A CATALYTIC APPROACH TO CYCLOPENTENONES: UNEXPECTED CHALLENGES IN SYNTHESIZING PENT-2,4-DIENALS

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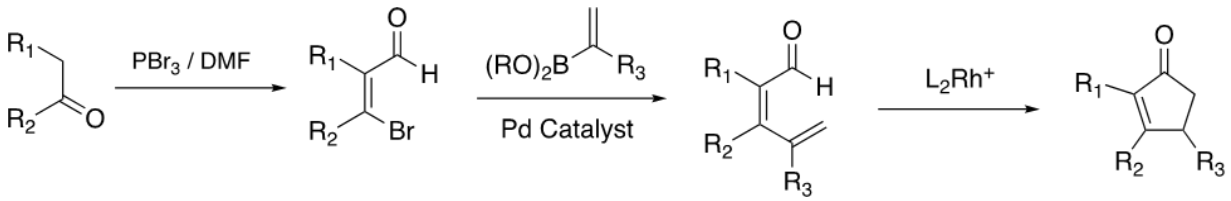
ABSTRACT

Transition metal catalysis has long been utilized to facilitate a number of chemical reactions outside the scope of traditional organic chemistry. Because of this, there has been a growing interest in the community in utilizing C-H bonds over C-X bonds as synthetic alternatives with better thermodynamic conditions (lower temperatures, pressures, energies, etc.) and forming C-C bonds. For example, rhodium-catalyzed hydroacylation can be used in the conversion of 4-pentenals to cyclopentanones. The mechanistic foundation of this reaction was applied to the synthesis of chiral 3-substituted indanones, unlocking a whole series of transformations towards the construction of biologically active molecules.

The Morehead group recently proposed an alternate synthesis of cyclopentenones via a rhodium-catalyzed intramolecular hydroacylation reaction of penta-2,4-dienals by the following reaction sequence: 1. Vilsmeier-Haack Formylation to form 3-bromo-2-enals, 2. Suzuki Cross-Coupling with vinylboronates, and 3. Hydroacylation. Indeed, all reaction steps were performed successfully starting from acetophenone and allylboronic acid pinacol ester, resulting in 4-methyl-3-phenyl-2-cyclopenten-1-one. However, some surprising results were obtained along the way. It was found that when 3-bromo-3-phenyl-2-propenal underwent Suzuki Cross-Coupling, an unexpected mixture of pent-2,4-dienal isomers was obtained.

To investigate this matter, a number of reaction conditions were examined in hopes of finding one with optimal yields and little to no isomerized pent-2,4-dienal product. In addition, a variety of cyclopentenones were synthesized to explore the steric effect in influencing the isomerization process. Some potential mechanistic details of this strange isomerization phenomenon along with results obtained from the synthesis will be reported and discussed.



A CATALYTIC APPROACH TO CYCLOPENTENONES: UNEXPECTED CHALLENGES IN SYNTHESIZING PENT-2,4-DIENALS

A Thesis

Presented to the Faculty of the Department of Chemistry

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In Partial Fulfillment of the Requirements for the Degree

Master of Science in Chemistry

By

Hunter Wade English

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Colin S. Burns, PhD

Brian E. Love, PhD

Shouquan Huo, PhD

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LIST OF SYMBOLS OR ABBREVIATIONS

ºC	Degrees centigrade
min	Minute/minutes
hr(s)	Hour/hours
rt	Room temperature
Ph	Phenyl
Me	Methyl
CF_3	Trifluoromethyl
PPh_3	Triphenylphosphine
OAc	Acetate
dba	Dibenyzlideneacetone
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppe	1,2-Bis(diphenylphosphino)ethane
nbd	Norbornadiene
BF_4^-	Tetrafluoroborate
DCM	Dichloromethane
THF	Tetrahydrofuran
DMF	Dimethylformamide

$CHCl_3$ Chloroform

mL Milliliter

TLC Thin Layer Chromatography

DFT Density Functional Theory

mol Mole

TMS Tetramethylsilane

d deuterated

MHz Megahertz

mg Milligram

g Gram

mmol Millimole

δ Chemical Shift

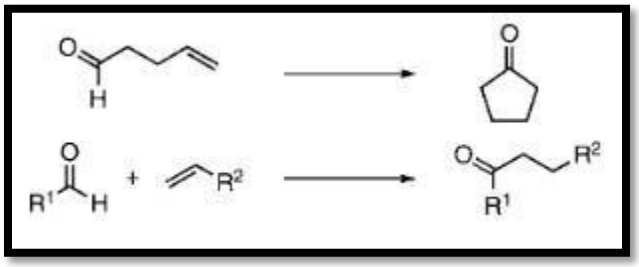
NMR Nuclear magnetic resonance

Hz Hertz

CHAPTER 1: INTRODUCTION

1.1. Hydroacylation

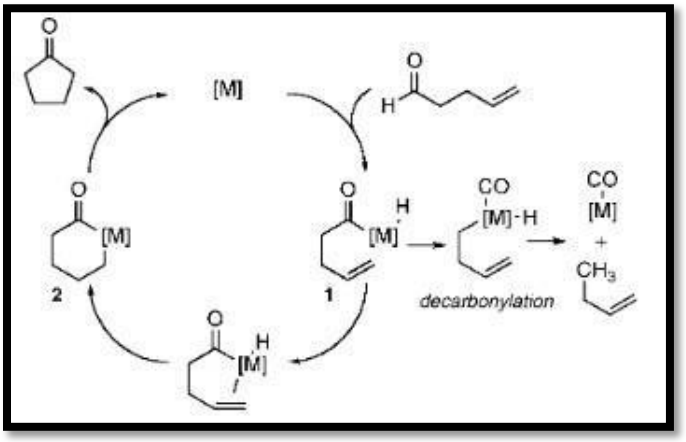
Transition-metal catalysis has long been used to enable a variety of useful transformations typically outside the scope of classical organic synthesis. These reactions are instrumental in converting normally unreactive and inexpensive starting materials into useful products under less demanding thermodynamic conditions. In particular, the catalytic activation and subsequent functionalization of C-H bonds is an attractive goal for synthetic chemists, with reactions that employ low catalyst loadings and result in the formation of new C-C bonds.[1] One of these transformations is hydroacylation (Scheme 1.1), a process in which, following C-H activation, an alkene or alkyne is inserted into the formyl C-H bond, producing a ketone either intramolecularly or intermolecularly. This process has been explored in detail for a variety of systems,[2] producing an assortment of natural products using mainly rhodium catalysts. Additionally, these processes are atom-economic and can be catalyzed by other transition metals,[3] producing little to no waste and with appropriate substrates and chiral products with high enantioselectivities typically in substantial yield.



Scheme 1.1. Hydroacylation reactions (top: intramolecular; bottom: intermolecular).

This process was initially discovered when aldehydes were decarbonylated by Wilkinson's catalyst, $RhCl(PPh_3)_3$.[4] When its mechanism was elucidated, the presence of acyl

metal hydride intermediates suggested that the use of those catalyst systems may be extended to the hydroacylation of unsaturated systems. Afterwards, to our knowledge, Sakai et al reported the first example of the intramolecular hydroacylation reaction,[5] involving the cyclization of a 4-pentenal to a cyclopentanone, applicable towards the construction of natural products including prostaglandins. A general mechanism (Scheme 1.2) for this reaction was later proposed and elucidated by Bosnich and Fairlie following deuterium-labeling studies: (1) oxidative addition to the C-H of 4-pentenal to metal catalyst [M], (2) migratory insertion of the olefin to the resulting metal hydride to generate a metallocomplex, and (3) reductive elimination.[6] Alternatively, the metal hydride intermediate may decarbonylate, which following hydride insertion results in an inactive metal catalyst. Regardless, the reactivity of the catalytic cycle has mostly been attributed to the open coordination site on the metal complex intermediates, allowing them to be filled by other coordinating, electron-rich species.

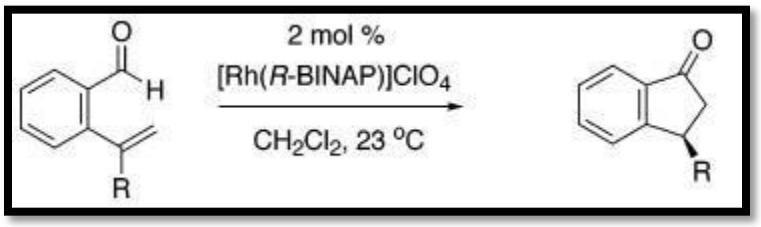


Scheme 1.2. Overview of the intramolecular hydroacylation catalytic cycle.

During the study,[6] the application of cationic rhodium complexes with diphosphine ligands was shown to reduce rates of decarbonylation while accelerating oxidative addition. Incorporation of a chiral diphosphine catalyst, (S)-BINAP, resulted in diastereoselective

production of cyclopentanones and 4-pentenal isomers in a kinetic resolution.[7] Mechanistic analysis showed that the enantioselectivity was largely determined by several reversible steps and intermediates. Since these notable findings, several synthetic and experimental studies[3] have been done in the pursuit of understanding more of this reaction, exploring its capabilities and limitations.

The Morehead group has developed an efficient method for the synthesis of chiral 3-substituted indanones by the intramolecular hydroacylation of 2-vinyl benzaldehydes (Table 1.1),[8] providing a rapid synthesis of these important synthetic building blocks. A dimer was the major product when R=H, but any substituent gave the desired 3-indanones with yields and enantioselectivities as high as 97% and 99%, respectively.



Entry	R=	Yield (%)	ee (%)
1	CH_3	97	99
2	CH_2CH_3	97	99
3	Ph	98	98
4	2-Napthalene	88	96
5	CH_2CH_2OH	97	96
6	$SiMe_3$	93	70
7	CF_3	90	99
8	$COOCH_2CH_3$	89	96

Table 1.1. Intramolecular hydroacylation of 2-vinyl benzaldehydes to indanones.

Computational studies[9,10] utilizing the nudged elastic band (NEB) method[11] provide a deeper insight into the mechanism of the hydroacylation catalytic cycle. Although results significantly differed from traditional QM/MM calculations,[9] NEB calculations proved to be

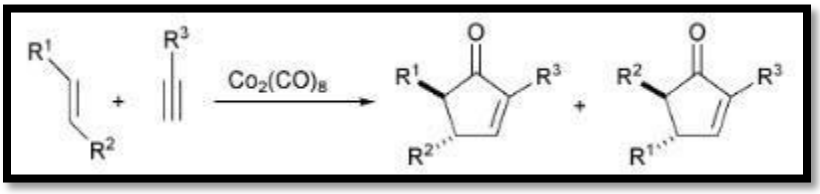
more consistent with experimental observations by identifying additional transition states and their energy levels not found originally. Specifically, higher concentrations of substrate have been shown to facilitate reductive elimination relative to decarbonylation. Upon re-examining and revisiting the oxidation addition step, it was found to contribute to both product and decarbonylation/catalyst deactivation rates. Thus, it is important to recognize the importance of each step of the catalytic cycle in the pursuit of bettering our knowledge of the hydroacylation reaction.

1.1 Approaches to Cyclopentenones

Since the initial reports by Sakai et al[5] and Fairlie and Bosnich,[6-7] many methods have been developed to synthesize carbocyclic and heterocyclic ketones, subunits which are ubiquitous in many natural products with biological activities. Cyclopentenones are key intermediates in asymmetric synthesis and are present in a number of bioactive compounds, including prostaglandins, prostanoid derivatives, and a variety of natural products (e.g. jasmone),[12] but are not typically available by hydroacylation. For this reason, a general catalytic synthesis thereof is highly sought after.

