_3)Pd **(12)** is formed, and subsequently converted to the butenoato intermediate **(18)** in our system. We planned to synthesize **(18)** starting from bis(η^3-allyl)Pd **(11)** and then adding PPh_3 to form bis(η^1,η^3-allyl)(PPh_3)Pd **(12)**. After NMR characterization of **(12)**, we planned to add CO_2, which would form **(18)** (Scheme 3-6).

Scheme 3-6
Proposed synthesis of (η^3-allyl)(3-butenoato)(PPh_3)Pd complex (18)

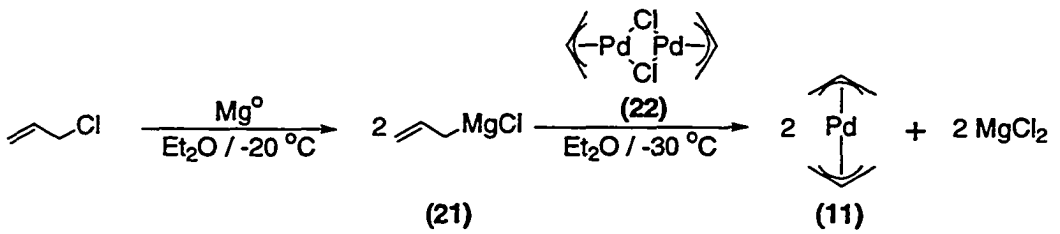


(11) **(12)** **(18)**

We attempted to synthesize **(18)** from the Grignard-based procedure for making bis(η^3-allyl)Pd **(11)**, which was reported by Wilke, *et al.*, (Scheme 3-7).[22] This procedure started by reacting allyl chloride and magnesium metal at –20 °C

to generate the allyl Grignard reagent **(21)**. We were able to synthesize the Grignard reagent without any trouble, however, the next step proved to be problematic. Wilke's procedure called for allylmagnesium chloride to be stirred with $[(\eta^3\text{-allyl})(\mu\text{-Cl})\text{Pd}]_2$ **(22)** overnight in Et_2O at –35 °C. At some point during the process of isolating the product, however, the color of the mixture changed from yellow to orange, indicating that the material had decomposed. Given that the procedure for the synthesis of **(11)** was quite difficult to perform, and since **(11)** is extremely air- and temperature-sensitive, we elected not to pursue this method any further.

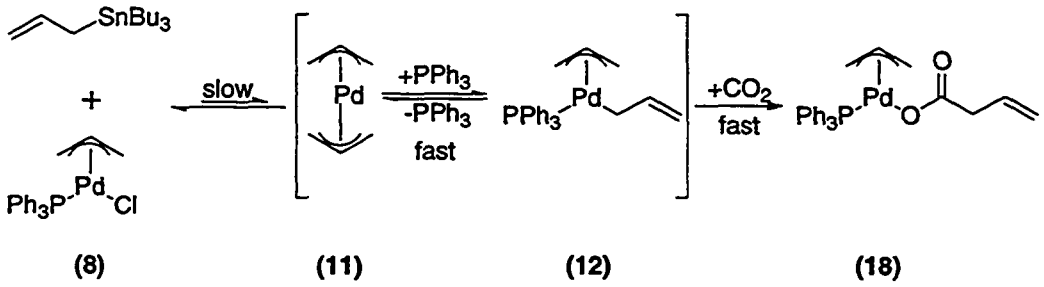
Scheme 3-7
Wilke's synthesis of bis(η^3-allyl)Pd (11)



Even if we had been successful in synthesizing **(11)**, we still might have encountered difficulties in producing complexes **(12)** and **(18)**. One important difference between our putative intermediate complexes **(11)**, **(12)**, and **(18)** and complexes **(13)** and **(14)**, which were synthesized by Wilke's group lies in the phosphine ligand. Wilke's group synthesized bis(η^1,η^3-allyl)(PR_3)Pd **(13)** and (η^3-allyl)(3-butenoato)(PR_3)Pd **(14)** using trialkylphosphine ligands (R = trimethylphosphine or tricyclohexylphosphine). Our proposed intermediates **(12)** and **(18)** both have triphenylphosphine, which is less basic than either

trimethylphosphine or tricyclohexylphosphine. It is interesting to note that in the Wilke group's structural studies of both bis(η^1,η^3-allyl)(PR_3)Pd and (η^3-allyl)(3-butenoato)(PR_3)Pd complexes, they *only* used tri*alkyl*phosphine ligands. Complexes with *aryl*phosphine ligands like **(12)** and **(18)** were conspicuously absent from their studies. This is most likely because the complex formed from triphenylphosphine, e.g. **(12)**, is not stable. This problem of instability resulting from the decreased Lewis basicity of PPh_3 relative to PMe_3 or PCy_3 could conceivably carry over into the carboxylato complex **(18)** also. It is true that triphenylphosphine is capable of forming **(12)** by coordinating to **(11)** *in solution*, however, complex **(12)** might not be stable enough to be isolated. Unlike Yamamoto, we did not observe any evidence for the formation of either **(11)** or **(12)** in our high-pressure NMR studies. It could be that the carboxylation step (and subsequent steps) occur very rapidly. If this were the case, then intermediates **(11)** and **(12)** would not be present in a very high concentration, as they would be consumed as soon as they were formed. Although we were not able to synthesize complexes **(11)**, **(12)**, or **(18)**, we still believe that they play an important role in the reaction mechanism.

Scheme 3-8
Relative rates of intermediate formation steps

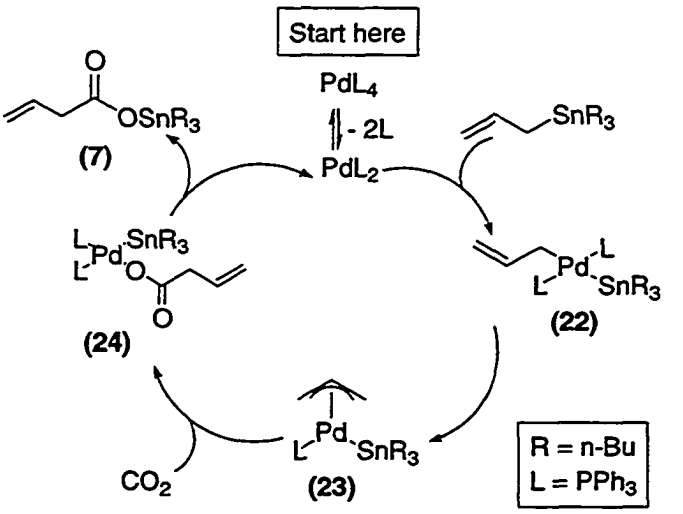


(8) **(11)** **(12)** **(18)**

3.3.3 Discussion of possible modes for the formation of tributyltin 3-butenoate

The mode postulated for the formation for the tin carboxylate is different than that which was originally postulated based on Shi's studies of the Pd-catalyzed carboxylation of allyltributyltin (Scheme 3-9). In the allyltin carboxylation mechanism, the allyltin is thought to undergo oxidative addition with palladium(0) forming (η^3-allyl)(PPh_3)($SnBu_3$)Pd **(22)**, which can then insert CO_2 forming (3-butenoato)(PPh_3)($SnBu_3$)Pd **(23)**. After isomerization to the cis complex **(24)**, tributyltin 3-butenoate **(7)** is then formed by reductive elimination.

Scheme 3-9
Tentative catalytic cycle for Pd-catalyzed carboxylation of allyltin



Although there is some literature evidence that allyltins can undergo oxidative addition with Pt(0) complexes, we do not believe that the tin carboxylate is formed this way in our system.[23] One important difference between our system and Shi's system is that our system contains allyl chloride. The electronic

structures of allyl chloride and allyltributyltin are very different (Figure 3-9). In allyl chloride, the C-Cl bond is polarized toward the Cl atom. The result is that allylic moiety is much more electrophilic in allyl chloride than in allyltributyltin. Hence, electron-rich complexes, like $Pd(PPh_3)_4$ will add to allyl chloride very easily. Conversely, in allyltributyltin, the C-Sn bond is polarized toward the C atom. The result in this case is that allyltributyltin is much more nucleophilic than allyl chloride. This type of bond polarization could account for the reactivity between allyltributyltin and electron-deficient Pd(II) complexes that was reported by Yamamoto (Scheme 3-2 & Scheme 3-4(a)).

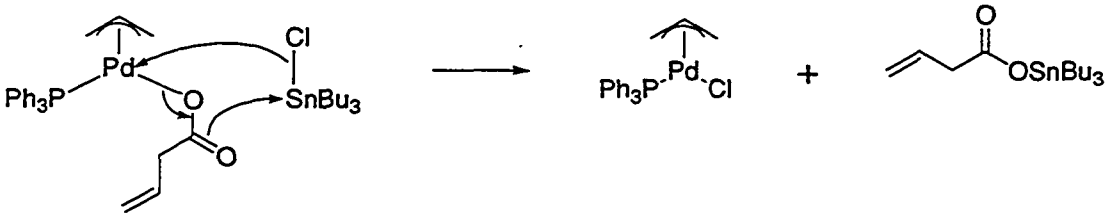
Figure 3-9
Allyl C-Z bond polarity differences between allyl chloride and allyltin



We have certainly seen these patterns of reactivity to be the case in our experience. Shi found that no reaction occurred between allyltributyltin and $Pd(PPh_3)_4$ when the two were stirred in THF overnight at room temperature. The reaction between allyl chloride and $Pd(PPh_3)_4$, on the other hand, occurs in less than 5-10 s at room temperature (eq. 3-13). Thus when allyl chloride and allyltributyltin are added to $Pd(PPh_3)_4$, the allyl chloride reacts much more rapidly with the Pd-complex than allyltributyltin, and only (η^3-allyl)$(PPh_3)PdCl$ **(8)** is formed. Thus, any consideration of how tributyltin 3-butenoate **(7)** is formed in our system must start from the point of complex **(8)**. We propose that the tin

carboxylate is formed through a metathesis reaction, in which the (η^3-allyl)(3-butenoato)(PPh_3)Pd complex **(18)** reacts with tributyltin chloride to form tributyltin 3-butenoate and (η^3-allyl)(PPh_3)PdCl **(8)** (Scheme 3-10). It must be emphasized that such a reaction is speculative on our part, but would be expected to be favorable thermodynamically. In addition to stability considerations based solely on bond energies, another possible thermodynamic driving force for the metathesis reaction could be the relative instability of complex **(18)**, as was discussed in the previous section (Section 3.3.2). Conversion of the presumably unstable butenoato intermediate **(18)** into **(7)** and **(8)**, both of which are stable at room temperature, would certainly be more favorable thermodynamically.

Scheme 3-10
Proposed metathesis reaction for tributyltin 3-butenoate formation



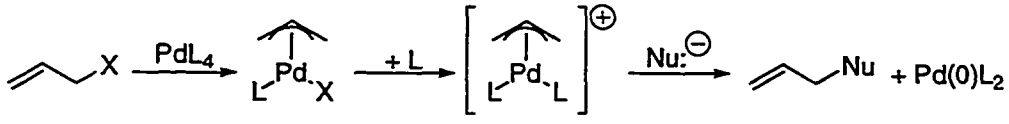
(18) **(8)** **(7)**

3.3.4 Discussion of possible modes of ester formation

One question that remains in the discussion of the revised catalytic model is, "How is the ester formed from tributyltin 3-butenoate **(7)**?" We have shown that tributyltin 3-butenoate and allyl chloride do react with $Pd(PPh_3)_4$ to form allyl 3-butenoate **(1)** (eq. 3-7), but we have not addressed the question of how exactly that happens. We have stated that we believe one of the key intermediates in

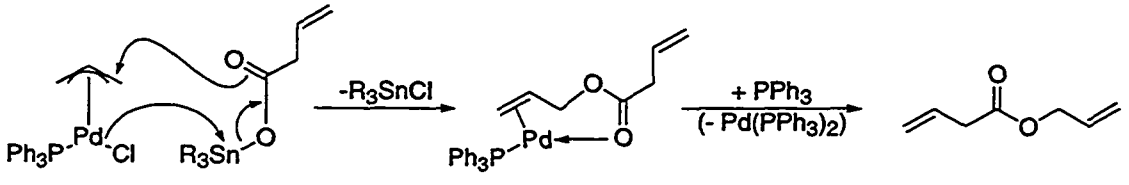
the mechanism is (η^3-allyl)(PPh_3)PdCl **(7)**. These types of Pd-allyl complexes are known to be quite electrophilic, as has been demonstrated in the case of the extensive allylic alkylation chemistry of electrophilic allylic compounds developed by Trost, Tsuji, and others (Scheme 3-11).[24]

Scheme 3-11
Pd-catalyzed allylic alkylation



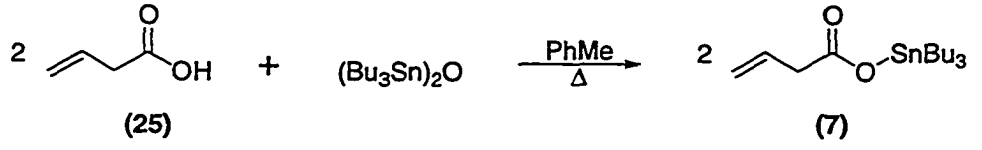
We believe that, given the electrophilic nature of **(8)**, the ester could be formed by attack of the tin carboxylate at either of the termini of the η^3-allyl ligand. Attack at the terminus of the allyl ligand has also been proposed by Stille in the case of allyl-allyl Stille couplings (*vide infra*), and has been supported by Trost.[25] Such an attack would likely form an η^2-coordinated intermediate **(20)**, from which the ester can then be displaced by addition of another equivalent of phosphine ligand (Scheme 3-12).

Scheme 3-12
Mode of attack of (η^3-allyl)(PPh_3)PdCl by tin carboxylate



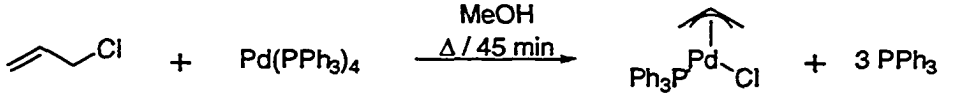
(8) **(20)** **(1)**

In an effort to explore the idea of ester formation via attack by the tin carboxylate **(18)** on the electrophilic allyl complex **(8)**, we tested whether or not **(8)** and **(18)** would react to form the ester. A literature procedure was used to prepare tributyltin 3-butenoate **(7)**.[26] Bis(tributyltin) oxide was treated with 3-butenoic acid **(25)** in toluene under azeotropic distillation conditions (eq. 3-18). The tin carboxylate **(7)** was formed in good yield (91%) using this method.



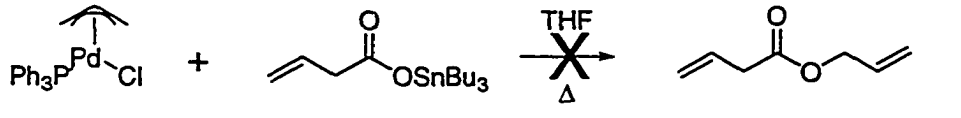
(25) **(7)** (3-18)

Pd-complex **(8)** was prepared using the method described by Powell and Shaw.[27] This method entailed a simple oxidative addition reaction of allyl chloride with $Pd(PPh_3)_4$ (eq. 3-19)



(8) (3-19)

After the two reactants had been prepared, equimolar amounts of each were reacted overnight in refluxing THF (eq. 3-20). The reaction mixture was then analyzed for the presence of the ester using gas chromatography. No ester product was detected by GC.

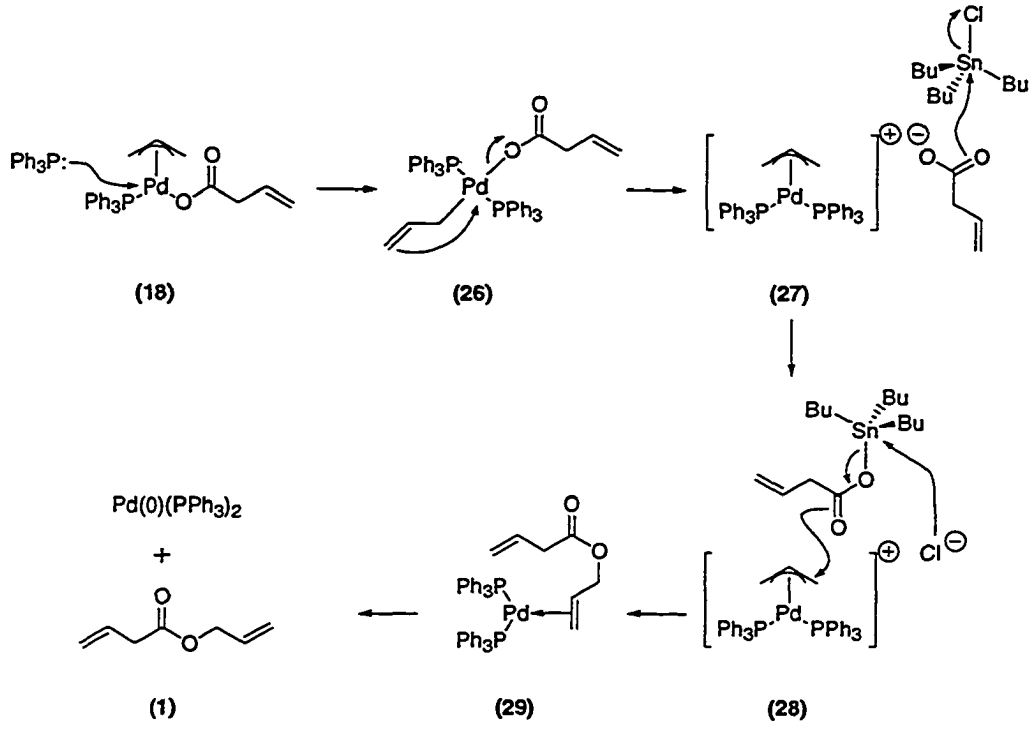


(8) **(7)** (3-20)

The failure of tributyltin 3-butenoate and (η^3-allyl)(PPh_3)PdCl to react directly to form the ester can be interpreted in several ways. First, it could be that the ester is not formed via the proposed attack of the η^3-coordinated allyl ligand by the tin carboxylate. One possible reason for this could be that the tin carboxylate is not sufficiently nucleophilic to attack the allyl ligand. Another possible reason for this is that the ester-forming step could be endothermic and also rate-limiting. Such a possiblity would be consistent with our failure to observe any ester formation in either the high-pressure NMR experiments or the preparative-scale stoichiometric experiments.

An alternative explanation might be that the lack of extra triphenylphosphine (present under catalytic conditions) in the reaction mixture inhibited the formation of the ester. It might be the case that an additional equivalent of triphenylphosphine adds to complex **(8)** in an associative process. This would necessitate a change in the hapticity of the allyl ligand from $\eta^3 \rightarrow \eta^1$ forming *trans*-(η^1-allyl)(3-butenoato)(PPh_3)$_2$Pd **(26)**. Isomerization of the allyl group back to η^3 geometry would displace the 3-butenoato group from the inner coordination sphere of Pd forming [(η^3-allyl)(PPh_3)$_2$Pd]$^+$[3-butenoate]$^-$ **(27)**. The 3-butenoate moiety and Bu_3SnCl could undergo metathesis in the outer coordination sphere to form [(η^3-allyl)(PPh_3)$_2$Pd]$^+$Cl$^-$ **(28)** and **(7)**.[24f] The cationic palladium complex **(28)** could then be attacked at the allyl ligand by **(7)** to form the η^2-coordinated complex **(29)** and Bu_3SnCl. The ester product **(1)** could then easily be formed by dissociation from **(29)**, regenerating the catalytically active Pd(0)(PPh_3)$_2$ species, which can restart the catalytic cycle (Scheme 3-13).

Scheme 3-13
Alternative mode for ester formation



(18) (26) (27)

(1) (29) (28)

3.4 The importance of the allylic substrate

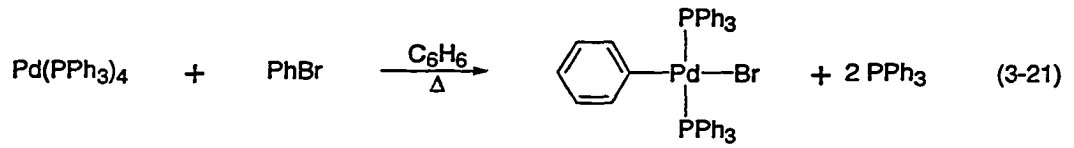
As was discussed in the previous chapter, after Shi's initial discovery of catalytic carboxylation of allyltins, he tried unsuccessfully to carboxylate a number of non-allylic substrates. In addition, after our discovery of the catalytic carboxylative coupling of allyltins and allyl chloride, we also tried unsuccessfully to effect carboxylative coupling with a variety of non-allylic organotin and organohalogen substrates, as was discussed in the previous chapter. Our attention began to focus on the obvious importance of the allyl group in these reactions. We began by examining the chemistry of the allyl group in other catalytic reactions in the literature.[28] First among these was the behavior of allyl-

allyl couplings in the Stille reaction.[29] Both types of coupling reactions, the "normal" allyl-X/allyl-Sn coupling and the carbonylative allyl-x/allyl-Sn/CO coupling work well with Pd-catalysis. We found a few other carboxylations of Group 10 allyls in the literature[30] in addition to those already cited, however, we found few examples of non-allylic organopalladium compounds that react with CO_2.[31] In an effort to expand the synthetic scope of our reaction to include non-allylic substrates, we began to look at carboxylating aryl-Pd complexes.

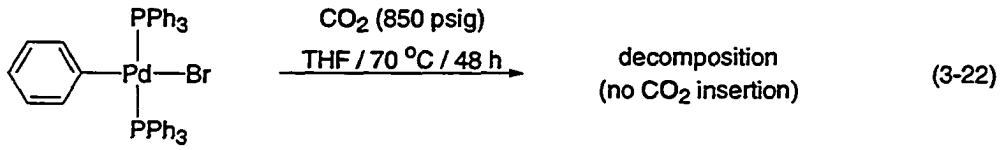
3.4.1 Attempted carboxylation of Pd- & Pt-aryl complexes

We were eager to induce carboxylation of other organopalladium complexes, and thus we investigated the possibility of carboxylating arylpalladium complexes. We hoped to modify the ligand environment around the metal center to make the complex more nucleophilic. We began our studies by attempting to carboxylate *trans*-$PhPd(PPh_3)_2Br$ **(30)**. Complex **(30)** was synthesized by heating bromobenzene with $Pd(PPh_3)_4$ overnight in refluxing benzene (eq. 3-21).[32] We were able to isolate the complex and recrystallize it from $CHCl_3$/MeOH. The product was characterized by ^1H-, ^{13}C-, and ^{31}P-NMR. The ^1H- and ^{13}C-NMR spectra of the sample contained only aromatic signals. The trans geometry of the complex was confirmed by the presence of only one ^{31}P resonance at δ 24.1. We then attempted to carboxylate complex **(30)** using conditions that were similar to those that were used in the successful carboxylative coupling experiments, e.g. high CO_2 pressure, elevated temperatures, THF solvent (eq. 3-22). Unfortunately, when the autoclave was

opened, the complex appeared to have decomposed, perhaps due to the high temperature used in the reaction.

