# The Metal-Catalyzed Cross-Coupling Reactions of n-Butylketene Dimer

by

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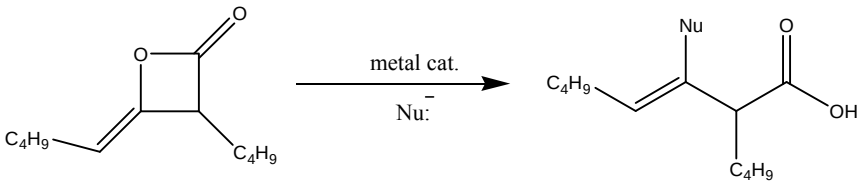
# ABSTRACT




The research project on which this thesis is based is the total synthesis of (-)-hexylitaconic acid. (-)-hexylitaconic acid is a natural product which has been shown to inhibit the degradation of the tumor suppressor protein p53. P53 degradation is the pathogenic factor in many cancers and so prevention of this process is of tremendous promise to cancer treatments. Our proposed synthesis of (-)-hexylitaconic acid involves the asymmetric formation of a ketene dimer and the selective cleavage of this dimer to produce a β-substiuted-β,γ-unsaturated carboxylic acid which can be transformed into (-)-hexylitaconic acid.

The research described here investigates the selective cleavage of n-butylketene dimer via metal-catalyzed cross-coupling of the dimer with organic nucleophiles. In our investigation of the cross-coupling reactions of n-butylketene dimer we explored three categories of nucleophiles: non-organometallics, organozincs and organomagnesiums, and three types of metal catalysts: palladium, nickel and cobalt. n-Butylketene dimer was reacted with non-organometallic nucleophiles in the

presence of palladium catalysts. The reactions produced the desired cross-coupling product in addition to polymeric compounds. We also attempted the nickel-catalyed reaction of n-butylketene dimer with organomagnesium and organozinc compounds but found that the nickel-catalyzed method was not able to produce the β-substiuted-β,γ-unsaturated carboxylic acid we desired. Cobalt catalysts, on the other hand, were able to produce the desired product when used with organomagnesium nucleophiles. n-Butylketene dimer reacted with ethyl and methylmagnesium bromide to produce β-ethyl and β-methyl carboxylic acids in fairly low yields. The results obtained from the reactions we performed suggest that cobalt catalysis may be a viable method for producing a β-substiuted-β,γ-unsaturated carboxylic acid which can be used in the synthetic route to (-)-hexylitaconic acid.

# INTRODUCTION

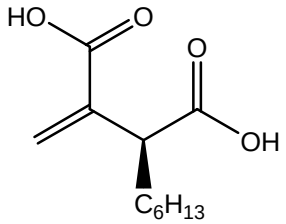
## History of Natural Product Synthesis

In 1828, German chemist Friedrich Wöhler performed what is widely referred to as the first organic synthesis when he serendipitously synthesized urea from silver cyanate.[1] Wöhler's synthesis of urea, which was first isolated from urine by the French chemist Hilaire Rouelle in 1773, challenged the prevailing theory of vitalism which stated that organic compounds could only be synthesized in living systems and never from inorganic compounds.[1] Since Wohler's discovery, the field of organic synthesis has mushroomed and immeasurably impacted everyday life. The total synthesis of natural products that possess pharmacological properties has had profound impact on medicine and on the study of organic chemistry. For example, the need for large-scale production of penicillin during World War II fueled research which culminated in the total chemical synthesis of penicillin by Sheehan in 1959.[2] The characterization and synthesis of penicillin gave birth to an entirely new field of chemistry focused on the β-lactam functionality.[3] The importance of natural product synthesis is evident to this day. Twenty-eight percent of new drugs developed between 1981 and 2006 were natural products or natural product derivatives. Natural products and their derivatives make up forty-seven percent of anticancer drugs developed from the 1940s to the present. [4]

## Total Synthesis of Hexylitaconic Acid

### Hexylitaconic Acid: A Natural Product Inhibitor of P53 Ubiquitination

The subject of this thesis – the cross-coupling reactions of n-butylketene dimer – is part of a larger research project of the Calter group: the total synthesis of the natural product (-)-hexylitaconic acid. Isolated from the marine fungus *Arthrinium* sp., (-)-hexylitaconic acid has been shown to inhibit the interaction of the enzyme HDM2 and the p53 protein *in vitro*.[5] P53 is a tumor suppressor protein that initiates programmed cell death (apoptosis) of tumor cells and its inactivity is involved in the majority of human cancers. HDM2 is an ubiquitin-protein ligase which recognizes p53 and signals its degradation by apoptosis. HDM2 is overexpressed in several cancers, especially cancers with poor prognoses.[6] The inhibition of HDM2-p53 interaction is a strategy currently being investigated in cancer chemotherapy. Small-molecule inhibitors of MDM2-p53 interaction have been shown to prevent p53 ubiquitination and thereby reactivate p53-mediated apoptosis of cancer cells *in vivo*.[7] The development of novel HDM2-p53 inhibitors such as (-)-hexylitaconic acid is an important front in current cancer research.

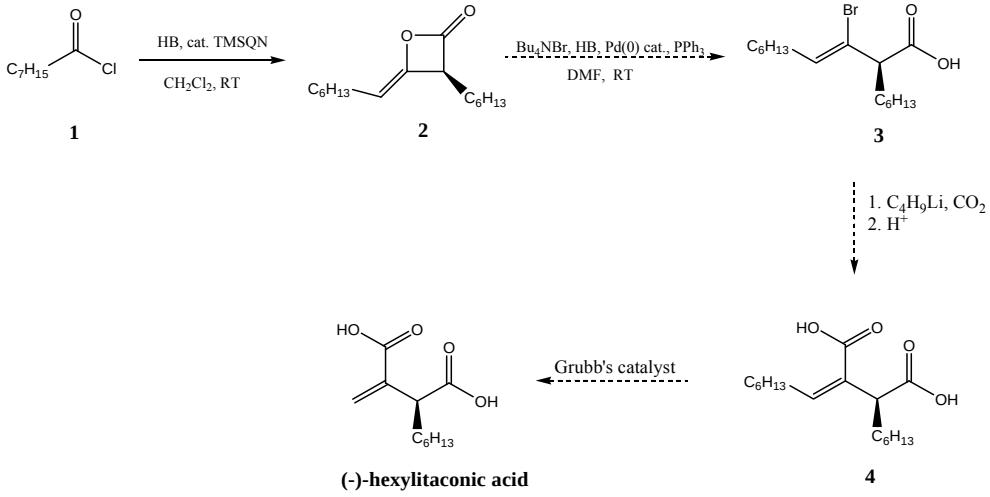



**(-)-hexylitaconic acid**

**Synthetic Route to Hexylitaconic Acid**

The Calter research group seeks to create a synthetic route from a commercially-available acid chloride to (-)-hexylitaconic acid via the asymmetric synthesis and subsequent transformation of a ketene dimer intermediate. Previous research by Calter *et al*. has produced novel syntheses of ketene dimers from acid chlorides, using cinchona-alkaloid analogs as asymmetric catalysts.[8] Scheme 1 shows the initially proposed synthetic route to (-)-hexylitaconic acid.

*Scheme 1. Proposed total synthesis of (-)-hexylitaconic acid*

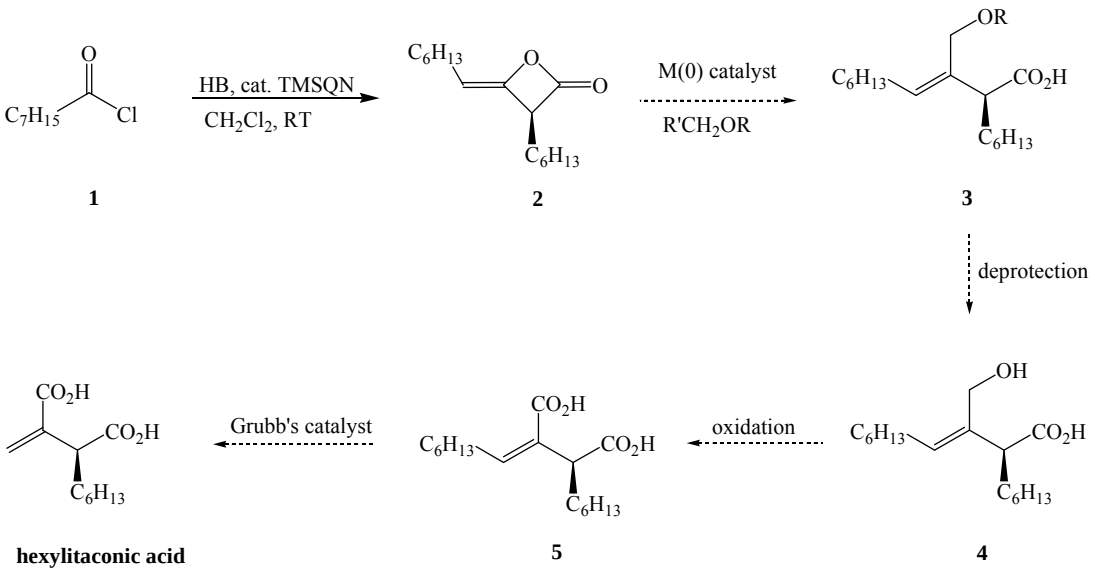



In Scheme 1, octanoyl chloride (**1**) is converted to hexylketene dimer (**2**) using the method developed by Calter *et al.* Palladium(0) then catalyzes the cleavage of the dimer ring and the subsequent coupling to bromine. The β,γ-unsaturated carboxylic acid (**3**) is produced, which is then transformed to the dicarboxylic acid (**4**) by

halogen-metal exchange followed by carbonylation. Olefin metathesis using Grubb's catalyst then converts (**4**) to the desired product, (-)-hexylitaconic acid.

The results obtained after initial attempts to produce the (**4**) by the two-step carbonylation of the dimer (Scheme 1) necessitated the proposal of an alternative route in which the bromination and halogen/metal exchange reactions are replaced by transition metal-catalyzed C-C bond formation between the dimer and an organic nucleophile. Scheme 2 depicts the coupling of the dimer to a $-CH_2OR$ moiety which is deprotected and oxidized to produce dicarboxylic acid (**5**). This is then transformed via olefin metathesis to hexylitaconic acid.

*Scheme 2: Revised synthetic route to (-)-hexylitaconic acid*



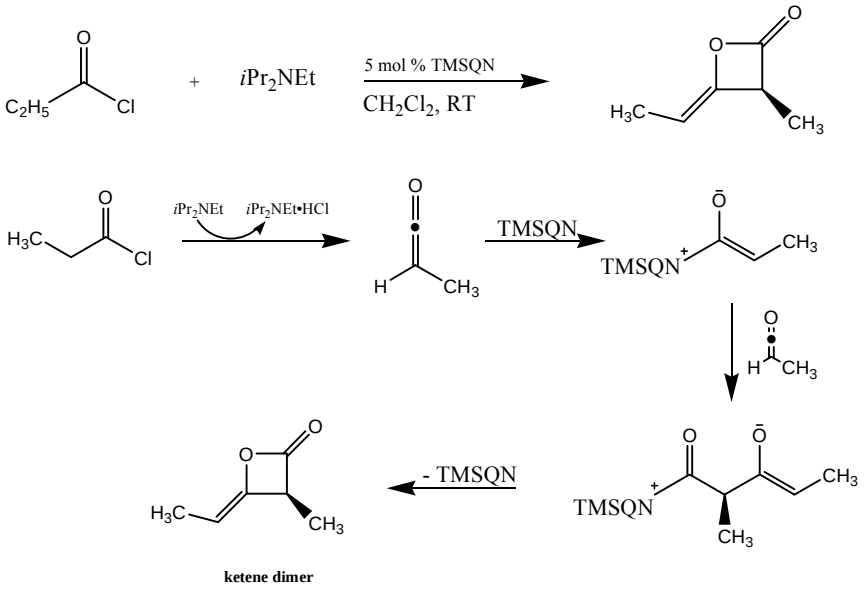
This thesis focuses on the second step in the synthetic route: the metal-catalyzed ring-opening of the ketene dimer. A variety of methods utilizing both organometallic and non-organometallic reagents are investigated. In addition, several catalyst systems are explored to optimize the formation of the desired ring-opening products.

In the proposed synthesis of hexylitaconic acid, octanoyl chloride is first converted to hexylketene dimer. In the research conducted for this thesis, the properties of the reactions of ketene dimers are investigated using n-butylketene dimer. It is expected that the reactions developed using n-butylketene dimer will yield the analogous products when repeated with hexylketene dimer.

## Synthesis of n-Butylketene Dimer

The first step in the synthetic route is the preparation of the ketene dimer. When an acid chloride is treated with Hünig's base (a tertiary amine) and a catalytic amount of 9-trimethylsilylquinine (TMSQN), the corresponding ketene dimer is obtained (Scheme 3).

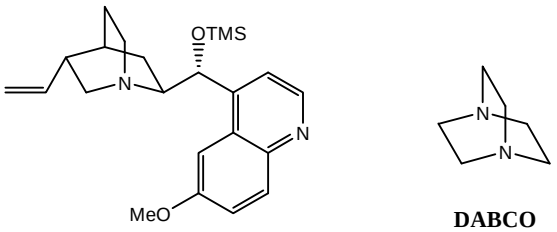
*Scheme 3. Ketene Dimerization*




The dimerization mechanism proposed by Calter[8] begins with the deprotonation of the chloride by Hünig's base and the *in situ* generation of the ketene. TMSQN (also a tertiary amine) then reacts with the ketene to form an acyl ammonium enolate. The enolate subsequently reacts with another ketene molecule and dimerizes, regenerating the TMSQN catalyst.

The stereochemistry-determining step is the reaction of the acyl ammonium enolate with the ketene electrophile. The cinchona alkaloid catalyst controls the facial selectivity of the ketene electrophile, thus determining the stereochemistry of the product. The use of TMSQN catalyst produces the *(R)* enantiomer with high selectivity. Ketene dimerization can also be carried out symmetrically using 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyst to produce the racemic product. The [2.2.2] fused ring moiety of DABCO is similar to that of TMSQN, however it noticeably lacks the bulky quinoline moiety that enables TMSQN to direct the facial selectivity.