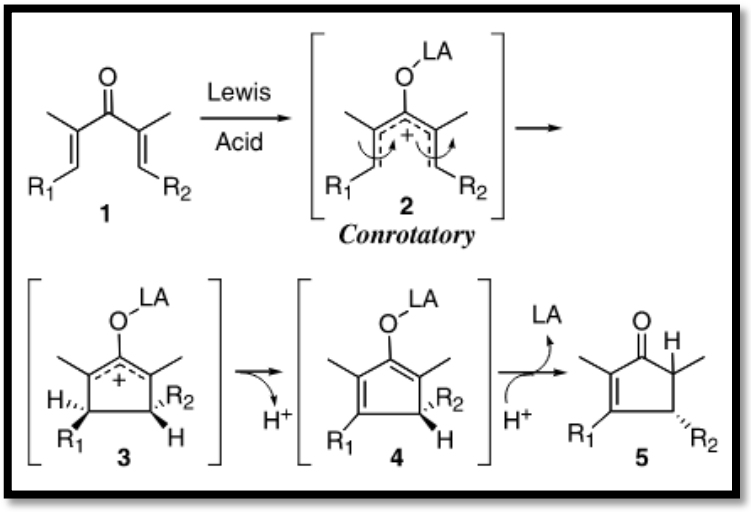
Despite the vast utility cyclopentenones have in total synthesis and pharmacology, few general protocols have been employed in their construction, most notably via Pauson-Khand[13] and Nazarov cyclization[14] reactions. Both approaches, however, have specific reactivity and regioselectivity concerns that need to be addressed. For example, Pauson-Khand reactions often have poor conversions and are limited to a relatively low scope of suitable substrates, usually requiring sterically strained, electron-deficient olefins. In addition, unsymmetrical alkenes give

mixtures of regioisomers (Scheme 1.3). Finally, additives or promoters are often needed in not easily rationalized ways to improve the CO-transfer from the metal catalyst onto the olefin.



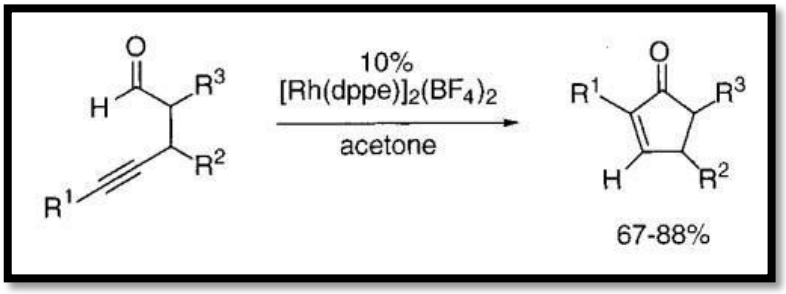
Scheme 1.3. Pauson-Khand approach to cyclopentenones.

In Nazarov cyclization, the reaction proceeds by activation of a divinyl ketone **1** with a Lewis acid to provide a pentadienyl cation **2**. Conrotatory rotation allows for cyclization to occur, giving an oxyallyl cation **3**. Elimination of a proton, formation of the enolate **4**, and subsequent protonation results in the cyclopentenone product **5** (Scheme 1.4). While seemingly elegant, there are a number of limitations: (1) multiple equivalents of a strong Lewis acid are generally required to promote cyclization effectively, (2) elimination of the proton (**3➔4**) is not regioselective and leads to loss of a stereocenter, and (3) protonation of the enolate (**4➔5**) is not regioselective. Moreover, reactive substrates can be prone to polymerization if the Lewis acid is too strong.



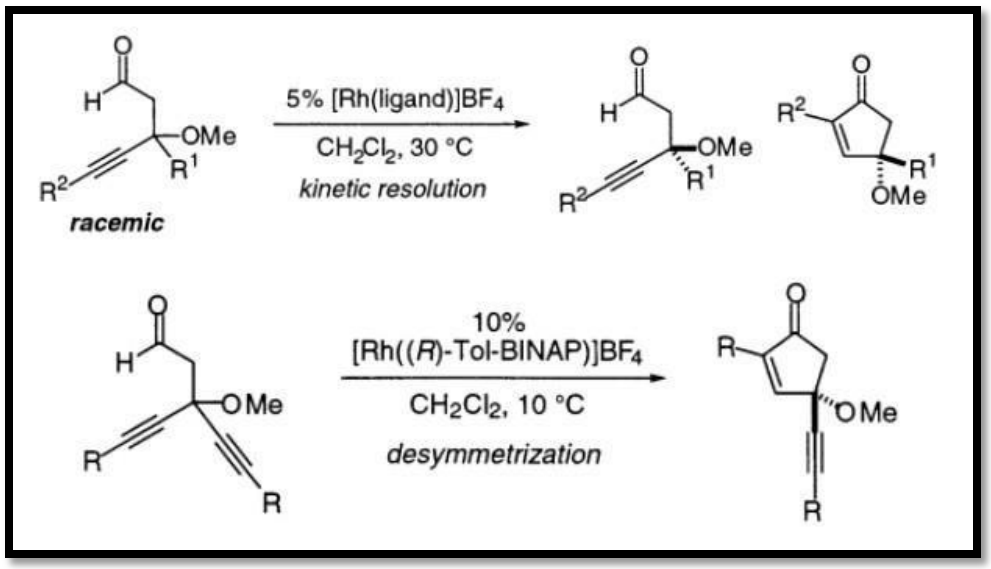
Scheme 1.4. Overview of the Nazarov approach to cyclopentenones.

Previously, Tanaka and Fu have developed the only hydroacylation-based synthesis of cyclopentenones by a rhodium-catalyzed intramolecular cyclization of 4-alkynals upon treatment with 10% $[Rh(dppe)]_2(BF_4)_2$ (Table 1.2).[15] While no stereocenters were generated in that study, they later demonstrated that enantioselective cyclopentenones can be obtained by conducting a kinetic resolution and a desymmetrization reaction (Scheme 1.5) on β-methoxy substituted 4-alkynals,[16] isolating the unreacted aldehyde and enantiopure cyclopentenone in excellent yields and selectivities. It was postulated that the stereoselectivity was enhanced by the coordinating effects of the methoxy-directed substituents to the rhodium via a multi-point complex,[17] resulting in higher reaction rates and selectivity factors.



Entry	R_1=	R_2=	R_3=	Yield (%)
1	n-$C_{10}H_{21}$	H	H	67
2	n-C_6H_{13}	CH_3	H	75
3	n-C_6H_{13}	H	CH_3	67
4	Ph	CH_3	H	88
5	Ph	CH_3O, CH_3	H	75
6	Cyclohex-1-ene	CH_3	H	84
7	n-$C_{10}H_{21}$-CC	H	H	76

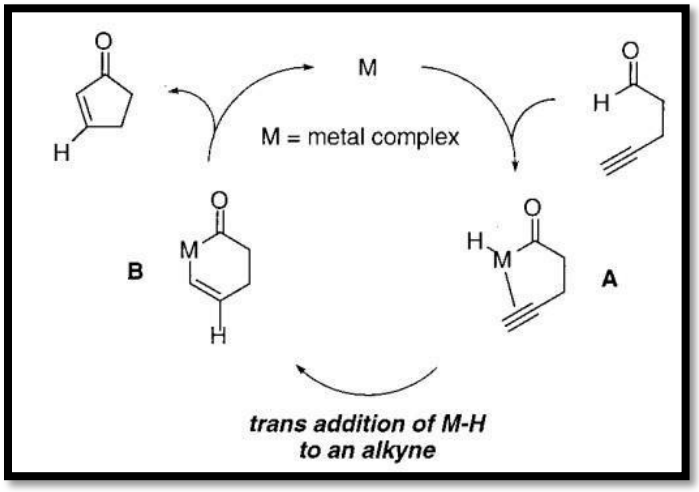
Table 1.2 Intramolecular hydroacylation of 4-alkynals to cyclopentenones.



Scheme 1.5. Kinetic resolution and desymmetrization cyclization reactions of 4-alkynals.

Based on these findings and the well-understood process of how a typical cyclization proceeds, they hypothesized that the reaction follows an unusual hydroacylation pathway: (1) oxidative addition of the aldehyde C-H to Rh(I) catalyst, (2) trans addition of the hydride to the alkyne that is coordinated to the metal center, and (3) reductive elimination, furnishing the

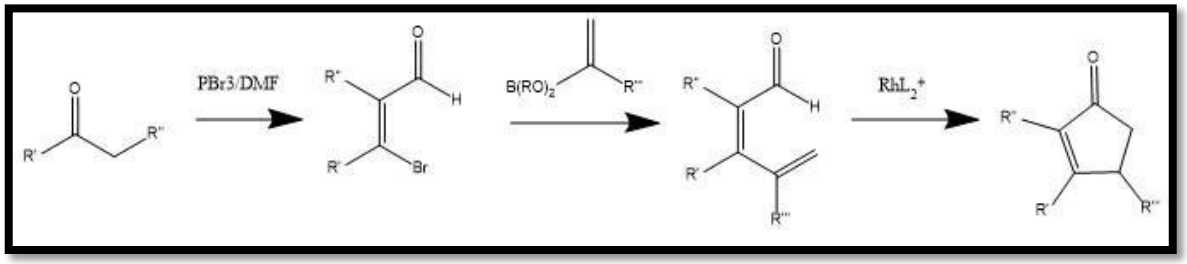
cyclopentenone product and regenerating the Rh(I) catalyst (Scheme 1.6). Sure enough, the mechanistic data gathered from crossover experiments does indicate that the reaction proceeds intramolecularly and through the addition of the aldehyde hydrogen to the β-position of the cyclopentenone. In contrast to alkenes in which the intramolecular hydroacylation proceeds via cis addition, alkynes undergo trans addition of the rhodium hydride.



Scheme 1.6. Intramolecular hydroacylation pathway of 4-alky

CHAPTER 2: RESEARCH OBJECTIVE

Following in the footsteps of these predecessors, the goal of this study is to develop an alternate synthetic approach to cyclopentenones by a three-step synthesis, culminating with a hydroacylation reaction. As established in the literature, α, β-unsaturated β-haloaldehydes are regarded as versatile synthons for several heterocyclic compounds[18] and are readily made by a Vilsmeier-Haack reaction, traditionally by a mixture of $POCl_3$ and DMF. However, for the purposes of incorporating the more reactive bromide needed for the Suzuki coupling, the bromo analogue (using PBr_3 and DMF) of the reagent was made instead. Control of the stereochemistry is a concern here in the synthesis of the bromo precursor, as Suzuki-coupling of α, β-unsaturated bromo aldehydes with vinyl boronic acids in the presence of a palladium catalyst can be anticipated to give the stereospecific replacement of the bromine to result in a pent-2,4-dienal. As the pentadienal must be in the appropriate configuration to allow for hydroacylation to occur, lack of control of the stereochemistry is a significant issue since the other diastereomer will not be in a position to insert. Given the similarities between pent-2,4-dienals and the previously reported 4-pentenals, we expect for them to serve as useful precursors towards the desirable cyclopentenone products when cyclized. As mentioned, since the cyclopentenone products obtained by Tanaka do not create chiral centers, we would also like to explore the possibility of creating a chiral center during the hydroacylation reaction for the purposes of expanding its synthetic utility.