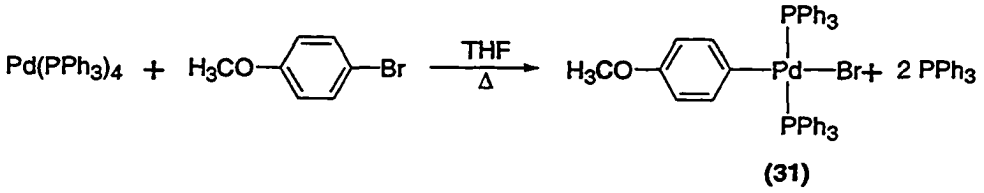


(30)

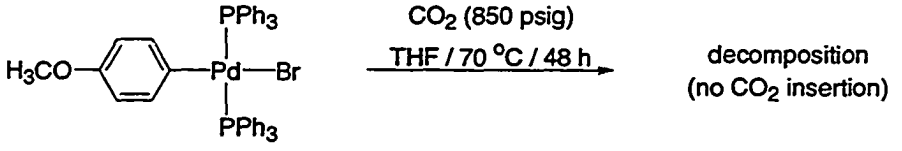


(30)

We hoped to improve our chances for carboxylation by increasing the nucleophilicity at the palladium center. We sought to accomplish this by using an aryl ligand with an electron-donating group attached at the para position in the ring. $Pd(PPh_3)_4$ was heated with p-bromoanisole overnight in refluxing THF (eq. 3-23). The resulting *trans*-(p-anisyl)$Pd(PPh_3)_2Br$ complex **(31)** was also characterized by ^1H-, ^{13}C-, and ^{31}P-NMR. As in the previous case, the ^1H- and ^{13}C-NMR spectra of complex **(31)** showed only aromatic signals, and the presence of only one ^{31}P signal at δ 24.1 confirmed the trans geometry. We then attempted to carboxylate complex **(31)** in the same manner that we had attempted for complex **(30)**, but the result in this case was also decomposition (eq. 3-24).

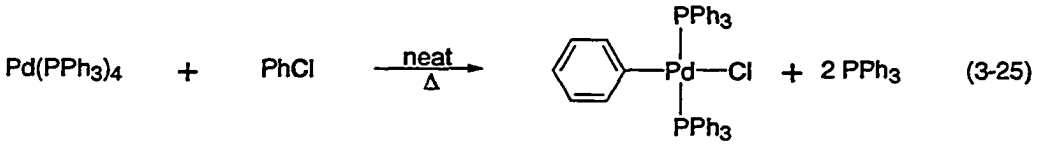


(31) (3-23)

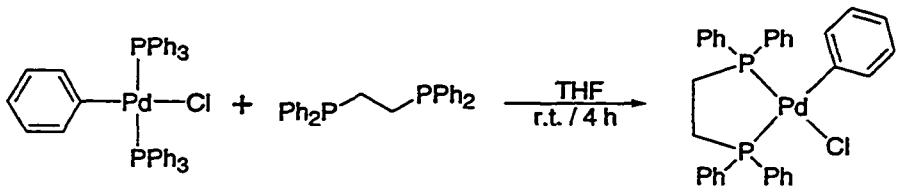


(31) (3-24)

Another approach that we were interested in using to try to enhance the nucleophilicity of the palladium center was to attempt the carboxylation using a *cis*-arylpalladium halide. We prepared *cis*-PhPd(dppe)Cl **(33)** from *trans*-$Ph(PPh_3)_2PdCl$ **(32)**[33] (eqs. 3-25 & 3-26) based on a procedure reported by Herrmann, *et al.*[34] The resulting cis complex **(33)** was then heated with CO_2 for 48 h (eq. 3-27). Again, as was the case in other attempted carboxylations of arylpalladium halides, the complex appeared to have decomposed.

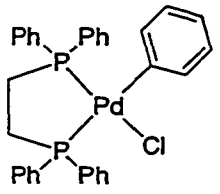


(32) (3-25)



(3-26)

(32) (33)



CO_2 (850 psig)
THF / 70 °C / 48 h

decomposition
(no CO_2 insertion)

(3-27)

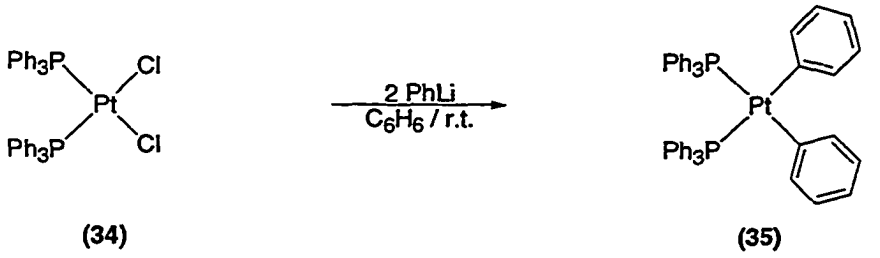
(33)

We were concerned that the presence of the halogen bonded to the palladium was still reducing the nucleophilicity of the complex and inhibiting possible reaction with CO_2. We then wanted to attempt carboxylating a *cis*-bis(aryl)Pd(II) complex. Unfortunately, an examination of the literature revealed that such complexes of palladium are not very thermally stable. However, *cis*-bis(aryl)Pt(II) complexes are more stable thermally, so we elected to use them instead.

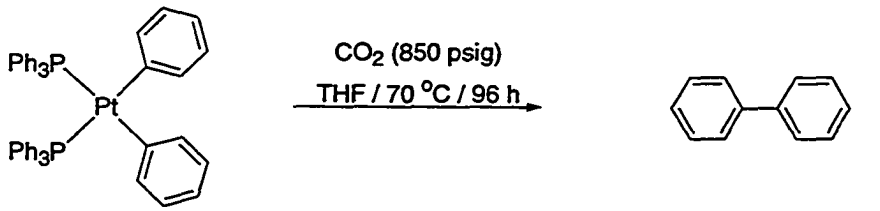
We synthesized *cis*-diphenylbis(triphenylphosphine)platinum(II) **(35)** from *cis*-$Pd(PPh_3)_2Cl_2$ **(34)** and phenyllithium according to a standard literature procedure (eq. 3-28).[35] Complex **(35)** was then heated with CO_2 for four days in an autoclave. The reaction mixture was analyzed by IR and NMR. Neither the NMR nor the IR spectra showed any evidence of carboxylation. The ^{1}H-NMR of the reaction mixture indicated that the σ-bonded aromatic groups had been lost from the complex. Further analysis of the reaction mixture by GC showed that the major organic product of the reaction was biphenyl. This was conclusive

evidence that complex **(35)** had not been carboxylated, but rather had suffered reductive elimination to form biphenyl **(36)** (eq. 3-29).

When we considered the results of our unsuccessful attempts to induce carboxylation of Pd- and Pt-aryl complexes, we arrived at two possible conclusions: (1) It is possible that the Pd- and/or Pt-aryl complexes are simply unreactive toward CO_2, and (2) It is possible that the complexes reacted with CO_2, but the resulting carboxylates were unstable under the reaction conditions and, hence, were not able to be isolated. Some halide-carboxylate complexes of Pd(II) and Pt(II) have been reported, but this type of complex normally exists as a (μ-carboxylato) dimer.[36] We believe that these results underscore the unique reactivity characteristics of the allylic ligand.



(34) (35) (3-28)



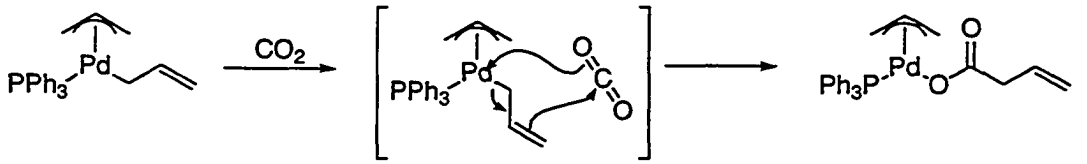
(35) (36) (3-29)

3.4.2 The amphiphilic nature of the allylic ligand

We believe that the allyl group plays two different roles in the carboxylative coupling reaction. First, it reacts as a nucleophile when CO_2 is

attacked by bis(η^1,η^3-allyl)(PPh_3)Pd **(12)**. Later, it must react as an electrophile when (η^3-allyl)(PPh_3)PdCl **(8)** is attacked by the tin carboxylate in the ester-forming step of the mechanism. The only difference in these two cases is the anionic ligand that is bound to the (η^3-allyl)(PPh_3)Pd moiety. In the case of nucleophilic attack on CO_2, the reacting palladium species is believed to be the bis(allyl) complex **(12)**. The presence of the second allyl group bound to the palladium results in a much more nucleophilic complex, as was evidenced by our findings, and by those of Yamamoto, which were discussed earlier (*vide supra*). A possible mode for nucleophilic attack on CO_2 by complex **(12)** is shown in Scheme 3-14.

Scheme 3-14
Nucleophilic attack on CO_2 by bis(η^1,η^3-allyl)(PPh_3)Pd (12)



(12) **(18)**

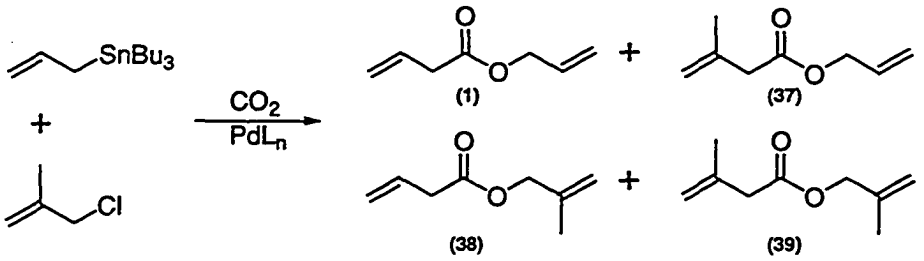
In contrast, when chloride is bound to palladium instead of a second allyl group, as in the case of (η^3-allyl)(PPh_3)PdCl **(8)**, the resulting character of the complex is changed from being nucleophilic to being electrophilic. The electronegativity of the chloride ligand could make the allyl ligand more susceptible to nucleophilic attack by the tin carboxylate, as was shown in Schemes 3-12 & 3-13. We believe that the allyl group is one of the only organic ligands that can behave in such an amphiphilic manner. The other organic groups that we tried to

carboxylate are not able to behave in such an amphiphilic manner, and we believe that this is the reason that we were not able to carboxylate them.

3.4.3 Mixed allyl/2-methallyl coupling revisited

3.4.3.1 Application of the mechanistic model to account for product distribution in mixed coupling experiments

In addition to the aforementioned effects on reactivity exhibited by the allyl ligand, we believe that the allyl ligand is also responsible for the unique mixture of products that resulted when 2-methallyl chloride was heated with allyltributyltin under CO_2 pressure (eq. 3-30).



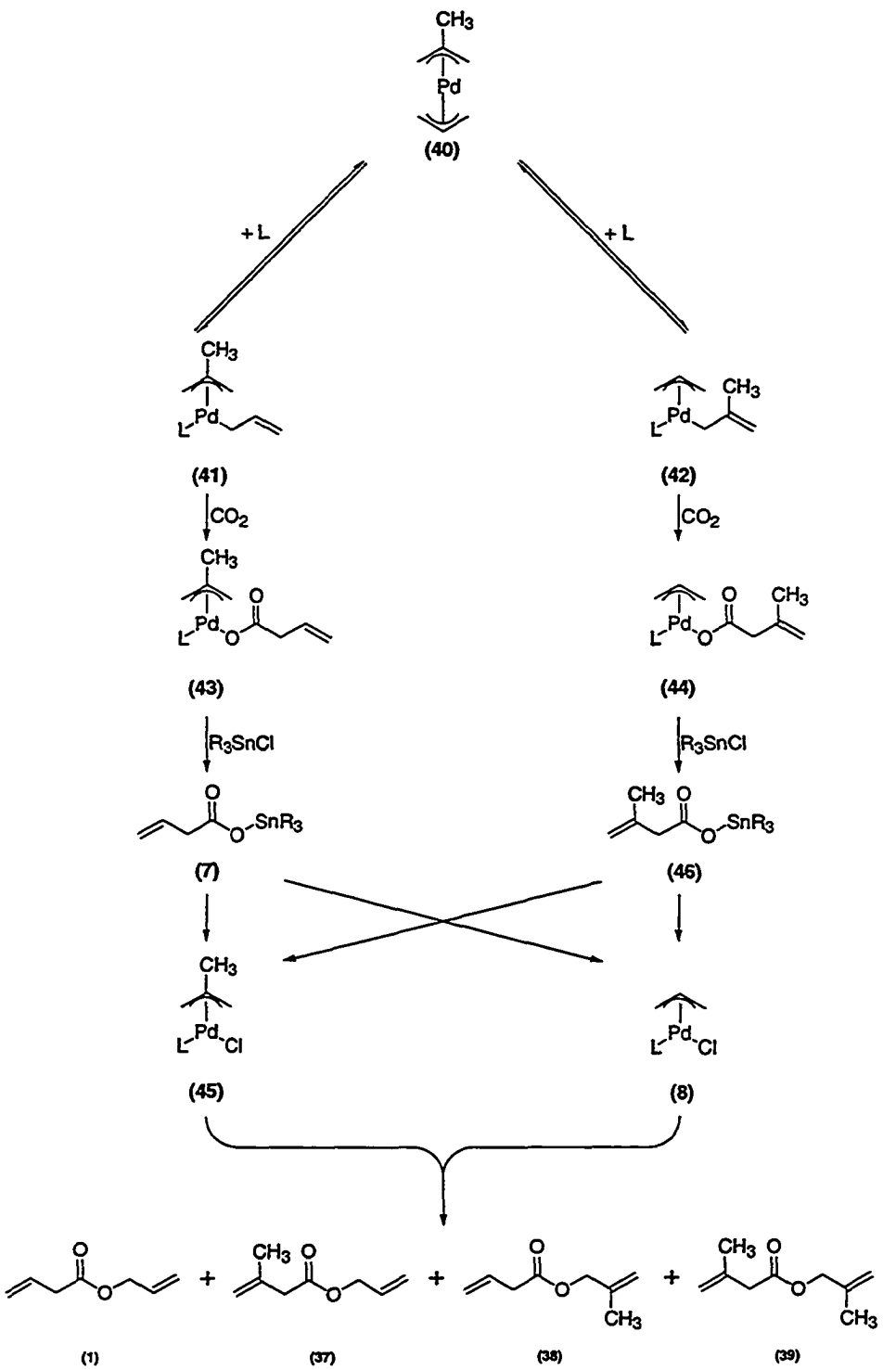
(3-30)

We now believe that the formation of both the heterocoupled esters **(37)** and **(38)** *and* the rather mysterious formation of the homocoupled esters **(1)** and **(39)** can be accounted for by application of our mechanistic model to the mixed substrate system, as was shown in Scheme 3-5.

In the case of the mixed substrate system, the key intermediate formed after the initial reaction of the starting Pd-complex with the substrates would be (η^3-allyl)(η^3-2-methallyl)Pd **(40)**. PPh_3 can then add to complex **(40)** to form to different products (η^1-allyl)(η^3-2-methallyl)(PPh_3)Pd **(41)** and (η^1-2-methallyl)(η^3-allyl)(PPh_3)Pd **(42)**. Each of these can then undergo CO_2 insertion forming (η^3-2-

methallyl)(3-butenoato)(PPh_3)Pd **(43)** and (η^3-allyl)(3-methyl-3-butenoato)(PPh_3)Pd **(44)** respectively. Subsequent metathesis of complexes **(43)** and **(44)** with tributyltin chloride would yield tributyltin 3-butenoate **(7)** and (η^3-2-methallyl)(PPh_3)PdCl **(45)**, and tributyltin 3-methyl-3-butenoate **(46)** and (η^3-allyl)(PPh_3)PdCl **(8)**. The four ester products can be formed by combination of each of the tin carboxylates with each of the (allyl)(PPh_3)PdCl complexes formed in this step. Reaction of tributyltin 3-butenoate **(7)** with (η^3-allyl)(PPh_3)PdCl **(8)** would form the allyl-allyl coupled ester **(1)**. Reaction of **(7)** with (η^3-2-methallyl)(PPh_3)PdCl **(45)**, on the other hand, would form the allyl-methallyl heterocoupled ester **(38)**. If, instead tributyltin 3-methyl-3-butenoate **(46)** were to react with (η^3-allyl)(PPh_3)PdCl **(8)**, the result would be other heterocoupled ester **(37)**. The especially curious formation of the methallyl-methallyl homocoupled ester **(39)** can be accounted for by the reaction of **(46)** with (η^3-2-methallyl)(PPh_3)PdCl **(45)**. This is shown in Scheme 3-15. We were pleased finally to have a mechanistic model that could reasonably account for the previously enigmatic appearance of all four esters in the mixed substrate system.

Scheme 3-15
Formation of homocoupled & heterocoupled esters



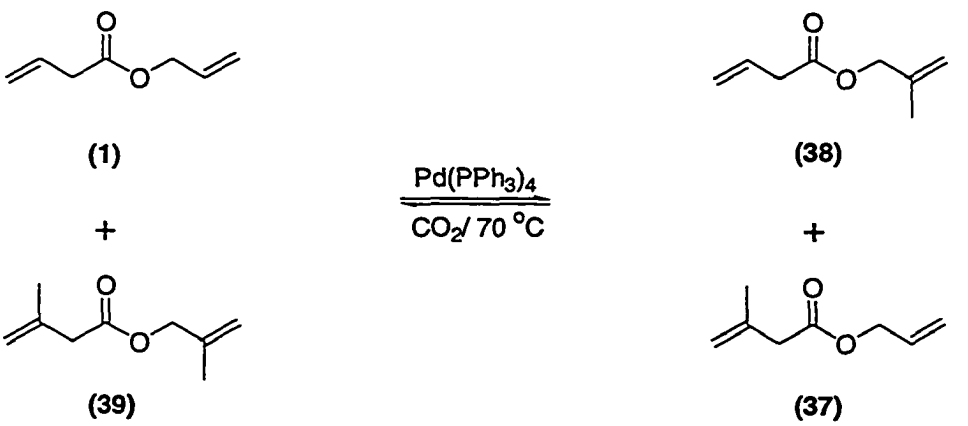
3.4.3.2 Allyl/2-methallyl crossover experiments

Another possibility that we considered was that the ester formation reaction could be reversible. The propensity for allyl esters to undergo oxidative addition is the foundation of the extensive Pd-catalyzed allylic alkylation chemistry developed by Trost and others.[24] We were concerned what the effects of reaction reversibility could be on our system, given that we were forming an allyl ester, and that there was Pd(0) present in the system. We conducted a series of "crossover" experiments to test this idea. The first experiment was performed by loading an autoclave with a catalytic amount of $Pd(PPh_3)_4$ and an equimolar mixture of the heterocoupled esters **(37)** and **(38)**. The reagents were then dissolved in THF and the autoclave was pressurized with CO_2 (750 psig). The system was then heated at 70 °C for 48 h. After 48 h, the reaction mixture was analyzed by GC, and four product peaks were detected. In addition to peaks for the starting *heterocoupled* esters **(37)** and **(38)**, peaks for the *homocoupled* esters **(1)** and **(39)** were also observed (Scheme 3-16). As had been the case in the original mixed coupling experiments, all four of the esters were formed in approximately equal amounts.

The second "crossover" experiment in this series was very similar to the first. This time the autoclave was again charged with a catalytic amount of $Pd(PPh_3)_4$ and equimolar amounts of the homocoupled esters allyl 3-butenoate **(1)** and 2-methallyl 3-methyl-3-butenoate **(39)**. The reagents were dissolved in THF, the reactor was pressurized with CO_2 (750 psig), and the system was heated at 70 °C for 48 h. GC analysis of the reaction mixture again indicated the

presence of the two starting *homocoupled* esters **(1)** and **(39)** along with the two *heterocoupled* esters **(37)** and **(38)**. As was the case in the previous experiment, all four ester were present in almost equimolar amounts (Scheme 3-16). These crossover experiments clearly demonstrated that tributyltin chloride, or any other tin-containing species, was unnecessary for the homocoupled esters **(1)** and **(39)** to form. The crossover experiments showed that it was indeed possible to form the homocoupled esters by means of a solely Pd-centered pathway.