*Figure 1. TSMQN and DABCO catalysts*



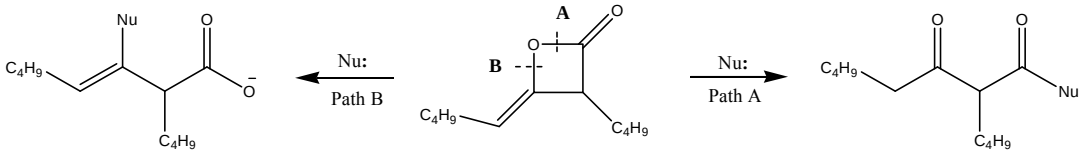

**TMSQN** **DABCO**

## Cross-Coupling Reactions of n-Butylketene Dimer

### General Strategy

The next step in the synthetic route - and the focus of this thesis - is the cleavage of the ketene dimer. Ketene dimers are β,γ-unsaturated β-lactones. Like other carbonyl compounds, β-lactones are readily cleaved by nucleophilic reagents which attack the carbonyl group. The carbonyl carbon-oxygen bond, when cleaved, forms an enolate which tautomerizes to form a β-diketo product. The proposed synthetic route (Schemes 1 and 2) requires the conversion of the ketene dimer to an acyclic β,γ-unsaturated carboxylic acid, thus precluding the formation of an enolate in the ring-opening mechanism. For this to occur, the nucleophile must instead react at the β-carbon and effect cleavage of the vinyl carbon-oxygen bond.

*Scheme 4. Selective cleavage of n-butylketene dimer*




Interestingly, despite the usefulness of β,γ-unsaturated carboxylic acids in the synthesis of terpenoids,[9] which are an important class of natural products, reactions producing them from ketene dimers have not been extensively studied in the existing literature. Itoh *et al.*[10] reported the first example of ring-opening of diketene by selective cleavage of the vinyl-oxygen bond via the use of a nickel catalyst. Since

then, Abe *et al.*[11] and Fujisawa *et al.*[12] have reported similar reactions of diketene using nickel, palladium, iron and cobalt catalysts.

The main challenge in performing nucleophilic substitution at the β-carbon of the ketene dimer is the fact that the molecule possesses a carbonyl center which is significantly more electrophilic than the alkenyl group. A nucleophile will react almost exclusively with the carbonyl to form a diketo product. Fortunately, transition-metal chemistry provides a means of getting around this problem. In the presence of a transition metal catalyst, an organic nucleophile can be coupled to the dimer at the β- carbon, thereby cleaving lactone ring to form the desired acyclic β,γ-unsaturated carboxylate.

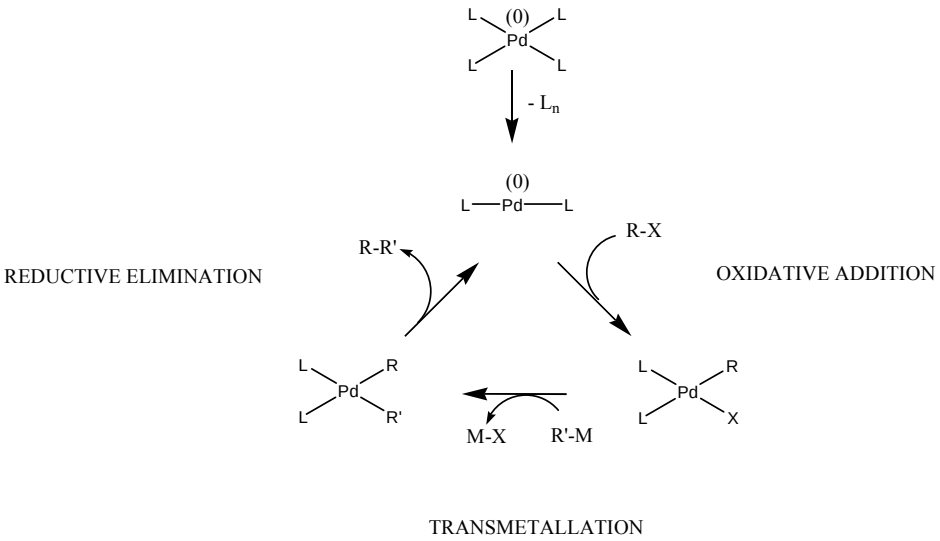
**General Properties of Metal-catalyzed Cross-Coupling Reactions**

The metal-catalyzed cross-coupling reactions developed in the 1970s presented the first direct method of forming C-C bonds at $sp^2$ and sp carbon centers.[13] Pioneering work done by Kumada,[14] Suzuki[15] and Negishi[16] produced the first metal-catalyzed coupling of vinyl halides to organomagnesium, organoboron and organozinc reagents, respectively. The scope of these reactions has since expanded to include an ever-increasing range of functional groups. Palladium and nickel catalysts are historically the most widely utilized catalysts; however other metals such as iron, cobalt and zirconium have also been used successfully.[17] Research investigating the reactions of

non- palladium and non-nickel catalysts has increased given the limitations of palladium and nickel catalysts in cross-coupling of $sp^3$ carbons. Of these alternative metals, cobalt is of particular interest to our research into the cross-coupling of ketene dimers.

Transition metals possess partially-filled *d* subshells which allow the metal to exist in a number of oxidation states as well as form dative covalent bonds with ligands. These properties of transition metals enable them to effect catalysis of cross-coupling reactions. Metal-catalyzed cross-coupling is initiated by the oxidative addition of the electrophile to the zero-valent metal. The nucleophile is then transferred from an organometallic reagent to the catalyst i.e. transmetallation occurs. The metal complex thus formed then undergoes reductive elimination in which the organic ligands from the electrophile and nucleophile are coupled and the zero-valent catalyst is regenerated. Scheme 5 depicts the general mechanism using a palladium catalyst.

*Scheme 5. General cross-coupling mechanism*



Traditionally, organic halides are the electrophiles used in cross-coupling reactions of this nature. Organic phosphates, ethers, and triflates have also been used.[18] Although unligated metals have been used as catalysts in cross-coupling reactions, metal-phosphine complexes of palladium and nickel are most widely used, with triphenylphosphine often being the ligand of choice. It is hypothesized that ligands stabilize intermediate species and prevent the precipitation of the metal, thus keeping the catalyst in solution where it can react.[19] Triphenylphosphine ligands have been reported to impact the rate of reductive elimination most favourably.[20]

The choice of which, if any, organometallic reagent is used in cross-coupling reactions greatly depends on the functional group tolerance of the organometallic group. Organozincs tolerate a wide range of functional groups whereas organomagnesiums are considered to be less chemoselective in their reactivity and so their use is more limited. Non-organometallic nucleophiles such as carboxylates and aryl compounds have been used in cross-coupling reactions.[21]

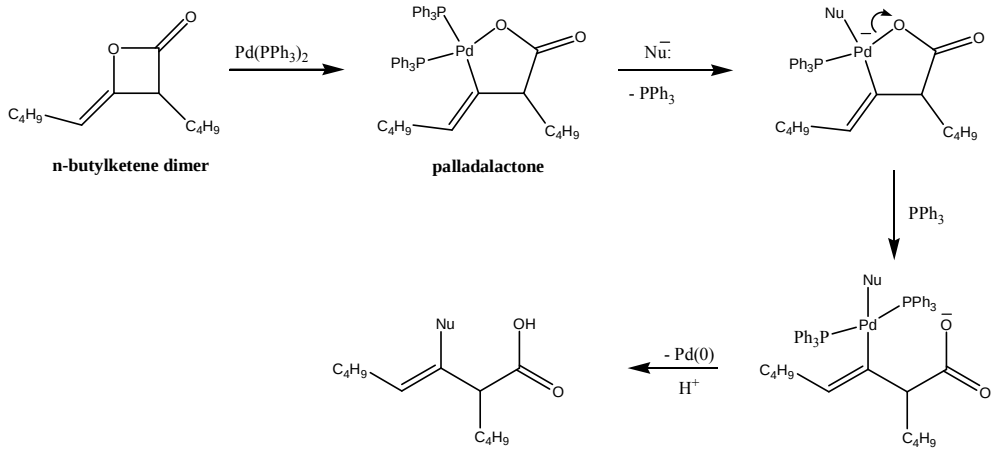
Carbon-carbon bond formation is arguably the most useful process in organic synthesis. The use of transition metal-catalyzed cross-coupling to achieve C-C bond formation is of great utility to the synthesis of natural products. This utility fuels research that seeks to expand the range of functionalities that can be used in these reactions. Research into the cross-coupling of ketene dimers is important not only to the body of work on the dimers themselves, but also to research on vinyl esters which, so far, has been poorly explored.

## Reactions Catalyzed by Palladium and Nickel

### Non-organometallic Reagents

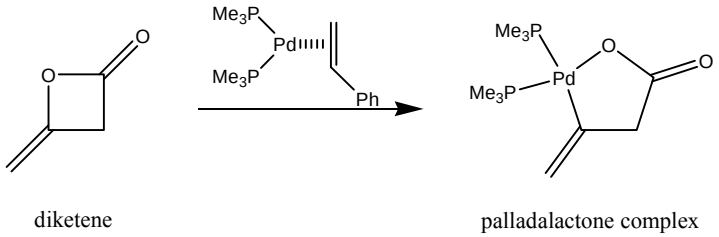
In the initially-proposed synthetic route to hexylitaconic acid (Scheme 1 above), the ketene dimer is reacted with tetrabutylammonium bromide the presence of a (triphenylphosphine)palladium(0) [$Pd(PPh_3)_n$] catalyst. Scheme 6 shows the general mechanism for the palladium-catalyzed coupling reactions of ketene dimers. The reaction begins with coordination of palladium to the double bond of the dimer and the subsequent insertion of palladium across the vinyl C-O bond. The palladium is oxidized to the + 2 state and a palladalactone intermediate is formed. Vinyl esters react with palladium (and nickel) much more slowly than the corresponding vinyl halides or triflates[20] and are typically not utilized in cross-coupling reactions.[22] The driving force for the addition of the ketene dimer to palladium is the relief of ring strain that occurs upon transition from the 4-membered lactone to the 5-membered palladalactone. After the palladalactone is formed, the nucleophile then adds to palladium, displacing a ligand and carboxylate ion. (This is analogous to the transmetallation step in the cross-coupling of organometallics.) Finally, by reductive elimination, the nucleophile is coupled to the vinyl carbon and zero-valent palladium is regenerated. The appropriate work-up should yield the desired substituted β,γ-unsaturated carboxylic acid.

*Scheme 6. Mechanism of palladium-catalyzed coupling of n-butylketene dimer*




Yammamoto *et al*. fairly recently isolated and spectroscopically determined the structure of a palladalactone complex formed from the reaction of diketene with $Pd(PMe_3)_2$(styrene) as shown in Scheme 7.[23] The structure of the isolated palladalactone is consistent with the palladalactone intermediate believed to be formed in the ring-opening of n-butylketene dimer (Scheme 6 above).

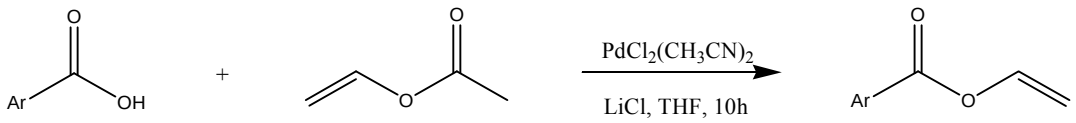
*Scheme 7. Formation of palladalactone complex*



When bromide is used as the nucleophile, the bromine-substituted β,γ-unsaturated carboxylic acid obtained by the mechanism shown above can be transformed to the dicarboxylic acid by halogen/metal exchange (Scheme 1 above) or by using metal-catalyzed cross-coupling to directly couple carbon monoxide to the bromine-substituted acid. The presence of the vinyl halide moiety makes the bromine-substituted acid (**3,** Scheme 1) a more anticipated substrate for metal-catalyzed cross-coupling than even the ketene dimer and metal-catalyzed carbonylation would be expected to occur readily.

The coupling reaction shown in Scheme 6 can be performed using other non-organometallic nucleophiles. The cross-coupling reaction of n-butylketene dimer with a benzoate nucleophile was investigated. Palladium has been reported to catalyze the exchange reactions of vinyl esters with carboxylic acids to form the vinyl esters of the acids (Scheme 8).[24] The reaction is expected to proceed by the mechanism outlined above.

*Scheme 8. Palladium-catalyzed coupling of vinyl esters and carboxylic acids*



## Organometallic Reagents

The coupling reactions of bromide and benzoate nucleophiles to n-butylketene dimer described above have no direct precedent in the existing literature. As mentioned earlier however, Itoh, Abe, and Fujisawa *et al.* have explored the cross-coupling of diketene to organometallic compounds. To further our research into cross-coupling of ketene dimers developed by Calter's method, the metal-catalyzed reactions of organometallics to n-butylketene dimer was investigated.

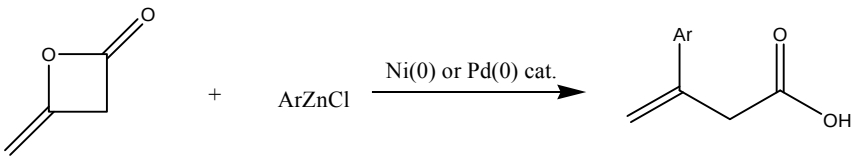
## Cross-coupling using Organozinc Reagents (Negishi Coupling)

In 1977, Negishi *et al.* reported the first reaction of arylzinc compounds with aryl halides using nickel(0) and palladium(0) catalysts.[16] Since then scope of the Negishi reaction has been expanded beyond the synthesis of biaryls. Negishi coupling has been used in the coupling of alkyl, alkenyl, alkynyl halides and organozincs. The mechanism of Negishi coupling is believed to be consistent with the general metal-catalyzed cross-coupling mechanism (Schemes 5 and 6) although the transmetallation step, in which the organic nucleophile is transferred from zinc to palladium (or nickel) has ben poorly characterized.

Abe *et al.*[11] investigated the reactions of diketene with several organozinc, organomagnesium and organoaluminium compounds and found that zero-valent

nickel-phosphine catalysts enabled reactivity unattainable with nickel (II) chloride [$NiCl_2$] or bis(triphenylphosphine)nickel (II) chloride [$NiCl_2(PPh_3)_2$]. They reported the coupling of alkynyl and arylzincs to produce the desired β,γ-unsaturated acids in moderate yields. Nickel and palladium catalysts, prepared *in situ* from $NiCl_2(PPh_3)_2$ and $Pd(PPh_3)_2Cl_2$/DIBAH, respectively, gave comparable conversion of starting material.

*Scheme 9. Negishi-type metal-catalyzed reaction of diketene with organozinc compounds*




The ability to carry-out organozinc-mediated coupling to the ketene dimer is of particular interest to the synthetic route to hexylitaconic acid. The use of O-protected methoxyzinc reagents would introduce the -$CH_2OR$ functionality which can subsequently be oxidized to yield the dicarboxylic acid (**5**, Scheme 2). The Negishi-type reaction of n-butylketne dimer and benzylzinc bromide was investigated using both nickel and palladium catalysts. In the reaction of benzylzinc bromide with n-butylketene dimer, the nickel catalyst, $Ni(PPh_3)_4$, is generated *in situ* via the reduction of $NiCl_2(PPh_3)_2$ by ethylmagnesium bromide. In the palladium-catalyzed reaction, $Pd(PPh_3)_4$ is generated from $Pd_2(dba)_3$ and triphenylphosphine.