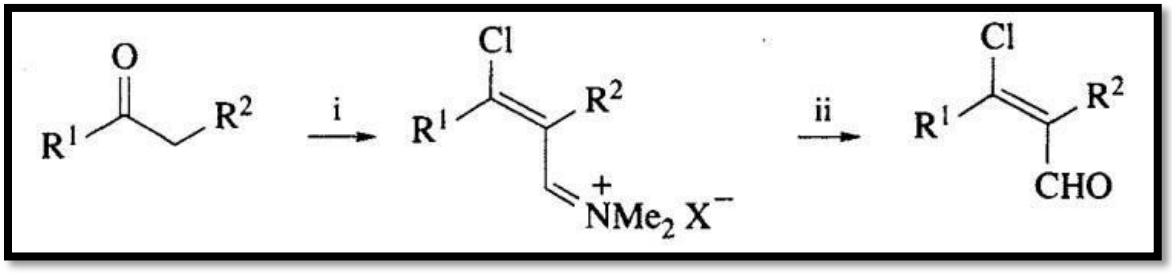
Scheme 2.1. General scheme for the anticipated synthesis of cyclopentenones via intramolecular hydroacylation of pent-2,4-dienals.

CHAPTER 3: REACTION SEQUENCE

3.1 Preparation of Aldehydes for Anticipated Suzuki-Coupling

The Vilsmeier-Haack reaction has been regarded as a classic method of installing formyl groups directly onto aromatic rings.[19] This method has also been shown to work well for converting enolizable ketones into aldehydes.[20] In general, the reaction involves the electrophilic substitution of an aromatic, electron-rich nucleophile with a halogenated methyleneiminium salt, which is generated by a mixture of DMF and either $POCl_3$ or PBr_3 for the chloro- or bromo-analogue, respectively. Hydrolysis of the iminium salt affords the aldehyde derivative.

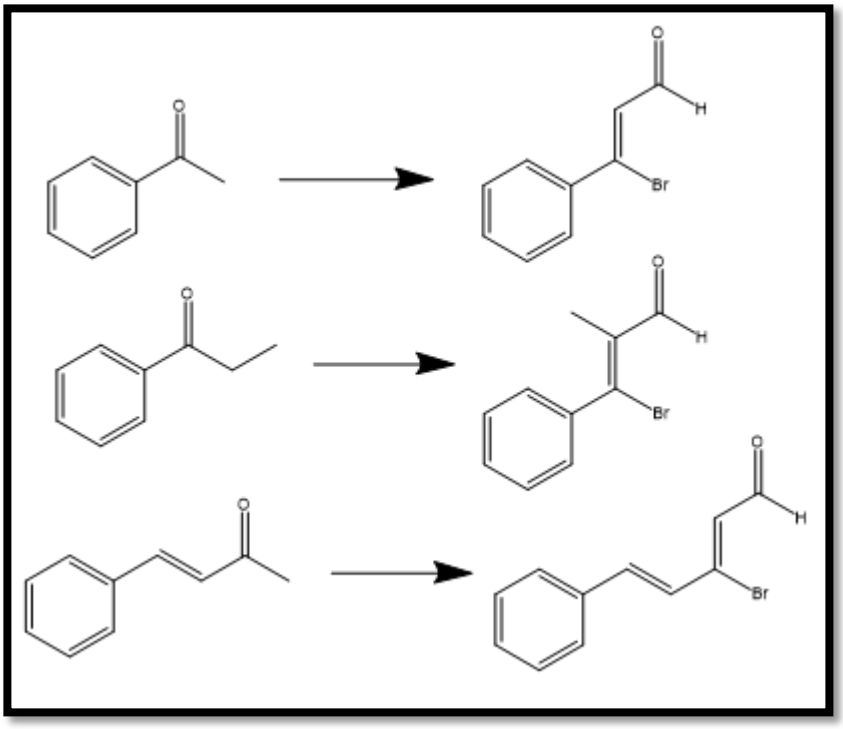
As mentioned above, ketones that possess activated methyl and methylene groups at an α-position can readily enolize to generate enol nucleophiles. As an example, upon attacking a chloromethyleneiminium salt, an iminium salt is formed. Subsequent hydrolysis yields a β-chloroacrolein (Scheme 3.1),[21] an α,β-unsaturated aldehyde. Note that the synthetic scheme above, the Z-stereoisomer must be the one made rather than the one illustrated in Scheme 3.1. Moreover, the bromo analogue will be prepared instead, but following the same reaction mechanism.



Scheme 3.1. Vilsmeier-Haack reaction of an activated ketone undergoing substitution (i) and then hydrolysis (ii).

To examine the viability of this synthetic approach, a few ketones were selected as potential suitable starting materials for the Vilsmeier-Haack reaction along with their expected products (Table 3.1). Since polysubstitution can occur with ketones containing two α-carbons, resulting in pyrones[20,21], only ketones with one α-carbon were selected for this initial screening. This will guarantee regioselectivity, as only one enol intermediate can be formed, thereby forming only one final product. Additionally, it is important that these ketones contain electron-rich π-bonds to enhance the substitution.[21]

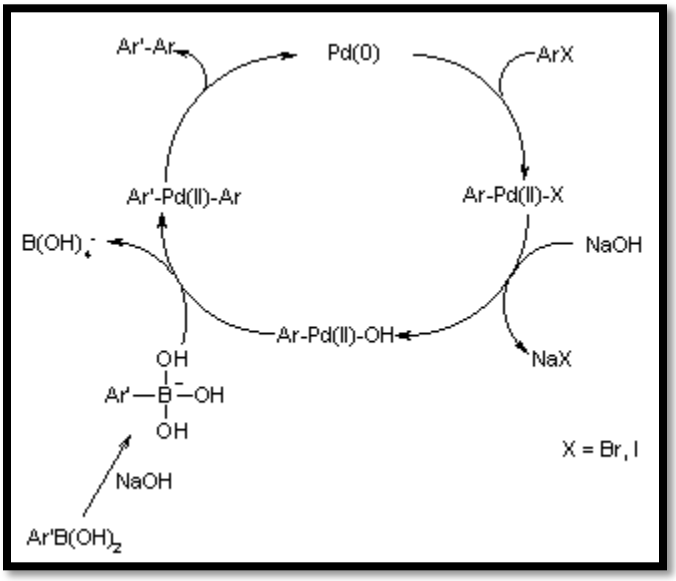
The reaction (Scheme 3.2) was first tested using acetophenone as starting material. In accordance with the literature,[22] its bromo aldehyde was obtained following work-up (64%). As illustrated in Scheme 3.2, this procedure was repeated for the other ketones, including propiophenone and benzalacetone, resulting in their corresponding bromo aldehydes (32% and 46%, respectively). Although most methods report running reactions overnight at room temperature, we found that a slightly higher elevated temperature (30 °C) and for 12-16 hrs resulted in better yields. Even so, the reasoning behind the moderately-low yields may be due to their propensity to polymerize,[23] especially given their structural relationship in reactivity to other acrolein derivatives.[24,25] The reaction was attempted with 2-phenylacetophenone but was very sluggish, resulting in only trace amounts of the desired product. This may be attributed to increased steric demand brought forth by the adjacent phenyl substituents in the product. In addition, although control of stereochemistry may be a concern at first glance, fortunately, the products obtained for these substrates almost exclusively favored the Z-alkene.



Scheme 3.2. Vilsmeier-Haack reaction of starting ketones with PBr_3 and DMF.

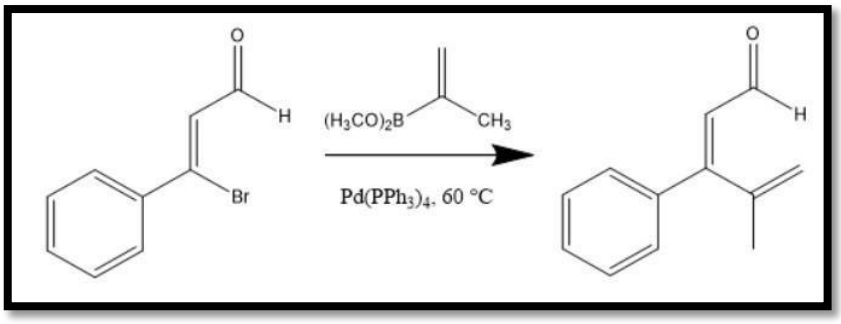
Now that the ready access to the required bromo aldehydes has been established, they can be used as suitable precursors for the next step of the synthesis. The Suzuki reaction is well established as an excellent approach to forming carbon-carbon bonds by the joining of two fragments with the addition of a palladium catalyst, a boron reagent, and a base.[26,27] The reaction typically requires the use of a sp^2 vinylic or aromatic halide or pseudohalide, often with the use of an electron-withdrawing group, like the bromo aldehydes made previously. Boronic acids are typically the boron reagent of choice for conducting this reaction, given their enhanced reactivity, higher atom economy, and ease of preparation.[28] Even so, several alternatives have been developed in recent years to accompany a wider substrate scope, while still upholding mild conditions.[29] This may be relevant in expanding the scope of the reaction step in future developments.

The mechanism is generally thought to proceed by the oxidative addition of the active palladium catalyst, Pd(0), to the halide, followed by displacement with the base, forming its salt. The intermediate reacts with the boronic acid, which is activated by the base, to undergo transmetalation. Subsequent reductive elimination affords the coupling product and regenerates the palladium catalyst (Scheme 3.3).



Scheme 3.3. General Suzuki coupling mechanism with an aryl halide.

The reaction (Scheme 3.4) was first conducted using 3-bromo-3-phenyl-2-propenal in accordance with the literature.[30] As such, its coupled product was obtained in a yield (85%) close to what was originally reported. Under normal circumstances, one could proceed with making the rest of the 2,4-pentadienals (Table 3.1) and later cyclize into their respective cyclopentenones during hydroacylation. However, upon further inspection, a very peculiar observation was made.



Scheme 3.4. Suzuki reaction of 3-bromo-3-phenyl-2-propenal.

3.2 Unexpected Results and Discussion

Upon analysis of the initial reaction forming 3-bromo-3-phenyl-2-propenal, an unusual set of isomeric aldehyde protons (9.9 and 9.4 ppm), which were originally speculated to be rotamers, had appeared (Figure 3.1). To investigate if these were rotamers, the cyclization was carried out with an achiral rhodium catalyst ([Rh(dppe)(nbd)](BF_4)).