Scheme 3-16
Ester scrambling from crossover experiments



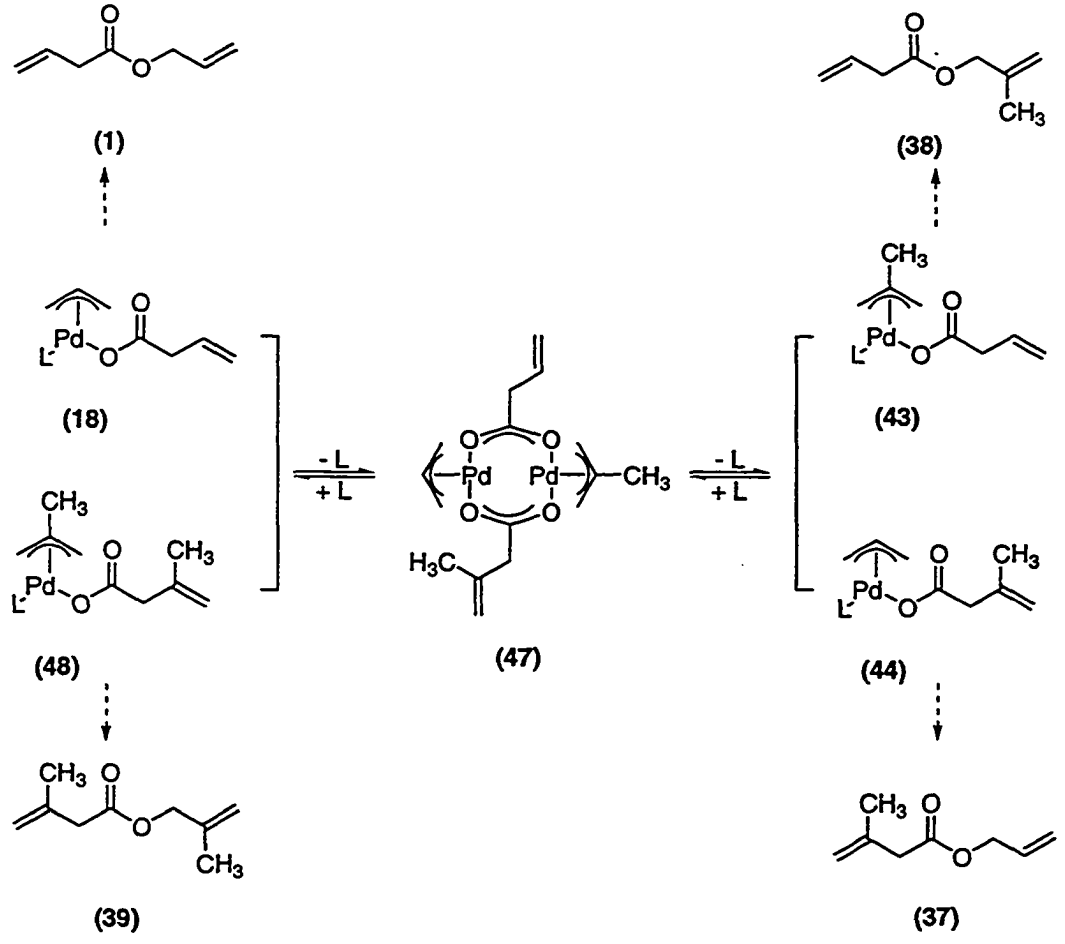
Again, the literature provided insight into these interesting results. Pratt and van Leeuwen studied the structures of various (η^3-allyl)(acetato)(PPh_3)Pd complexes.[37] They reported that it was possible for such complexes to exist not only in the in the monomeric form, but also in equilibrium with a dimeric form [(η^3-allyl)(μ-acetato)Pd]$_2$, which contained bridging acetato ligands. We believe that a similar equilibrium can account for the results we obtained in our crossover experiments, and by extension, to our original mixed carboxylative coupling system.

3.4.3.3 Pd-carboxylate dimerization to account for mixed ester formation

The formation of the two heterocoupled esters **(37)** and **(38)** in our mixed allyl/2-methallyl coupling studies did not come as a surprise. We did not expect for CO_2 to exhibit any type of regioselectivity in such a system. The formation of the homocoupled esters **(1)** and **(39)** was actually a shock to us, *especially* the formation of the 2-methallyl/2-methallyl coupled ester **(39)**. Furthermore, the fact that all four ester products were formed in approximately equal amounts was also very surprising. In the crystal-clear vision of hindsight, this type of product distribution should have suggested to us at the beginning that we were dealing with an equilibrium process, however, we did not consider such an equilibrium. We then used our observations from the crossover experiments and the evidence for the formation of bridging carboxylato Pd-complexes reported by van Leeuwen to devise a scheme for the formation of the homocoupled ester products in our original mixed allyl/2-methallyl substrate system (Scheme 3-17). As was the case in the tin-mediated scrambling model described in Scheme 3-5, (η^3-allyl)(η^3-2-methallyl)Pd **(40)** forms the cornerstone of our alternative equilibrium-based scrambling model. PPh_3 can add to complex **(40)** to form (η^1-allyl)(η^3-2-methallyl)(PPh_3)Pd **(41)** and (η^1-2-methallyl)(η^3-allyl)(PPh_3)Pd **(42)**. Each of these can then undergo CO_2 insertion forming (η^3-2-methallyl)(3-butenoato)(PPh_3)Pd **(43)** and (η^3-allyl)(3-methyl-3-butenoato)(PPh_3)Pd **(44)** respectively. Complexes **(43)** and **(44)** can then follow the "tin metathesis" pathway to form the heterocoupled esters **(37)** and **(38)** respectively. Another possible mechanistic pathway that complexes **(43)** and **(44)** could follow,

however, is to form a dimeric (η^3-allyl)(η^3-2-methallyl)(μ-3-butenoato)(μ-3-methyl-3-butenoato)dipalladium(II) complex **(47)**. Under the equilibrium conditions of the reaction, the dimeric complex could simply add PPh_3 and revert to the monomeric mixed allyl/2-methallyl complexes **(43)** and **(44)**, *or* it could add PPh_3 and form the monomeric non-mixed complexes **(18)** and **(48)**. The ester products could then be formed from any of the four complexes **(18)**, **(43)**, **(44)**, and **(48)** by following either the "direct coupling" or the "tin metathesis" pathways described in Scheme 3-17.

Scheme 3-17
Mixed ester formation from bridging carboxylato Pd-complex



The fact that we even were able to observe such scrambling in the crossover experiments was perhaps even more surprising, given the lack of any tin-containing species that could mediate any type of tin metathesis reaction of the carboxylato complex. Clearly, the crossover reactions had to proceed through a pathway that did not include tin. We propose a similar mechanistic scheme for the allyl/2-methallyl scrambling that occurred in the crossover experiments. Since the reaction began with the allylic esters, it is reasonable to postulate that the mechanism begins by the ester undergoing oxidative addition with $Pd(0)L_2$. If the reaction were carried out using the heterocoupled esters **(37)** and **(38)**, then the products of oxidative addition would be (η^3-2-methallyl)(3-butenoato)(PPh_3)Pd **(43)** and (η^3-allyl)(3-methyl-3-butenoato)(PPh_3)Pd **(44)** respectively. Complexes **(43)** and **(44)** could then undergo a dimerization forming complex **(47)**. The dimeric intermediate **(47)** could then either revert to the starting complexes, or alternatively, could form the precursor complexes for the homocoupled esters **(1)** and **(39)**. In either case, the ester products could be formed by reversal of the initial oxidative addition reaction, i.e. reductive elimination.

In the case of the original mixed carboxylative coupling of allyltributyltin and 2-methallyl chloride, it is indeed possible that both mechanistic pathways, that resulting from dimerization of the original carboxylato complexes and that resulting from oxidative addition of the ester products to form the dimeric intermediate, could be operating to give the mixture of products that was

observed. It is difficult to know to what extent each of the pathways is at work in the overall course of the reaction.

3.5 CONCLUSIONS

Our mechanistic studies yielded some very interesting results. After beginning our mechanistic work, we quickly discovered that our seemingly straightforward Pd-catalyzed allyl-allyl carboxylative coupling reaction was more complicated than it had first appeared. The high-pressure NMR studies showed that (η^3-allyl)(PPh_3)PdCl **(8)** was formed initially in the reaction, and then was subsequently converted to tributyltin 3-butenoate **(7)**. The formation of **(7)**, and its importance in the reaction was confirmed by our preparative-scale reactions, ^{119}Sn-NMR experiments, and our allyl chloride/tributyltin 3-butenoate metathesis results. We used the results published by Yamamoto's and Wilke's groups along with our own results to formulate a putative catalytic model for the reaction. This model was much more complex than we had originally imagined, as it contained the possibility of ester formation through two different pathways, a more conventional "direct coupling" pathway, and a novel "tin metathesis" pathway. The "tin metathesis" pathway featured ester formation via attack of (η^3-allyl)(PPh_3)PdCl **(8)** by tributyltin 3-butenoate.

Perhaps the most important result of our mechanistic studies was our conclusion that the allylic moiety possesses unique characteristics that enable it to undergo carboxylative coupling. The allyl group can behave amphiphilically, depending on the other ligands bound to palladium, and this dual reactivity

accounts for much of our results. It accounts for why the carboxylative coupling reaction occurs in the first place, but it also accounts for our inability to effect carboxylative coupling for non-allylic substrates. We undertook these mechanistic studies with the hope that by learning about the reaction mechanism, we could manipulate the catalyst so that we could expand the scope of the reaction to include non-allylic substrates. Although we were not successful in this endeavor, we did learn a great deal about the unique and interesting chemistry of (η^3-allyl)Pd complexes in the process.

Finally, we were able to apply our mechanistic model, literature results, and the results of our crossover studies to propose a mechanistic scheme that accounted for the anomalous formation of both heterocoupled and homocoupled esters that we observed in our mixed allyltributyltin/2-methallyl chloride carboxylative coupling reactions. We believe that mixture of esters is produced as a result of the formation of a dimeric bis(carboxylato)palladium(II) intermediate **(47)**.

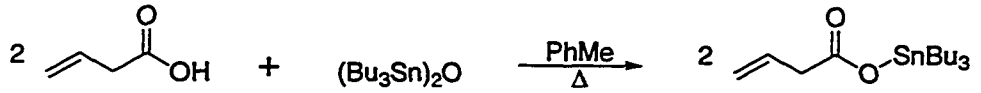
Our lack of success in expanding the synthetic scope of the reaction to achieve carboxylative coupling of non-allylic substrates led us to conclude that we should investigate metal systems other than Pd-Sn. After surveying the relevant literature, we decided to continue our work by attempting carboxylative coupling of Cu-Zn systems.

3.6 EXPERIMENTAL SECTION

All reagents were used as received from the suppliers. All glassware was oven-dried prior to use. THF, diethyl ether, and benzene were distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from calcium hydride. CO_2 was anaerobic grade (Mattheson). High pressure reactions were carried out in Parr stainless steel autoclaves. The high-pressure NMR tube used was purchased from Wilmad. GC analysis was carried out on a Hewlett-Packard HP 5790A GC using a 3 m column packed with 10 % OV-101 on Supelcort B, with nitrogen or helium as the carrier gas, and a flame ionization detector. GC-MS analysis was carried out on a Hewlett-Packard HP 5985 using a 30 m capillary column packed with 3% SE-54. NMR analysis was performed using Varian VXR-500S, Varian Unity/Inova 400, or Varian XL-300 instruments. NMR references were tetramethylsilane for ^{1}H and ^{13}C (internal standard), 85 % H_3PO_4 for ^{31}P (external standard), and tetramethyltin for ^{119}Sn (external standard). IR analysis was done using a Bio-Rad model FTS 135 FT-IR spectrometer.

Preparation of tributyltin 3-butenoate

Reaction:



Reference: Okawara, R.; Wada, M. In *Organotin Compounds*; Sawyer, A.K., Ed.; M. Dekker: New York, 1971; Vol. 2, p 253.

Procedure:

A 250-mL round bottom flask was charged with a stir bar, 3-butenoic acid (1.0 mL, 1.0 g, 12 mmol, 2.0 equiv.), bis(tributyltin)oxide (3.0 mL, 3.5 g, 5.9 mmol, 1.0 equiv.), and toluene (100 mL). A Dean-Stark trap was attached, and additional toluene was added to the trap. The system was heated at reflux for 20 h. The system was cooled to room temperature. Toluene was removed first by rotary evaporation and then under vacuum. The product was an off-white solid. The yield of product was 4.04 g (91 % yield based on bis(tributyltin)oxide).

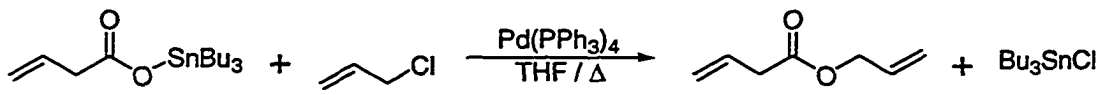
^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 9 H), 1.20-1.40 (m, 12 H), 1.60 (m, 6 H), 3.10 (d, 2 H, J = 7 Hz), 5.05-5.10 (overlapping d, 2 H), 5.90 (m, 1 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.6, 16.4, $^{1}J_{C\text{-}Sn}$ = 173 Hz, 27.0, $^{2}J_{C\text{-}Sn}$ = 33 Hz; 27.7 ,$^{3}J_{C\text{-}Sn}$ = 10 Hz; 39.8, 117.0, 132.0.

^{119}Sn-NMR (184 MHz, $CDCl_3$) δ 116.9.

Metathesis reaction of allyl chloride and tributyltin 3-butenoate

Reaction:

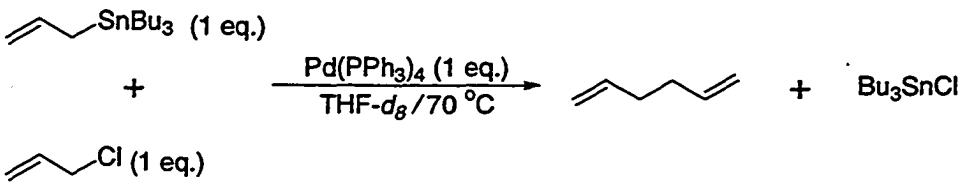


Procedure:

A flask was charged with a stir bar, naphthalene (53.7 mg, internal standard), and tributyltin 3-butenoate (292 mg, 0.779 mmol). $Pd(PPh_3)_4$ (156 mg, 0.135 mmol, 17.3 mol %) was then added. The flask was then sealed and purged with nitrogen. Dry THF (25 mL) was then added. Allyl chloride (100 μL, 1.23 mmol) was then added by syringe. The mixture was refluxed under nitrogen overnight. The yield of the reaction was determined by GC to be 126.5 mg (>99 % yield).

High-pressure NMR tube reaction of allyltributyltin, $Pd(PPh_3)_4$ (no CO_2)

Reaction:



Procedure:

NMR tube loading was done in the glove box. $Pd(PPh_3)_4$ (18.0 mg, 15.6 μmol) was dissolved in d_8-THF (300 μL) in a small glass vial. Allyl chloride (1.4 μL, 17 μmol) and allyltributyltin (5.0 μL, 16 μmol) was added by syringe. The

mixture was swirled until all of the reagents had dissolved. A 200 μL portion of this solution was transferred to a Wilmad high-pressure NMR tube. TMS (~1-2 drops) was added as a standard. The tube was sealed, removed from the glove box, and then was heated in refluxing THF. ^{1}H-NMR spectra were recorded at 0 h and 5 h.

^{1}H-NMR (300 MHz, d_8-THF):

Starting material: δ 0.80-1.80, 4.60, 4.75, 5.92, 7.20-7.70

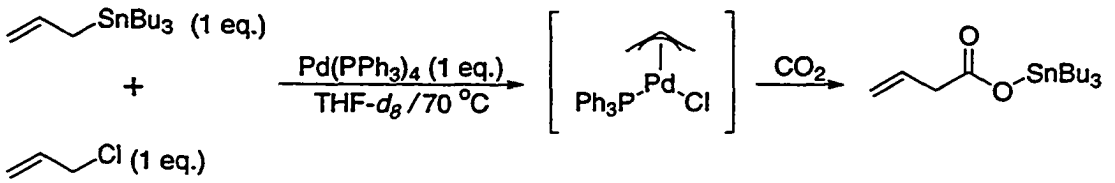
1,5-hexadiene: δ 2.12 (overlapping dd, 4 H), 4.92 (d, 2 H, J = 10 Hz), 4.99 (d, 2 H, J = 17 Hz), 5.79 (br m, 2 H)

t = 0 h starting material peaks plus δ 3.38-3.61 (br s), 4.92 (d, J = 11 Hz), 5.00 (d, J = 17 Hz), 5.61 (quintet, J = 10 Hz), 5.92 (br m)

t = 5 h starting material peaks plus δ 2.13 (d, 2 H), 4.92 (d, J = 10 Hz), 5.00 (d, J = 18 Hz), 5.72-5.84 (br m)

High-pressure NMR tube reaction of allyltributyltin, allyl chloride, $Pd(PPh_3)_4$, and CO_2

Reaction:



Procedure:

NMR tube loading was done in the glove box. $Pd(PPh_3)_4$ (16 mg, 14 μmol) was dissolved in d_8-THF (400 μL) in a small glass vial. Allyltributyltin (4.0

μL, 13 μmol) and allyl chloride (1.0 μL, 12 mmol) were added by syringe. The mixture was swirled until all of the reagents had dissolved. A 200 μL portion of this solution was transferred to a Wilmad high-pressure NMR tube. TMS (~1-2 drops) was added as a standard. The tube was sealed, removed from the glove box, and was then filled with CO_2 (4 atm). An initial ^{1}H-NMR spectrum was recorded. The tube was then heated in refluxing THF. ^{1}H-NMR spectra were recorded again at 22 h and 48 h.

^{1}H-NMR (300 MHz, d_8-THF):

Starting material: δ 0.80-1.80, 4.60, 4.75, 5.92, 7.20-7.70

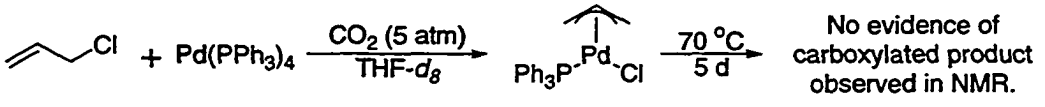
t = 0 h starting material peaks plus δ 3.50 (d, J = 10 Hz), 4.20 (d, J = 7 Hz) 5.15 (d, J = 10 Hz), 5.61 (quintet, J = 10 Hz), 5.92 (br m)

t = 22 h starting material peaks plus δ 2.96 (d, J = 7 Hz), 4.85-5.10 (br m), 5.20 (d, J = 17 Hz), 6.10-6.40 (br m)

t = 48 h starting material peaks plus δ 2.96 (d, J = 7 Hz), 4.78-5.10 (br m), 5.20 (d, J = 17 Hz), 6.10-6.40 (br m)

High-pressure NMR tube reaction of allyl chloride, $Pd(PPh_3)_4$, and CO_2

Reaction:



Procedure:

A 25-mL flask was charged with $Pd(PPh_3)_4$ (11.0 mg, 9.52 μmol). The flask was then evacuated and purged with N_2. The Pd-complex was dissolved in THF-d_8 (500 μL). A syringe was used to add allyl chloride (1.0 μL, 12 μmol).

The color of the solution rapidly changed from yellow to colorless. A 250 μL aliquot of this was then transferred into a Wilmad high-pressure NMR tube. The tube was then sealed and pressurized with CO_2 (5 atm). An initial ^{1}H-NMR spectrum was recorded. The tube was then heated in a bath of refluxing ethanol. Additional spectra were recorded after 24 h and 120 h of heating.

^{1}H-NMR (400 MHz, d_8-THF):

Allyl chloride peaks: δ 4.06 (d, 2 H, J = 7 Hz), 5.15 (d, 1 H, J = 11 Hz), 5.32 (d, 1 H, J = 17 Hz), 5.95 (br m, 1 H)

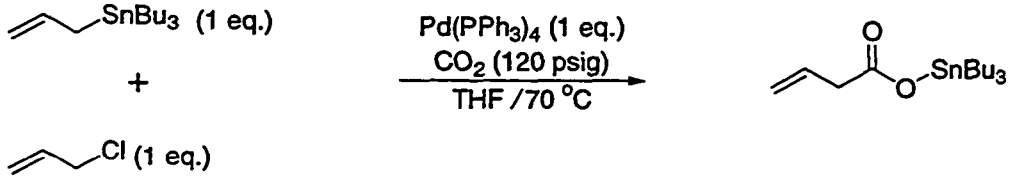
t = 0 h no peaks for allyl chloride; peaks at δ 3.50 (d, J = 10 Hz), 5.59 (m, J = 10 Hz), 7.2-7.4 (br m)

t = 24 h no peaks for allyl chloride; peaks at δ 3.50 (d, J = 10 Hz), 5.59 (m, J = 10 Hz), 7.2-7.4 (br m)

t = 120 h δ 1.85, 3.8 (from THF-*d*$_8$); 7.2-7.8 (br m)

Preparative-scale stoichiometric reaction of allyl chloride, allyltributyltin, $Pd(PPh_3)_4$, and CO_2

Reaction:



Procedure:

A glass liner was charged with a stir bar and $Pd(PPh_3)_4$ (1.28 g, 1.11 mmol). The liner was then put into a stainless steel autoclave body and connected to a special inert gas adapter. The autoclave was then evacuated and

purged with N_2. A syringe was then used to add THF (~20 mL), allyl chloride (100 μL, 1.23 mmol) and allyltributyltin (350 μL, 1.13 mmol). The head of the autoclave was then attached and the system was pressurized with CO_2 (120 psig, 8 atm). The system was heated at 80 °C in an oil bath for 24 h.

After 24 h, the reactor was cooled and vented. The contents of the autoclave were transferred to a 250-mL round bottom flask. The solvent was removed under vacuum. A small portion of this crude material was taken for an initial ^{1}H-NMR spectrum. The remaining material was washed several times with hexane. The hexane washes were decanted into another flask. The hexane-insoluble material was yellow-white in color and was a very gummy, viscous oil.

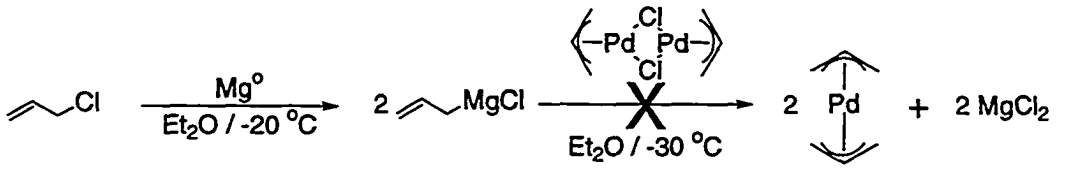
^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.80-1.90 (br m), 3.10 (d, 2 H, J = 7 Hz), 5.1-5.2 (overlapping d, 2 H), 5.9 (m, 1 H)

^{31}P-NMR (162 MHz, $CDCl_3$): δ 23.8, 29.7, 33.6

^{119}Sn-NMR (184 MHz, $CDCl_3$): δ 116.7

Attempted preparation of bis(η^3-allyl)Pd

Reaction:



Reference: Wilke, G. *Angew. Chem. Intl. Ed. Engl.* **1963**, *2*, 105.

Procedure:

A 50-mL round bottom flask was charged with a stir bar and granular magnesium metal (570 mg, 23.4 mmol, 20 mesh). A small iodine crystal was added to help initiate formation of the Grignard reagent. Dry ether (10 mL) was then transferred to the flask through a cannula. In a separate flask a solution of allyl chloride (600 μL, 7.37 mmol) dissolved in ether (10 mL) was made. This solution was then drawn into a syringe. The allyl chloride solution was slowly added to the suspension of magnesium metal over a 1 h period. A syringe pump was used to control the rate of addition (~200 μL/min). During addition of the allyl chloride, the flask was cooled to –20 °C in a dry ice/ethylene glycol bath. After all of the allyl chloride had been added, the mixture was stirred at –20°C for an additional 30 min. The mixture was then dried under vacuum. This was done to remove any unreacted allyl chloride and/or 1,5-hexadiene that might have been present in the system. Fresh ether (10 mL) was then added to redissolve the Grignard reagent.