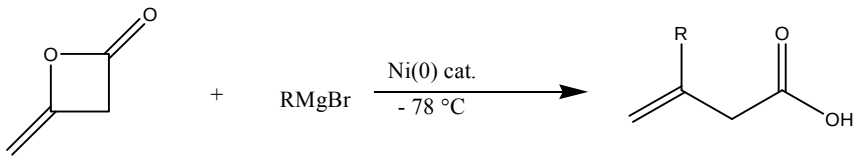
**Cross-coupling using Organomagnesium Reagents (Kumada Coupling)**

The metal-catalyzed reaction of diketene with a Grignard reagent was first reported by Itoh *et al.*[10] Itoh reported the reaction of diketene with trimethylsilylmagnesium chloride in the presence of nickel (II) chloride to yield 3-trimethylsilylmethyl-3-butenoic acid in 95% yield. Abe *et al.*[11] expanded the range of applicable Grignards to include aryl and alkylmagnesiums. They reported that $NiCl_2$ catalyzed the coupling of arylmagnesiums to give the substituted 3-butenoic acid in moderate yields, but failed to convert alkyl and alkenyl-magnesiums. For the reactions with alkylmagnesiums, $NiCl_2(PPh_3)_2$ and $NiCl_2$(dppp) produced the desired product in low to moderate yields.

Abe *et al*. did not report the formation of diketone-derived by-products of the reaction of Grignards with the carbonyl center. Their results do, however, confirm that it is possible for organomagnesiums to selectively react at the β-carbon and produce the desired ring-opening product. Based these results, we investigated the reactions of n-butylketene dimer with organomagnesium bromides in the presence of a nickel catalyst. The utility of the reaction of organomagnesiums with ketene dimers to the synthesis of hexylitaconic aicd would depend on the availability of a Grignard reagent bearing a functional group that can be facilely converted to a carboxylate. Ethers are known to be stable to organomagnesiums and at least one alkoxymethyl Grignard reagent has been synthesized.[25] To effect the transformation from the ring-opening

product to the dicarboxylic acid (**5**, Scheme 2), the ether moiety would be hydrolyzed and subsequently oxidized.

*Scheme 10. Kumada-type coupling of diketene with organomagnesium compounds*

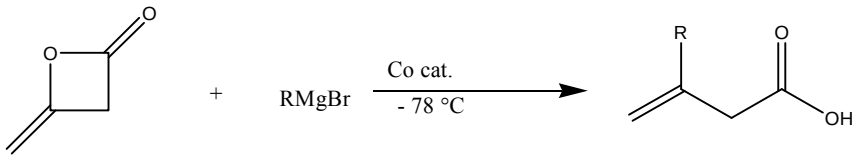


## Cobalt-Catalyzed Reactions

Although palladium and nickel are the most widely researched metals used as catalysts in cross-coupling reactions, other transition metals have successfully been used as catalysts. Despite their popularity, there are drawbacks to the large-scale use of palladium and nickel: palladium is expensive and nickel has been associated with high levels of toxicity.[26] Given these concerns, the development of cheaper, more-easily accessible and less toxic alternatives is beneficial. Cobalt salts are increasingly being explored as a greener alternative to conventional metal catalysts and have been employed in traditional cross-coupling reactions utilizing functionalized organometallic compounds such as organomagnesiums, organozincs, and organocoppers. One of the most promising aspects of cobalt catalysis is its application in the cross-coupling of organic compounds without the use of intermediary organometallic groups. For example, the synthesis of unsymmetrical biaryls – traditionally carried out by Negishi organozinc coupling – can be carried out in the presence of cobalt and without the use of an arylmetallic halide.[27] Cobalt catalysts are also superior to palladium and nickel catalysts in $sp^3$ C – C bond formation. Oxidative addition of alkyl halides to nickel and palladium is slower than that of aryl and alkyl halides thus making them poor substrates for cross-coupling reactions. Cobalt however, reacts with alkyl groups via SET mechanisms to produce reactive alkyl radicals which undergo rapid addition.[28] Additionally, decomposition of organocobalt compounds by β-elimination is not as problematic as with organonickel and organopalladium compounds.

Fujisawa *et al*. investigated the reaction of diketene with alkylmagnesium compounds in the presence of cobalt catalysts.[12] They reported that cobalt (II) iodide [$CoI_2$] and cobalt (III) acetoacetonate [$Co(acac)_3$] gave the highest conversion to the desired substituted 3-butenoic acids.

*Scheme 11. Cobalt-catalyzed coupling of diketne with organomagnesiums*




Based on the Fujisawa's results, the reactions of n-butylketene dimer with ethyl- and methyl- magnesium bromide in the presence of the iodide, chloride and acetoacetonate salts of cobalt were attempted. In addition, the coupling of n-butylketene dimer and benzylzinc bromide was attempted using cobalt (II) iodide instead of a nickel-phosphine catalyst.

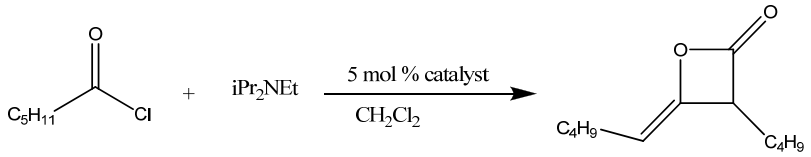
It is evident from the information given that research into metal-catalyzed cross-coupling reactions has been mainly empirical in approach. Not much has been determined experimentally about the mechanisms of specific coupling reactions. This empirical approach is reflected in the range of catalysts and reagents used in this research in our aim to produce the desired ring-opening of n-butylketene dimer.

# RESULTS

## Synthesis of n-Butylketene Dimer

To produce n-butylketene dimer, hexanoyl chloride was reacted with Hunig's base (iPr2NEt) in the presence of a catalyst containing a 1-azobicyclo[2.2.2]octane moiety (Figure 1). Trimethylsilylquinine (TMSQN) afforded the (*R*) enantiomer of n-butylketene dimer in 81% yield. 1,4-Diaobicyclo[2.2.2]octane (DABCO) afforded the racemic dimer, but in significantly lower yields than TMSQN. Table 1 shows the results of the reactions.

*Table 1. Synthesis of n-butylketene dimer*



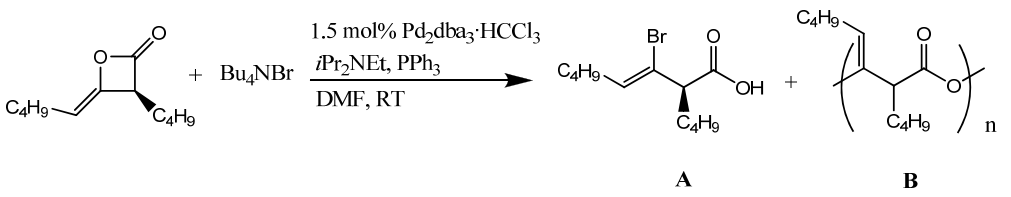

| Reaction | Catalyst | Reaction Time | % Yield |
|---|---|---|---|
| 1.0 | TMSQN | 24 hrs | 81 |
| 1.1 | DABCO | 24 hrs | 28 |

## Reactions With Non-organometallic Compounds

### Palladium-catalyzed Coupling of n-Butylketene Dimer and Tetrabutylammonium Bromide

Our investigation into the ring-opening coupling reactions on n-butylketene dimer began with the reaction of the dimer with a bromide nucleophile obtained from tetrabutylammonium bromide in the presence of a palladium(0) catalyst (Table 2). As described earlier, the reaction was expected to proceed via addition of palladium across the vinyl carbon-oxgyen bond of the dimer followed by addition of the bromide ion to palladium and, finally, formation of the vinyl bromide bond via reductive elimination of the palladium complex (Scheme 6). Zero-valent palladium was obtained commercially as tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] which was transformed *in situ* to tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$]. The dibezylideneacetone ligands are labile and readily displaced *in situ* by triphenylphosphine to form $Pd(PPh_3)_4$. $Pd(PPh_3)_4$ dissociates reversibly in solution to form the diphosphino-palladium complex $Pd(PPh_3)_2$ which is believed to be the active catalyst.

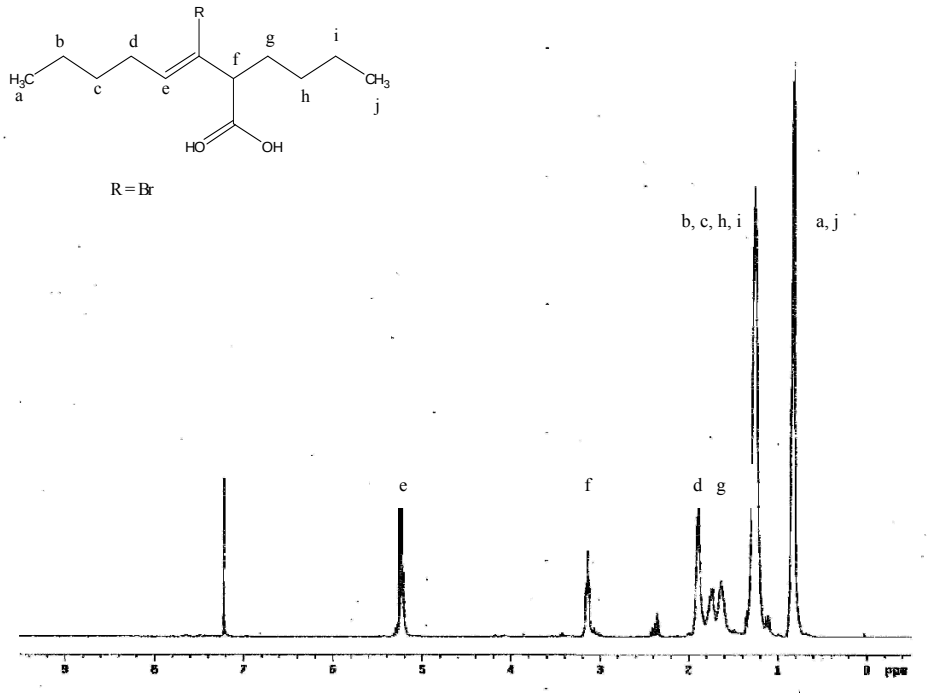
*Table 2. Reaction of n-butylketene dimer with tetrabutylammonium bromide*




| Reaction | Catalyst | Reaction Time | % Yield A | % Yield B |
|---|---|---|---|---|
| 2.0 | $Pd(PPh_3)_4$ | 19 hrs | 0 | 56 |

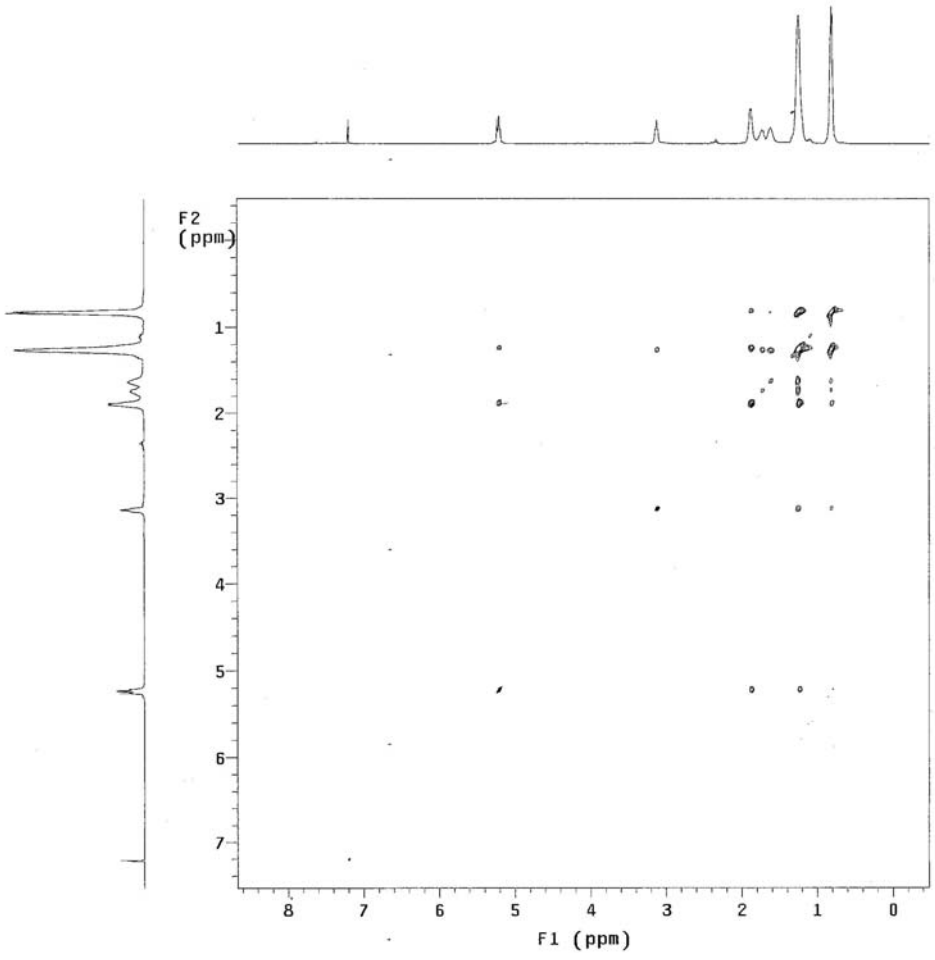
The $^1$H NMR spectrum of the product appeared consistent with the formation of **A**. The peaks at 5.26 and 3.17 ppm represented the vinyl and methine protons, (e) and (f), respectively. The allylic methylene protons, (d), appeared at 1.94 ppm.

*Figure 2. 1H NMR spectrum of the product of Reaction 2.0*



TOCSY and HMBC experiments were used to confirm that the carbon skeleton of the product was also consistent with **A**. The TOCSY spectrum is shown in Figure 2.0 The vinyl proton (e) at 5.26 ppm is immediately coupled to the two allyl protons (d) at 1.94 ppm and further down the alkyl chain to the methylene protons (c). The methine proton (f) at 3.17 is coupled to the methylene protons (h) and (i). Coupling of (f) to the β-methylene protons (g) is not visible in the spectrum shown here but was confirmed to be present.