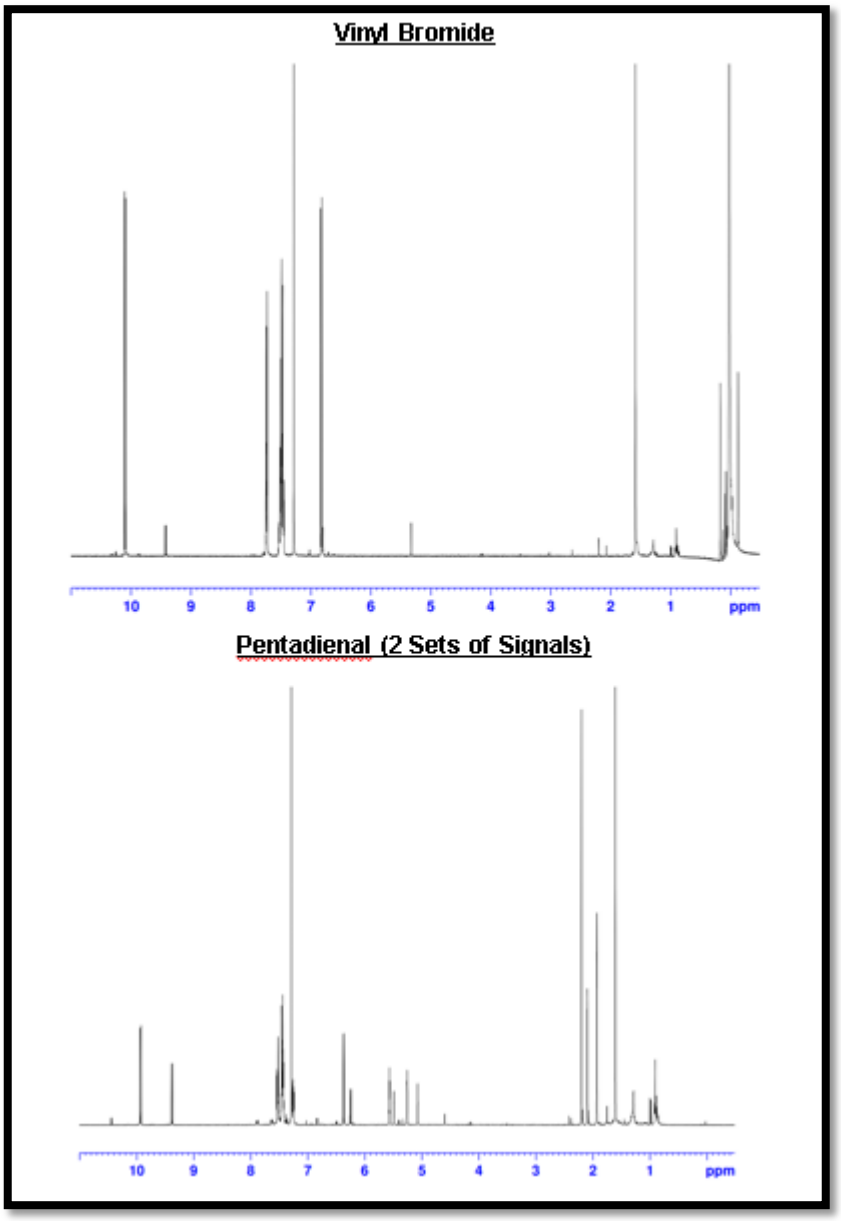


Figure 3.1. ^{1}H NMR spectra of the vinyl bromide starting material (3-bromo-3-phenyl-2-propenal) and the pent-2,4-dienal product (4-methyl-3-phenyl-2,4-pentadienal).

To our surprise, the resulting crude ^{1}H NMR spectrum not only contained the desired cyclopentenone, but also unreacted starting material (Figure 3.1), meaning these were likely E/Z isomers and not rotamers. This was an unusual finding, since Suzuki-coupling reactions generally proceed with retention of stereochemistry.[31] However, since only one of the isomers

was left unreacted, it must have been in a configuration such that the terminal alkene of the dienal is facing away from the aldehyde C-H, rendering it unable to cyclize – presumably due to the lack of coordination of the metal catalyst (Figure 3.2). For this reason, as mentioned above, it is the dienal with the aldehyde and alkene group cis that must be sought after for the purposes of this synthesis. Therefore, we conclude that the pair of 4-methyl-3-phenyl-2,4-pentadienal isomers detected were actually diastereomers (E: 9.9 ppm, Z: 9.4 ppm), whereby the E diastereomer corresponds to the desired cis alkene.

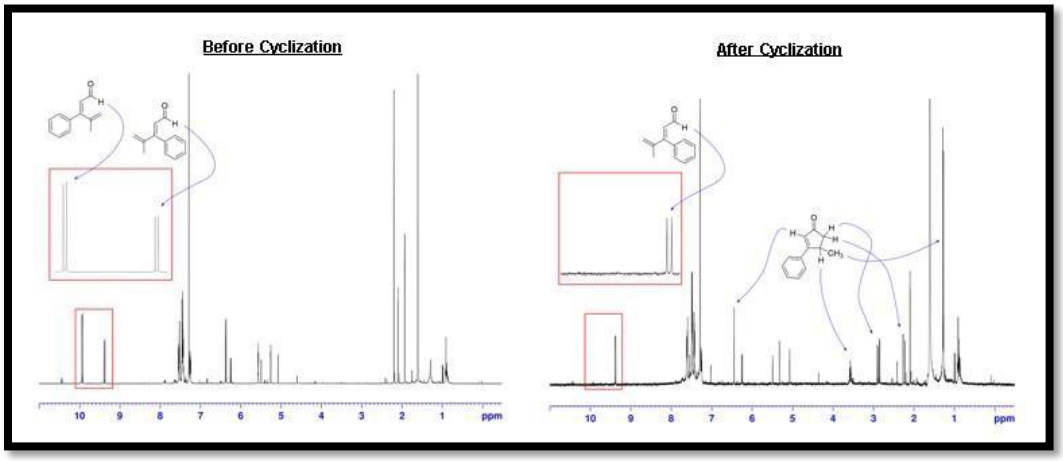
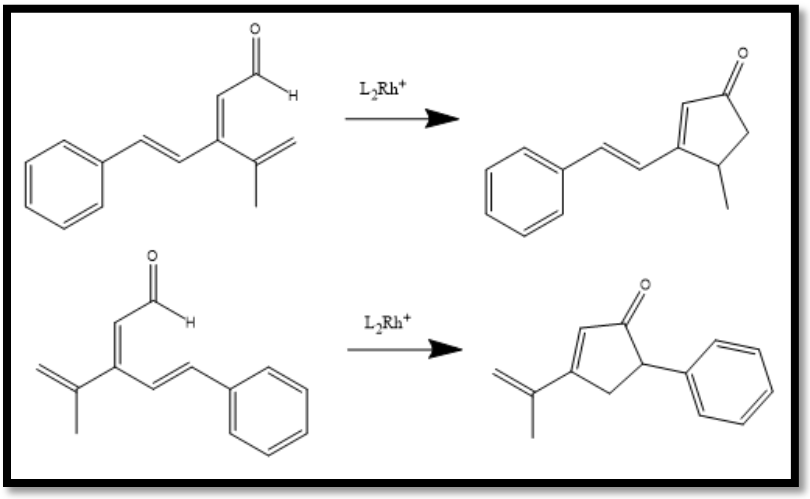


Figure 3.2. ^{1}H NMR spectra containing the pent-2,4-dienal before being cyclized (left) and of the crude reaction mixture (right) containing the cyclopentenone product (4-methyl-3-phenyl-2-cyclopenten-1-one*)* and the unreacted diastereomer after being cyclized.

This phenomenon was also observed when coupling took place with 5-phenyl-3-prop-1-en-2-ylpenta-2,4-dienal, derived from benzalacetone, with the same boronic acid pinacol ester. Likewise, its resulting ^{1}H NMR spectrum reveals two aldehydic peaks as before, but with slightly different chemical shifts and inversed integrations. To verify which represents the desired diastereomer, the cyclization was repeated for the set of dienals. Interestingly, however, unlike what was illustrated in Figure 3.2, both pent-2,4-dienals reacted – one forming the

predicted cyclopentenone (4-methyl-3-[(E)-2-phenylethenyl] cyclopent-2-en-1-one), and the other presumably forming its own cyclopentenone product from an another adjacent π-bond (Scheme 3.5). Having this extended conjugation in place may serve to its benefit as a useful intermediate in other cycloaddition reactions.

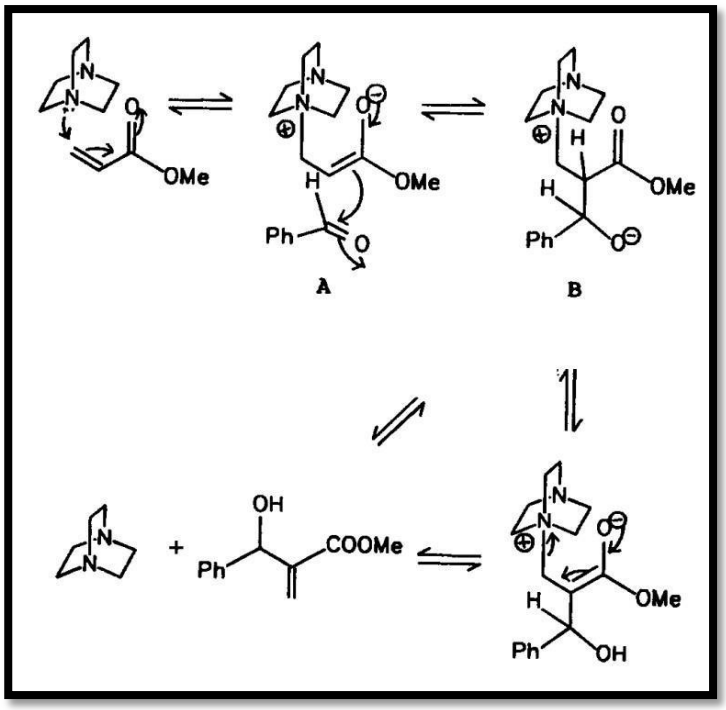


Scheme 3.5. Hydroacylation reaction of (E) and (Z) pent-2,4-dienals from 5-phenyl-3-prop-1-en-2-ylpenta-2,4-dienal.

To investigate this unusual outcome further, a thermal study was conducted at room temperature of the isolated dienal to measure its supposed isomerism. After 24 hours, no noticeable isomerization took place. Three Suzuki-coupling reactions were monitored at 45, 60, and 70 °C for 6 hrs, and the crude reaction mixtures were stored in the freezer (-10 °C) for later workup. After three days, a large decrease in E/Z ratio was observed when crude reaction mixtures, all reverting to an E/Z of 0.4. This evidence strongly suggests that there exists a reactant in the mixture that is initiating this process regardless of temperature sustained during the reaction.

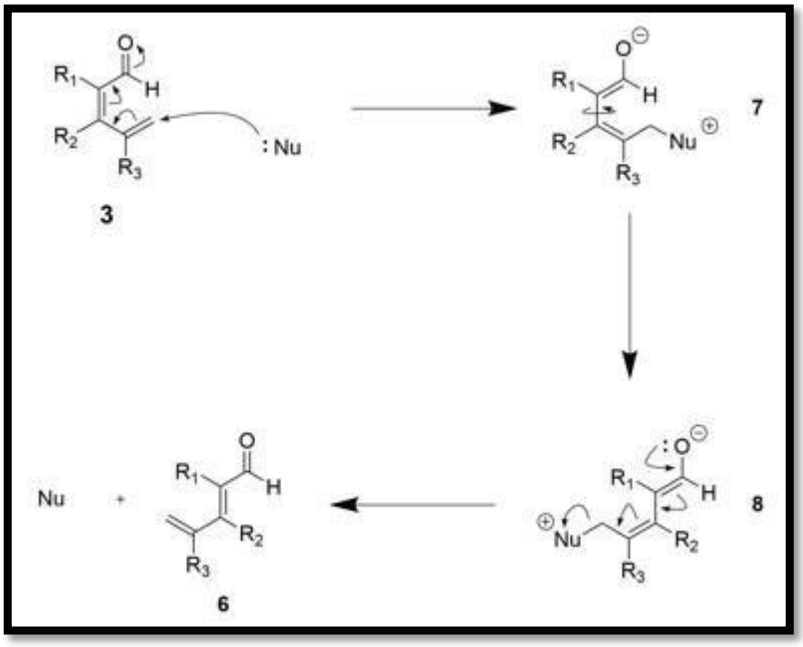
We initially proposed a mechanism (Scheme 3.7) similar to the well-established Morita-Baylis-Hillman (MBH) reaction,[32] attempting to explain the isomerization taking place. This reaction formally involves the addition of an activated alkene to an aldehyde or ketone with the assistance of a nucleophilic catalyst, usually containing a tertiary amine, resulting in the formation of aldol-type products. Several alkenes such as acrylic esters, vinyl ketones, and acrolein have been employed in the MBH reaction with many kinds of functionalized aldehydes,[33] including those with α, β-unsaturation.