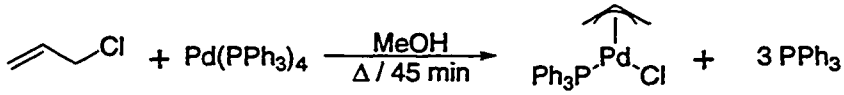
A separate 100-mL RBF was loaded with [(η^3-allyl)(μ-Cl)Pd]$_2$ (450 mg, 1.23 mmol) in the glove box. The flask was then sealed, removed from the glove

box, connected to an inert gas manifold, evacuated, and purged with N_2. The Pd-complex was then suspended in ether (20 mL), which was added by cannula. The flask containing the Pd-complex was then cooled to –78 °C in a dry ice/acetone bath. The solution of allylmagnesium chloride was then slowly cannulated into the flask containing the Pd-complex. A 15 mL portion of ether was used to rinse any residual material from the flask that contained the allylmagnesium chloride reagent into the flask containing the Pd-complex. The mixture was then stirred at –78 °C for 30 min.

At the end of the 30 min stirring period, there appeared to be a good deal of the unreacted $[(\eta^3\text{-allyl})(\mu\text{-Cl})\text{Pd}]_2$ complex remaining in the flask. The flask was then kept cool in an ice bath while the ether was removed from the reaction mixture under vacuum. The product was then triturated with pentane (25 mL), which was cannulated into the flask. The pentane suspension was then filtered using a special Schlenk filtration apparatus. The filtrate was collected in a Schlenk flask that was cooled in an ice bath. The solvent was then removed from the cold filtrate under vacuum. A small amount of pale yellow solid material remained in the Schlenk flask. The Schlenk flask was then purged with N_2, sealed, and stored in the freezer overnight. The next day the Schlenk flask was transferred into the glove box in order to prepare an NMR sample of the product material. The product material turned from yellow to orange while being transferred into the glove box. This indicated that the product had most likely decomposed.

Preparation of (η^3-allyl)(PPh_3)PdCl

Reaction:



Reference: Powell, J.; Shaw, B.L. *J. Chem. Soc. (A)* **1968**, 774.

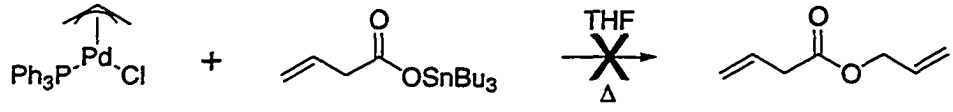
Procedure:

A 250-mL round bottom flask was charged with a stir bar and $Pd(PPh_3)_4$ (1.08 g, 0.937 mmol). The flask was then sealed with a septum, connected to an inert gas manifold, evacuated, and purged with N_2. Degassed methanol (~125 mL) was then added into the flask through a cannula. A syringe was used to add allyl chloride (4.0 mL, 49 mmol, 52 equiv). A condenser was added and the mixture was heated at reflux for 45 min. After heating, the system was cooled to room temperature. The solvent was removed under vacuum. A yellow residue remained in the flask. This residue was washed several times with degassed hexane. Each time the hexane was removed from the flask by decantation. The remaining solids were then dried under vacuum. A portion of the solid material was analyzed by ^{1}H-NMR.

^{1}H-NMR (400 MHz, THF-d_8) δ 3.52 (d, 4 H, J = 7 Hz), 5.59 (m, 1 H, J = 7 Hz), 7.25-7.45 (br m)

Reaction of tributyltin 3-butenoate and (η^3-allyl)(PPh_3)PdCl

Reaction:

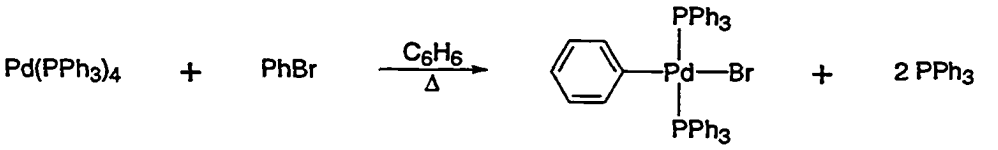


Procedure:

A 100-mL round bottom flask was charged with a stir bar, (η^3-allyl)(PPh_3)PdCl (459 mg, 1.03 mmol), and tributyltin 3-butenoate (379 mg, 1.01 mmol). The flask was then sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (50 mL) was then cannulated into the flask. A condenser was then attached and the system was refluxed under N_2 overnight. The solution was clear yellow in color at the beginning, but darkened slightly to clear yellow-orange at the beginning of the heating period. The following day, the system was cooled to room temperature. The solvent was removed by rotary evaporation. During the rotary evaporation process, ice was added to the water bath of the rotovap in order to prevent loss of the ester. The concentrated residue was then stirred with CH_2Cl_2 (1 mL) for 15 min. The CH_2Cl_2 solution was then filtered through a microcolumn filled with silica gel. The filtered solution was then analyzed by GC. The chromatogram of the reaction mixture showed a number of small peaks, however, none of the retention times for these peaks corresponded to that for authentic allyl 3-butenoate. In order to confirm the absence of ester, an aliquot of the sample from the reaction mixture was spiked with a drop of the authentic ester. GC analysis of this material confirmed that the ester had not been formed in the reaction.

Preparation of *trans*-$PhPd(PPh_3)_2Br$

Reaction:



References: (a) Fitton, P.; Rick, E.A. *J. Organomet. Chem.* **1971**, *28*, 287.
(b) Moser, W.R.; Wang, A.W., Kildahl, N.K. *J. Am. Chem. Soc.* **1988**, *110*, 2816.
(b) Monteil, F.; Kalck, P. *J. Organomet. Chem.* **1994**, *482*, 45.

Procedure:

A 250-mL round bottom flask was charged with a stir bar and $Pd(PPh_3)_4$ (647 mg, 0.560 mmol). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. Benzene (100 mL) was then cannulated into the flask. A syringe was used to add bromobenzene (2.0 mL, 19 mmol, 34 equiv.) to the flask. A condenser was added and the system was refluxed overnight under N_2.

The following day, the color of the solution had changed from bright yellow to pale yellow. The benzene was removed under vacuum. After the benzene had been removed, ether (50 mL) was cannulated into the flask and the mixture was stirred for 15 min. This was done to remove any free triphenylphosphine and any unreacted bromobenzene. The mixture was filtered using a cannula filter device and was then dried under vacuum. The remaining solid material was then recrystallized from $CHCl_3$/MeOH. The crystals formed were then filtered and dried under vacuum. The yield of product was 308.3 mg (70% yield based on $Pd(PPh_3)_4$). The product was characterized using ^1H-, ^{13}C-, and ^{31}P-NMR.

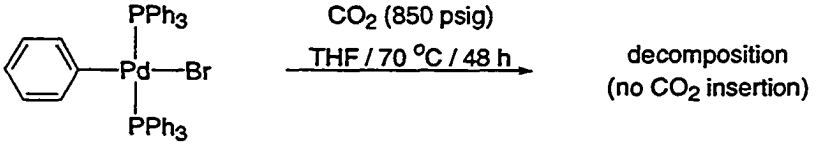
^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.21 (overlapping dd, 2 H, J = 7.1 Hz), 6.35 (overlapping dd, 1 H, J = 5.4 Hz), 6.62 (d, 2 H, J = 8.3 Hz), 7.23 (app t, 12 H, J = 7.2 Hz), 7.31 (app t, 6 H, J = 6.2 Hz), 7.49 (dd, 12 H, J = 6.0, 5.6 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 121.8, 1127.7, 127.8 (J_{C-P} = 5 Hz), 129.7, 131.5 (J_{C-P} = 22 Hz), 134.7 (J_{C-P} = 134.7 Hz), 136.2

^{31}P-NMR (162 MHz, $CDCl_3$) δ 24.1

Attempted carboxylation of *trans*-PhPd(PPh_3)$_2$Br

Reaction:



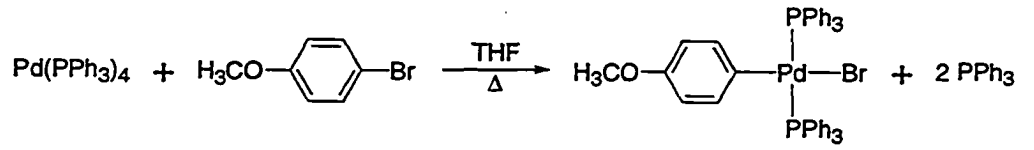
Procedure:

A glass liner was charged with a stir bar and *trans*-Ph(PPh_3)$_2$PdBr (85.6 mg, 0.109 mmol). The liner was then placed into a stainless-steel autoclave body and a special inert gas adapter was attached. The system was connected to an inert gas manifold and was then evacuated and purged with N_2. THF (25 mL) was then added to the liner using a syringe. The adapter was replaced with an autoclave head, which was then sealed. The system was pressurized with CO_2 (850 psig). The system was then heated at 70 °C for 48 h in an oil bath.

After 48 h, the autoclave was cooled, vented, and opened. The solution in the glass liner had turned a dark orange-brown color, indicating that the Pd-complex had most likely decomposed.

Preparation of *trans*-(p-$MeOC_6H_4$)Pd(PPh_3)$_2$Br

Reaction:



References: (a) Moser, W.R.; Wang, A.W., Kildahl, N.K. *J. Am. Chem. Soc.* **1988**, *110*, 2816.
(b) Monteil, F.; Kalck, P. *J. Organomet. Chem.* **1994**, *482*, 45.

Procedure:

A 50-mL round bottom flask was charged with a stir bar and $Pd(PPh_3)_4$ (1.03 g, 0.891 mmol). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (25 mL) was then cannulated into the flask. A syringe was used to add p-bromoanisole (500 μL, 3.99 mmol, 4.50 equiv.) to the flask. A condenser was added and the system was refluxed overnight under N_2.

The following day, the color of the solution had changed from bright yellow to pale yellow. The THF was removed under vacuum. After the THF had been removed, ether (50 mL) was cannulated into the flask and the mixture was stirred for 15 min. This was done to remove any free triphenylphosphine and any unreacted p-bromoanisole. The mixture was filtered using a cannula filter device and was then dried under vacuum. The remaining solid material was then recrystallized from $CHCl_3$/MeOH. The crystals formed were then filtered and dried under vacuum. The yield of product was 302.3 mg (41% yield based on $Pd(PPh_3)_4$). The product was characterized using ^{1}H-, ^{13}C-, and ^{31}P-NMR.

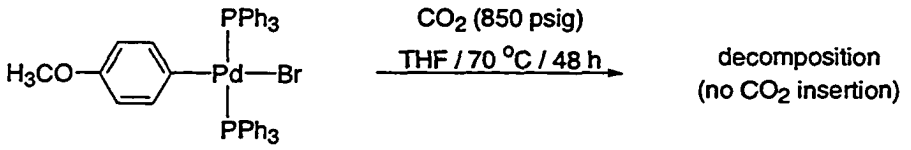
^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3 H), 6.215 (overlapping dd, 2 H, J = 7.4 Hz), 6.348 (overlapping dd, 2 H, J = 6.8 Hz), 7.20-7.75 (br m, 30 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 61.2, 113.7, 121.6, 127.9, 128.6, 129.9, 130.3, 134.9, 135.2

^{31}P-NMR (162 MHz, $CDCl_3$) δ 24.1

Attempted carboxylation of *trans*-(p-$MeOC_6H_4$)Pd(PPh_3)$_2$Br

Reaction:



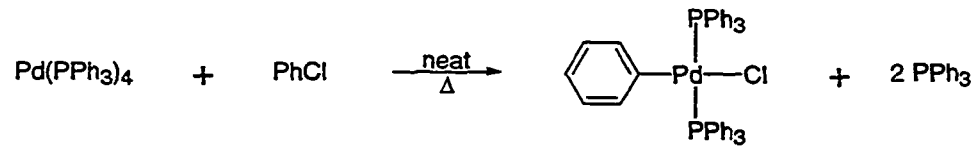
Procedure:

A glass liner was charged with a stir bar and *trans*-(p-$MeOC_6H_4$)(PPh_3)$_2$PdBr (41.3 mg, 50.5 μmol). The liner was then placed into a stainless-steel autoclave body and a special inert gas adapter was attached. The system was connected to an inert gas manifold and was then evacuated and purged with N_2. THF (25 mL) was then added to the liner using a syringe. The adapter was replaced with an autoclave head, which was then sealed. The system was pressurized with CO_2 (850 psig). The system was then heated at 70 °C for 48 h in an oil bath.

After 48 h, the autoclave was cooled, vented, and opened. The solution in the glass liner had turned a dark orange-brown color, indicating that the Pd-complex had most likely decomposed.

Preparation of *trans*-$PhPd(PPh_3)_2Cl$

Reaction:



References: (a) Coulson, D.R. *J. Chem. Soc., Chem. Commun.* **1968**, 1530.
(b) Fitton, P.; Rick, E.A. *J. Organomet. Chem.* **1971**, *28*, 287.
(c) Flemming, J.P.; Pilon, M.C. Borbulevitch, O.Y.; Antipin, M.Y.; Grushin, V.V. *Inorg. Chim. Acta* **1998**, *280*, 87.

Procedure:

A 100-mL round bottom flask was charged with a stir bar and $Pd(PPh_3)_4$ (999 mg, 0.864 mmol). Chlorobenzene (40.0 mL, 393 mmol, 455 equiv.) was added by syringe. The system was degassed by subjecting it to several evacuation/purge cycles with N_2. A condenser was added and the system was refluxed overnight under N_2. The following day, the system was allowed to cool to room temperature and the chlorobenzene was removed under vacuum. The residue was triturated with ether to remove any free triphenylphosphine and unreacted chlorobenzene. The solid material was recrystallized from CH_2Cl_2/hexane. The product was collected by filtration. The yield of product was 569.6 mg (89 % yield based on $Pd(PPh_3)_4$). The product was characterized by ^1H-, ^{13}C-, and ^{31}P-NMR. The NMR spectral data for the product compared favorably with the data reported by Flemming, *et al.*

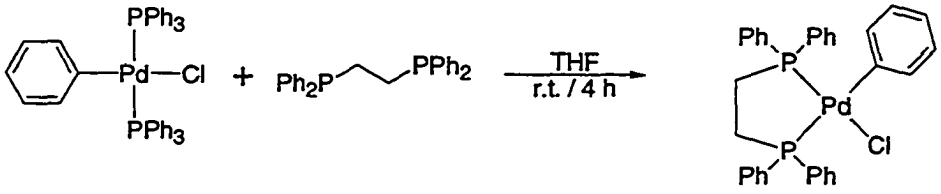
^1H-NMR (400 MHz, $CDCl_3$) δ 6.22 (overlapping dd, 2 H, J = 7.6 Hz), 6.37 (overlapping dd, 1 H, J = 7.6 Hz), 6.62 (overlapping dd, 2 H, J = 6.8, 1.2 Hz), 7.20-7.60 (m, 30 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 121.7, 127.6, 127.9 (J_{C-P} = 9 Hz), 129.7, 131.2 (J_{C-P} = 45.6 Hz), 134.6 (J_{C-P} = 13 Hz), 136.4 (J_{C-P} = 4 Hz)

^{31}P-NMR (162 MHz, $CDCl_3$) δ 24.1

Preparation of *cis*-PhPd(dppe)Cl

Reaction:



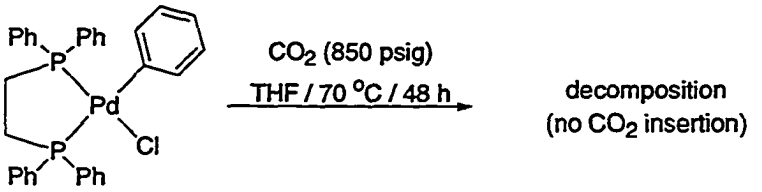
Reference: Herrmann, W.A.; Broßmer, C.; Priermeier, T.; Öfele, K. *J. Organomet. Chem.* **1994**, *481*, 97.

Procedure:

A 25-mL round bottom flask was charged with a stir bar, *trans*-$PhPd(PPh_3)_2Cl$ (319 mg, 0.428 mmol), and bis-1,2-(diphenylphosphino)ethane (dppe)(191 mg, 0.478 mmol, 1.11 equiv.). The flask was then sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (7.5 mL) was then added using a syringe. The mixture was stirred under N_2 at room temperature. After stirring for 4 h, the mixture was then filtered. The filtered solid material, was then washed with ether (3 x 50 mL). The solids were then dried under vacuum. The product was recrystallized from CH_2Cl_2/hexane. The recrystallized product was then collected by filtration and dried under vacuum. yield of product was 150 mg (57 % yield based on *trans*-$PhPd(PPh_3)_2Cl$).

Attempted carboxylation of *cis*-PhPd(dppe)Cl

Reaction:



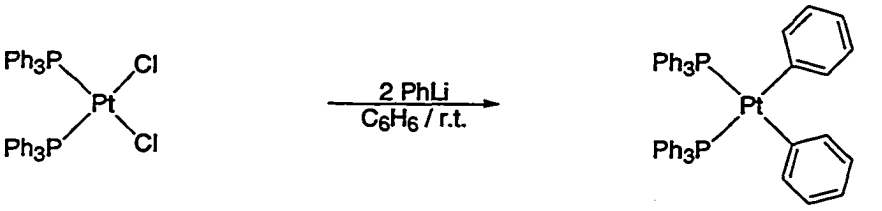
Procedure:

A glass liner was charged with a stir bar and *cis*-PhPd(dppe)Cl (93.0 mg, 0.150 mmol). The liner was then placed into a stainless-steel autoclave body and a special inert gas adapter was attached. The system was connected to an inert gas manifold and was then evacuated and purged with N_2. THF (25 mL) was then added to the liner using a syringe. The adapter was replaced with an autoclave head, which was then sealed. The system was pressurized with CO_2 (850 psig). The system was then heated at 70 °C for 48 h in an oil bath.

After 48 h, the autoclave was cooled, vented, and opened. The solution in the glass liner had turned a dark orange-brown color, indicating that the Pd-complex had most likely decomposed.

Preparation of *cis*-$(Ph)_2(PPh_3)_2Pt$

Reaction:



Reference: Glockling, F.; McBride, T.; Pollock, R.J.I. *J. Chem. Soc., Chem. Commun.* **1973**, 650.

Procedure:

A 250-mL round bottom flask was charged with a stir bar and *cis*-$Pt(PPh_3)_2Cl_2$ (700 mg, 0.885 mmol). The flask was then sealed, connected to an inert gas manifold, evacuated, and purged with N_2. Benzene (100 mL) was then cannulated into the flask. A 1.8 M solution of phenyllithium (4.0 mL, 7.2 mmol, 4.1 equiv.) was then added to the Pt-complex suspension using a syringe. The Pt-complex was initially insoluble in the benzene solvent, however, after the PhLi was added, the reaction mixture was homogeneous and red in color. The mixture was stirred at room temperature under N_2 for 2 h.

The reaction was worked up by first cooling the mixture to 0 °C in an ice bath. The excess PhLi was hydrolyzed by dropwise addition of dilute HCl (50 mL, 0.24 M) to the reaction mixture. The color of the solution changed from red to milky yellow-white after the HCl was added. The organic solution was isolated using a separatory funnel, and dried with anhyd. Na_2SO_4. The solvent was removed by rotary evaporation. The product was purified by recrystallization from $CHCl_3$/hexane. The product was isolated as yellow rhombohedral crystals.

Yield of product was 165.3 mg (31% yield based on *cis*-$Pt(PPh_3)_2Cl_2$). The product was characterized by FAB-MS, ^1H-, ^{13}C-, and ^{31}P-NMR.

^1H-NMR (400 MHz, $CDCl_3$) δ 6.32 (t, 2 H), 6.43 (t, 4 H), 7.05 (m, 16 H), 7.17 (m, 6 H), 7.31 (m, 12 H)

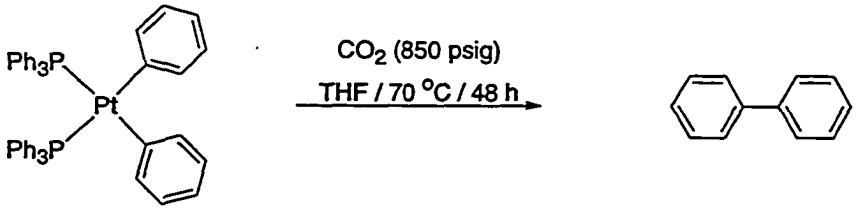
^{13}C-NMR (100 MHz, $CDCl_3$) δ 120.1,126.6, 127.5 (t, J_{C-P} = 5 Hz), 129.0, 132.5, 133.0, 134.2 (t, J_{C-P} = 5.4 Hz), 136.5

^{31}P-NMR (162 MHz, $CDCl_3$) δ 19.5 (t, J_{P-Pt} = 879 Hz)

FAB-MS (3-nitrobenzyl alcohol matrix) *m/z* 873.2 (6.6%, M^+), 719.2 (100%, M^+-2Ph)

Attempted carboxylation of *cis*-$(Ph)_2(PPh_3)_2Pt$

Reaction:



Procedure:

A glass liner was charged with a stir bar and *cis*-$(Ph)_2(PPh_3)_2Pt$ (190 mg, 0.217 mmol). The liner was then placed into a stainless-steel autoclave body and a special inert gas adapter was attached. The system was connected to an inert gas manifold and was then evacuated and purged with N_2. THF (25 mL) was then added to the liner using a syringe. The adapter was replaced with an

autoclave head, which was then sealed. The system was pressurized with CO_2 (850 psig). The system was then heated at 70 °C for 48 h in an oil bath.