*Figure 3. TOCSY spectrum of the product of Reaction 2.0*



Based on the 1D and 2D spectra, the product obtained from Reaction 2.0 was treated with the reagents listed in Table 3 below. [a]

*Table 3. Reactions of* ***A***[a]

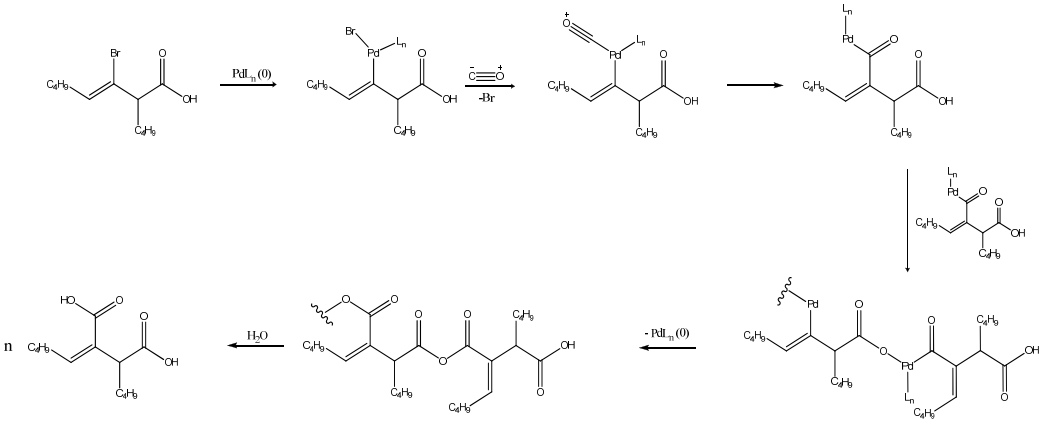
| Reaction | Reagent | Reaction Time | % Yield |
|---|---|---|---|
| 2.1 | $C_4H_9Li/CO_2$ | 1 hr | - |
| 2.2 | pyrrolidine | > 24 hrs | No reaction |
| 2.3 | CO | 23 hrs | - |

A halogen/metal exchange and carbonylation reaction sequence was carried out on the compound believed to be **A**[a] (Reaction 2.1, Table 3). In the halogen/metal exchange, Li replaces Br as the vinyl substituent. The exchange occurs with retention of stereochemistry at the double bond. In the carbonylation step, the *in situ* generated vinyllithium reacts with solid carbon dioxide to produce the dicarboxylic acid. The exchange was carried out at -78 °C to minimize the occurrence of competing reactions such as addition of nucleophilic butyllithium to the carbonyl. The NMR spectrum of the crude product obtained from the reaction indicated that the starting material had decomposed under the reaction conditions.

[a] Reactions were performed on product of Reaction 2.0 which was later shown to be B, not A as expected.

The failure of the halogen-metal exchange and carbonylation sequence led us to investigate a direct approach to carbonylation using palladium-catalyzed coupling of carbon monoxide to **A**[a] (Reaction 2.3, Table 3). The reaction is initiated by the oxidative addition of palladium(0) via insertion into the vinyl - bromide bond. Carbon monoxide then adds to palladium and subsequently rearranges to form an acylpalladium complex. The carboxylate oxygen from another molecule of **A** replaces the palladium ligand. Reductive elimination regenerates palladium (0) and an anhydride is formed. Hydrolysis should generate the desired dicarboxylic acid (Scheme 12).

*Scheme 12. Palladium-catalyzed carbonylation of* ***A***



The reaction with carbon monoxide was allowed to proceed for 23 hours. A crude NMR of the filtered, concentrated reaction mixture indicated the presence of a mixture of compounds, however only unreacted starting material was recovered after purification on silica gel.

An amidation reaction was also carried out on the compound believed to be **A**. The compound was treated with pyrrolidine in the presence of DCC/DMAP to form the pyrrolidine amide of A (*Reaction 2.2,* Table 3). Again, the unconverted starting material was recovered after purification of the crude product on silica gel.

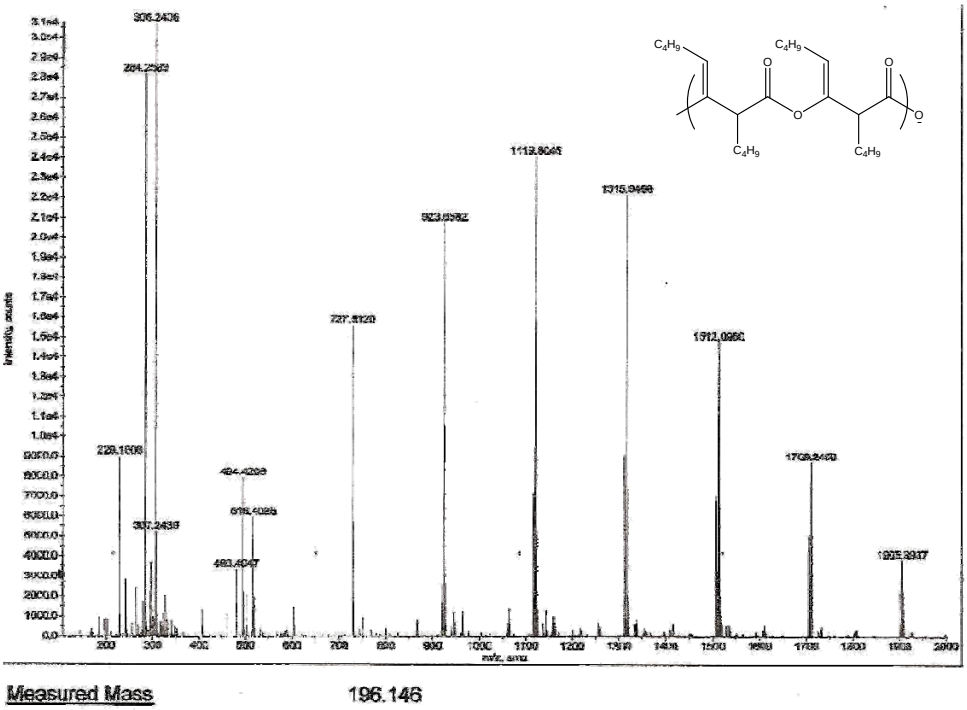
The failure of the reactions shown in Table 3 to yield the desired products led us to consider that the compound isolated from Reaction 2.0 may not have been **A** as expected. A Beilstein test (in which the color of the flame produced upon combustion of the compound is observed) indicated the compound did not contain a halogen. The IR spectrum of the product noticeably lacked the characteristic OH stretch at 3000 $cm^{-1}$.

Our first hypothesis as to the identity of the uknown product was that a stable palladalactone complex had formed. Yammamoto *et al*. previously reported that diketene reacted with a palladium-phosphine complex to form an isolable bis(trimethylphoshino)-palladalactone (Scheme 7). The absence of aromatic peaks in the product spectrum indicated that the palladalactone, if present, contained no phosphine ligands. To test this hypothesis, an NMR experiment was conducted on a sample of the compound (Reaction 3.0). A proton spectrum of the product was obtained, after which 2 equivalents of triphenylphosphine were added to the sample and the spectrum re-run. A change in the chemical shift of the methine or vinyl proton

would suggest that phosphine had complexed to any palladium present. The chemical shifts of the methine (3.17 ppm) and vinyl proton (5.26) did not shift, leading us to employ other spectroscopic techniques to determine the structure of the unknown compound.

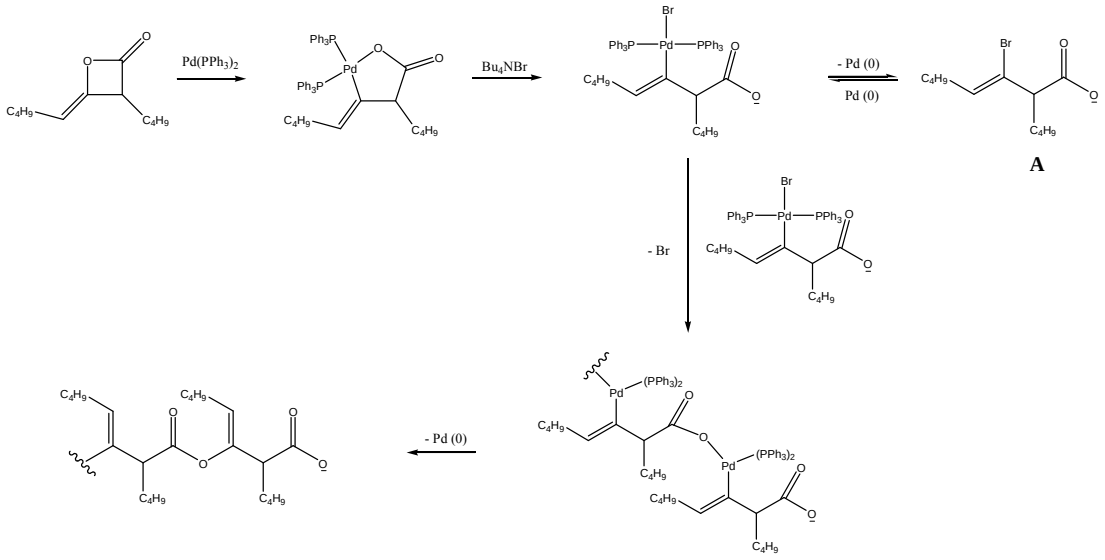
The mass spectrum of the compound was obtained (Figure 4). The mass spectrum revealed that no bromide-containing compound was present: the bromide had not coupled with the dimer. Instead, a mixture of products including polymerized dimer (**B**, Table 2) had been produced. The polymers were of varying chain lengths and differed by a molecular weight of 196, the molecular weight of n-butylketene dimer.

*Figure 4. Mass spectrum of the product of Reaction 2.0*



Scheme 13 shows a probable mechanism of the palladium-catalyzed polymerization of n-butylketene dimer. It is possible that the bromide may facilitate polymerization by displacing the carboxylate oxygen of the palladalactone intermediate, thus making the carboxylate available to bond to the palladium of another identical complex. The formation of a vinyl ester bond between the monomeric units forms the polymer and regenerates the catalyst. Alkenyl halides are typically used as reagents in metal-catalyzed cross-coupling reactions because of the facile addition of metal catalysts across the vinyl halide bond and the fact that halide ions are good leaving groups. It is therefore possible that even if the bromine-substituted product (**A**) formed transiently during the reaction, it reacted rapidly with palladium to reform the R-Pd-Br complex.

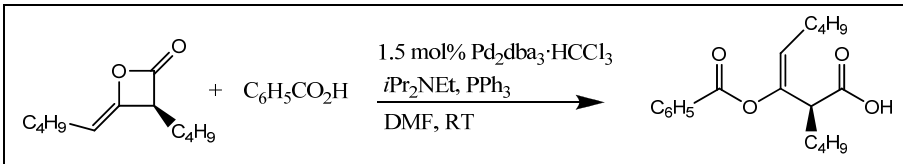
*Scheme 13. Polymerization of n-butylketene dimer*



**Palladium-catalyzed Coupling of n-Butylketene Dimer and Benzoic Acid**

We then investigated the reaction of n-butylketene dimer with benzoic acid in the presence of $Pd(PPh_3)_4$ (Reaction 4.0, Table 4). The reaction yielded the expected 3-benzoyl substituted acid in addition to polymers of the expected product with n-butylketene dimer. Evidently the homocoupling of n-butylketene dimer and cross-coupling of n-butylketene dimer with the benzoyl group were competing processes and this resulted in the formation of heteropolymeric products. The $^1H$ NMR and mass spectrum of the product with peak assignments are shown in Figures 5 and 6 respectively.

*Table 4. Reaction of n-butylketene dimer with benzoic acid*




| Reaction | Catalyst | Reaction Time | % Yield[b] |
|---|---|---|---|
| 4.0 | $Pd(PPh_3)_4$ | 18 hrs | 21 |

[b] Obtained as a mixture of polymers.

*Figure 5. 1H NMR spectrum of the product of Reaction 4.0*

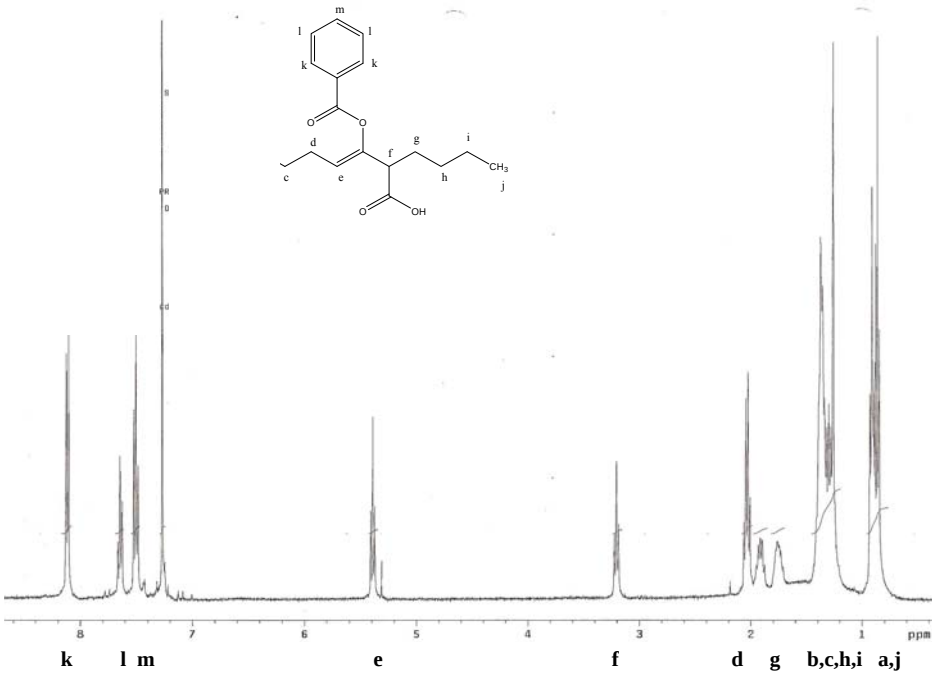
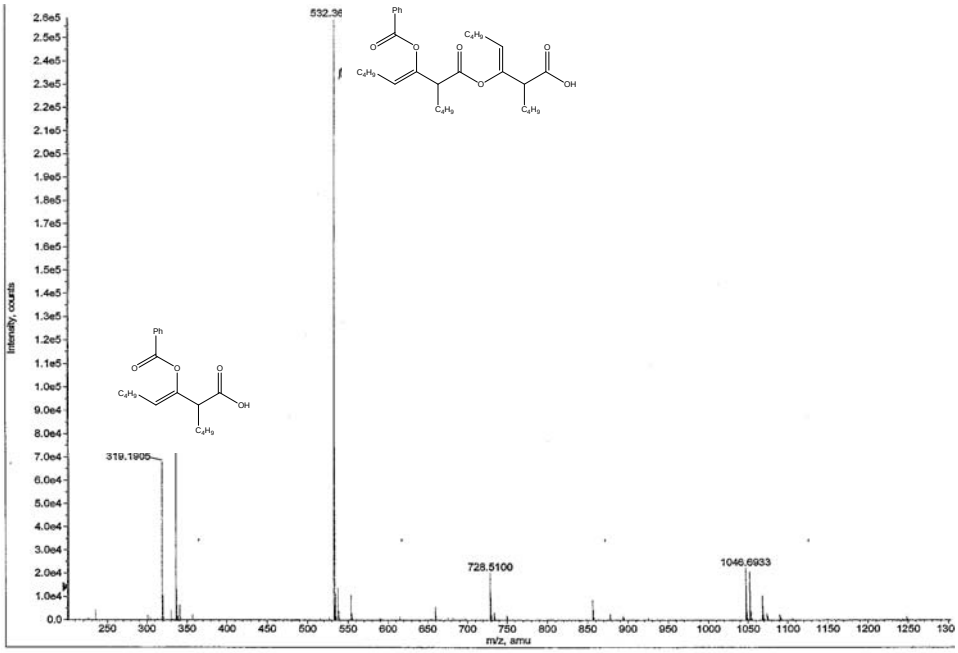