The general mechanism (Scheme 3.6) begins with the Michael addition of the catalyst to the activated alkene, forming a zwitterionic enolate intermediate **A** which subsequently attacks the electrophilic aldehyde. Proton migration and elimination of the tertiary amine either by E2 or E1cb mechanism from the adduct **B** to give the final product. Tertiary phosphines have also been shown to contribute to this process by the same mechanism.[34,35] However, if the alkene is β-substituted, much like our system, a mixture of E/Z isomers will be obtained – the extent of which depending largely on factors such as the solvent polarity, nucleophilicity of the ligand, and other thermodynamic parameters.[36] Therefore, even if retention of stereochemistry is still probable in the case of Suzuki reactions, it is crucial for each factor to be considered on a case-by-case basis.



Scheme 3.6. Morita-Baylis-Hillman (MBH) reaction mechanism with DABCO.

Due to the resemblance between MBH and Suzuki catalysts, combined with the electron-deficient properties of the aldehyde, it is likely that this process may be the primary initiator behind this undesired isomerism. In particular, it would seem that a nucleophile, especially one that is phosphine-based, can attack a terminal olefin of the E isomer **3** to produce the enolate intermediate **7,** which can freely rotate about the α-β bond to afford the Z isomer intermediate **8**. Dissociation forms the corresponding Z isomer **6**.



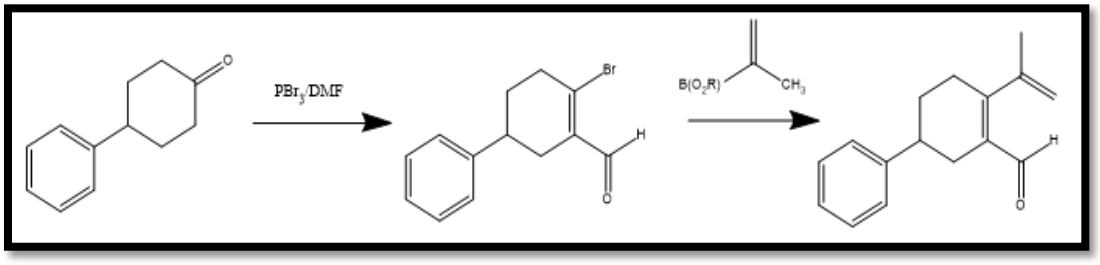
Scheme 3.7. Proposed isomerization mechanism of pent-2,4-dienals.

In an attempt to examine this model, two isomerization reactions were carried out and monitored at room temperature with the pent-2,4-dienal in question (Table 3.1). As expected, the one containing just the palladium catalyst ($Pd(PPh_3)_4$) resulted in a decrease by roughly half of its initial E/Z ratio. Counter to the model, however, the one containing the same molar quantity of catalyst as the prior with the addition of triphenylphosphine resulted in a significant increase in E/Z ratio. While the trend that took place over time is not completely clean, likely due to temperature fluctuations influencing the E-Z equilibrium, the overall outcome still indicates that it is clearly not the ligand alone that is influencing this process, but rather the metal center.

Time (hrs)	1 mol% $Pd(PPh_3)_4$ (E/Z)	1 mol% $Pd(PPh_3)_4$ + 1.00 eq PPh_3 (E/Z)
0	7.84	9.73
4	2.03	8.85
6	5.13	10.4
8	6.00	14.5
22	4.26	23.8

Table 3.1. E/Z ratios recorded in the presence of either catalyst or catalyst and ligand.

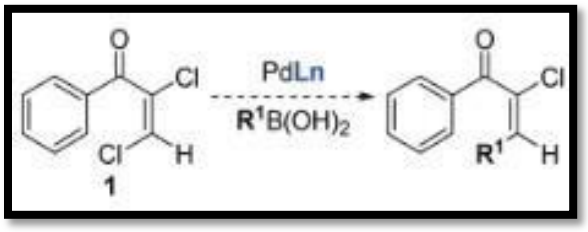
To further support the notion that this phenomenon is specific to acyclic dienals or dienones, the synthesis was carried out using 4-phenylcyclohexanone (Scheme 3.8). Since the ketone is symmetrical about the axis containing the carbonyl and phenyl functional groups, enolization on either α-carbon will produce identical aldehydes. In addition, because this vinyl bromide is cyclic in nature unlike the prior one, it would stand to reason that it is incapable of isomerizing during the Suzuki-coupling. As anticipated, Suzuki-coupling of its bromoenal resulted in the desired diastereomer with no complications. Therefore, the overall synthesis is also capable of producing bicyclic fused cyclopentenones once hydroacylation has been achieved.



Scheme 3.8. Synthesis of 4-phenyl-2-prop-1-en-2-ylcyclohexene-1-carbaldehyde.

To see if removing the phosphine addressed the isomerization issue, another method[37] detailing a ligand-free Suzuki cross-coupling reaction at room temperature with α,β-unsaturated bromo aldehydes with boronic acids was found and replicated using the 4-methyl-3-phenyl-2,4-pentadienal. While reaction times were improved considerably in comparison to the original method,[30] yields and E/Z ratios were still not satisfactory. In fact, using the first phosphine-free catalyst, $Pd(OAc)_2$, almost exclusively favored the Z-configuration, even with additional triphenylphosphine added to solution.

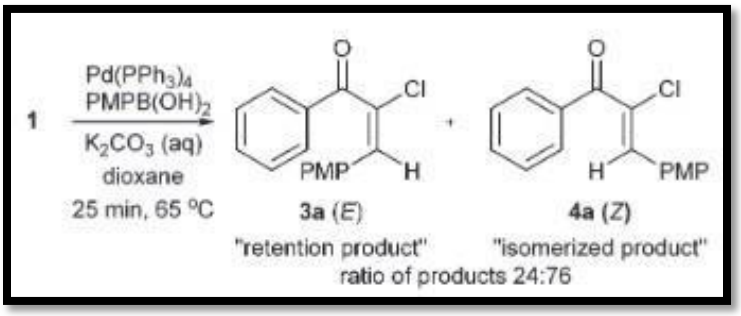
In addition, it was brought to our attention that a Suzuki cross-coupling of a similar substrate (E-1,2-dichlorovinyl phenyl ketone) was attempted.[38] Coupling was anticipated to occur with regio- and stereo-selectivity in mind, favoring the β- over the α-position (Scheme 3.9). Although the predicted regioselectivity was observed, E-Z isomerization of the double bond took place depending on the ligand employed. A model similar to that of the proposed isomerization mechanism of pent-2,4-dienals was speculated. However, some more elaborate experiments carried out suggest an entirely separate catalytic cycle.



Scheme 3.9. Predicted cross-coupling of E-1,2-dichlorovinyl phenyl ketone.

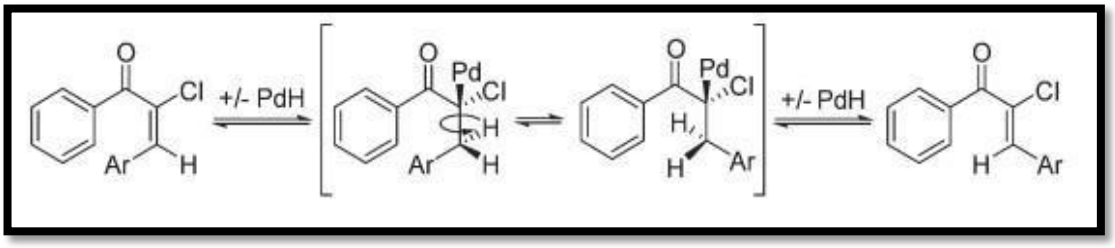
When treated with p-methoxyphenylboronic ($PMPB(OH)_2$) acid in the presence of $Pd(PPh_3)_4$ and aq. K_2CO_3 in dioxane at 65 ºC, full conversion was observed in 25 minutes, forming a ratio of the kinetic retention product and thermodynamic isomerized product (24:76) (Scheme 3.10). This strongly suggests that the retention product is formed first, and the

phosphine ligand influences the rate at which isomerization occurs. Furthermore, when the isomerization of the 1,2-dichlorovinyl phenyl ketone and its retention product were investigated further, neither the palladium catalyst nor the phosphine ligand alone promoted the isomerization to a significant extent. Instead, a mixture of the two was found to be the primary contributor to this process. Specifically, lower isomerization rates relative to cross-coupling rates were observed when lowering the catalyst concentration.



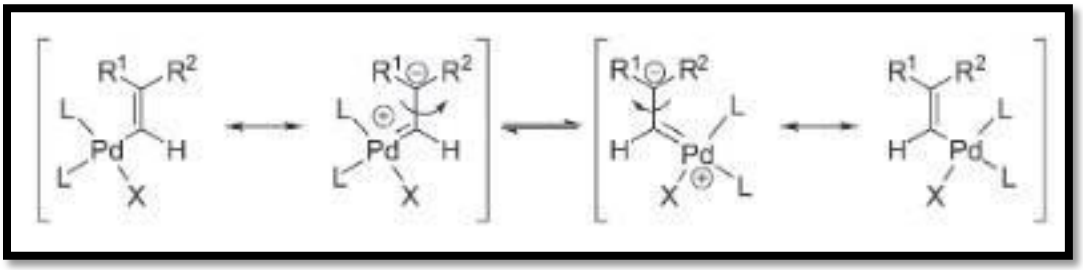
Scheme 3.10. Mixture of diastereomers obtained from the cross-coupling.

A few models[39,40,41] have been proposed that may explain the E-Z isomerization taking place for systems involving vinyl halides. It is plausible, for example, that trace Pd-H species could have initiated this process (Scheme 3.11), given what is known about how they affect many types of alkenes in undergoing positional and/or geometric isomerization.[39]As such, anti-addition of the Pd-H source to the alkene, followed by free rotation and reductive elimination, can afford the Z-isomer.



Scheme 3.11. Palladium-hydride mediated isomerization pathway.

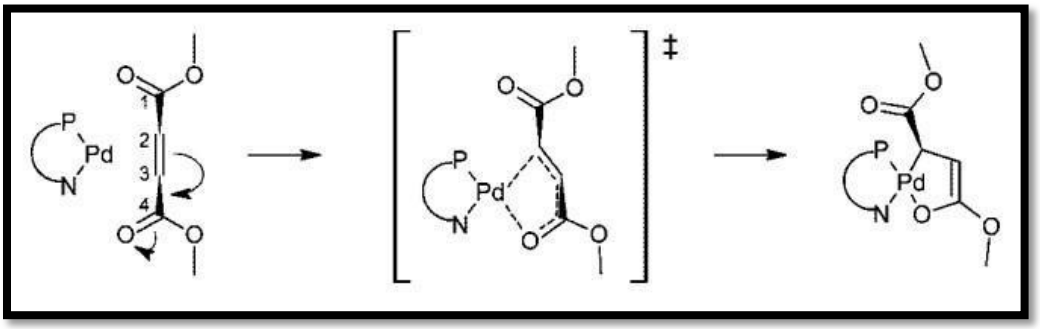
On the other hand, it is also plausible to suggest that the presence of the conjugated carbonyl plays a crucial role in the isomerization mechanism, presumably via a vinyl palladium intermediate (Scheme 3.12).[40] The stability of the palladium species permits a resonance structure involving a zwitterion which can undergo free rotation to form the other stereochemical configuration. A similar model was proposed by Krasovskiy[41] while studying the ligand effects of alkenyl halides during Negishi coupling, another reaction that operates off the same principles as Suzuki-coupling but with the use of an organozinc reagent.[42]



Scheme 3.12. Stereochemical interconversion involving a zwitterionic vinyl palladium carbene intermediate.

Despite the rationality of these proposed models, DFT calculations and computational studies[39] are inconsistent with their observations. Instead, the results point to a mechanism (Scheme 3.13) first proposed by Canovese et al.,[43,44] involving the presence of the conjugated C=O of the carbonyl and the electron-withdrawing substituents of the alkene. Their findings

highlight the importance of both electron-rich Pd(0) species and the groups conjugated to the electron-deficient alkene in stabilizing the low oxidation state of palladium by back donation from the metal center to the π^* orbitals of the alkene.[44] Thus, the Pd(0) species performs a 1,4-addition of the α,β-unsaturated alkene to generate a cyclopalladated intermediate. Subsequent rearrangement of the double-bond from the 2,3- to the 3,4- position generates another cyclopalladated intermediate. The trans influence by the phosphine ligand attached will then determine the configuration of the substituents attached to the alkene.