After 48 h, the system was allowed to cool to room temperature and the autoclave was vented and opened. The contents of the autoclave liner were transferred to a 250-mL round bottom flask and the solvent was removed under vacuum. A dark reddish-brown residue remained in the flask. The material was analyzed by NMR, IR, and GC. No evidence of carboxylation was observed by ^{1}H-, ^{13}C-NMR, or IR. The ^{31}P-NMR spectrum of the material contained three peaks, none of which corresponded to that of the starting material. A portion of the mixture was stirred with CH_2Cl_2 and filtered through a microcolumn containing silica gel. This sample was analyzed by GC. The GC data indicated that the major organic material present was biphenyl. The presence of biphenyl in the GC of the sample was confirmed by comparing the retention time of the main peak in the sample mixture with that of a commercially purchased sample of biphenyl.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.5-7.8 (br m)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 127.2, 128.4, 128.6, 128.8, 129.9, 132.1, 133.7, 133.9, 141.2

^{31}P-NMR (162 MHz, $CDCl_3$) δ 9.3, 29.6, 165.2

IR (CH_2Cl_2 solution) 3050, 1620, 1512 cm^{-1}

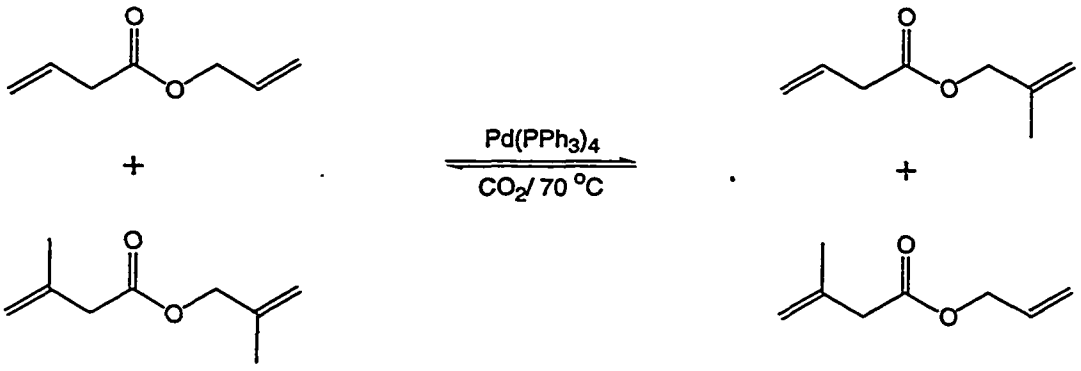
GC retention times:

reaction mixture: 13.93 min

authentic biphenyl: 13.92 min

Crossover experiment with allyl 3-butenoate, methallyl 3-methyl-3-butenoate, and $Pd(PPh_3)_4$:

Reaction:



Procedure:

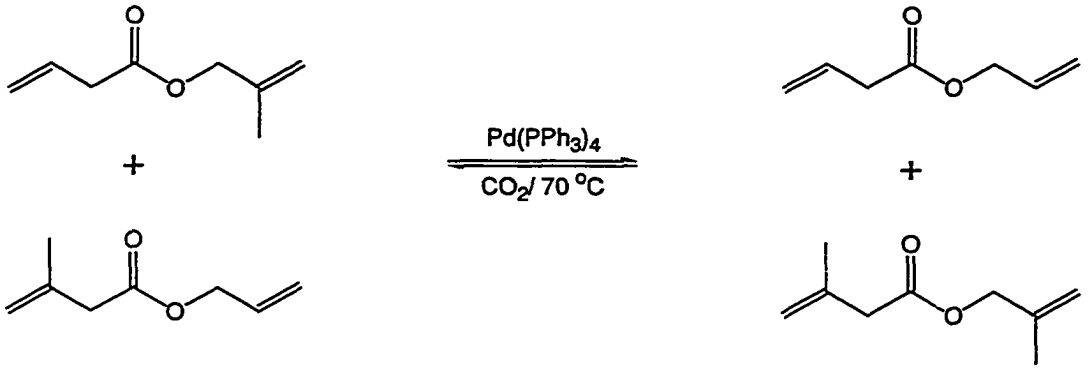
A glass liner was charged with allyl 3-butenoate (150 mg, 1.14 mmol), methallyl 3-methyl-3-butenoate (154 mg, 0.999 mmol), and $Pd(PPh_3)_4$ (55 mg, 48 μmol, 2.2 mol %). The liner was then placed into a stainless-steel autoclave body and a special inert gas adapter was attached. The system was connected to an inert gas manifold and was then evacuated and purged with N_2. THF (25 mL) was then added to the liner using a syringe. The adapter was replaced with an autoclave head, which was then sealed. The system was pressurized with CO_2 (750 psig). The system was then heated at 70 °C for 24 h in an oil bath.

At the end of the 24 h period, the autoclave was cooled to room temperature, vented, and opened. The contents were then removed and filtered through a microcolumn containing silica gel, diluted with CH_2Cl_2, and analyzed by GC. GC analysis of the reaction mixture showed four ester peaks, two of which corresponded to the two starting esters, as well as two peaks that corresponded to allyl 3-methyl-3-butenoate, and 2-methallyl 3-butenoate. The identity of the

four esters was confirmed by comparison of retention time data from the reaction mixture with retention time data for authentic samples. The four esters were present in approximately equal amounts.

Crossover experiment with allyl 3-methyl-3-butenoate, 2-methallyl 3-butenoate, and $Pd(PPh_3)_4$:

Reaction:



Procedure:

A glass liner was charged with 2-methallyl 3-butenoate (340 mg, 2.43 mmol), allyl 3-methyl-3-butenoate (350 mg, 2.50 mmol), and $Pd(PPh_3)_4$ (210 mg, 182 μmol, 3.7 mol %). The liner was then placed into a stainless-steel autoclave body and a special inert gas adapter was attached. The system was connected to an inert gas manifold and was then evacuated and purged with N_2. THF (25 mL) was then added to the liner using a syringe. The adapter was replaced with an autoclave head, which was then sealed. The system was pressurized with CO_2 (750 psig). The system was then heated at 70 °C for 24 h in an oil bath.

At the end of the 24 h period, the autoclave was cooled to room temperature, vented, and opened. The contents were then removed and filtered through a microcolumn containing silica gel, diluted with CH_2Cl_2, and analyzed by

GC. GC analysis of the reaction mixture showed four ester peaks, two of which corresponded to the two starting esters, as well as two peaks that corresponded to allyl 3-butenoate and 2-methallyl 3-methyl-3-butenoate. The identity of the four esters was confirmed by comparison of retention time data from the reaction mixture with retention time data for authentic samples. The four esters were present in approximately equal amounts.

3.7 BIBLIOGRAPHY

1) (a) Shi, M.; Nicholas, K.M. *J. Am. Chem. Soc.* **1997**, *119*, 5057. (b) Shi, M.; Franks, R.; Nicholas, K.M. In *Advances in Chemical Conversions for Mitigating Carbon Dioxide*; Inui, T.; Anpo, M.; Izui, K.; Yanaguida, S.; Yamaguchi, T., Eds.; Elsevier: New York, NY, 1998; pp 165-170.

2) Franks, R.J.; Nicholas, K.M. *Organometallics* **2000**, *8*, 1458.

3) (a) Stille, J.K. *Pure Appl. Chem.* **1985**, *57*, 1771. (b) Stille, J.K. *Angew. Chem. Intl. Ed. Engl.* **1986**, *25*, 508. (c) Mitchell, T.N. In *Metal-catalyzed Cross-coupling Reactions*; Diedrich, F.; Stang, P.J., Eds.; Wiley-VCH: New York, NY, 1998; pp 167-202. (d) Farina, V.; Krishnamurthy, V.; Scott, W.J. *Org. React.* **1997**, *50*, 1-652. (e) Farina, V.; Krishnamurthy, V.; Scott, W.J. *The Stille Reaction*; Wlley: New York, NY, 1998.

4) (a) Fitton, P.; McKeon, J.E. *J. Chem. Soc., Chem. Commun.* **1968**, 4. (b) Ugo, R.; Pasini, A.; Fusi, A.; Cenini, S. *J. Am. Chem. Soc.* **1972**, *94*, 7364. (c) Kudo, K.; Sato, M.; Hidai, M.; Uchida, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2820. (d) Kramer, A.V.; Osborn, J.A. *J. Am. Chem. Soc.* **1974**, *96*, 7832. (e) Stille, J.K.; Lau, K.S.Y. *J. Am. Chem. Soc.* **1976**, *98*, 5841. (f) Stille, J.K.; Lau, K.S.Y. *Acc. Chem. Res.* **1977**, *10*, 434. (g) Fauvarque, J.-F.; Pflüger, F. *J. Organomet. Chem.* **1981**, *208*, 419. (h) Amatore, C.; Azzabi, M.; Jutand, A. *J. Organomet. Chem.* **1989**, *363*, C41. (i) Amatore, C.; Pflüger, F. *Organometallics* **1990**, *9*, 2276. (j) Amatore, C.; Azzabi, M.;

Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 1670. (k) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.

5) Casado, A.L; Espinet, P. *Organometallics* **1998**, *17*, 954.

6) (a) Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* **1983**, *105*, 6129. (b) Beletskaya, I.P. *J. Organomet. Chem.* **1983**, *250*, 551. (c) Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (d) Davies, G.; El-Sayed, M.A.; El-Toukhy, A. *Chem. Soc. Rev.* **1992**, *21*, 101. (e) Vedejs, E.; Haight, A.R.; Moss, W.O. *J. Am. Chem. Soc.* **1992**, *114*, 6556. (f) Crisp, G.T.; Gebauer, M.G. *Tetrahedron Lett.* **1995**, *36*, 3389. (g) Cianfriglia, P.; Narducci, V.; Lo Sterzo, C.; Viola, E.; Bocelli, G.; Kodenkandath, T.A. *Organometallics* **1996**, *15*, 5220. (h) Cotter, W.D.; Barbour, L.; McNamara, K.L.; Hechter, R.; Lachicotte, R.J. *J. Am. Chem. Soc.* **1998**, *120*, 11016.

7) (a) Cárdenas, D.J.; Mateo, C.; Echavarren, A.M. *Angew. Chem. Intl. Ed. Engl.* **1994**, *33*, 2445. (b) Mateo, C.; Cárdenas, D.J.; Fernández-Rivas, C.; Echavarren, A.M. *Chem. Eur. J.* **1996**, *2*, 1596. (c) Mateo, C.; Fernández-Rivas, C.; Echavarren, A.M.; Cárdenas, D.J. *Organometallics* **1997**, *16*, 1997. (d) Mateo, C.; Fernández-Rivas, C.; Cárdenas, D.J.; Echavarren, A.M. *Organometallics* **1998**, *17*, 3661.

8) (a) Casado, A.L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978. (b) Casado, A.L.; Espinet, P.; Gallego, A.M. *J. Am. Chem. Soc.* **2000**, *122*, 11771.

9) (a) Liebeskind, L.S.; Fengl, R.W. *J. Org. Chem.* **1990**, *55*, 5359. (b) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73. (c) Farina, V.; Roth, G.P. *Tetrahedron Lett.* **1991**, *32*, 4243. (d) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (e) Farina, V.; Krishnan, B.; Marshall, D.R.; Roth, G.P. *J. Org. Chem.* **1993**, *58*, 5434. (f) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L.S. *J. Org. Chem.* **1994**, *59*, 5905.

10) (a) Braterman, P.S.; Cross, R.J. *Chem. Soc. Rev.* **1973**, *2*, 271. (b) Braterman, P.S.; Cross, R.J.; Young, G.B. *J. Chem. Soc., Dalton Trans.* **1976**, 1306. (c) Braterman, P.S.; Cross, R.J.; Young, G.B. *J. Chem. Soc., Dalton Trans.* **1976**, 1310. (d) Moravskiy, A.; Stille, J.K. *J. Am. Chem. Soc.* **1980**, *103*, 4182. (e) Gillie, A.; Stille, J.K. *J. Am. Chem. Soc.* **1980**, *102*, 4933. (f) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457. (g) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J.K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857. (h) Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1868. (i) Loar, M.K.; Stille, J.K. *J. Am. Chem. Soc.* **1981**, *103*, 4174. (j) Ozawa, F.; Fujimori, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1986**, *5*, 2144. (k) Brown, J.M.; Cooley, N.A. *Chem. Rev.* **1988**, *88*, 1031. (l) Goldberg, K.I.; Yan, J.; Winter, E.L. *J. Am. Chem. Soc.* **1994**, *116*, 1573. (m) Goldberg, K.I.; Yan, J.; Breitung, E.M *J. Am. Chem. Soc.* **1995**, *117*, 6889. (n) Lin, Y.-S.; Yamamoto, A. *Organometallics* **1998**, *17*, 3466. (o) Roy, A.H.; Hartwig, J.F. *J. Am. Chem. Soc.* **2001**, *123*, 1232.

11) Forngren, T.; Andersson, Y.; Lamm, B.; Långstrom, B. *Acta Chim. Scand.* **1998**, *52*, 475.

12) (a) Nicholas, K.M. *J. Organomet. Chem.* **1980**, *188*, C10. (b) Dickson, M.K.; Dixit, N.S.; Roundhill, D.M. *Inorg. Chem.* **1983**, *22*, 3130. (c) Lawson, H.J.; Atwood, J.D. *J. Am. Chem. Soc.* **1989**, *111*, 6223. (d) Ziegler, W.; Nicholas, K.M. *J. Organomet. Chem.* **1992**, *423*, C35. (e) Yin, C.; Xu, Z.; Yang, S.-Y.; Ng, S. M.; Wong, K. Y.; Lin, Z.; Lau, C. P. *Organometallics* **2001**, *20*, 1216.

13) (a) Statton, G.L.; Ramey, K.C. *J. Am. Chem. Soc.* **1966**, *88*, 1327. (b) Cotton, F.A.; Faller, J.W.; Musco, A. *Inorg. Chem.* **1967**, *6*, 179. (c) Powell, J.; Shaw, B.L. *J. Chem. Soc. (A)* **1968**, 774. (d) Powell, J.; Shaw, B.L. *J. Chem. Soc. (A)* **1967**, 1839. (e) Hartley, F.R.; Jones, S.R. *J. Organomet. Chem.* **1974**, *66*, 465. (f) Sakakibara, M.; Takahashi, Y.; Sakai, S.; Ishii, Y. *J. Organomet. Chem.* **1971**, *27*, 139. (g) Kurosawa, H.; Kajimaru, H.; Ogoshi, S.; Yoneda, H.; Miki, K.; Kasai, N.; Murai, S.; Ikeda, I. *J. Am. Chem. Soc.* **1992**, *114*, 8417.

14) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641.

15) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Nakamura, H.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1273. (c) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1459. (d) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.

16) (a) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113. (b) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372. (c) Solin, N.; Narayan, S.; Szabó, K.J. *J. Org. Chem.* **2001**, *66*, 1686.

17) Jolly, P.W. *Angew. Chem. Intl. Ed. Engl.* **1985**, *24*, 283.

18) (a) Henc, B.; Jolly, P.W.; Salz, R.; Wilke, G.; Benn, R.; Hoffmann, E.G.; Mynott, R.; Schroth, G.; Seevogel, K.; Sekutowski, J.C.; Krüger, C. *J. Organomet. Chem.* **1980**, *191*, 425. (b) Henc, B.; Jolly, P.W.; Salz, R.; Stobbe, S.; Wilke, G.; Benn, R.; Mynott, R.; Seevogel, K.; Goddard, R.; Krüger, C. *J. Organomet. Chem.* **1980**, *191*, 449.

19) (a) Hung, T.; Jolly, P.W.; Wilke, G. *J. Organomet. Chem.* **1980**, *190*, C5. (b) Trinh, H. Doctoral Dissertation, Max-Planck-Institut für Kohlenforschung, 1980.

20) Santi, R.; Marchi, M. *J. Organomet. Chem.* **1979**, *182*, 117.

21) Ito, T.; Kindaichi, Y.; Takami, Y. *Chem. Ind. (London)* **1980**, 83.

22) Wilke, G. *Angew. Chem. Intl. Ed. Engl.* **1963**, *2*, 105.

23) Christofides, A.; Ciriano, M.; Spencer, J.L.; Stone, F.G.A. *J. Organomet. Chem.* **1979**, *178*, 273.

24) (a) Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* **1978**, *100*, 3416. (b) Trost, B.M. *Acc. Chem. Res.* **1980**, *13*, 385. (c) Trost, B.M.; Schmuff, N.R. *Tetrahedron Lett.* **1981**, *22*, 2999. (d) Tsuji, T.; Sato, K.; Okumoto, H. *Tetrahedron Lett.* **1982**, *23*, 5189. (e)

Trost, B.M.; Van Vranken, D.L. *Chem. Rev.* **1996**, *96*, 395. (f) Amatore, C.; Jutand. A.; Meyer, G.; Mottier, L. *Chem. Eur. J.* **1999**, *5*, 466.

25) Trost, B.M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595.

26) Okawara, R.; Wada, M. In *Organotin Compounds*; Sawyer, A.K., Ed.; M. Dekker: New York, 1971; Vol. 2, p 253.

27) See Reference 13(c)

28) (a) Kurosawa, H. *J. Organomet. Chem.* **1987**, *334*, 243. (b) Kurosawa, H.; Ogoshi, S. *Bull. Chim. Soc. Jpn.* **1998**, *71*, 973. (c) Marshall, J.A. *Chem. Rev.* **2000**, *100*, 3163.

29) (a) Godschalx, J.; Stille, J.K. *Tetrahedron Lett.* **1980**, *21*, 2599. (b) Godschalx, J.P.; Stille, J.K. *Tetrahedron Lett.* **1983**, *24*, 1905. (c) Merrifield, J.H.; Godschalx, J.P.; Stille, J.K. *Organometallics* **1984**, *3*, 1108.

30) (a) Jolly, P.W.; Stobbe, S.; Wilke, G.; Goddard, R.; Krüger, Sekutowski, J.; Tsay, Y.-H. *Angew. Chem. Intl. Ed. Engl.* **1978**, *17*, 124. (b) Tsuda, T.; Chujo, Y.; Saegusa, T. *Synth. Commun.* **1979**, *9*, 427. (c) Flid, V.R.; Kuznetsov, V.B.; Dmitriev, D.V. *Kinetics and Catalysis* **1999**, *40*, 301.

31) (a) Amatore, C.; Jutand, A.; Khalil, F.; Nielsen, M.F. *J. Am. Chem. Soc.* **1992**, *114*, 7076. (b) Sugimoto, H.; Kawata, I.; Taniguchi, H.; Fujiwara, Y. *J. Organomet. Chem.* **1984**, *266*, C44.

32) (a) Fitton, P.; Rick, E.A. *J. Organomet. Chem.* **1971**, *28*, 287. (b) Moser, W.M.; Wang, A.W.; Kildahl, N.K. *J. Am. Chem. Soc.* **1988**, *110*, 2816. (c) Monteil, F.; Kalck, P. *J. Organomet. Chem.* **1994**, *482*, 45.

33) (a) Coulson, D.R. *J. Chem. Soc., Chem. Commun.* **1968**, 1530. (b) Fitton, P.; Rick, E.A. *J. Organomet. Chem.* **1971**, *28*, 287. (c) Flemming, J.P.; Pilon, M.C. Borbulevitch, O.Y.; Antipin, M.Y.; Grushin, V.V. *Inorg. Chim. Acta* **1998**, *280*, 87.

34) Herrmann, W.A.; Broßmer, C.; Priermeier, T.; Öfele, K. *J. Organomet. Chem.* **1994**, *481*, 97.

35) Glockling, F.; McBride, T.; Pollock, R.J.I. *J. Chem. Soc., Chem. Commun.* **1973**, 650.

36) Kannan, S.; Jain, V.K. *Magn. Reson. Chem.* **1990**, *28*, 1007.

37) (a) Robinson, S.D.; Shaw, B.L. *J. Organomet. Chem.* **1965**, *3*, 367. (b) van Leeuwen, P.W.N.M.; Pratt, A.P. *J. Organomet. Chem.* **1970**, *21*, 501. (c) Brown, R.G.; Chaudhari, R.V.; Davidson, J.M. *J. Chem. Soc., Dalton Trans.* **1977**, 176. (d) Wemer, H.; Kraus, H.-J. *Chem. Ber.* **1980**, *113*, 1072.

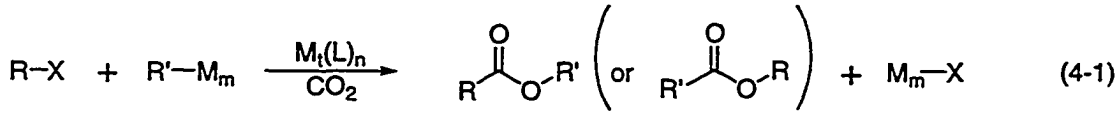
Chapter 4

Cu-MEDIATED CARBOXYLATION OF ORGANOZINC REAGENTS

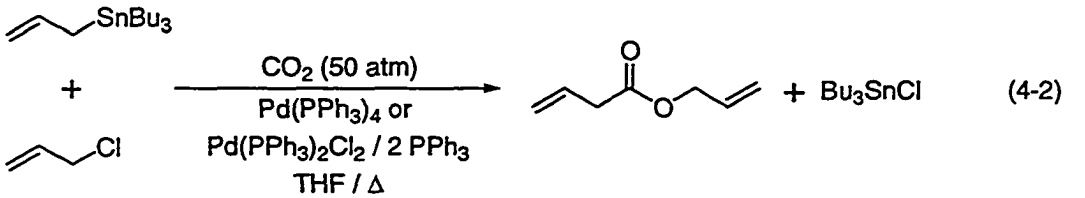
4.1 INTRODUCTION

4.1.1 Summary of previous results

This project began with the goal of developing a metal-catalyzed carboxylative coupling reaction (eq. 4-1). We did indeed discover that allyltributyltin and allyl chloride could be carboxylatively coupled at high CO_2 pressures in the presence of a Pd(0) or Pd(II) catalyst (eq. 4-2).[1] After this initial discovery we studied the effects of different Group 10 catalysts and different ligands on the reaction. Attempts were also made to broaden the synthetic scope of the reaction to include non-allylic substrates. Unfortunately, these attempts were unsuccessful. Neither carboxylation (Scheme 4-1(a) and (b)) nor carboxylative coupling (Scheme 4-1(c)) for non-allylic substrates was achieved. The mechanism of the allyl-allyl coupling reaction was also studied. Through a series of high-pressure NMR studies and preparative-scale experiments, and using literature precedents, we were able to postulate a catalytic mechanism for the reaction (Scheme 3-5).