*Figure 6. Mass spectrum of the product of Reaction 4.0*




Measured Mass 319.1905

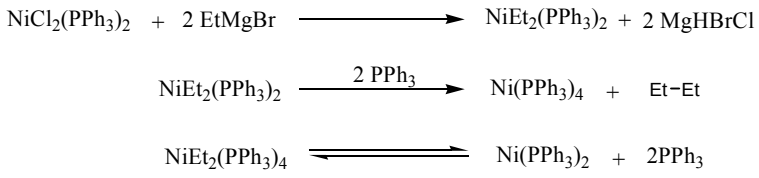
## Reactions with Organozinc Compounds

### Nickel- and Palladium-catalyzed Reactions of n-Butylketene Dimer with Organozincs

Given the tendency of n-butylketene dimer to form polymeric products when reacted with the non-organometallic nucleophiles investigated in the previous reactions, we then decided to investigate organometallic-mediated reactions in the hope of obtaining the desired heterocoupling product. Organometallic nucleophiles such as organozincs are known to react quickly with transition metals in cross-coupling reactions. It was therefore anticipated that heterocoupling between n-butylketene dimer and the organic fragment of the chosen organometallic compound would occur faster than the homocoupling of dimer molecules.

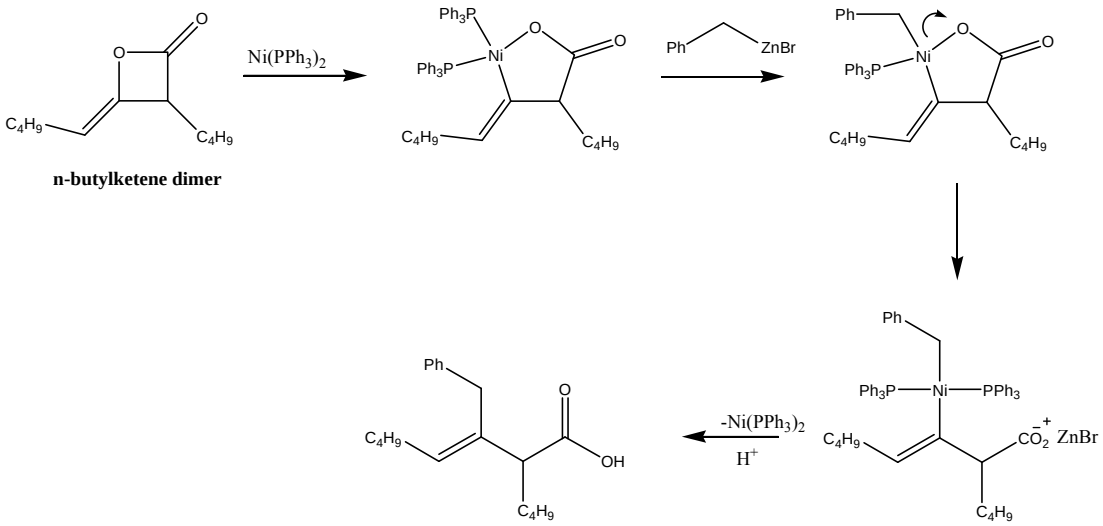
The metal-catalyzed reaction of n-butylketene dimer with benzylzinc bromide was investigated. For the nickel-catalyzed reactions, $Ni(PPh_3)_4$ was generated *in situ* from the reduction of $NiCl_2(PPh_3)_2$ with 2 equivalents of ethylmagnesium bromide at 0°C. To generate zero-valent nickel, the chlorine atoms are substituted by ethyl groups which are transmetallated from magnesium to nickel. Reductive elimination then occurs, forming butane and nickel(0). As with the palladium-catalyzed reactions described earlier, the active form of the nickel catalyst is believed to be the bisphosphino-nickel $Ni(PPh_3)_2$.

*Scheme 14. In-situ formation of Nickel(0) catalyst*



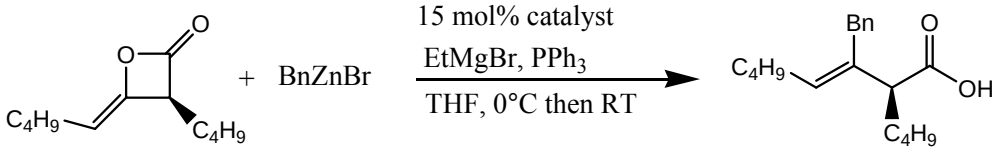

The reaction of n-butylketene dimer and benzylzinc bromide is then expected to occur via the oxidative addition – transmetallation – reductive elimination mechanism shown in Scheme 15.

*Scheme 15. Reaction of n-butylketene with benzylzinc bromide*



As shown in Scheme 15, nickel is added across the vinyl C – O bond of the dimer and is oxidized to the +2 state. The nickel-lactone complex undergoes transmetallation with zinc; the benzyl group is transferred to nickel and the carboxylate of the dimer is displaced. This may or may not occur as a concerted step. The benzyl group is then coupled to the opened dimer, yielding the cross-coupling product and the regenerated catalyst. The reactions of n-butylketene dimer with benzylzinc bromide are shown in Table 5.

*Table 5. Reactions of n-butylketene dimer with benzylzinc bromide*




| Reaction | Catalyst | Reaction Time |
|---|---|---|
| 5.0 | $Ni(PPh_3)_4$ | 4 hrs |
| 5.1[c] | $Ni(PPh_3)_4$ | 3 hrs |
| 5.2[d] | $Ni(PPh_3)_4$ | 3.5 hrs |
| 5.3 | $Pd(PPh_3)_4$[e] | 5 hrs |

[c] Two molar equivalents of BnZnBr were used.

[d] One molar equivalent of BnZnBr was used.

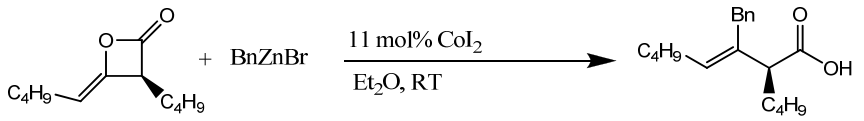
[e] $Pd(PPh_3)_4$ was generated in situ from $Pd_2(dba)_3$ as in Reaction 2.0. No EtMgBr was needed to generate Pd(0).

In the first entry, n-butylketene dimer was added slowly over 4 hours to a mixture of the catalyst and benzylzinc bromide in THF (Reaction 5.0, Table 5). The $^{1}H$ NMR spectrum of the crude product of Reaction 5.0 revealed incomplete conversion of n-butylketene dimer to a mixture of products. A singlet peak characteristic of 1,2-diphenylethane was observed at 2.83 ppm which indicated that homocoupling of the benzylzinc reagent had occurred. The presence of the homocoupling product and unreacted dimer suggested that the nickel catalyst reacted with the benzylzinc reagent more rapidly than with the dimer. In an attempt to limit benzyl homocoupling in favor of the formation of heterocoupled product, the reaction was repeated via slow addition of the both the dimer and benzylzinc bromide to a solution of the catalyst. This was done using 2 equivalents (Reaction 5.1) and 1 equivalent (Reaction 5.2) of benzylzinc bromide. Although each run appeared to produce a similar mixture of products, none of the compounds obtained after purification produced spectra consistent with the formation of the desired product. The use of $Pd(PPh_3)_4$ catalyst (Reaction 5.3) produced similar results to the nickel-catalyzed reactions.

**Cobalt-catalyzed Reactions of n-Butylketene Dimer with Organozincs**

The nickel-catalyzed and palladium-catalyzed reactions of n-butylketene dimer and benzylzinc bromide did not yield the desired β-substituted β,γ-unsaturated carboxylic acid. We then decided to investigate if cobalt-based catalysis would produce better results. n-Butylketene dimer was reacted with 1.5 equivalents of benzylzinc bromide in the presence of a catalytic amount of $CoI_2$ at room temperature (Table 6). This reaction also failed to produce the desired coupling product.

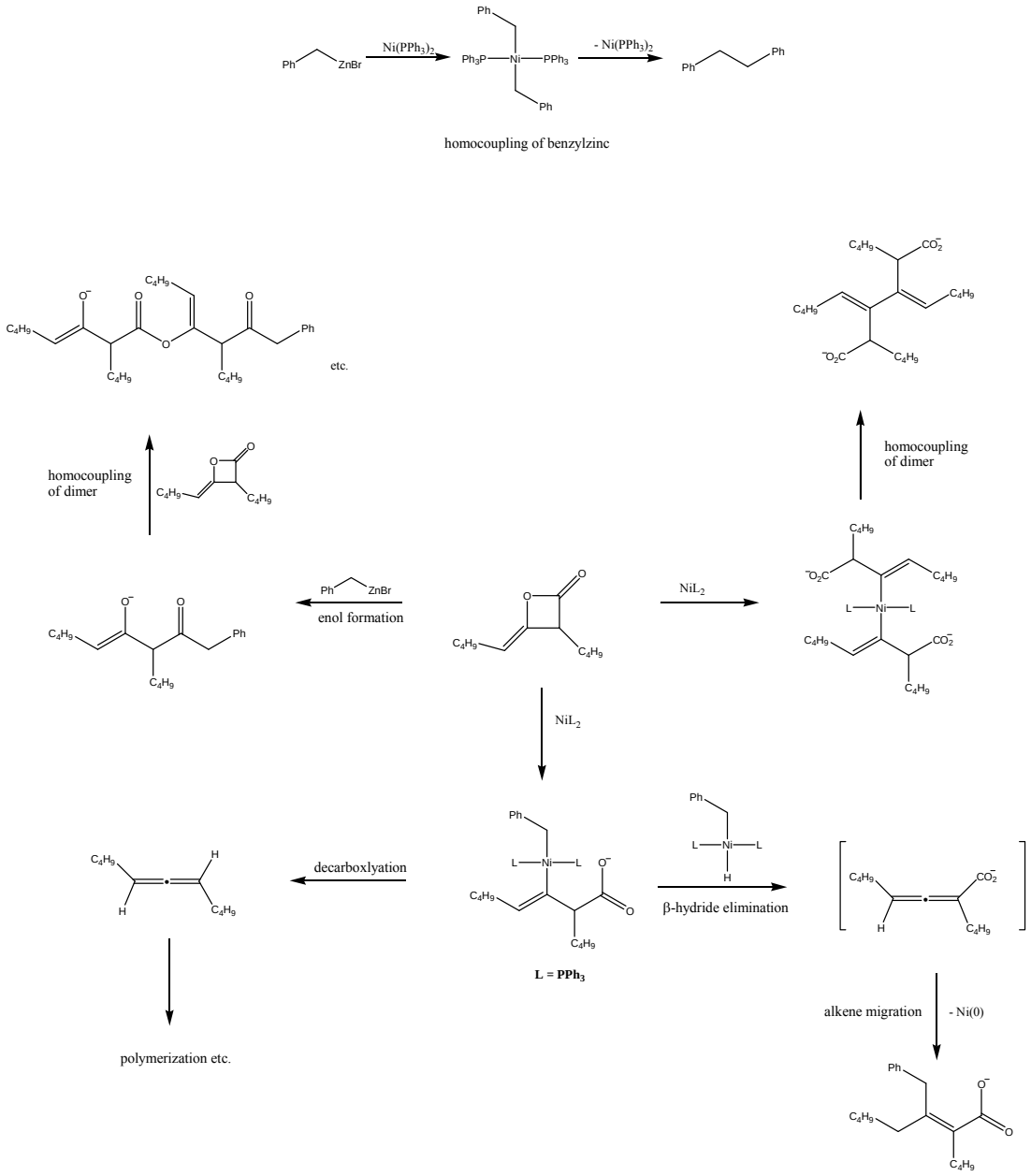
*Table 6. Cobalt-catalyzed reaction of n-butylketene dimer with benzylzinc bromide*




| Reaction | Catalyst | Reaction Time | % Yield |
|---|---|---|---|
| 7.0 | $CoI_2$ | > 24 hrs | 0 |

The results obtained from the reaction of the n-butylketene with benzylzinc bromide under the conditions outlined above suggest that the reactions proceeded via alternative routes than outlined in Scheme 15 to produce side products. Scheme 16 shows a few probable pathways that could have lead to a mixture of products.

*Scheme 16. Alternative pathways for product formation in reaction of dimer with benzylzinc bromide*



The structure of n-butylketene dimer makes it susceptible to several side reactions that may competitively inhibit the desired cross-coupling reaction. Even in the presence of catalyst, the carbonyl carbon – oxygen bond is susceptible to attack by the organozinc nucleophile. Benzyl and allylzincs are known to be especially reactive to carbonyl centers , exhibiting Grignard-like reactivity.[29] The enolate that results from cleavage of the carbonyl carbon – oxygen bond of the ketene dimer can tautomerize to form an asymmetrical ketone or react with other species present, including unreacted dimer. This occurs, for example, in the formation of dehydroacetic acid from diketene.[30] The fact that the organozinc reactions were carried out at room temperature increases the likelihood of nucleophilic attack of the carbonyl C – O bond and the associated enolate formation. As stated earlier, the driving force behind the insertion of the metal catalyst into the dimer is the relief of ring strain that occurs when the 4-membered lactone forms a 5-membered metallolactone. It should be noted, however, that oxidative addition of vinyl esters to transition metals is significantly slower than the addition of other functional groups including organometallic halides. This may also result in significant benzyl-benzyl homocoupling being observed.