Scheme 3.13. Pathway involving nucleophilic attack of Pd(0) species.

Regardless of model, there is no doubt that steric and electronic characteristics of the ligands attached to the metal play a great role in the E-Z isomerization during coupling. Furthermore, it is known that phosphine-based ligands are often desirable and enhance the rate in Suzuki reactions. However, it is also evident that they can contribute to undesirable, stereochemical outcomes in the case of unsaturated ketones and aldehydes with β-halo or similar substituents. For these reasons, we will explore ligand as well as steric and electronic effects of this step of the synthesis on yield and E/Z ratios.

CHAPTER 4: E/Z RATIO OPTIMIZATION STUDY

4.1. Results and Discussion

Given the extensive literature review previously mentioned, we are now more familiar with the mechanistic issues of the coupling reaction to hopefully tackle the stereochemical outcomes. Having said that, it is critical to optimize this reaction step of the synthesis for the development of the hydroacylation approach to cyclopentenones. Therefore, we continued to use 3-bromo-3-phenyl-2-propenal as starting material for the optimization studies.

One obvious variable to alter is temperature, considering what is known about its impact on how many other catalytic reactions proceed. Indeed, when three identical Suzuki reactions, with the exception being their temperatures, were simultaneously run and monitored by NMR until completion, the highest temperature (70 °C) of the three resulted in the sharpest and quickest decrease of its E/Z ratio Table 4.1). The yields of 4-methyl-3-phenyl-2,4-pentadienal for reactions run at 45, 60, and 70 °C after work-up were found to be 63%, 59%, and 48%, respectively. It is apparent, therefore, that higher temperatures, even with short reaction times, contribute considerably to the formation of the unwanted diastereomer and side products, presumably due to polymerization and/or decomposition.

Time (hours)	Rxn at 45 °C (E/Z)	Rxn at 60 °C (E/Z)	Rxn at 70 °C (E/Z)
1	n.d.	n.d.	n.d.
2	1.6	n.d.	0.73
3	1.8	1.4	0.67
4	1.7	0.61	0.66
5	1.8	0.59	0.66
6	2.0	0.45	0.57

Table 4.1. E/Z ratios recorded every hour for three reactions held at 45, 60, and 70 °C.

It is worth noting that time duration also plays a role, as the coupling and isomerization reactions must take place at different rates. The highest E/Z ratio (Entry 1) recorded when using $Pd(PPh_3)_4$ took 2 hrs with modest heating (45 °C) as shown in Table 4.2. However, reaction times extending beyond six hours dramatically lowered the E/Z ratio, even at temperatures as low as room temperature (Entry 5). This result was also observed with $Pd(OAc)_2$, favoring the isomerized product regardless of amounts of PPh_3 (Table 4.3). Despite the observation made in Table 3.1, the presence of PPh_3 worsened stereochemical outcomes when $Pd(OAc)_2$ was used.

Entry	Time (hrs)	Temperature (°C)	Amount of Catalyst (mol%)	Yield (%)	E/Z
1	2	45	1	45	5.6
2	6	45	1	63	2.0
3	6	60	1	59	0.45
4	6	70	1	48	0.57
5	9	rt	1	n.d.	All Z
6	24	60	2	46	0.46
7	72	45	2	85	1.0

Table 4.2. E/Z ratios and yields obtained using $Pd(PPh_3)_4$ catalyst at various temperatures.

Entry	Time (hrs)	PPh_3 (mol eq.)	E/Z
1	9	1	0.73
2	9	2	All Z
3	9	3	All Z

Table 4.3. E/Z ratios obtained using 1 mol% $Pd(OAc)_2$ catalyst with triphenylphosphine at room temperature.

Furthermore, exchanging the ligands should have a direct impact on the rate of oxidative addition, and thus, indirectly, the rate of isomerization. It is also apparent that the presence of the phosphine moiety is important in ensuring adequate reaction rates. Because of this, it was hypothesized that increasing the steric bulkiness of the ligand while tethering the phosphine to

said ligand should significantly lower isomerization rates. Therefore, we continued to optimize reaction conditions, but with the use of $PdCl_2$(dppf) as our catalyst system.

Sure enough, out of all the catalysts used, $PdCl_2$(dppf) resulted in consistently higher yields and E/Z ratios – even at room temperature (Table 4.4, Entries 5-7). In fact, out of all Suzuki reactions attempted, the highest E/Z ratio and yield obtained were 20:1 and 75%, respectively. For reference, the Suzuki reaction in question, originally reported to take 24 hours at 60 °C, monitored with TLC and GC-MS, only took (if not less than) one hour at 50 °C to reach completion in the transformation of the pent-2,4-dienal. Although one would likely obtain better E/Z ratios at 60 °C for only 20-30 min, yields would likely suffer as indicated in Entry 2. This reemphasizes the importance of time and temperature as crucial variables when conducting Suzuki reactions, especially with sensitive substrates.

Indeed, reactions which were run at lower temperatures contributed less to the isomerization of the pent-2,4-dienal than those run at higher temperatures. This is rather unambiguously the case for virtually all catalytic systems, including the use of $Pd_2(dba)_3$ (Table 4.5). Again, we obtained lower yields of the pentadienal when reactions were run at higher temperatures when time is held constant. Despite this phosphine-free catalyst being used with α,β-unsaturated aldehydes previously, we found little success in obtaining as good of yields and E/Z ratios as with $PdCl_2$(dppf). Thus, we have determined the following optimized reaction conditions to be in accordance with Table 4.4, Entry 1.

Entry	Time (hrs)	Temperature (°C)	Amount of Catalyst (mol%)	Yield (%)	E/Z
1	1	50	2	75	20
2	1	60	2	40	12
3	3	30	2	32	7.9
4	3	40	2	43	3.5
5	4.5	rt	1	28	14
6	4.5	rt	2	54	6.4
7	4.5	rt	3	21	15

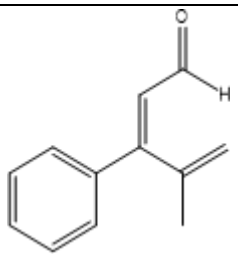
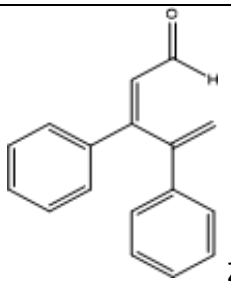
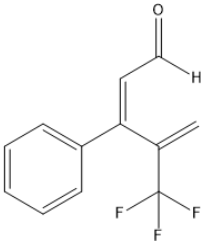
Table 4.4. E/Z ratios and yields obtained using $PdCl_2$(dppf) catalyst at various temperatures.

Entry	Time (hrs)	Temperature (°C)	Yield (%)	E/Z
1	1.5	50	22	13
2	1.5	60	11	0.82
3	5	30	49	13
4	5	40	34	2
5	7.5	rt	26	1.5

Table 4.5. E/Z ratios and yields obtained using 2 mol% $Pd_2(dba)_3$ catalyst at various temperatures.

Now that the optimized conditions were obtained, Suzuki reactions were conducted from the previously made bromo-3-enals: 3-bromo-3-phenyl-2-propenal (Entries 1-3), 3-bromo-5-phenylpenta-2,4-dienal (Entries 4-6), and 2-bromo-5-phenylcyclohexene-1-carbaldehyde (Entries 7-9), each coupled with a different boronic acid pinacol ester (Table 4.6). Since the other cis pent-2,4-dienal products differ in their stereochemical assignment, both their E/Z and Z/E ratios were reported along with their indicated stereochemistry (note that the stereochemistry shown with the aldehyde and alkene cis is the desired outcome). As expected, only one product was obtained from coupling with 2-bromo-5-phenylcyclohexene-1-carbaldehyde, thus no E/Z or Z/E ratio was reported for those substrates.

In general, higher yields and E/Z ratios of pent-2,4-dienals were obtained from simple aliphatic or aromatic substituents (Me or Ph) at the 4-position. Interestingly, however, Entry 2 was found to have the lowest yield and exclusively favored the E-product. This is likely due to the strong preferability associated with phenyl groups being trans to aldehydes as also seen in Entry 5. Moreover, those with CF_3 substituents at the 4-position produced mixed results but are generally associated with lower yields and E/Z ratios as is often the case with other electron-withdrawing groups on boronic acids. In general, deactivated α,β-unsaturated aldehydes tend to work best with electron-rich coupling partners in the presence of strongly activated and soft-nucleophilic catalysts.

Entry	Pent-2,4-dienal	Yield (%)	E/Z	Z/E
1	 E	75	20	0.1
2	 Z	29	All Z	All Z
3	 Z	61	0.4	2.3

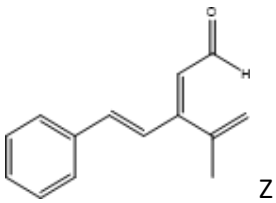
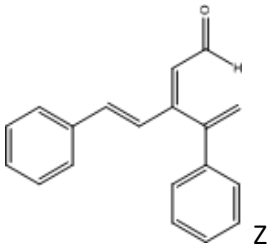
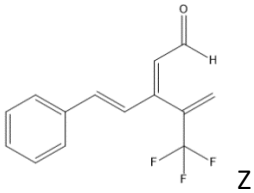
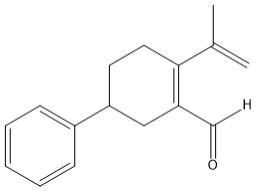
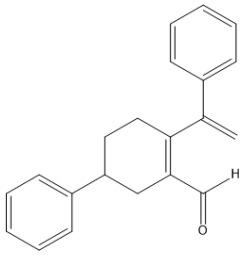
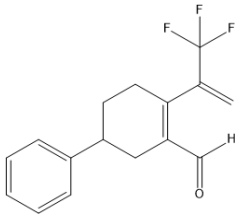
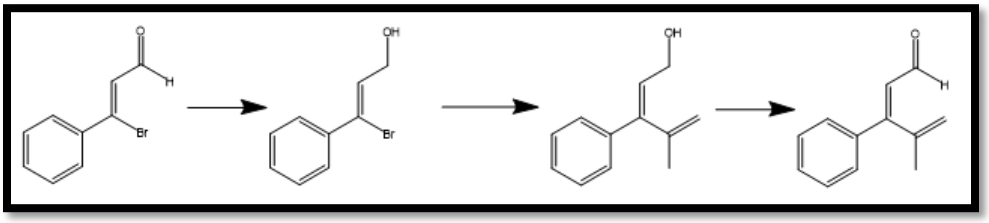
4		40	0.2	4.6
5		44	0.1	9.4
6		40	0.2	5.4
7		45	NA	NA
8		55	NA	NA
9		36	NA	NA

Table 4.6. Yields and E/Z ratios of pent-2,4-dienals using the optimized conditions.

4.2 Alternate Routes

Increasing frustrations from not being able to completely prevent the E/Z isomerization in the Suzuki coupling reaction has led us to consider other synthetic alternatives entirely. Considering that unsaturated aldehydes are one of many substrates that are prone to isomerizing, even at mild-to-moderate temperatures, a functional group interconversion may be beneficial. Specifically, the 3-bromo-2-enal made from the Vilsmeier-Haack formylation can be reduced to an alcohol prior to coupling. Thus, subsequent oxidation of the coupled alcohol would yield the pent-2,4-dienal once again, except corresponding to the appropriate diastereomer (Scheme 4.1).