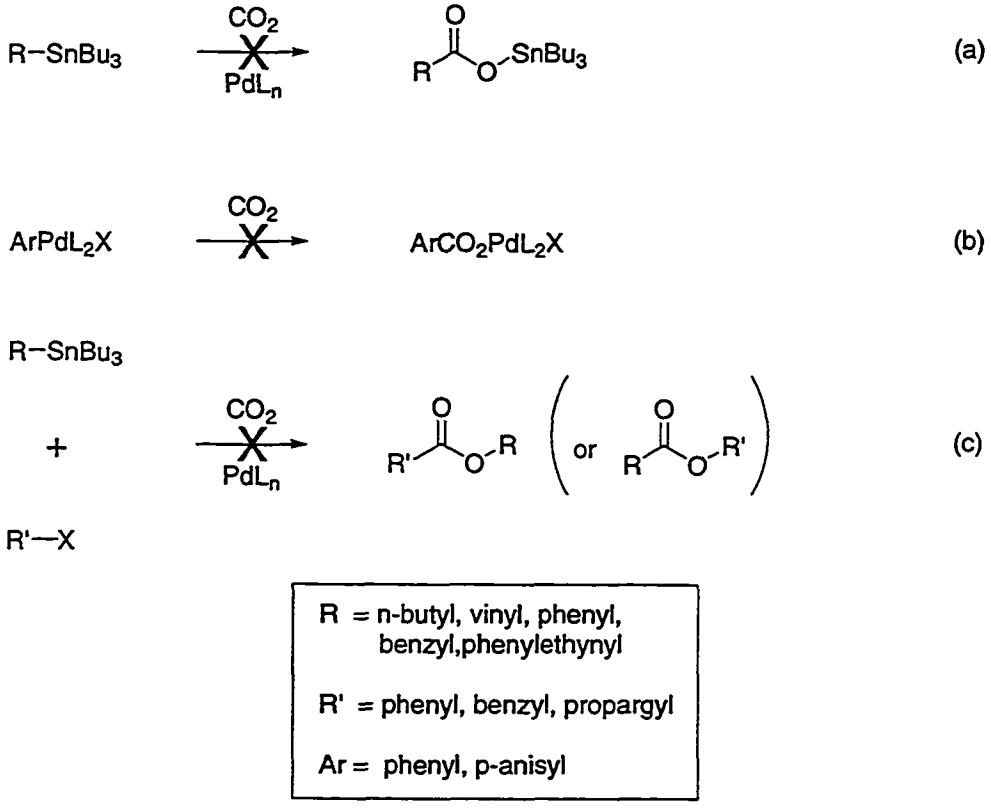


(4-1)



(4-2)

Scheme 4-1
Attempted carboxylation/carboxylative coupling of non-allylic substrates



R = n-butyl, vinyl, phenyl, benzyl,phenylethynyl

R' = phenyl, benzyl, propargyl

Ar = phenyl, p-anisyl

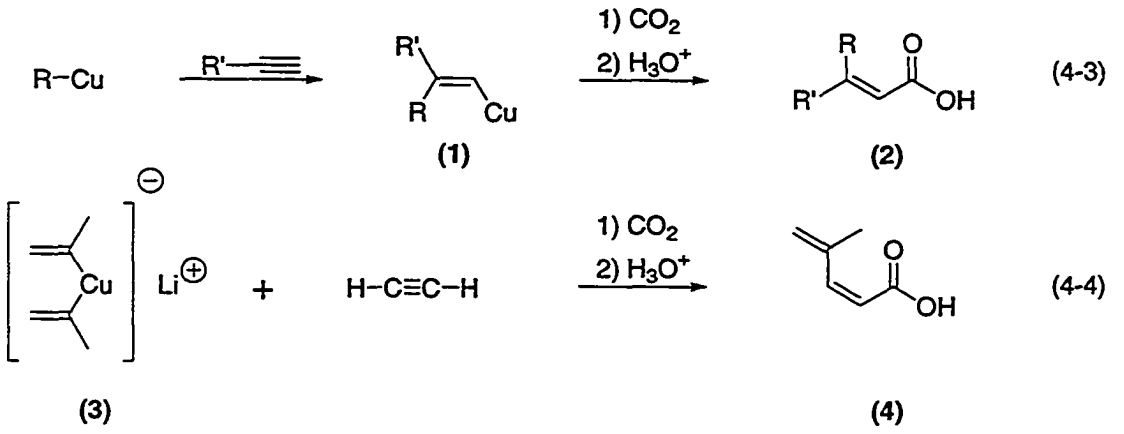
Based on this work, we concluded that the allylic ligand possesses unique amphiphilic reactivity characteristics that enable it to undergo the carboxylative coupling reaction. We attributed our inability to carboxylate other non-allylic substrates to the lack of reactivity of non-allylic organopalladium complexes toward CO_2. This assertion was based not only on our own work, but also by the lack of literature precedent for carboxylation of non-allylic organopalladium complexes.[2] In order to develop a carboxylative coupling reaction for non-allylic substrates, we felt that we needed to move away from the Sn-Pd system and consider other organometal systems that were more likely to be reactive toward CO_2.

4.1.2 Could a Zn-Cu system be used for carboxylative coupling?

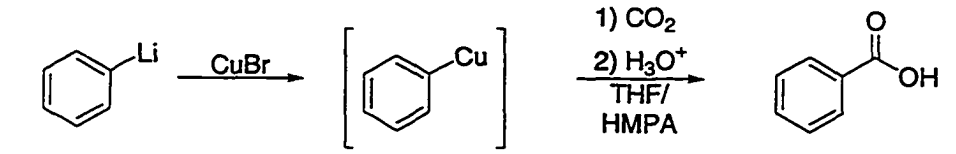
Although there have been relatively few carboxylations of non-allylic organopalladium complexes reported in the literature, there have been a number of carboxylations of organocopper complexes reported.[3] These systems caught our interest, not only because they do react with CO_2, but also because of the existence of Zn-Cu cross-coupling reactions (*vide infra*).

4.1.2.1 Carboxylation of organocopper complexes

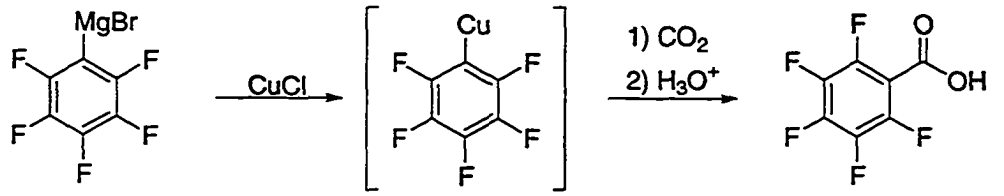
Most of the CO_2 chemistry of copper complexes has featured Cu(I) complexes, although some carboxylation of organocuprate complexes has also been reported. Some interesting stoichiometric carboxylations of organocopper compounds were reported by Normant and co-workers. They were able to react vinylcopper complexes **(1)** with CO_2 producing, after acid workup, α,β-unsaturated carboxylic acids **(2)** (eq. 4-3). Interestingly, they began their synthesis with alkylcopper reagents, which react with alkynes to form the vinylcopper species *in situ* by means of an "addition" of the alkylcopper reagent to the alkyne. The reaction also was achieved with good stereocontrol: the reaction formed the β,β-disubstituted acid, and the alkyl group R from the copper reagent was cis to the new carboxyl moiety.[4] In a similar fashion, Normant's group was also able to effect a reaction of diisopropenyllithium cuprate **(3)** with acetylene and CO_2 to form 4-methyl-2,4-pentadienoic acid **(4)** (eq. 4-4).[5]



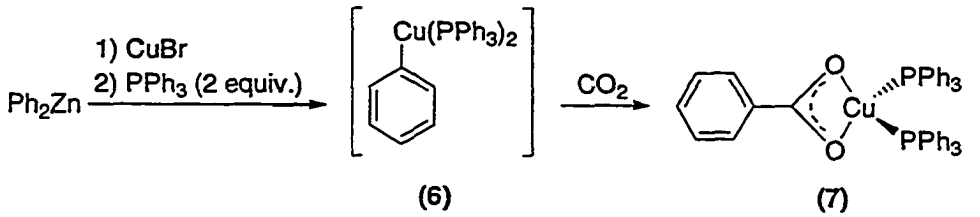
Normant's group was also able to form benzoic acid by carboxylating phenylcopper, which was formed from phenyllithium and CuBr (eq. 4-5). Notable in this system was that they found that the reaction occurred best using a mixed solvent system of THF-HMPA. Apparently, the use of HMPA is necessary in order to sequester lithium cations, which were found to inhibit the carboxylation.[6] DePasquale and Tamborski were also able to carboxylate an arylcopper reagent. They synthesized pentafluorobenzoic acid **(5)** from C_6F_5Cu, which was made from C_6F_5MgBr and CuCl (eq. 4-6).[7] Additionally, Marisch and co-workers reported that $PhCu(PPh_3)_2$ **(6)** can be carboxylated easily at 0 °C (eq. 4-7). They noted that the reaction does not occur with simple PhCu, but only with $PhCu(PPh_3)_2$.[8] They had synthesized PhCu by transmetallation reaction between Ph_2Zn and CuBr.[9] They were able to isolate (benzoato)bis(triphenylphospine)Cu(I) **(7)** and obtained an X-ray crystal structure. They also reported that methyl benzoate could be liberated from **(7)** by heating it with methyl iodide (eq. 4-8). We decided to use their work as a guide in our studies.



(4-5)

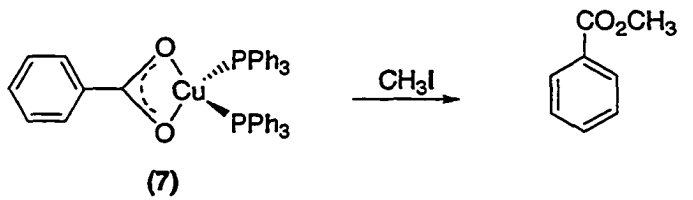


(4-6)



(6) (7)

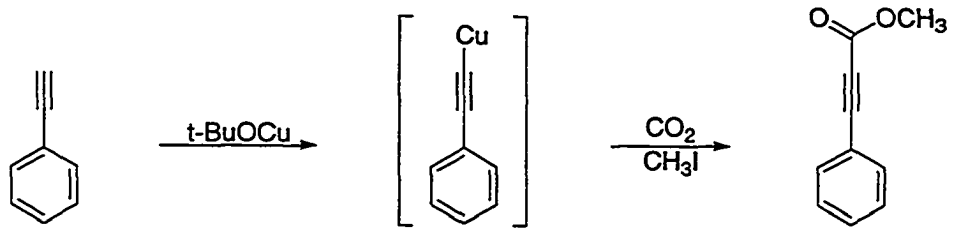
(4-7)



(7)

(4-8)

Alkynylcopper complexes have also been carboxylated. Saegusa reported that they were able to form methyl phenylpropiolate **(8)** by reacting copper(I) t-butoxide and phenylacetylene in the presence of CO_2. The initial product of the reaction was presumably a copper carboxylate, as the ester was formed after treating the reaction mixture with methyl iodide (eq. 4-9).[10] Interestingly, Inoue has reported being able to perform the same reaction catalytically.[11]



(4-9)

(8)

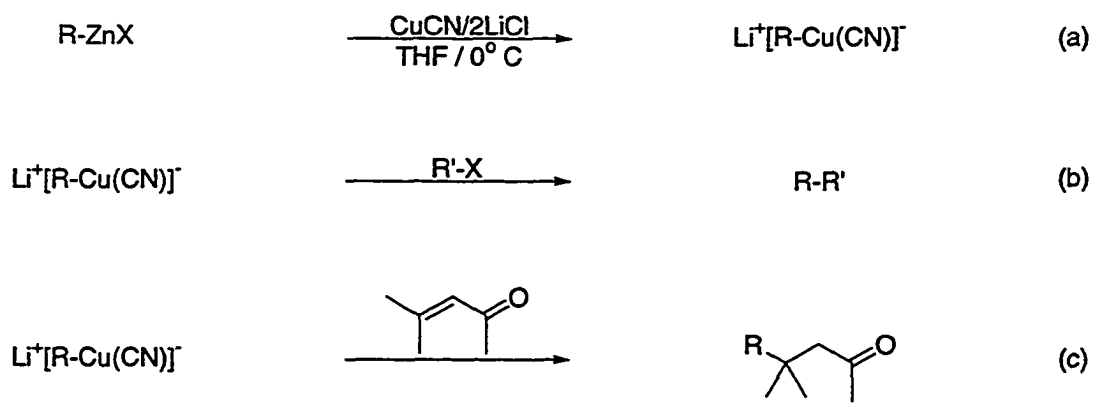
After considering these literature reports, we were certainly interested in studying in more detail the reactivity of organocopper compounds toward CO_2. Our hope was that in doing so we might find something that would give us insights into how to develop a Cu-catalyzed carboxylative coupling reaction.

4.1.2.2 Cross-coupling of organozinc halides and CuCN

Although organocopper(I) compounds are very reactive, i.e. they are usually air-, moisture-, and temperature-sensitive, they can easily be generated from more stable precursors. Most of the literature reports mentioned in the previous section generated the organocopper compound by reacting organolithium or Grignard reagents with copper(I) salts. While this method does work, it also carries with it all of the constraints associated with organolithium or Grignard reagents, i.e. problems with functional group incompatibility. More recently, however, a new way of synthesizing reactive organocopper complexes has been developed. This method uses a transmetallation reaction between an organozinc halide R-Zn-X and CuCN/2LiCl to generate the organocopper complex (Scheme 4-2(a)). The advantage of this method is that the R-Zn-X group is much more tolerant of other functional groups in the substrate, e.g. it is possible to form an organozinc halide with the substrate containing ester, nitrile,

and nitro groups. One of the advantages of using CuCN, as opposed to a different Cu salt, in the reaction is that the CN^- ligand is believed to have a significant stabilizing effect on the complex. For example, the coupling reactions using CuCN are typically performed at 0 °C (Scheme 4-2(a)), however, "simple" organocopper (R-Cu) complexes are not thermally stable and normally must be kept < -20 °C. One of the leading figures in this area of study is Prof. Paul Knochel of Phillips Universität Marburg in Germany. Knochel's group has studied these systems for over ten years and they continue to be in the vanguard of new discoveries in this field.[12] In addition to "simple" coupling reactions (Scheme 4-2(b)), Knochel's group has also extended their methodology to include 1,4-conjugate additions (Scheme 4-3(c)).

Scheme 4-2
Reactions of organozinc halides and CuCN/2LiCl

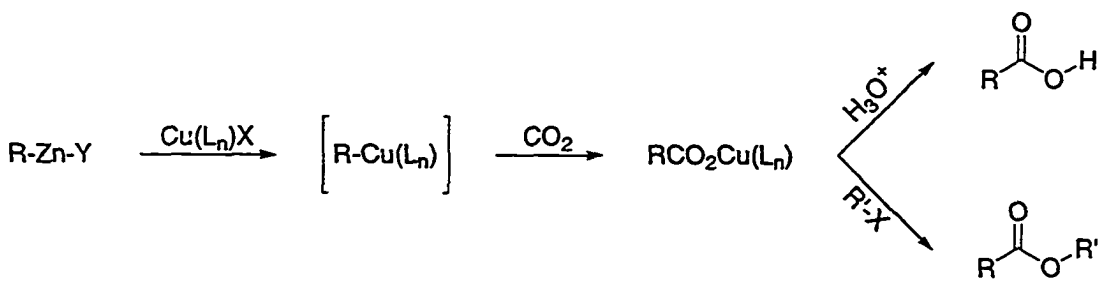


4.1.2.3 A Zn-Cu based system for carboxylative coupling

The literature precedents of reactions of organocopper compounds and CO_2 and the C-C bond-forming methodology developed by Knochel's group

stimulated a lot of thought among us, as we envisioned the possibility of developing a Zn-Cu based system for carboxylative coupling (Scheme 4-3).

Scheme 4-3
Zn-Cu based system for carboxylative coupling



This idea had the potential of offering a tremendous expansion of the synthetic scope of the reaction. A number of organozinc halides are available commercially. In addition, a number of new methods for their synthesis have been published recently.[13] Such a system would be stoichiometric in copper in the beginning phases of discovery, but we hoped that we could eventually make the system catalytic in copper.[14]

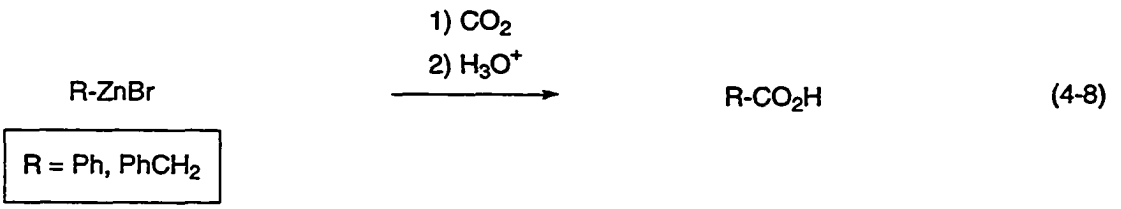
4.2 RESULTS AND DISCUSSION

4.2.1 Selection of organozinc halides and Cu(I) salts

We elected to begin investigating this idea using phenylzinc bromide and benzylzinc bromide, as they were both available commercially, and the derived products would have well known spectral characteristics. We decided to use a variety of common, commercially available copper(I) salts including CuCN, CuI, and CuBr.

One of the first concerns that we had to address in this new work was to determine whether or not the organozinc halides reacted by themselves with CO_2.

Literature reports indicated that allylzinc bromide does react directly with CO_2.[9e] This fact itself was not terribly surprising to us given our experiences with allyl compounds (see Chapters 1-3). However, if either of the compounds reacted with CO_2, then we would not be able to use that compound in our studies. We wanted to be able to control the point in the reaction where the CO_2 reacts. If it simply reacted with the zinc reagent at the beginning, the prospect of developing a catalytic reaction would not be very good. In separate control reactions, phenylzinc bromide and benzylzinc bromide were stirred overnight under CO_2. Carboxylation did not occur at ambient or elevated (50 atm) CO_2 pressures. Acidification and subsequent IR analysis of the reaction mixture indicated that carboxylation had not occurred (eq. 4-8).



(4-8)

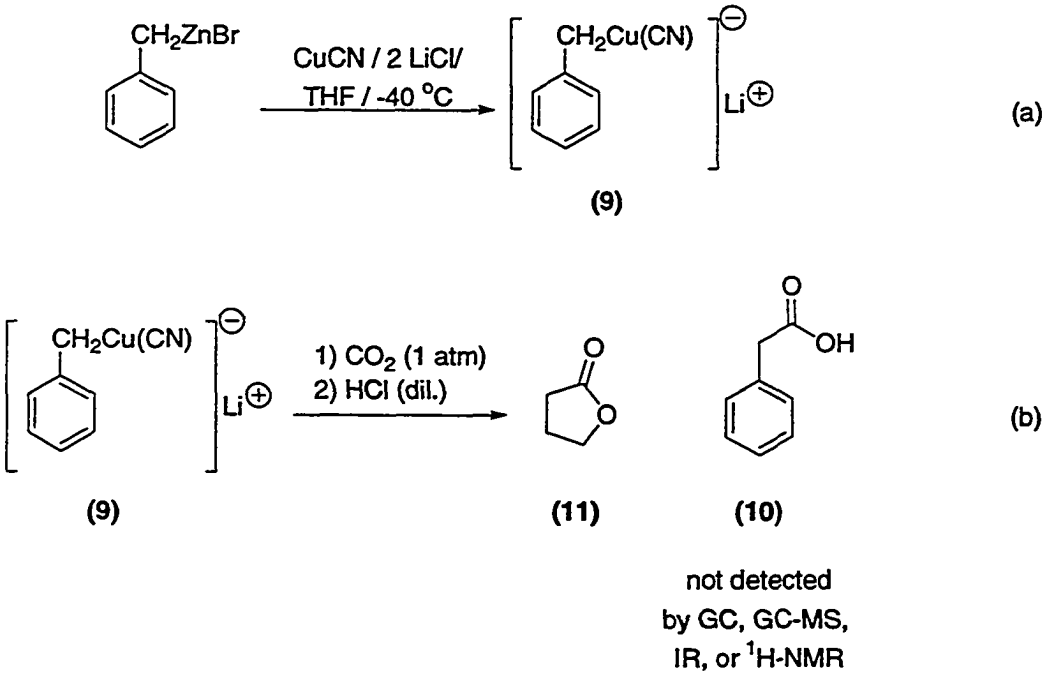
Since the organozinc reagent did not react with CO_2, we were able to continue in our investigations.

4.2.2 Attempted transmetallation/carboxylation using CuCN/2LiCl

We began by attempting to carboxylate benzylzinc bromide using Knochel's system CuCN/2LiCl. One advantage of the LiCl is that it makes CuCN

soluble in THF. The reaction was performed at low temperatures due to the thermal instability of the benzylcopper(I) intermediate **(9)**. After complex **(9)** was generated, CO_2 was bubbled through the solution for 1 h. The mixture was then acidified, extracted, and analyzed. None of the desired acid product **(10)** was formed. The GC, GC-MS, IR, and NMR data indicated that the major organic product of the reaction was actually γ-butyrolactone **(11)**. Most likely **(11)** was formed from a side reaction with the solvent THF (Scheme 4-4(b)).

Scheme 4-4
Attempted carboxylation of benzylzinc with CuCN/LiCl



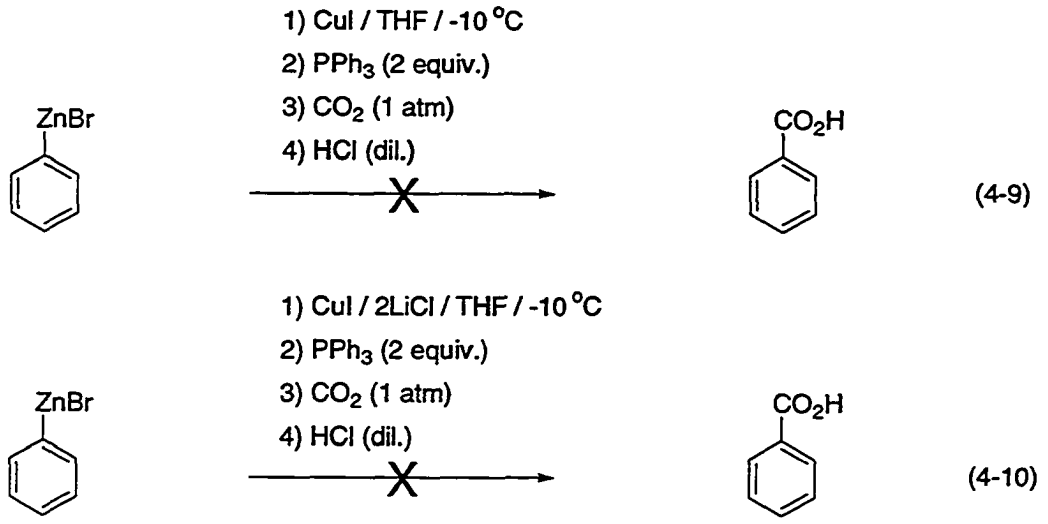
We believed that the failure of the benzyl substrate to react with CO_2 was due to the fact that the anionic copper(I) complex **(9)** formed upon reaction of CuCN and $PhCH_2ZnBr$ was deactivated to reaction with CO_2 by the presence

of the CN^- ligand. This type of complex is very different electronically than the neutral copper(I) complexes, or even the anionic copper (I) complexes (eq. 4-4) that were carboxylated in Section 4.1.2.1. We thought that it would be better to try the carboxylation with a neutral copper(I) complex.