Even if the anticipated nickel-lactone intermediate is formed as shown in Scheme 15, a number of decomposition pathways could account for the formation of unintended products. Take, for example, β-hydride elimination. The R-M-R′ complex formed between the benzyl group, metal and ketene dimer possesses two β-hydrogens which

could produce different β-elimination products. Vinyl acetate has been shown to react with $Ni(PPh_3)_4$ to form butadiene from the coupling of vinyl carbons of two vinyl acetate molecules; $Ni(OCOCH_3)_2$ is eliminated. [31] The analogous reaction of n-butylketene dimer would produce an allenyl product. Homocoupling of the ketene dimer (previously encountered with the reaction of n-butylketene dimer with tetrabutylammonium bromide) may also occur.

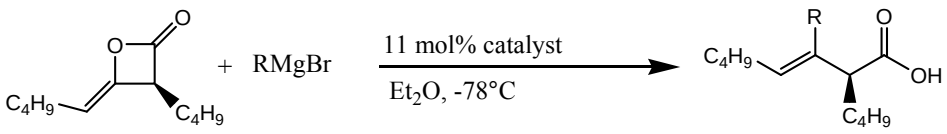
Although cobalt catalysis provides a means of avoiding the some of the problems associated with palladium and nickel catalysts, there are drawbacks to its application. Organometallic reagents have been shown to readily decompose in the presence of cobalt salts to form homocoupling products, even at low temperatures. Cobalt also reacts via SET transfers that produce radicals which may form a variety of radical combination products. The alkyl groups present in n-butylketene dimer can stabilize radical intermediates which can then form undesired by-products.

The compounds obtained in the benzylzinc coupling reactions were not further purified or characterized in order to pursue the main goal of this research: the synthesis of a β,γ-unsaturated compound that can be employed in the synthesis of hexylitaconic acid. However in the future characterization may be useful in determining the mechanism of the metal-catalyzed reaction of benzylzinc with the dimer.

## Reactions with Organomagnesium Compounds

Based on the reports of Fujisawa et al. that diketene reacts with alkyl Grignard reagents in the presence of cobalt catalysts, we decided to apply the metal-catalyzed Grignard reactions to n-butylketene dimer. Fujisawa reported that ethyl- and methyl-magnesium bromides reacted with diketene in the presence of 10 mol% $CoI_2$ to afford the corresponding 3-methylenealkanoic acid in 65 and 84% yields, respectively.[12] We reacted n-butylketene dimer with ethyl and methyl-magnesium bromides in the presence of $CoI_2$, $COCl_2$, and $Co(acac)_3$ catalysts. We also carried out the reaction with ethylmagnesium bromide using a nickel-phosphine catalyst. A summary of the reactions performed is shown in Table 7. The All the reactions were carried out at -78 °C.

*Table 7. Reaction of n-butylketene dimer with Grignard reagents*




| Reaction | R | Catalyst | Reaction | % Yield |
|---|---|---|---|---|
| 6.0 | $C_2H_5$ | $NiCl_2(PPh_3)_2$ | 3 hrs | 0 |
| 8.0 | $C_2H_5$ | $CoI_2$ | 6 hrs | 21 |
| 8.1 | $C_2H_5$ | $CoI_2$ | 12 hrs | 28 |
| 8.2 | $C_2H_5$ | $CoI_2$ | > 24 hrs | nd[f] |

[f] No data. Product decomposed upon addition of pyrrolidine.

| | | | | |
|---|---|---|---|---|
| 8.3 | $CH_3$ | $CoI_2$ | > 24 hrs | < 14 |
| 8.4 | $C_2H_5$ | $CoCl_2$ | > 24 hrs | 0 |
| 8.5 | $C_2H_5$ | $Co(acac)_3$ | 24 hrs | 14 |

The reaction of n-butylketene dimer with ethylmagnesium bromide was first investigated using nickel-phosphine catalyst (Reaction 6.0). The NMR of the crude product indicated that the dimer remained largely unreacted with traces of undetermined products present. The reaction was also performed using cobalt (II) iodide (Reaction 8.0 and Reaction 8.1). The $^1$H NMR spectrum of the major product obtained after flash chromatography on silica gel suggested that the desired β-ethyl-β,γ-unsaturated carboxylic acid was formed (Figure 7 below). Another product was also obtained which, based on the NMR spectrum, was determined to be an isomeric product caused by alkene migration (Figure 8 below). In Reaction 8.2, the reaction mixture was treated with pyrrolidine to form the amide however an NMR taken after the addition of pyrrolidine indicated that the product had decomposed. No reaction occurred when cobalt chloride was used (Reaction 8.4). Cobalt (III) acetoacetonate produced similar results as the iodide (Reaction 8.5). The reaction of n-butylketene dimer with methylmagnesium bromide appeared to have produced the desired β-methyl-β,γ-carboxylic acid (Reaction 8.3 and Figure 9 below).

*Figure 7. HNMR spectrum of β-ethyl-β,γ-unsaturated carboxylic acid*

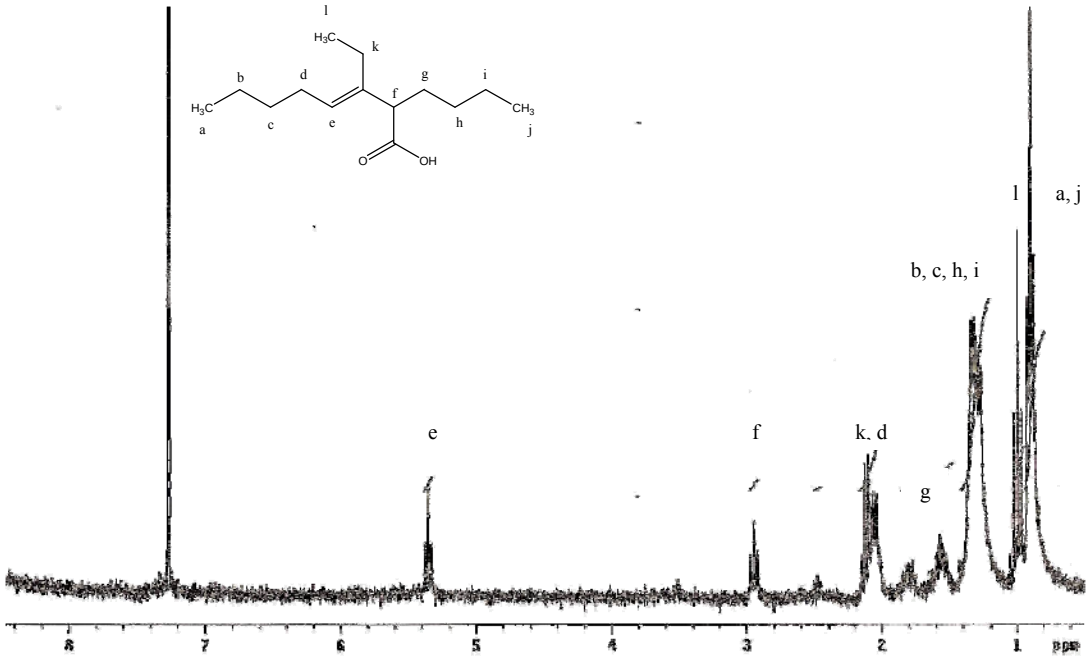


*Figure 8. HNMR product of isomeric product obtained from reaction of dimer with ethylmagnesium bromide*

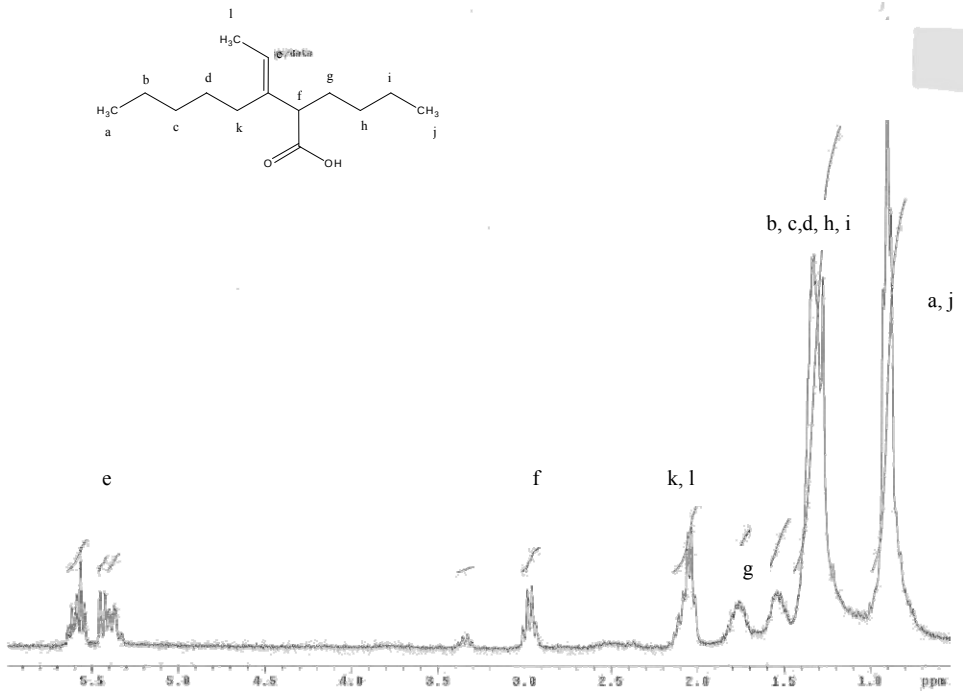
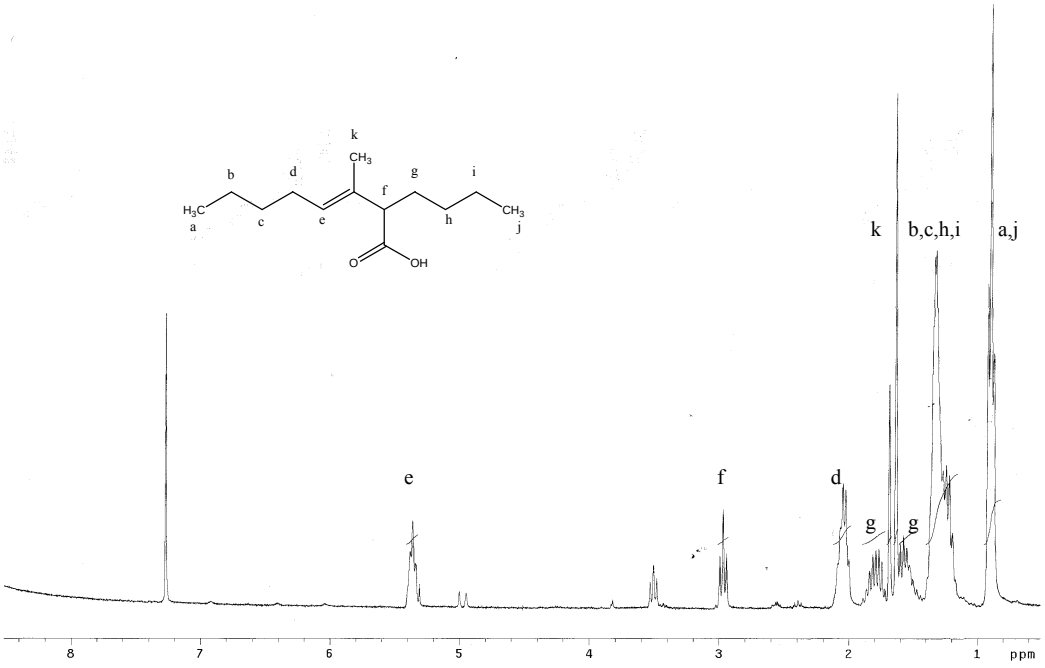


*Figure 9. HNMR spectrum of β-methyl-β,γ-unsaturated carboxylic acid*




As shown in Figure 7, the signals at 5.35 and 2.94 ppm were assigned to the vinyl and methine protons, respectively, of the ethyl-substituted product. The spectra obtained after our first attempts at isolating the product via flash chromatography contained a peak at ~3.5 ppm which was determined to belong to an impurity. We attempted to improve the purification protocol thereafter and found that starting with a 3:97 mixture of ethyl acetate and hexanes and increasing the concentration of ethyl acetate via 2% increments to 9% allowed the desired compound to be isolated in greater purity. The proton NMR spectrum of the methyl-substituted product contained a similar peak at ~3.5 ppm which is visible in Figure 9. COSY experiments were performed on both the methyl- and ethyl- substituted compounds to provide supporting evidence for the identity of the product.

The COSY spectrum of the ethyl-substituted product is shown in Figure 10. As expected, the signal at 5.35 ppm produces a cross-peak with the signal at 2.13 ppm which was assigned to the methylene allylic protons (d). signal at 2.94 exhibits coupling to the β-methylene protons (g) which are inequivalent and are seen as multiplets centered at 1.79 and 1.51 ppm. These protons were further coupled to methylene protons further along the alkyl chain (not visible in Figure 10). The impurity at 3.5 ppm is visible in the COSY spectrum as the experiment was performed on a sample taken before the optimal purification protocol was determined.