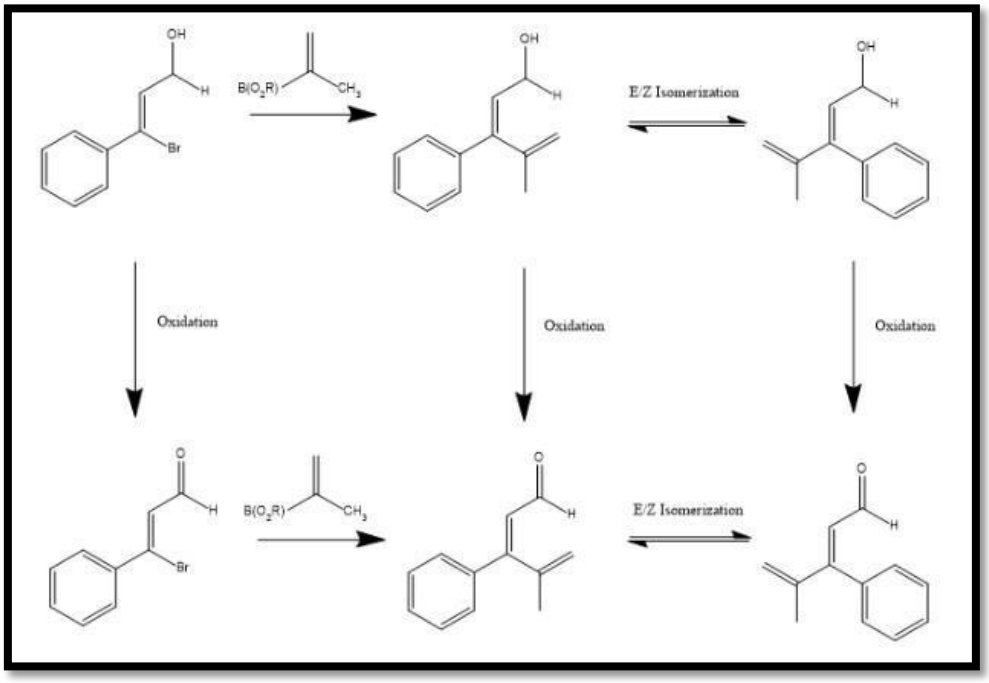
Scheme 4.1. Alternate route to diastereoselective pent-2,4-dienals via reduction and oxidation.

As mentioned previously, in the absence of carbonyl, the possibility of conjugate addition taking place should be eliminated, thereby allowing for coupling to proceed stereoselectivity. Despite the synthesis taking an additional two steps to account for the separate reduction and oxidation, we hope that the diastereoselectivity of the coupling and yields will compensate for the tedious nature of this alternative route compared to that of the proposed.

As such, the reduction was classically carried out with sodium borohydride and iodine as a catalyst. Following acidic workup, the alcohol was obtained cleanly with little impurities. Afterwards, two coupling reactions were attempted with the bromoenol with equal molar concentrations of $PdCl_2(dppf)$ and $Pd(PPh_3)_4$, respectively. Although the latter catalyst system

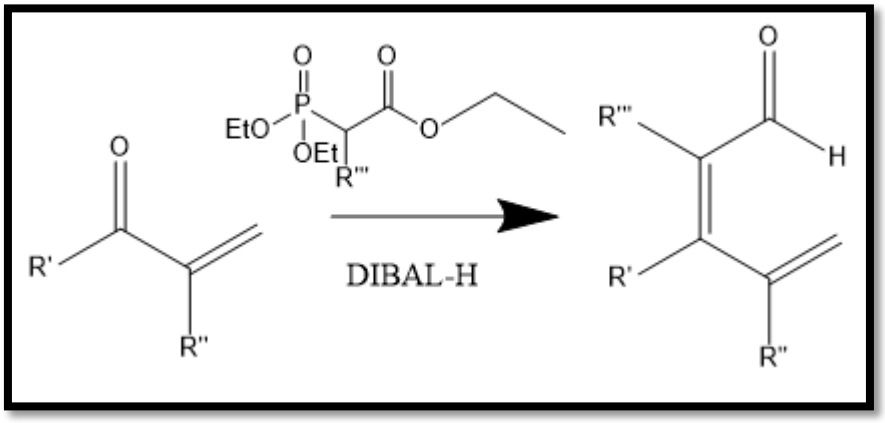
was found to be undesirable in the case of the bromoenal, it was speculated that without the possibility of the new substrate isomerizing, phosphine-rich and dissociable catalysts may work in our favor in this instance in accelerating the reaction rate. However, when the coupling was attempted using the optimal reaction conditions, no transformation was noticeable by TLC in either reaction – even when left for 6 days.

The Suzuki reactions were attempted once more, but in exchange of toluene rather than THF as a higher boiling point solvent and at reflux. Complete transformation of the starting material was noticed in 25 hrs, and the reactions were worked up as usual. Interestingly, the resulting TLC revealed two pairs of two spots with each pair having a similar Rf. Following purification and ^{1}H NMR, it was determined that one pair of spots corresponded to the desired and isomerized products of the pent-2,4-dienol, whereas the other pair corresponded to the pent-2,4-dienal diastereomers from before. This is an indication that either the substrate, intermediate, or product was oxidized prematurely back to the aldehyde, presumably by the metal complex, coupled, and then isomerized into their stereoisomers (Scheme 4.2). However, given that the rate of the coupling reaction is strongly influenced positively (in the forward direction) by the presence of the carbonyl, the first oxidation pathway seems to be the most likely outcome.



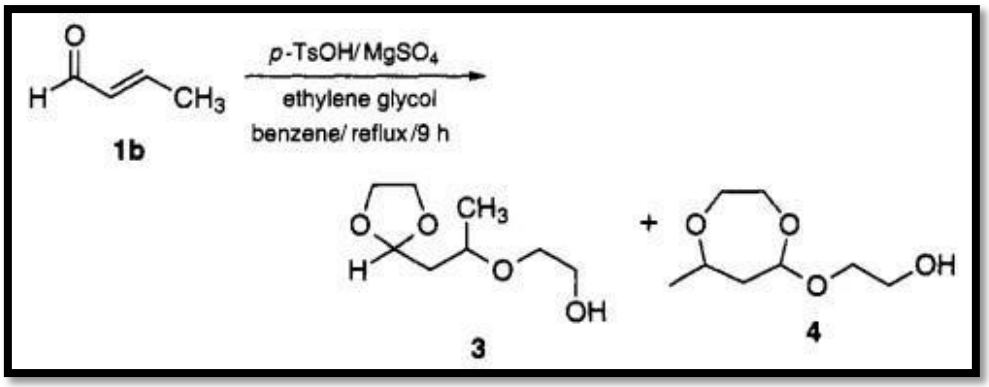
Scheme 4.2. Proposed rationale for the formation of E/Z stereoisomers from the alcohol and aldehyde.

Other alternate syntheses could be carried out to circumnavigate the isomerization process entirely, even if additional steps are necessary. One possibility, for example, could be via a modified Horner-Wadsworth-Emmons (HWE) reaction (Scheme 4.3),[45,46] since it generally favors the formation of (E)-alkenes. This reaction generally utilizes phosphonate-stabilized carbanions that are more nucleophilic but less basic than their ylide counterpart used in the classic Wittig reaction. As illustrated in Scheme 4.3, reduction of the ester following the HWE reaction with DIBAL-H or equivalent should result in the desired aldehyde.



Scheme 4.3. Proposed alternate synthesis to pent-2,4-dienals via Horner-Wadsworth-Emmons (HWE) reaction.

On the other hand, it may be wise to protect the aldehyde via formation of the acetal instead if one wishes to continue working with α, β-unsaturated aldehydes for coupling. An acidic environment, however, may be a cause for concern if an acetalization were performed. Although the alkene itself should not be too reactive, the use of strong Lewis acids can potentially trigger polymerization as observed while conducting the Vilsmeier-Haack reactions, especially at elevated temperatures. Additionally, conjugate addition to the double-bond is also likely as detected by Lu[47] under the reaction conditions with crotonaldehyde (Scheme 4.4). Fortunately, this was reduced by adding magnesium sulfate and by reducing amounts of ethylene glycol and p-toluenesulfonic acid, making this method potentially viable.



Scheme 4.4. Undesired byproducts from the acetalization of crotonaldehyde.

CHAPTER 5: CONCLUSION

This study highlights a new protocol for the synthesis of pent-2,4-dienals for the development of substituted cyclopentenones. All steps of the synthesis carried out in this investigation worked successfully, albeit with poor to modest yields (36-75%). The most significant challenge is the E/Z isomerization during the Suzuki Coupling. However, we have significantly reduced the rate of this process to an extent that may still be beneficial for industry and other applications.

Future work will certainly need to be done to optimize the reaction conditions for Suzuki-coupling of β-bromoacroleins, especially to account for varying steric and electronic effects by different substituents during coupling. This should be done accordingly by adjusting the ligands of the catalyst – perhaps utilizing those mentioned in the literature. Once chosen, a variety of solvents with a range of polarities can be tested to best facilitate reaction conditions. From there, the scope of the Suzuki reaction should be expanded upon by utilizing additional boronic acids and α, β-unsaturated bromo-3-enals based on electronic factors.

Moreover, the Suzuki coupling method used for this study will need to be improved upon or revised entirely. This is due to the sensitivity of both the bromo-3-enals and pent-2,4-dienals to polymerize and undergo inevitable side reactions under its conditions. However, if one were to revise the synthesis and/or its methodology, it would be best to do so with special considerations of its unique stereochemical outcomes and underlying mechanisms as a result of functionality.

Experimental

General. All reactions were done in oven-dried glassware under dry N_2. Tetrahydrofuran was distilled over sodium metal. HPLC grade hexane and ethyl acetate were used as developing solvents for flash column chromatography. Analytical thin-layer chromatography was carried out using EM Science silica gel and analyzed by a UV lamp (254 nm). ^{1}H NMR spectra were recorded using a Bruker 400 (400 MHz). Samples were dissolved in deuterated chloroform and referenced to TMS (0.00 ppm). E/Z ratios were recorded using the Bruker 400 (400 MHz) ^{1}H NMR integration feature.

Preparation of α,β-Unsaturated Bromo Aldehydes. To a three-necked, round-bottomed flask was attached an addition funnel charged with PBr_3 (20 mmol), which was added dropwise to a mixture of DMF (22 mmol) and chloroform (8 mL) under continuous stirring in an ice-water bath (0 ºC) for 60 minutes. The ketone (7.36 mmol) was then added, and the resulting the solution allowed to slowly come to 30 ºC and was stirred for 12-16 hours or overnight. The solution was then neutralized with solid sodium bicarbonate, transferred to a separatory funnel containing ice-cold water (100 mL), and extracted with dichloromethane (3-40 mL portions). The combined organic layers were washed with saturated NaCl solution (40 mL), dried under anhydrous $MgSO_4$, and concentrated to a crude oil. Purification by column chromatography with portions of hexane and ethyl acetate produced the corresponding bromo aldehyde.

(Z)-3-bromo-2-methyl-3-phenylprop-2-enal. In accordance with the procedure, PBr_3 (1.96 mL) was added dropwise to DMF (1.73 mL) and chloroform (7.87 mL) under stirring. Propiophenone (0.995 mL) was added, and the solution was stirred for 12 hours. Work-up resulted in a clear, colorless oil (31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.42-7.69 (m, 5H), 1.96 (s, 3H).