4.2.3 Attempted transmetallation/carboxylation using CuI

We decided to apply the same idea to our system and generate PhCu via transmetallation from PhZnBr to CuI. PhZnBr was added to a suspension of CuI in THF. The mixture was stirred at $-10^{\circ}C$ for 45 min. This system was quite problematic. The CuI was not soluble in THF. After the organozinc reagent was added, the mixture was dark black, brown. It was almost impossible to tell whether the solids had dissolved or not. A solution of PPh_3 (2 equiv.) in THF was added. CO_2 was bubbled through the mixture for 1 h. After the reaction mixture was hydrolyzed and extracted, there was no evidence that any benzoic acid had formed (Scheme 4-5(a)). The experiment was repeated using the same reagents, but two equivalents of anhydrous LiCl were added in the hope of improving the solubility of the CuI. The CuI did dissolve with the addition of the LiCl, however, subsequent addition of CO_2 did not lead to the formation of any carboxylated product (Scheme 4-5(b)).

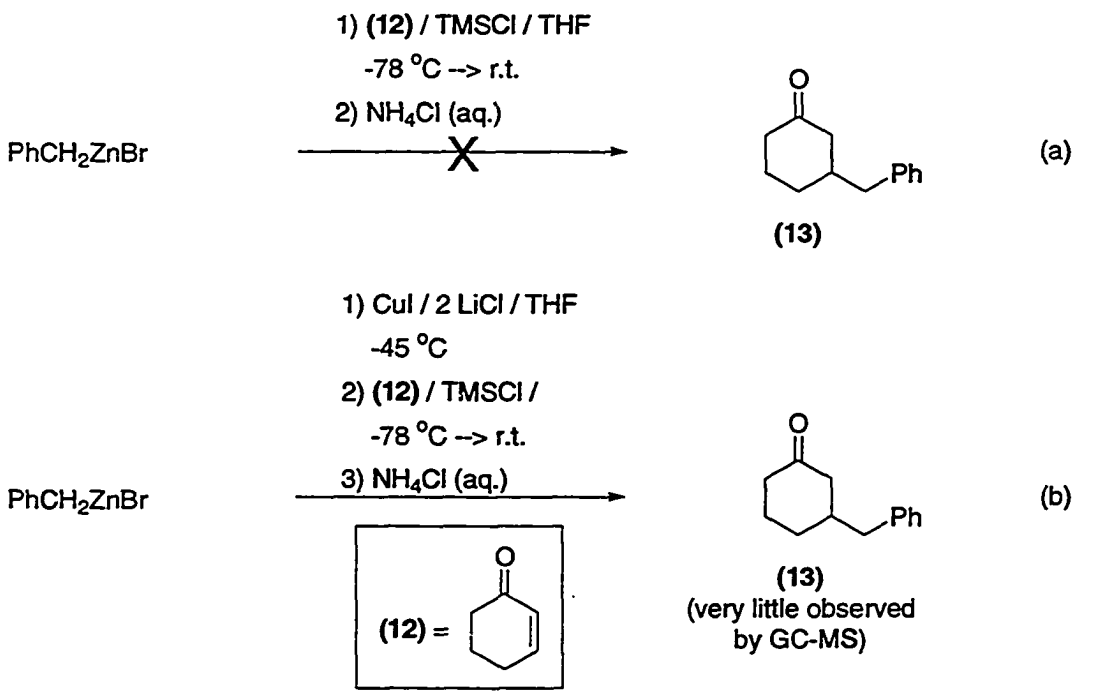
Scheme 4-5
Attempted carboxylation of PhZnBr with CuI



The insolubility of CuI in THF caused a number of experimental problems. One of our principal concerns was that we were unable to determine visually whether or not the transmetallation of the organic group from Zn to Cu was even occurring. We conducted a trapping experiment to find out if the transmetallation was taking place or not. We decided to try to trap the organic group using a 1,4-conjugate addition reaction. Our idea was to try to generate the organocopper reagent under our experimental conditions, i.e. using R-ZnBr and CuI, and add a substrate that was known to undergo conjugate addition easily.[11b,15] We decided to use 2-cyclohexen-1-one **(12)** as the substrate. We conducted a pair of experiments to test this idea. The first reaction was a control experiment in which benzylzinc bromide and **(12)** were mixed without any copper salt added (Scheme 4-6(a)). Chlorotrimethylsilane was used in both cases to activate the substrate. The second reaction was done using benzylzinc bromide, CuI with 2 equivalents of LiCl, and **(12)** (Scheme 4-6(b)). The control experiment did not

produce any of the conjugate addition product 3-benzylcyclohexanone **(13)**. GC-MS data from the second experiment were ambiguous. A peak of moderate intensity in the GC (retention time = 14.6 min) produced a mass spectrum that had peaks at *m/z* = 188.1, 130.1, and 91.1 these were taken to be indications that at least a small amount of **(13)** might have been formed in the reaction. The results of our trapping experiments indicated that even if $PhCH_2Cu$ were being formed in our system, the transmetallation was not occurring to any appreciable (or synthetically useful) extent. The trapping experiments did give us reason to believe that we should consider using other CuX salts.

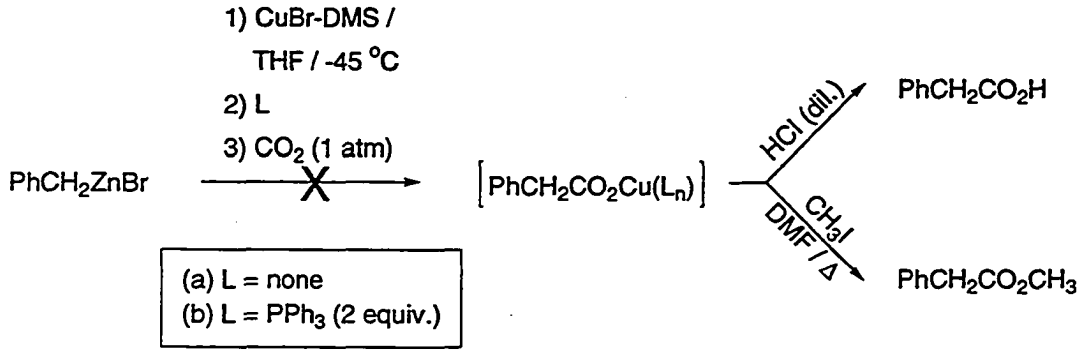
Scheme 4-6
Trapping of $PhCH_2Cu$ by 1,4-conjugate addition



4.2.4 Attempted transmetallation/carboxylation using other Cu(I) salts

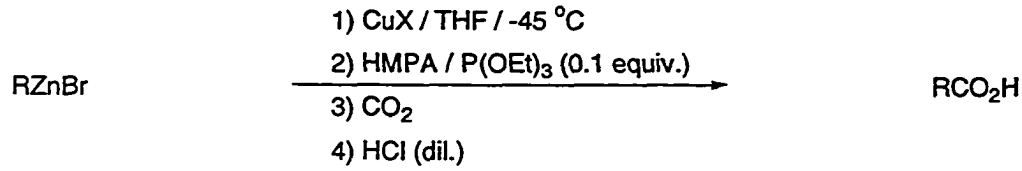
We decided to attempt the transmetallation-carboxylation process using other copper(I) salts in the hope of finding a copper(I) salt that was more soluble in THF. We decided to use the dimethyl sulfide adduct of CuBr (CuBr-DMS), which had been reported to have better solubility in THF than CuI or CuBr.[16] We did not find this to be the case in our experience. It was necessary to add LiCl to the CuBr-DMS in order to dissolve the Cu salt. We conducted a pair of experiments to find out whether or not using CuBr-DMS would lead to formation of carboxylated product. The first experiment was performed using CuBr-DMS with two equivalents of LiCl, but without any added PPh_3 (Scheme 4-7(a)). The second experiment had CuBr-DMS, two equivalents of LiCl, and two equivalents of PPh_3 (Scheme 4-7(b)). We also used a new experimental technique to probe for the presence of carboxylated product in these experiments. After the period of bubbling CO_2 into the reaction mixture had been completed, the mixture was divided into two separate portions. One portion was subjected to the usual acidification/extraction process that had been done previously. The other portion was dissolved in DMF and heated in a sealed tube with excess methyl iodide. Our hope was that, if any carboxylated product were present, it would be converted to the methyl ester, which would be more easily detected by gas chromatography. Unfortunately, neither one of these experiments gave any detectable amounts of carboxylated products.

Scheme 4-7
Attempted carboxylation of benzylzinc bromide using CuBr-DMS



We decided to attempt a series of carboxylations of arylcopper complexes using conditions similar to those reported by Normant.[6] The main variable investigated in these experiments was the effect of using a variety of copper(I) salts on the reaction. We also decided to try the carboxylation at elevated CO_2 pressures. RZnBr and CuX were allowed to react at low temperature in THF:HMPA (1:4) with 0.1 equiv. of $P(OEt)_3$. The first experiment was a control experiment conducted at ambient CO_2 pressure without using any CuX (Scheme 4-8(a)). In the second experiment using CuBr-DMS, CO_2 was bubbled through the reaction mixture (Scheme 4-8(b)). In the remaining experiments, after the $P(OEt)_3$ had been added, the reaction mixture was transferred into a stainless-steel autoclave and pressurized with CO_2 (58 atm)(Scheme 4-8(c)-(h)). In all cases, after the addition of CO_2 had been completed, the mixture was stirred and allowed to warm up to room temperature. The reaction mixture was subjected to the previously described acidification-extraction protocol and analyzed for the presence of carboxylated product. These experiments are summarized in Scheme 4-8.

Scheme 4-8
Attempted carboxylations of organozinc bromides with THF/HMPA solvent



Entry	CuX	R	$P(CO_2)$ (atm)	Product	Yield (mg)	Yield (%)
a	none	Ph	1	none	0	0
b	CuBr-DMS	Ph	1	none	0	0
c	CuBr-DMS	Ph	58	none	0	0
d	CuI	Ph	58	$PhCO_2H$	< 20	< 5
e	CuCN/2LiCl	Ph	58	$PhCO_2H$	< 20	< 5
f	$[CuPF_6][MeCN]_4$	Ph	58	$PhCO_2H$	0	0
g	$[CuOTf]_2[PhMe]$	Ph	58	$PhCO_2H$	0	0
h	CuI	$PhCH_2$	58	$PhCH_2CO_2H$	< 20	< 5

The experiments conducted at ambient CO_2 pressure did not produce any detectable amounts of benzoic acid (entries (a) and (b)). No benzoic acid was observed when CuBr-DMS was used, even at high CO_2 pressure (entry (c)). A small amount of benzoic acid (< 20 mg) was isolated when CuI (entry (d)), and when CuCN/2LiCl (entry (e)) were used. We decided to try other Cu(I) salts with weakly coordinating anions. No benzoic acid was detected when tetrakis(acetonitrile)copper(I) hexafluorophosphate (entry (f)) or when the toluene

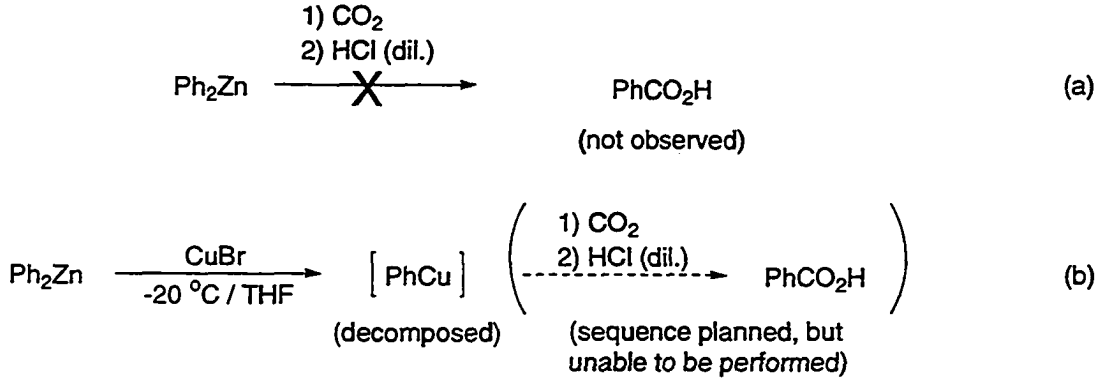
adduct of copper(I) triflate (entry (g)) were used. When benzylzinc bromide was used with CuI, a small amount (< 20 mg) of phenylacetic acid was isolated (entry (h)).

Although these experiments did produce small amounts of carboxylated products, the yield of the reaction was so low that we decided not to make a dedicated attempt to improve the yield. We began to consider using other organozinc reagents to generate the organocopper species.

4.2.5 Attempted carboxylations of Ph_2Zn and CuBr

Diphenylzinc was used by Marisch to form phenylcopper and phenylzinc bromide (eq. 4-7).[9c] We decided to investigate the possibility of using this approach to generate PhCu and attempt carboxylation under our conditions (high CO_2 pressure, mixed THF/HMPA solvent). We first performed a control reaction to determine if Ph_2Zn reacts with CO_2 without any added copper(I) salt (Scheme 4-9(a)). No carboxylated product was isolated after the standard acidification-extraction protocol was done at the end of the reaction. We attempted to carry out a simple transmetallation-carboxylation sequence using CuBr (Scheme 4-9(b)). Unfortunately, we had many problems (insolubility, decomposition) while generating the PhCu reagent. Since the PhCu was so sensitive to air and moisture, we ultimately decided to discontinue these efforts.

Scheme 4-9
Attempted transmetallation/carboxylation using Ph_2Zn and CuBr



4.3 CONCLUSIONS

Although our idea of developing a carboxylative coupling reaction based on transmetallation from Zn to Cu appeared to have promise at the beginning, we soon discovered that there were many practical difficulties that would ultimately lead to the failure of this project. The main difficulty encountered in this project was solubility. CuX salts have low solubility in THF, especially at low temperatures, as was often the case in these experiments. Additionally, the low solubility made it difficult to monitor visually the progress of the transmetallation reaction. The low solubility of these salts most likely meant that the transmetallation reaction was not taking place to any great extent. The solubility of the copper(I) salt is improved by addition of LiCl, but the addition of the LiCl does not appear to improve the transmetallation reaction. Of course, Knochel's work with the Zn-Cu transmetallation has been done using CuCN/2LiCl, which is soluble in THF. We found that, although this salt is indeed very soluble in THF, the resulting organocopper species are not especially reactive toward CO_2. The

instability of the PhCu species generated using Ph_2Zn/CuBr precludes it from being a reasonable choice for use in developing a synthetically practical carboxylative coupling reaction.

4.4 PROJECT SUMMARY

This project still has potential to achieve the goal we had originally established, i.e. to develop a carboxylative coupling reaction based on the Zn-Cu transmetallation-carboxylation sequence. In the Sn-Pd system, there were not very many examples of non-allylic organopalladium complexes that reacted with CO_2. Unlike non-allylic organopalladium complexes, however, there are a number of non-allylic organocopper(I) complexes that do react with CO_2, hence there is much more of a solid literature precedent for establishing a Zn-Cu based carboxylative coupling. The difficulties that we experienced were practical ones.

There were two major problems encountered in exploring the Zn-Cu system. The most serious problem was the insolubility of the copper(I) salts in THF. Simple halide salts, e.g. CuBr, CuBr-DMS, and CuI, were very insoluble in THF. Other Cu(I) salts with weakly-coordinating counterions, e.g. $[(MeCN)_4Cu]^+[PF_6]^-$ and $[(PhMe)(CuOTf)_2]$ were also insoluble. Addition of LiCl improved the solubility of the salts, but appeared to deactivate the resulting copper(I) species to transmetallation. This could be attributed to the possible formation of an anionic copper(I) complex, e.g. $CuX + LiCl \rightarrow Li^+[CuXCl]^-$. Such a complex would be fairly electron-rich and, hence, would be less reactive toward transmetallation. The combination of CuCN/2LiCl that was used by Knochel in

his coupling reactions,[12] is much more reactive toward transmetallation, however, it is unreactive toward CO_2. What needs to be developed, therefore, is a Cu-complex that is soluble and reactive to both transmetallation and carboxylation. It appears as if the conditions favoring transmetallation, i.e. a more electrophilic copper center, are opposite those favoring carboxylation, i.e. a more nucleophilic copper center. A balance must be established between increasing the solubility of the Cu-complex and maintaining an appropriate level of reactivity. This could be accomplished by variation of the ligands and/or counterion on copper, with the hope that a soluble ligand/counterion combination favorable to both transmetallation and carboxylation could be discovered. The use of different solvent systems could also possibly solve the solubility problem.

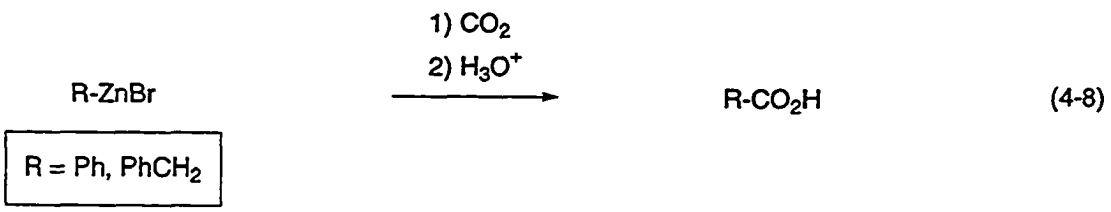
The major outstanding goal on this project is the development of a Zn-Cu carboxylative coupling reaction that is catalytic in Cu. An empirical approach to this idea might be the best way of accomplishing the goal. A combinatorial approach using parallel reactions with different Cu-salts, ligands, and counterions could be attempted. The goal of a Zn-Cu carboxylative coupling is not unrealistic, but there is a lot of work to be done. The synthetic potential of such a reaction makes it a worthwhile endeavor.

4.5 EXPERIMENTAL SECTION

All reagents were used as received from the suppliers. All glassware was oven-dried prior to use. THF and diethyl ether were distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from calcium hydride. CO_2 was anaerobic grade (Mattheson). Phenylzinc bromide and benzylzinc bromide were purchased from Aldrich and were stored under N_2 in a Sure-Seal® bottle. All transfers of these reagents were performed using syringes or cannulae and standard techniques for handling air- and moisture-sensitive reagents. High-pressure reactions were carried out in Parr stainless steel autoclaves. GC analysis was carried out on a Hewlett-Packard HP 5790A GC using a 3 m column packed with 10 % OV-101 on Supelcort B, with nitrogen or helium as the carrier gas, and a flame ionization detector. NMR analysis was done using a Varian Unity/Inova 400 or a Varian XL-300. NMR references were tetramethylsilane for ^{1}H and ^{13}C (internal standard), 85 % H_3PO_4 for ^{31}P (external standard), and tetramethyltin for ^{119}Sn (external standard). IR analysis was done using a Bio-Rad model FTS 135 FT-IR spectrometer. GC-MS analysis was carried out on a Hewlett-Packard HP 5985 using a 30 m capillary column packed with 3% SE-54.

General procedure for attempted ambient-pressure carboxylation of organozinc bromides (control reaction)

Reaction:



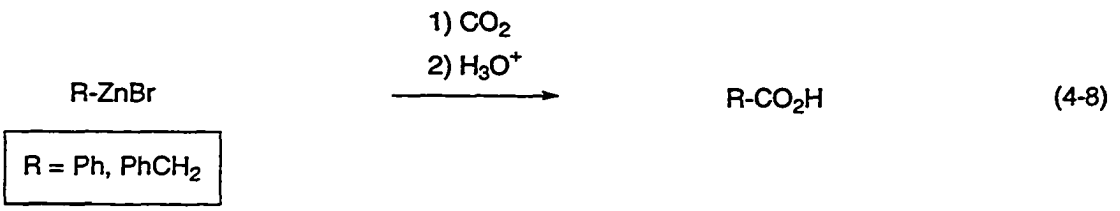
(4-8)

Procedure:

A 50-mL round bottom flask was charged with a stir bar. The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. The organozinc bromide reagent (1.0 mL, 0.5 mmol [0.5 M solution in THF] was added to the flask using a syringe. THF (25 mL) was added to the flask using a cannula. CO_2 was bubbled into the solution through a long needle for 1 h. The solvent was removed from the mixture using rotary evaporation. The residue remaining in the flask was treated with 1 M HCl (1 mL). The acidic solution was extracted with 2 x 1 mL portions of CH_2Cl_2. The organic extract was dried, filtered, and concentrated by rotary evaporation. In both cases (R = Ph and $PhCH_2$), IR and ^{1}H-NMR analysis of the residual material showed no evidence of the presence of the corresponding carboxylic acid, $PhCO_2H$ and $PhCH_2CO_2H$ respectively.

General procedure for attempted high-pressure carboxylation of organozinc bromides (control reaction)

Reaction:



(4-8)

Procedure:

A 50-mL round bottom flask was charged with a stir bar. The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. The organozinc bromide reagent (1.0 mL, 0.5 mmol [0.5 M solution in THF] was added to the flask using a syringe. THF (25 mL) was added to the flask using a cannula.

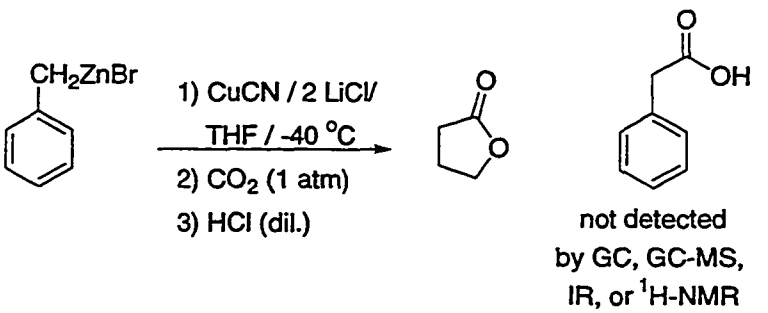
A glass liner was charged with a stir bar and placed inside of a stainless steel autoclave body. A special inert gas adapter was added and the apparatus was connected to an inert gas manifold. The system was evacuated and purged with N_2. The solution of the organozinc bromide reagent was transferred under positive N_2 pressure from the round bottom flask, through a stainless steel cannula, and into the autoclave. The head of the autoclave was attached and sealed. The system was pressurized with CO_2 (850 psig). The system was allowed to stir at room temperature for 1 h.

The autoclave was vented and opened. The contents of the autoclave were poured into a 250-mL round bottom flask. The solvent was removed from the mixture using rotary evaporation. The residue remaining in the flask was

treated with 1 M HCl (1 mL). The acidic solution was extracted with 2 x 1 mL portions of CH_2Cl_2. The organic extract was dried, filtered, and concentrated by rotary evaporation. In both cases (R = Ph and $PhCH_2$), IR and ^{1}H-NMR analysis of the residual material showed no evidence of the presence of the corresponding carboxylic acid, $PhCO_2H$ and $PhCH_2CO_2H$ respectively.