*Figure 10. COSY spectrum of ethyl-substituted product*

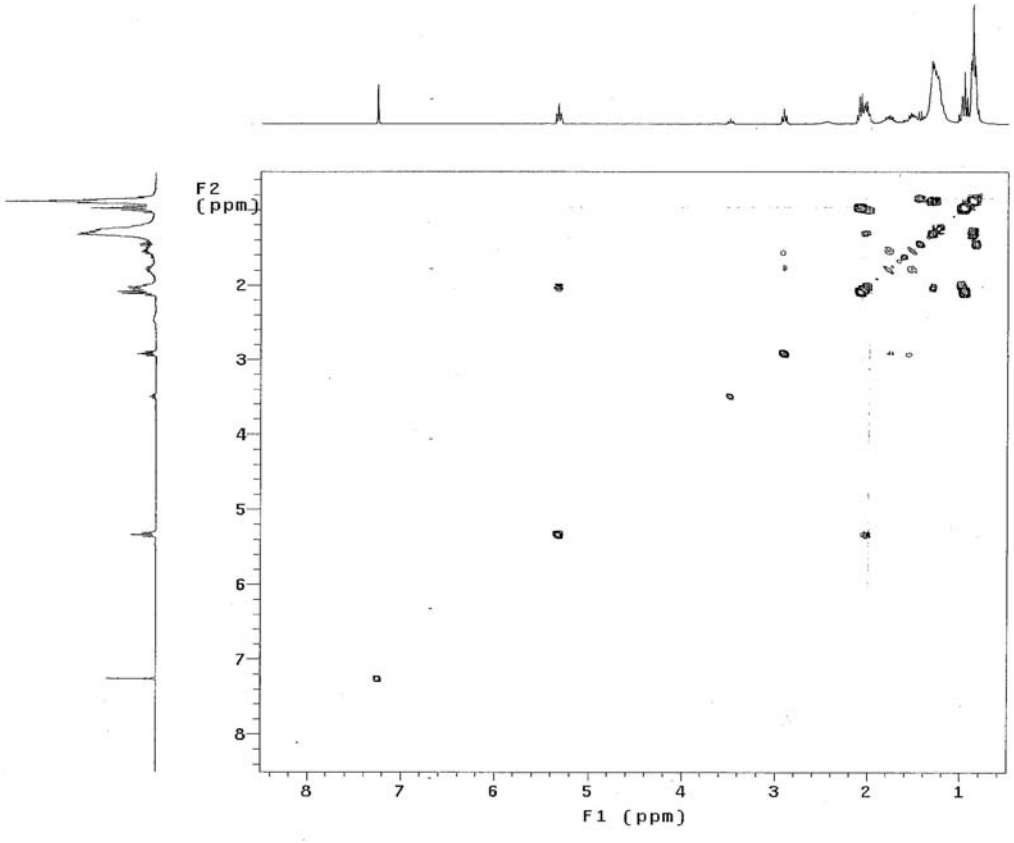
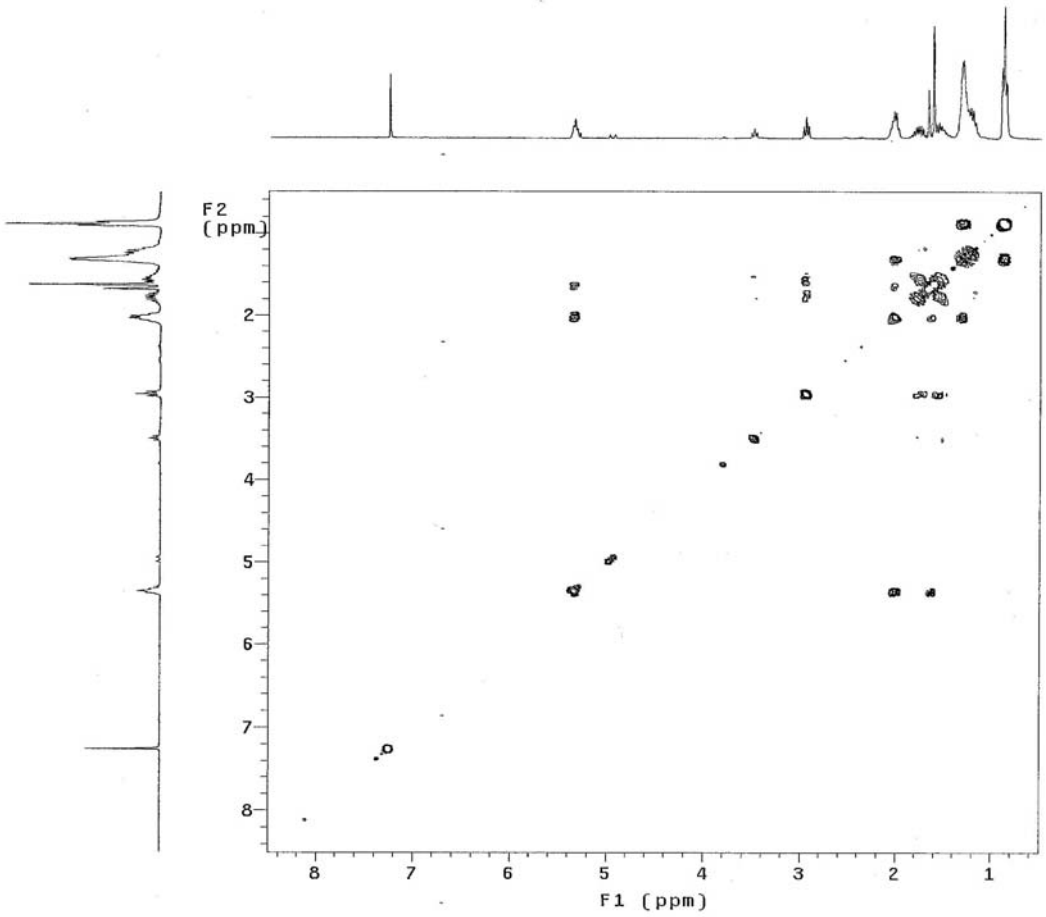


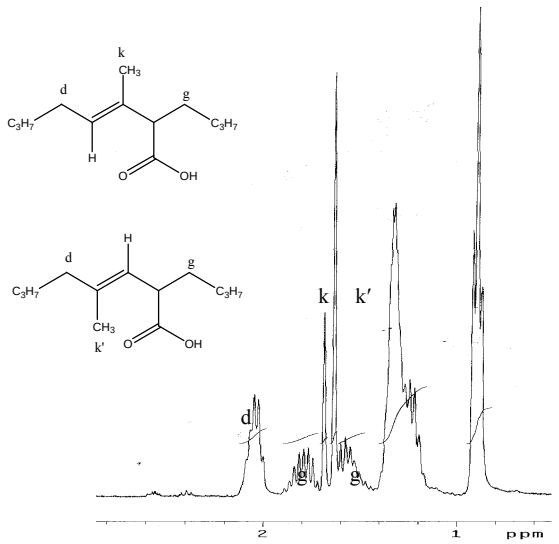
Figure 11 shows the COSY spectrum of the methyl-substituted product. The methine proton (f) at 2.96 is coupled to the β-methylene protons (g) at 1.79 and 1.58 ppm. Coupling between the vinyl proton (e) at 5.36 ppm and the allyl methylene protons (f) at 2.03 ppm protons is also observed as expected. The vinyl proton also appears to be coupled to the peaks at 1.69 and 1.64 ppm. The peaks at 1.69 and 1.64 also appear to be weakly coupled to the allyl methylene protons (d) located at 2.03 ppm.

*Figure 11. COSY spectrum of methyl-substituted product*



The assignment of these peaks at 1.69 and 1.64 ppm was somewhat difficult since it was predicted that the methyl protons bonded to the double bond would produce a singlet peak in this region. A possible explanation is that a product in which the methyl group is bonded to the γ-vinyl carbon was formed. This would possibly account for the slight coupling of the allylic methylene protons observed. This product and its assignment on the NMR spectrum are shown in Figure 11 below. However the fact that only one peak is observed in the alkene region of the spectrum (Figure 9) casts some doubt on the validity of this hypothesis. The vinyl protons of the two products have different chemical environments and would thus be expected to appear at slightly different chemical shifts. Further purification and additional NMR experiments would be needed to unequivocally assign the peaks.

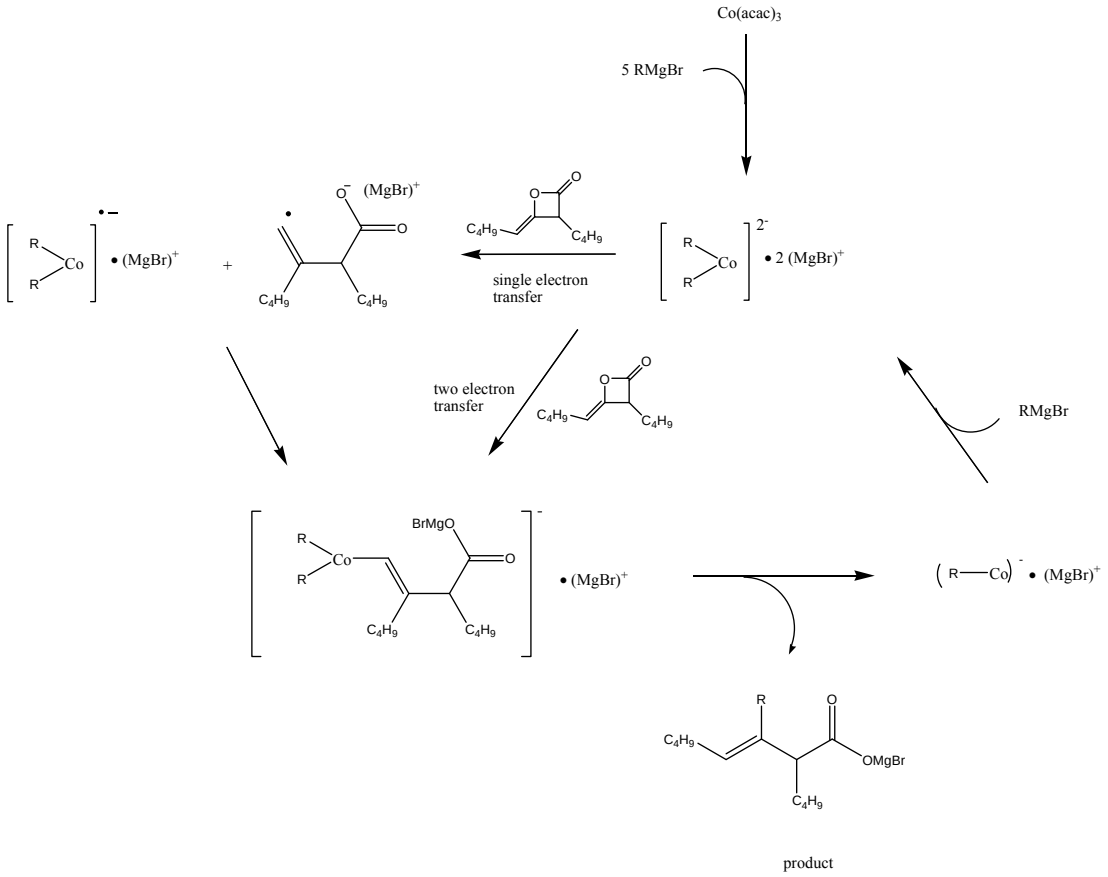
*Figure 8. Possible by-products of the reaction of n-butylketene dimer with methylmagnesium bromide*



**Reaction Mechanism**

A possible mechanistic scheme for the formation of product in the cobalt-catalyzed reaction is shown in Scheme 17 below. The cobalt complex that interacts with n-butylketene dimer is the zero-valent diorganocobalt (0) complex formed from the reduction of the cobalt salt by the Grignard reagent. Scheme 17 shows the generation of the catalyst from cobalt (III) acetylacetonate, however catalyst-formation from cobalt (II) chloride is expected to proceed similarly. The cobalt-catalyzed reaction of nucleophiles with n-butylketene dimer differs from the palladium and nickel-catalyzed reactions as it does not necessarily involve a cobalt-lactone intermediate. Oxidative addition of the dimer to cobalt can occur via a single electron process in which an electron is transferred to the dimer from cobalt. The resulting radical anion formed from the dimer can then combine with the cobalt-centered radical cation. Reductive elimination of this complex forms the cross-coupled product. Alternatively, addition of the dimer to cobalt could occur via a concerted mechanism wherein cobalt adds to the β-vinyl carbon and the carboxylate is displaced. The mono-substituted cobalt (0) complex formed after formation of the product is converted back to the diorganocobalt complex by addition of another equivalent of Grignard reagent.

*Scheme 17. Possible mechanism for cobalt-catalyzed reactions*



# CONCLUSIONS

Of the cross-coupling reactions investigated here, the cobalt-catalyzed reaction with organomagnesiums is the most promising method for executing the selective cross-coupling of n-butylketene dimer which we set out to achieve. Cobalt selectively catalyzed the cleavage of the vinyl carbon –oxygen bond of the dimer. The cobalt-catalyzed reactions proceeded relatively cleanly and resulted in the addition of the organic nucleophile at the β-alkenyl carbon of the dimer.

The reactions of n-butylketene catalyzed by traditional palladium and nickel complexes were less successful in forming the desired products. Although palladium catalyzed the cleavage of the vinyl carbon –oxygen bond, significant homocoupling and polymerization were observed. In the presence of bis(triphenylphosphino)-palladium, the ketene dimer was coupled to carboxylate nucleophiles via the formation of a vinyl ester bond. The formation of vinyl ester bonds between dimer molecules resulted in the polymerization of the ketene dimer. In the presence of carboxylate nucleophiles derived from other reagents, cross-coupling between the reagent and the dimer was observed in addition to homocoupling of the dimer. In future research, the reactions of ketene dimers with carboxylate nucleophiles may be optimized to favor cross-coupling rather than homocoupling by utilizing more electron-rich nucleophiles which can react with the oxidized palladium (II) intermediate more rapidly than the carboxylate of the dimer.

The reactions of n-butylketene dimer with organozinc compounds were unsuccessful in producing the desired cross-coupling product regardless of the metal catalyst used. A mixture of products was obtained, suggesting that several decomposition pathways had occurred. These results may be explained by the fact that oxidative addition of the dimer is a relatively slow process when compared to the reactivity of benzylzincs with metals and carbonyls. The fact that the organozinc-mediated catalyzed reactions need to occur at relatively high temperatures makes control of side reactions difficult and limits the utility of this method of cross-coupling for our purposes. Although organomagnesiums are more reactive towards carbonyls than organozincs, the cobalt-catalyzed reaction of organomagnesiums with the dimer benefits from the fact that the reaction can be carried out at lower temperatures where reactivity is more controlled.

The future application of the cobalt-catalyzed reaction to our proposed synthesis of (-)-hexylitaconic acid will depend on our ability to synthesize an appropriate β-oxygen-containing Grignard reagent and also on the reactivity of such a compound under the conditions of cobalt catalysis. A likely organomagnsium target would be a benzyloxymethylmagnesium halide. If successfully coupled to the dimer, the oxygen can be deprotected using DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) and oxidized to form the dicarboxylic acid which can then be transformed to hexylitaconic acid.

# EXPERIMENTAL METHODS

## General Methods

The following reagents were purchased from Aldrich Chemical Company and were used as received: tetrabutylammonium bromide, ethylmagnesium bromide, methylmagnesium bromide, benzylzinc bromide, benzoic acid, pyrrolidine, and triphenylphosphine. $Ni(PPh_3)_2Cl_2$ was obtained from Strem Chemicals Inc. $Pd_2(dba)_3$, $CoI_2$ and $Co(acac)_3$ were purchased from Alfa Aesar. Hexanoyl chloride and Hunig's base were obtained commercially and distilled before use. TMSQN was prepared from TMSCl and quinine. All reactions were carried out under nitrogen. NMR experiments were performed on a Varian 300MHz spectrometer.