3-bromo-3-phenyl-2-propenal. In accordance with the procedure, PBr_3 (3.86 mL) was added dropwise to DMF (3.49 mL) and chloroform (30.7 mL) under stirring. Acetophenone (1.72 mL) was added, and the solution was stirred for 12 hours. Work-up resulted in a yellow oil (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (d, 1H), 7.45-7.75 (m, 5H), 6.82 (d, 1H).

3-bromo-5-phenylpenta-2,4-dienal. In accordance with the procedure, PBr_3 (3.92 mL) was added dropwise to DMF (3.49 mL) and chloroform (29.9 mL) under stirring. Benzalacetone (2.185 g) was added, and the solution was stirred for 14 hours. Work-up resulted in a yellow, crystalline solid (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (d, 1H), 7.38-7.56 (m, 6H), 6.93 (d, 1H), 6.48 (d, 1H).

2-bromo-5-phenylcyclohexene-1-carbaldehyde. In accordance with the procedure, PBr_3 (1.32 mL) was added dropwise to DMF (1.19 mL) and chloroform (10.3 mL) under stirring. 4-Phenylcyclohexanone (0.8722 g) was added, and the solution was stirred for 12 hours. Work-up resulted in a clear, colorless oil (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.22-7.37 (m, 5H), 2.77-2.97 (m, 5H), 2.27 (m, 1H), 2.08 (m, 1H).

Preparation of Pent-2,4-dienals (in accordance with literature method[16]). To a Schlenk flask was added the bromo aldehyde (1.08 mmol), THF (10 mL), boronic acid pinacol ester (1.30 mmol), cesium carbonate (3.24 mmol), and $Pd(PPh_3)_4$ (0.022 mmol). The mixture was heated to 60 ºC and stirred under reflux for 24 hours. The solution was diluted with water (20 mL) and extracted with ethyl acetate (3-15 mL portions). The combined organic layers were washed with saturated NaCl solution (25 mL), dried under $MgSO_4$, and concentrated to oil. Purification by column chromatography with portions of hexane and ethyl acetate produced the pentadienal.

4-methyl-3-phenyl-2,4-pentadienal. In accordance with the procedure, a mixture of 3-bromo-3-phenyl-2-propenal (0.202 g), THF (10 mL), 2-isopropenyl boronic acid pinacol ester (0.236 g), cesium carbonate (1.062 g), and $Pd(PPh_3)_4$ (28 mg) was heated and stirred. Work-up resulted in a yellow oil (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 E (d, 1H), 9.38 Z, 7.41-7.54 (m, 5H), 6.38 (d, 1H), 5.57 (d, 1H), 5.33 (d, 1H), 1.93 (s, 3H).

Preparation of Cyclopentenones. To a Schlenk flask was added $[Rh(dppe)(nbd)]^+(BF_4)^-$ (5 mol%) and dichloromethane (4 mL). Hydrogen gas was allowed to permeate throughout the system for 5 minutes to activate the catalyst. The remaining amount of dichloromethane (3 mL) was added to dissolve the pentadienal and the solution was transferred by syringe to the hydrogenated catalyst. The solution was stirred at 30 °C for 2-12 hrs, passed through silica and concentrated to oil. Purification by column chromatography with portions of hexane and ethyl acetate produced the corresponding cyclopentenone.

4-methyl-3-phenyl-2-cyclopenten-1-one. In accordance with the procedure, the catalyst (30 mg) was dissolved with dichloromethane (4 mL) and activated with hydrogen gas. A solution of 4-methyl-3-phenyl-2,4-pentadienal (0.141 g) and dichloromethane (3 mL) was added and allowed to stir for 2 hrs. Work-up resulted in a black oil.

4-methyl-3-[(E)-2-phenylethenyl] cyclopent-2-en-1-one. In accordance with the procedure, the catalyst (6.2 mg) was dissolved with dichloromethane (0.7 mL) and activated with hydrogen gas. A solution of 4-methyl-3-phenyl-2,4-pentadienal (24 mg) and dichloromethane (0.5 mL) was added and allowed to stir for 12 hrs. Work-up resulted in gold oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.58 (m, 5H), 7.10 (s, 1H), 6.16 (s, 1H), 3.34 (m, 1H), 2.80 (dd, 1H), 2.11-2.20 (m, 2H), 1.36 (d, 3H).

Preparation of Pent-2,4-dienals (updated and optimized). To a Schlenk flask was added the bromo aldehyde (1.08 mmol), THF (10 mL), boronic acid pinacol ester (1.30 mmol), cesium carbonate (3.24 mmol), and $PdCl_2$(dppf) (2 mol%). The mixture was heated to 50 ºC and stirred for 1 hour. The solution was passed through silica with dichloromethane and concentrated to oil. Purification by column chromatography with portions of hexane and ethyl acetate produced the corresponding pentadienal.

4-methyl-3-phenyl-2,4-pentadienal. In accordance with the procedure, a mixture of 3-bromo-3-phenyl-2-propenal (0.1216 g), THF (12.3 mL), 2-isopropenyl boronic acid pinacol ester (0.649 g), cesium carbonate (0.649 g), and $PdCl_2$(dppf) (8.6 mg) was heated and stirred. Work-up resulted in a yellow oil (75%, 20:1 E/Z). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 E (d, 1H), 7.41-7.54 (m, 5H), 6.38 (d, 1H), 5.57 (d, 1H), 5.33 (d, 1H), 1.93 (s, 3H).

3,4-diphenylpent-2,4-dienal. In accordance with the procedure, a mixture of 3-bromo-3-phenyl-2-propenal (0.0682 g), THF (6.4 mL), 4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (0.0988 g), cesium carbonate (0.3488 g), and $PdCl_2$(dppf) (5.5 mg) was heated and stirred. Work-up resulted in a yellow oil (29%, All E). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (d, 1H), 7.33-7.59 (m, 10H), 6.74 (d, 1H), 6.17 (d, 1H), 5.51 (d, 1H).

3-phenyl-4-(trifluoromethyl)pent-2,4-dienal. In accordance with the procedure, a mixture of 3-bromo-3-phenyl-2-propenal (0.0654 g), THF (6.7 mL), 4,4,5,5-tetramethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborolane (0.0956 g), cesium carbonate (0.3476 g), and $PdCl_2$(dppf) (6.0 mg) was heated and stirred. Work-up resulted in a yellow oil (61%, 2.3 E/Z). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 E (d, 1H), 9.40 Z, 7.44-7.55 (m, 5H), 6.65 (d, 1H), 6.44 (d, 1H), 5.86 (d, 1H).

4-phenyl-2-prop-1-en-2-ylcyclohexene-1-carbaldehyde. In accordance with the procedure, a mixture of 2-bromo-5-phenylcyclohexene-1-carbaldehyde (0.0852 g), THF (6.4 mL), 2-isopropenyl boronic acid pinacol ester (0.0760 g), cesium carbonate (0.3517 g), and $PdCl_2$(dppf) (4.7 mg) was heated and stirred. Work-up resulted in a yellow oil (45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.22-7.36 (m, 5H), 5.22 (d, 1H), 4.93 (d, 1H), 2.81 (m, 2H), 2.54 (m, 2H), 2.22 (m, 1H), 2.10 (m, 1H), 1.99 (s, 3H), 1.78 (m, 1H).

5-phenyl-2-(1-phenylethenyl)cyclohexene-1-carbaldehyde. In accordance with the procedure, a mixture of 2-bromo-5-phenylcyclohexene-1-carbaldehyde (0.0844 g), THF (6.4 mL), 4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (0.0972 g), cesium carbonate (0.347 g), and $PdCl_2$(dppf) (5.2 mg) was heated and stirred. Work-up resulted in a clear, colorless oil (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.25-7.44 (m, 10H), 5.83 (d 1H), 5.26 (d, 1H), 2.92 (m, 2H), 2.49 (m, 3H), 2.04 (m, 1H), 1.85 (m, 1H).

5-phenyl-2-(3,3,3-trifluoroprop-1-en-2-yl)cyclohexene-1-carbaldehyde. In accordance with the procedure, a mixture of 2-bromo-5-phenylcyclohexene-1-carbaldehyde (0.0830 g), THF (6.5 mL), 4,4,5,5-tetramethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborolane (0.0923 g), cesium carbonate (0.3467 g), and $PdCl_2$(dppf) (4.4 mg) was heated and stirred. Work-up resulted in a yellow oil (36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (d, 1H), 7.24-7.37 (m, 5H), 6.12 (d, 1H), 5.59 (d, 1H), 2.81-2.86 (m, 2H), 2.60 (m, 2H), 1.84-2.13 (m, 3H).

5-phenyl-3-prop-1-en-2-ylpenta-2,4-dienal. In accordance with the procedure, a mixture of 3-bromo-5-phenylpenta-2,4-dienal (0.0739 g), THF (6.6 mL), 2-isopropenyl boronic acid pinacol ester (0.0746 g), cesium carbonate (0.3482 g), and $PdCl_2$(dppf) (4.3 mg) was heated and stirred. Work-up resulted in a yellow oil (40%, 4.6 E/Z). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 Z,

9.90 E (d, 1H), 7.34-7.51 (m, 6H), 7.01 (d, 1H), 5.97 (d, 1H), 5.47 (d, 1H), 5.07 (d, 1H), 2.08 (s, 3H).

5-phenyl-3-(1-phenylethenyl)penta-2,4-dienal. In accordance with the procedure, a mixture of 3-bromo-5-phenylpenta-2,4-dienal (0.0730 g), THF (7.2 mL), 4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (0.1004 g), cesium carbonate (0.3516 g), and $PdCl_2$(dppf) (4.8 mg) was heated and stirred. Work-up resulted in a yellow oil (44%, 9.4 E/Z). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 Z, 9.82 E (d, 1H), 7.02-7.41 (m, 10H), 6.94 (m, 2H), 6.28 (d, 1H), 6.09 (d, 1H), 5.28 (d, 1H).

5-phenyl-3-(3,3,3-trifluoroprop-1-en-2-yl)penta-2,4-dienal. In accordance with the procedure, a mixture of 3-bromo-5-phenylpenta-2,4-dienal (0.0737 g), THF (6.2 mL), 4,4,5,5-tetramethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborolane (0.1014 g), cesium carbonate (0.3487 g), and $PdCl_2$(dppf) (4.8 mg) was heated and stirred. Work-up resulted in a yellow oil (40%, 5.4 E/Z). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 Z, 9.83 (d, 1H), 7.34-7.54 (m, 6H), 6.99 (d, 1H), 6.41 (d, 1H), 6.28 (d, 1H), 5.76 (d, 1H).

3-bromo-3-phenyl-2-propen-1-ol. To a three-necked, round-bottomed flask equipped with an addition funnel was added $NaBH_4$ (0.0905 g) in dry THF (2 mL). A solution of 3-bromo-3-phenyl-2-propenal (0.4172 g) and THF (3 mL) was added slowly under stirring. The reaction mixture was cooled in an ice-water bath (0 °C) and was gradually added iodine (0.2615 g) in THF (3 mL) in a period of 30 min. After 14 hrs, the mixture was quenched with 3 M HCl (2x5 mL) and extracted with ether (3x10 mL). The organic layers were washed with 3 M NaOH (3x5 mL), dried over anhydrous Na_2SO_4, and concentrated to oil (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.38 (m, 5H), 6.50 (t, 1H), 4.50 (d, 2H).

Suzuki Coupling of 3-bromo-3-phenyl-2-propenol. In accordance with *Preparation of 2,4-Pentadienals* (updated and optimized), a mixture of 3-bromo-3-phenyl-2-propenol (0.1180 g), THF (5 mL), 2-isopropenyl boronic acid pinacol ester (0.1104 g), cesium carbonate (0.5496 g), and $PdCl_2$(dppf) (8.8 mg) was heated and stirred. Work-up resulted in a yellow oil containing multiple products.

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