Attempted transmetallation-carboxylation using $PhCH_2ZnBr$ and CuCN/2LiCl

Reaction:



Reference: Berk, S.C.; Yeh, M.C.P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053.

Procedure:

A 50-mL round bottom flask was taken into the glove box and charged with a stir bar, CuCN (46.3 mg, 0.517 mmol, 1.03 equiv.) and anhydrous LiCl (45.7 mg, 1.08 mmol, 2.09 equiv.). The flask was sealed, removed from the glove box, connected to an inert gas manifold, evacuated, and purged with N_2. THF (10 mL) was added using a syringe. The mixture was stirred to dissolve the solids. The flask was cooled to –78 °C in a dry ice-acetone bath. Benzylzinc

bromide (1.0 mL, 0.50 mmol [0.5 M solution in THF]) was added using a syringe. A long needle was used to bubble CO_2 through the solution for 1h. The system was allowed to warm to room temperature and was stirred overnight. The solvent was removed from the mixture by rotary evaporation. The residual solid material was treated with 1 M HCl (1 mL) **CAUTION!! THE ACID HYDROLYSIS PROCEDURE MUST BE PERFORMED IN A GOOD FUME HOOD!!!** The mixture was extracted with CH_2Cl_2 (2 x 1 mL), dried, filtered, and concentrated under vacuum. The residual material was analyzed by IR and ^{1}H-NMR. The data from the reaction were consistent not with phenylacetic acid, but rather γ-butyrolactone. This was confirmed by comparison of data from the reaction with ^{1}H-NMR data for authentic γ-butyrolactone.

Data for authentic γ-butyrolactone (from Aldrich spectral collection):

^{1}H-NMR: δ 2.35 (m, 2 H, β-CH_2), 2.50 (t, 2 H, α-CH_2), 4.35 (t, 2 H, γ-CH_2)

^{13}C-NMR: δ 22.2 (β-CH_2), 27.8 (α-CH_2), 68.6 (γ-CH_2), 177.8 (C=O)

IR: 2916, 1771, 1377, 1168, 1037, 992, 931 cm^{-1}

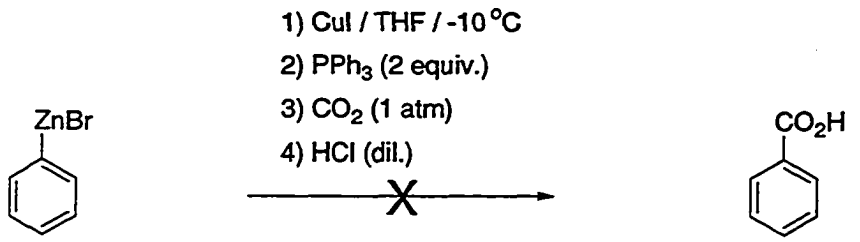
Data from reaction mixture:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.269 (m, 2 H, J = 1.2 Hz), 2.504 (t, 2 H, J = 8.7 Hz), 4.358 (t, 2 H, J = 7.2 Hz)

IR (CH_2Cl_2): 1771, 1173 cm^{-1}

Attempted transmetallation-carboxylation using PhZnBr and CuI/2PPh_3

Reaction:



Reference: Marisch, N.; Camus, A.; Nardin, G. *J. Organomet. Chem.* **1982**, *239*, 429.

Procedure:

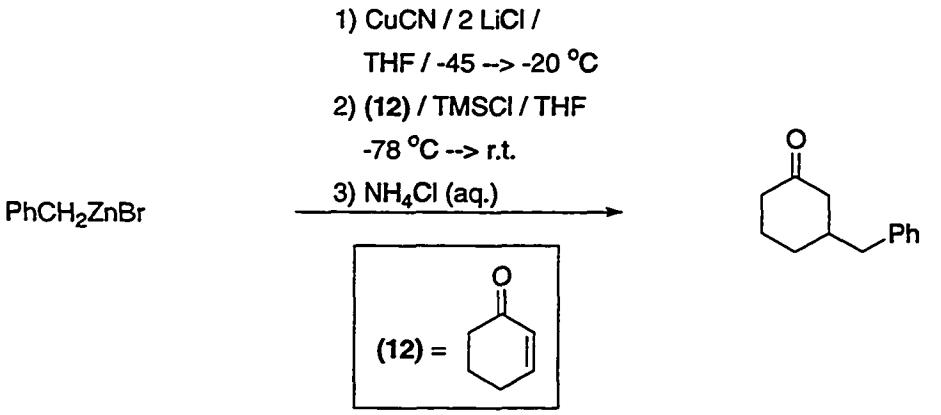
A 100-mL round bottom flask was charged with a stir bar and CuI (192.1 mg, 1.01 mmol). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (15 mL) was added to the flask using a syringe. The flask and contents were cooled to –10 °C in an ice-salt bath. A syringe was used to add phenylzinc bromide (2.2 mL, 1.10 mmol, 1.1 equiv. [0.5 M solution in THF]). The mixture was stirred under N_2 for 1 h. A separate 50-mL round bottom flask was charged with triphenylphosphine (529.6 mg, 2.02 mmol, 2.0 equiv.). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (10 mL) was added by syringe to dissolve the phosphine. The solution of triphenylphosphine was transferred via cannula into the flask containing the PhZnBr/CuI mixture. A long needle was used to bubble CO_2 through the mixture for 1 h.

The solvent was removed from the mixture by rotary evaporation. The residual material was treated with 1 M HCl (1 mL). The acidic solution was extracted with CH_2Cl_2 (2 x 1 mL), dried, filtered, and concentrated under vacuum.

The residual material was analyzed by IR and ^{1}H-NMR. There were no C=O stretching peaks seen in the IR of the residue. ^{1}H-NMR showed aromatic peaks, but these were most likely from PPh_3.

Preparation of authentic 3-benzylcyclohexanone

Reaction:



References: (a) Weissig, V.; Thiele, K.-H.; Beckhaus, R. *Z. Allorg. Alleg. Chem.* **1981**, *482*, 185.
(b) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.
(c) Berk, S.C.; Yeh, M.C.P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053.
(d) Van Heerden, P.S.; Bezuidenhout, B.C.B.; Steenkamp, J.A.; Ferreira, D. *Tetrahedron Lett.* **1992**, *33*, 2383.

Procedure:

A 100-mL round bottom flask was charged with a stir bar, CuCN (278.1 mg, 3.10 mmol), and anhydrous LiCl (282.4 mg, 6.66 mmol, 2.15 equiv.). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (5 mL) was added using a syringe. The mixture was stirred for 5 min. to dissolve the solids. The flask was cooled to –45 °C in a dry ice-acetonitrile bath. Benzylzinc bromide (6.0 mL, 3.0 mmol [0.5 M solution in THF],

0.97 equiv.) was slowly added using a syringe. After all of the $PhCH_2ZnBr$ had been added, the mixture was warmed to –20 °C, and held there for 5 min in an ice-salt bath. The mixture was cooled to –78 °C in a dry ice-acetone bath. Chlorotrimethylsilane (800 μL, 6.31 mmol, 2.04 equiv.) was added using a syringe. Next 2-cyclohexen-1-one (300 μL, 3.10 mmol, 1.0 equiv.) was added using a syringe. After all of the reagents had been added, the flask was removed from the dry ice-acetone bath, and the mixture was allowed to warm up to room temperature. A sample was taken from the mixture immediately after all of the reagents had been added. TLC analysis (20% Et_2O/ 80% hexane) of the sample showed two spots: one for 2-cyclohexen-1-one (Rf = 0.11) and one for the product (Rf = 0.38). The identity of 2-cyclohexen-1-one was confirmed by a running a spot of authentic 2-cyclohexen-1-one, and a co-spot of the reaction mixture and 2-cyclohexen-1-one. The reaction mixture was stirred overnight at room temperature.

The following day another sample was taken from the reaction mixture for TLC analysis. TLC analysis (20% Et_2O/ 80% hexane) of this sample showed only one spot (Rf = 0.37). No spot was seen for 2-cyclohexen-1-one. The mixture was poured into a solution of saturated NH_4Cl (50 mL) and stirred. Ether (20 mL) was added to the solution and the mixture was stirred for 10 min. A precipitate formed in the mixture, so the solution was filtered through Celite and transferred into a separatory funnel. The ether phase was removed and set aside. The aqueous phase was extracted with 3 x 25 mL portions of ether. The ether extracts were combined, dried using anhydrous $MgSO_4$, filtered, and

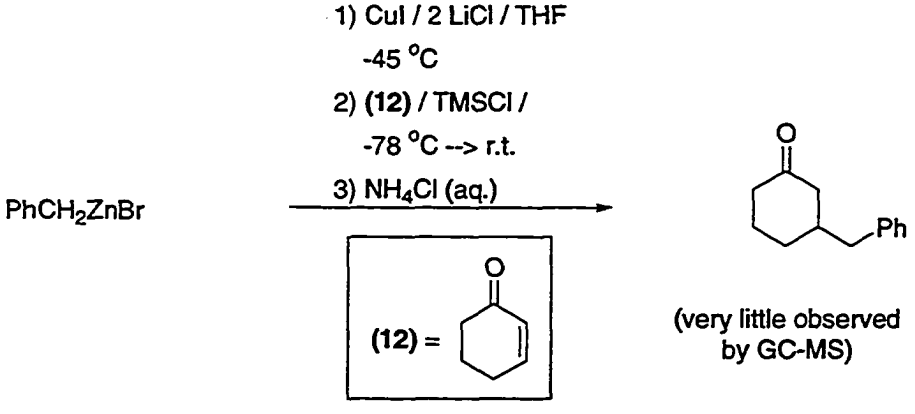
concentrated by rotary evaporation. Yield of product was 384 mg (68 % based on $PhCH_2ZnBr$). The product was analyzed by NMR.

^{1}H-NMR (300 MHz, $CDCl_3$): δ (1.3-2.6 complex m, 11 H), 7.1-7.4 (m, 5 H)

^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.5, 31.2, 41.3 (homobenzylic), 41.8, 43.3, 48.2, 126.4 (aromatic, para), 128.5, 129.3, 139.6 (aromatic, ipso), 211.8 (C=O) (*assignments made using DEPT*)

Trapping of $PhCH_2Cu$ by 1,4-conjugate addition

Reaction:



References: (a) Weissig, V.; Thiele, K.-H.; Beckhaus, R. *Z. Allorg. Alleg. Chem.* **1981**, *482*, 185.
(b) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.
(c) Berk, S.C.; Yeh, M.C.P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053.
(d) Van Heerden, P.S.; Bezuidenhout, B.C.B.; Steenkamp, J.A.; Ferreira, D. *Tetrahedron Lett.* **1992**, *33*, 2383.

Procedure:

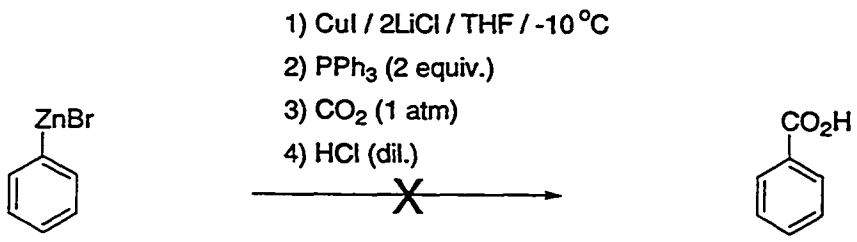
A 100-mL round bottom flask was charged with a stir bar, CuI (390.5 mg mg, 2.05 mmol), and anhydrous LiCl (197.4 mg, 4.66 mmol, 2.3 equiv.). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (25 mL) was added using a syringe. The mixture was stirred for 5 min. to dissolve the solids. The flask was cooled to –45 °C in a dry ice-acetonitrile bath. Benzylzinc bromide (6.0 mL, 3.0 mmol [0.5 M solution in THF], 0.97 equiv.) was slowly added using a syringe. After all of the $PhCH_2ZnBr$ had been added, the mixture was warmed to –20 °C, and held there for 5 min in an ice-salt bath. The mixture was cooled to –78 °C in a dry ice-acetone bath. Chlorotrimethylsilane (250 μL, 1.98 mmol, 0.97 equiv.) was added using a syringe. Next 2-cyclohexen-1-one (100 μL, 1.03 mmol, 1.0 equiv.) was added using a syringe. A small sample of the reaction mixture was removed from the flask at this point for GC analysis. After all of the reagents had been added, the flask was removed from the dry ice-acetone bath, and the mixture was allowed to warm up to room temperature.

The following day, the mixture was hydrolyzed by treating it with 1 M HCl (10 mL). The acidic solution was extracted using 3 x 20 mL portions of ether. The ether extracts were combined, dried using anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The product mixture was dissolved in CH_2Cl_2 and analyzed by GC and GC-MS.

GC-MS: peak at 14.6 min gave the following MS data: *m/z* = 188.1(5 %, M^+), 130.1 (100 %), and 91.1 (M^+-C_6H_9O)

Attempted transmetallation-carboxylation using PhZnBr and CuI/2LiCl/2PPh_3

Reaction:



Reference: Marisch, N.; Camus, A.; Nardin, G. *J. Organomet. Chem.* **1982**, *239*, 429.

Procedure:

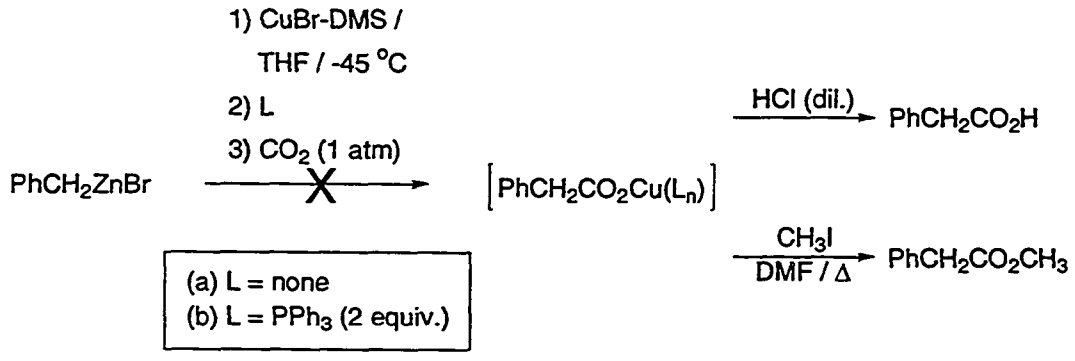
A 250-mL round bottom flask was charged with a stir bar, anhydrous LiCl (85.7 mg, 2.02 mmol, 2.02 equiv.), and CuI (190.5 mg, 1.00 mmol). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (20 mL) was added to the flask using a syringe. The flask and contents were cooled to –10 °C in an ice-salt bath. A syringe was used to add phenylzinc bromide (2.0 mL, 1:00 mmol, 1.0 equiv. [0.5 M solution in THF]). The mixture was stirred under N_2 for 1 h. A separate 50-mL round bottom flask was charged with triphenylphosphine (526.4 mg, 2.00 mmol, 2.0 equiv.). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (20 mL) was added by syringe to dissolve the phosphine. The solution of triphenylphosphine was transferred via cannula into the flask containing the PhZnBr/CuI mixture. A long needle was used to bubble CO_2 through the mixture for 3 h.

The solvent was removed from the mixture by rotary evaporation. The residual material was treated with 1 M HCl (1 mL). The acidic solution was

extracted with CH_2Cl_2 (2 x 1 mL), dried, filtered, and concentrated under vacuum. The residual material was analyzed by IR and ^{1}H-NMR. There were no C=O stretching peaks seen in the IR spectrum of the residue. ^{1}H-NMR showed only aromatic peaks. These were most likely from PPh_3.

General procedure for attempted transmetallation-carboxylation of $PhCH_2ZnBr$ and CuBr-DMS

Reaction:



Procedure:

A 250-mL round bottom flask was charged with a stir bar and CuBr-DMS (~410 mg, ~2 mmol). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (25 mL) was added to the flask using a syringe. The flask and contents were cooled to –45 °C in a dry ice-3-pentanone bath. A syringe was used to add benzylzinc bromide (2.0 mL, 1.00 mmol, 1.0 equiv. [0.5 M solution in THF]). The mixture was stirred under N_2 for 1 h. A separate 50-mL round bottom flask was charged with triphenylphosphine (526.4 mg, 2.00 mmol, 2.0 equiv.). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. THF (20 mL) was added by syringe to dissolve the phosphine. The solution of triphenylphosphine was transferred via

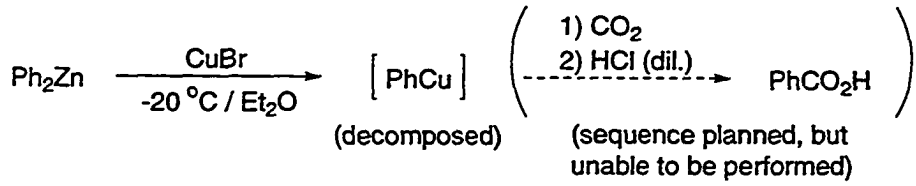
cannula into one of the flasks containing the PhZnBr/CuI mixture. No PPh_3 was added to the material in the other flask. A long needle was used to bubble CO_2 through the mixture for 3 h.

The solvent was removed from the mixture by rotary evaporation. The residual material roughly divided into equal halves. One half of the material was treated with 1 M HCl (1 mL). The acidic solution was extracted with CH_2Cl_2 (2 x 1 mL), dried, filtered, and concentrated under vacuum. The residual material was analyzed by IR. There were no C=O stretching peaks seen in the IR spectrum of the residue.

The other half of the material was dissolved in DMF and CH_3I (1 mL) was added. The mixture was heated overnight in a sealed tube. The solution was dissolved in CH_2Cl_2 and analyzed by GC. Comparison of retention time data from the reaction mixture with authentic samples of $PhCH_2CO_2CH_3$ showed no evidence that $PhCH_2CO_2CH_3$ had been formed in the reaction.

Attempted transmetallation-carboxylation using Ph_2Zn and CuBr

Reaction:



Reference: Hofstee, H.K.; Boersma, J.; van der Kirk, G.J.M. *J. Organomet. Chem.* **1978**, *144*, 255.

Procedure:

A 250-mL round bottom flask was charged with a stir bar and CuBr (160.6 mg, 1.12 mmol). The flask was sealed, connected to an inert gas manifold, evacuated, and purged with N_2. Ether (50 mL) was transferred into the flask via cannula. The flask was cooled to –20 °C using a dry ice-ethylene glycol bath. A solution of diphenylzinc in THF (20 mL, 2 mmol [0.1 M]) was added slowly to the CuBr suspension. The mixture was stirred at –20 °C for 10 h. The product mixture was supposed to be white, however, after the 10 h period had elapsed, the mixture in the flask was greenish-brown. This was taken to be evidence that the copper complex had decomposed somehow and the procedure was terminated.

4.6 BIBLIOGRAPHY

1) (a) Shi, M.; Nicholas, K.M. *J. Am. Chem. Soc.* **1997**, *119*, 5057. (b) Shi, M.; Franks, R.; Nicholas, K.M. In *Advances in Chemical Conversions for Mitigating Carbon Dioxide*; Inui, T.; Anpo, M.; Izui, K.; Yanaguida, S.; Yamaguchi, T., Eds.; Elsevier: New York, NY, 1998; pp 165-170. (c) Franks, R.J.; Nicholas, K.M. *Organometallics* **2000**, *8*, 1458.

2) See Reference 31, Chapter 3.

3) Behr, A. *Carbon Dioxide Activation by Metal Complexes*; Wiley-VCH: New York, NY, 1988, pp 29, 43-44.

4) Dubot, G.; Mansuy, H.; Lecolier, S.; Normant, J.F. *J. Organomet. Chem.* **1972**, *42*, C105.

5) Alexakis, A.; Normant, J.F. *Tetrahedron Lett.* **1982**, 5151.

6) Cahiez, G.; Normant, J.F.; Bernard, D. *J. Organomet. Chem.* **1975**, *94*, 463.

7) DePasquale, R.J.; Tamborski, C. *J. Organomet. Chem.* **1969**, *34*, 1736.

8) Marisch, N.; Camus, A.; Nardin, G. *J. Organomet. Chem.* **1982**, *239*, 429.

9) (a) Costa, G.; Camus, A.; Gatti, L.; Marisch, N. *J. Organomet. Chem.* **1966**, *5*, 568. (b) Costa, G.; Camus, A.; Marisch, N.; Gatti, L. *J. Organomet. Chem.* **1967**, *8*, 339. (c) Hofstee, H.K.; Boersma, J.; van der Kirk, G.J.M. *J. Organomet. Chem.* **1978**, *144*, 255.

10) Tsuda, T.; Ueda, K.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1974**, 380.

11) Fukue, Y.; Oi, S.; Inoue, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 2091.

12) (a) Majid, T.N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413. (b) Berk, S.C.; Yeh, M.C.P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053. (c) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5425. (d) Knochel, P.; Singer, R.D. *Chem. Rev.* **1993**, *93*, 2117. (e) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC: New York, NY, 1996; pp 160, 271-343. (f) Knochel, P. In *Metal-catalyzed Cross-coupling Reactions*; Diedrich, F.; Stang, P.J., Eds.; Wiley-VCH: New York, NY, 1998; pp 387-419. (g) Jackson, R.F.W. In *Organozinc Reagents: A Practical Approach*; Knochel, P.; Jones, P., Eds.; Oxford: New York, NY, 1999; pp 37-56. (h) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186.

13) Rieke, R.D. *Aldrichimica Acta* **2000**, *33*, 52.

14) (a) Knochel, P.; Rozema, M.J.; Tucker, C.E. In *Organocopper Reagents: A Practical Approach*; Taylor, R.J.K., Ed.; Oxford: New York, NY, 1994; pp 85-104. (b) Taylor, R.J.K.; Casy, G. In *Organocopper Reagents: A Practical Approach*; Taylor, R.J.K., Ed.; Oxford: New York, NY, 1994; pp 1-72.

15) (a) Weissig, V.; Thiele, K.-H.; Beckhaus, R. *Z. Allorg. Alleg. Chem.* **1981**, *482*, 185. (b) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349. (c) Van Heerden, P.S.; Bezuidenhout, B.C.B.; Steenkamp, J.A.; Ferreira, D. *Tetrahedron Lett.* **1992**, *33*, 2383.

16) (a) Bertz, S.H.; Gibson, C.P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251. (b) Bertz, S.H.; Dabbagh, G. *Tetrahedron Lett.* **1989**, *45*, 425.

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