## 1.0 Asymmetric synthesis of n-butylketene dimer

To trimethylsilylquinine (1.255 g, 3.2 mmol) in anhydrous $CH_2Cl_2$ (640 mL) under argon was added Hünig's Base (12.26 mL, 70.4 mmol), followed by hexanoyl chloride (8.615 g, 64 mmol). The reaction mixture was stirred overnight at room temperature, after which pentanes (640 mL) was added. The reaction mixture was then filtered on silica gel using 1:1 $CH_2Cl_2$: pentanes as the eluant until the yellow band reached the bottom of the column. The fractions were collected, dried over sodium sulfate and concentrated under vacuum to yield 5.101 g of product (81% yield). *N-butylketene dimer*: $^1$H NMR ($CDCl_3$, 300MHz) δ 4.69 (t, 1H), 3.93 (t, 1H), 2.13 (q, 2H), 1.77 (q, 2H), 1.42 – 1.31 (m, 8H), 0.95 – 0.88 (m, 6H)

**1.1 Racemic synthesis of n-butylketene dimer**

To 4-diazabicyclo[2.2.2]octane [DABCO] (0.14 g, 1.25 mmol) in anhydrous $CH_2Cl_2$ (250 mL) under nitrogen was added Hünig's Base (4.79 mL, 27.5 mmol), followed by hexanoyl chloride (3.49 mL, 25 mmol). The reaction mixture was stirred overnight at room temperature, after which pentanes (100 mL) was added. The reaction mixture was then filtered on silica gel using 1:1 $CH_2Cl_2$: pentanes as the eluant. The fractions were collected, dried over sodium sulfate and concentrated under vacuum to yield 1.35 g of product (28% yield).

**2.0 Reaction of n-butylketene dimer with bromide**

Tetrabutylammonium bromide (2.525 g, 7.6 mmol), $Pd_2dba_3.HCCl_3$ (0.060 g, 0.058 mmol), triphenylphosphine (0.099 g, 0.38 mmol) were added to a flask under nitrogen. To this was added anhydrous DMF (30 mL) followed by Hünig's Base (0.66 mL, 3.8 mmol) and (1) (0.760 g, 3.8 mmol) in that order. The reaction mixture was stirred overnight, after which it was diluted with 150 mL ether and extracted with 1M sodium bisulfate. The organic layer was dried over sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel (1:99 MeOH:$CH_2Cl_2$) to yield 0.28 g (56 %) of product **A**. $^1$H NMR ($CDCl_3$, 300MHz) δ= 5.26 (t, 1H), 3.17 (t, 1H), 1.94 (app d, 2H), 1.79 (m, 1H), 1.67 (m, 1H), 1.29 (m, 8H), 0.87 (app d, 6H); $^{13}$C NMR ($CDCl_3$, 300MHz) δ= 169.7, 144.6, 120.1, 50.1, 31.2, 29.8, 29.6, 25.5, 22.6, 22.5, 13.98, 13.96; IR ( KBr) $cm^{-1}$: 2959, 2861, 1751, 1103, 909, 732.

### 2.1 Halogen/metal exchange reaction of A

To **A** (0.14 g, 0.5 mmol) in anhydrous THF (10 mL) under nitrogen at -78°C was added butyllithium (0.59 mL, 1.0 mmol) dropwise over 5 minutes . The mixture was stirred for 1 hour and transferred via cannula to dry ice. The reaction mixture was allowed to warm to room temperature and quenched with 5 mL 1M HCl (aq.). The organic phase was dried over magnesium sulfate and concentrated *in vacuo* to yield 0.13 g of solid. The solid was treated with dilute aq. $NaHCO_3$ and extracted with diethyl ether. The aqueous layer was acidified to pH 2 using 1M HCl (aq.) and washed with ether. The organic layer was collected and concentrated *in vacuo* to yield < 0.01 g of untraceable product.

### 2.2 Amidation of A

To a solution of pyrrolidine (0.040 mL, 0.432 mmol), triethylamine (0.05 mL, 0.36 mmol), N,N'-dicyclohexylcarbodiimide [DCC] (0.089 mL, 0.432 mmol), and HOBt (0.058 mL, 0.432 mmol) in $CH_2Cl_2$ at 0°C was added **A** (0.100 g, 0.36 mmol). The mixture was stirred at 0°C for 2 hours and then at RT overnight, after which it was diluted with 20 mL ethyl acetate and filtered through glass wool to remove precipitate. The filtrate was washed with water, 1M HCl, sat. $NaHCO_3$ and brine in that order. The organic layer was treated with $CH_2Cl_2$ and subsequently dried over sodium sulfate and concentrated. The starting material was recovered after purification on silica gel (0.5% MeOH in $CH_2Cl_2$).

### 2.3 Carbon monoxide carbonylation of A

$Pd_2dba_3.HCCl_3$ (0.062 g, 0.06 mmol), triphenylphosphine (0.106 g, 0.4 mmol) and Hünig's Base (0.70 mL, 4 mmol) were added to a flask under nitrogen. To this was added a solution of **A** (1.17 g, 4 mmol) in anhydrous THF. Carbon monoxide was first bubbled through the reaction mixture and then placed above the reaction mixture. The reaction allowed to proceed for 24 hours, after which it was filtered to remove solid palladium. The filtrate was collected and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (1:9 EtOAc:Hexanes). 0.1808 g of an untraceable product was recovered along with starting material.

### 3.0 Test for palladalactone complex

**A** (0.0329 g) was dissolved in $CDCl_3$ and a $^1H$ NMR spectrum was obtained. Two equivalents of tri-tert-butylphosphine were added to the $CDCl_3$ solution and another $^1H$ NMR spectrum was obtained.

### 4.0 Reaction of n-butylketene dimer with benzoic acid

$Pd_2dba_3.HCCl_3$ (0.016 g, 0.015 mmol), triphenylphosphine (0.026 g, 0.099 mmol) and benzoic acid (0.181 g, 1.49 mmol) were added to a flask under nitrogen. To this Hünig's Base (0.17 mL, 0.99 mmol) and n-butylketene dimer (0.195 g, 0.99 mmol) in 10 mL anhydrous DMF were added. The reaction was allowed to proceed for 18 hours after which the mixture was separated in ether and pH 7 buffer. The organic layer was dried over sodium sulfate, concentrated and purified by flash

chromatography on silica gel (2:8 EtOAc:Hexanes). The reaction yielded 0.067g (21% yield) of product. $^{1}$H NMR ($CDCl_3$, 300MHz) δ= 8.12 (d, 2H), 7.64 (t, 1H), 7.50 (t, 2H), 5.38 (t, 1H), 3.20 (t, 1H), 2.04 (q, 2H), 1.91 (p, 1H), 1.80-1.70 (m, 1H), 1.44-1.18 (m, 10H), 0.96-0.80 (m, 6H); $^{13}$C NMR ($CDCl_3$, 300MHz) δ= 165.4, 145.1, 133.8, 130.3, 129.3, 128.7, 120.9, 50.3, 30.9, 30.3, 29.8, 29.5, 25.5, 22.5, 22.3, 14.0, 13.9; IR ( KBr) $cm^{-1}$: 2917, 1734, 1710, 1450.

**5.0 Nickel-catalyzed reaction of n-butylketene dimer with benzylzinc bromide via slow addition of dimer**

To a solution of $(PPh_3)_2NiCl_2$ (0.098 g, 0.15 mmol) and triphenylphosphine (0.079 g, 0.30 mmol) in THF at 0°C was added ethylmagnesium bromide[g] (0.1 mL, 0.30 mmol). The reaction was stirred at 0°C for 2 minutes after which it was warmed to RT and benzylzinc bromide[h] (4 mL, 2.0 mmol) added. To this was added n-butylketene dimer (0.196 g, 1.0 mmol) by slow addition over 4 hours. The reaction mixture was then taken up in 30 mL $CH_2Cl_2$ and extracted with 1M HCl. The aqueous layers were extracted with $CH_2Cl_2$. The organic layers were combined, dried, concentrated *in vacuo* and a crude NMR was taken. No purification of crude material was performed.

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[g] 3.0 M solution in diethyl ether

[h] 0.5 M solution in tetrahydrofuran

**5.1 Nickel-catalyzed reaction of n-butylketene dimer with benzylzinc bromide via slow addition of dimer and benzylzinc bromide**

To a solution of $(PPh_3)_2NiCl_2$ (0.098 g, 0.15 mmol) and triphenylphosphine (0.079 g, 0.30 mmol) in THF at 0°C was added ethylmagnesium bromide[g] (0.1 mL, 0.30 mmol). The mixture was stirred at 0°C for 2 minutes after which it was warmed to RT and benzylzinc bromide[h] (4 mL, 2.0 mmol) and n-butylketene dimer (0.196 g, 1.0 mmol) added by slow addition over 3 hours. The reaction mixture was then taken up in $CH_2Cl_2$ and extracted with 1M HCl. The aqueous layers were extracted with $CH_2Cl_2$. The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (5:95 EtOAc: Hexanes).

**5.2 Nickel-catalyzed reaction of n-butylketene dimer with benzylzinc bromide via slow addition of dimer and benzylzinc bromide[i]**

To a solution of $(PPh_3)_2NiCl_2$ (0.049 g, 0.075 mmol) and triphenylphosphine (0.039 g, 0.15 mmol) in THF at 0°C was added ethylmagnesium bromide[g] (0.05 mL, 0.15 mmol). The reaction was stirred at 0°C for 2 minutes after which it was warmed to RT and benzylzinc bromide[h] (1 mL, 0.5 mmol) and n-butylketene dimer (0.098 g, 0.5 mmol) added by slow addition over 3 hours. The reaction mixture was then taken up in $CH_2Cl_2$ and extracted with 1M HCl. The aqueous layers were extracted with

[i] One molar equivalent of benzylzinc bromide was used.

$CH_2Cl_2$. The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (1% EtOAc in hexanes).

### 5.3 Palladium-catalyzed reaction of n-butylketene dimer with benzylzinc bromide via slow addition of dimer and benzylzinc bromide

To a solution of $Pd_2dba_3.HCCl_3$ (0.126g, 0.122 mmol) and triphenylphosphine (0.871 g, 0.229 mmol) in THF was added benzylzinc bromide (2.4 mL, 1.22 mmol) and (1) (0.119 g, 0.61 mmol) slowly over 5 hours. The reaction mixture was then taken up in $CH_2Cl_2$ and extracted with 1M HCl. The aqueous layers were extracted with $CH_2Cl_2$. The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo*. No purification of crude material was performed

### 6.0 Nickel-catalyzed reaction of n-butylketene dimer with ethylmagnesium bromide

To a solution of $NiCl_2(PPh_3)_2$ (0.049 g, 0.075 mmol) in diethyl ether was added ethylmagnesium bromide[g] (0.25 mL, 0.75 mmol) followed by 1. The reaction was stirred at -78°C for 2 hours and then at -44°C for 1 hour after which 2M HCl (aq.) was added and the reaction mixture extracted with ether. The organic phase was extracted with saturated aq. bicarbonate solution. The organic phase was concentrated and analyzed by NMR. The aqueous phase was acidified to pH 1 using 2M HCl (aq.)

and extracted with ether. The second organic phase was concentrated and analyzed by NMR. No purification of crude material was performed

**7.0 Cobalt (II) iodide-catalyzed reaction of n-butylketene dimer with benzylzinc bromide**

To a solution of $CoI_2$ (0.017 g, 0.55 mmol) in diethyl ether was added n-butylketene dimer (0.098 g, 0.5 mmol) followed by benzylzinc bromide (1.7 mL, 0.85 mmol). The reaction was allowed to proceed overnight at RT after which it was diluted with $CH_2Cl_2$ and extracted with HCl. The organic phases were combined and concentrated *in vacuo*. No purification of crude material was performed

**General Procedure for cobalt -catalyzed reactions of n-butylketene dimer with Grignard reagent**

To a solution of cobalt catalyst (0.11 molar equivalents) in diethyl ether was added n-butylketene dimer. The mixture was cooled to -78C and Grignard reagent (1.1 molar equivalents) was added dropwise. The reaction was allowed to proceed at -78C after which it was diluted with organic solvent and extracted with hydrochloric. The organic phases were combined and the product purified by flash chromatography on silica gel.

**8.0 Cobalt (II) iodide- catalyzed reaction with ethylmagnesium bromide**

Reaction time = 6 hrs. The reaction mixture was diluted with ether and extracted with 1M HCl. Crude product was purified in 5:95 EtOAc: hexanes. Reaction yielded 0.024 g of product (21% yield)[j].

**8.1 Cobalt (II) iodide- catalyzed reaction with ethylmagnesium bromide**

Reaction time = 12 hr. The reaction was allowed to sit at RT overnight, after which it was diluted with $CH_2Cl_2$ and extracted with 2M HCl. Purification was started in 3% EtOAc in hexanes and the concentration of EtOAc increased incrementally to 20%, after which collection was stopped. Reaction yielded 0.1607 g of product (28% yield).

**8.2 Cobalt (II) iodide- catalyzed reaction with ethylmagnesium bromide and pyrrolidine**

Reaction time = 24 hr. The reaction was quenched with pyrrolidine (0.042 mL, 0.5 mmol). Product decomposed in the presence of pyrrolidine.

**8.3 Cobalt (II) iodide- catalyzed reaction with methylmagnesium bromide**

Reaction proceeded overnight. Purification was started in 5% $CH_2Cl_2$ in pentanes and gradually increased to 7%, 10% 20%, 50% and 100% $CH_2Cl_2$. Reaction yielded <

[j] Impurities present in product

0.01g of product (< 14% yield). δ = 5.36 (t, 1H), 2.97 (t, 1H), 2.03 (m, 2H), 1.79 (m, 1H), 1.66 (d, 3H), 1.58 (m, 1H), 1.40 – 1.18 (m, 8H), 0.96 – 0.84 (t, 6H).

### 8.4 Cobalt (II) chloride- catalyzed reaction with ethylmagnesium bromide [k]

The reaction was allowed to proceed overnight, after which it was diluted with $CH_2Cl_2$ and extracted with HCl. The organic phases were combined and concentrated *in vacuo*. No conversion of starting material was observed.

### 8.5 Cobalt (III) acetoacetonate- catalyzed reaction with ethylmagnesium bromide [l]

Reaction time = 24 hr. Reaction mixture was diluted with $CH_2Cl_2$ and extracted with 2M HCl. The product was purified by flash chromatography on silica gel starting with 3% EtOAc in hexanes as the eluant and increasing the EtOAc concentration to 5%, 7% and 9%. Reaction yielded 0.016 g product (14% yield). $^1$H NMR ($CDCl_3$, 300MHz) δ = 5.35 (t, 1H), 2.94 (t, 1H), 2.16 (q, 2H), 2.13 (q, 2H), 1.79 (m, 1H), 1.51 (m, 1H), 1.40 – 1.18 (m, 8H), 0.98 (t, 3H), 0.95 – 0.90 (t, 6H).

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[k] THF used as the solvent instead of diethyl ether

[l] 0.15 molar equivalents of $Co(acac)_3$ catalyst used

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