PALLADIUM COMPLEXES OF CHELATING CARBENES FOR CATALYTIC HECK REACTIONS AND 1,4-CONJUGATE ADDITION REACTIONS

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PREFACE

Activities of a series of modular palladium Chugaev-type carbene complexes were investigated in catalytic Heck and 1,4-conjugate addition reactions. Significant variations of catalytic activity with ligand structure were observed in the Heck reaction. A methyl hydrazine-derived palladium dicarbene dibromide complex was recognized as the most effective precatalyst for the Heck reaction. The best precatalyst selected mediated the Heck reaction of electron-poor aryl chlorides and a range of aryl bromides with styrene in high yields at 120 ºC. Heck reactions performed under air showed limited air tolerance.

The modular nature of the palladium Chugaev-type carbene complexes also allowed optimization of the catalytic 1,4-conjugate addition reaction of organoboranes. A methyl hydrazine-derived palladium dicarbene dichloride complex was identified as the most promising precatalyst for the addition of phenylboronic acid to acyclic and cyclic enones at 40 ºC. Monitoring the 1,4-conjugate addition reactions revealed the need to optimize the reaction time, because the yield of the product decreased in most cases as the reaction was allowed to proceed for longer durations.

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INTRODUCTION

Cross-coupling Reactions

The chemistry of organometallic complexes has allowed chemists to perform new types of carbon-carbon or carbon- heteroatom bond forming reactions known as coupling reactions. Coupling reactions were first developed independently in the work of Tsuji and Trost. These reactions now play a major role in organic chemistry and in the pharmaceutical industry.[1] The functionalization of aryl halides through cross-coupling reactions is a very significant field in modern arene chemistry. This is due to the role that aromatic and heteroaromatic units play in fine chemicals intermediates and allied pharmaceuticals, agrochemical, and new materials industries.[2] Among the most useful coupling reactions are the Kumada reaction -- coupling of Grignard reagents with organo halides; the Stille reaction -- carbon-carbon bond formation between organostannanes and organo halides; the Suzuki-Miyaura reaction -- coupling between organoboronic acid and organohalides; the Mizoroki-Heck reaction -- carbon-carbon bond formation between organo halides and alkenes; and the Buchwald-Hartwig amination -- coupling between

organo halides and amines.[1] The above named reactions are usually catalyzed by palladium complexes.[1,3]

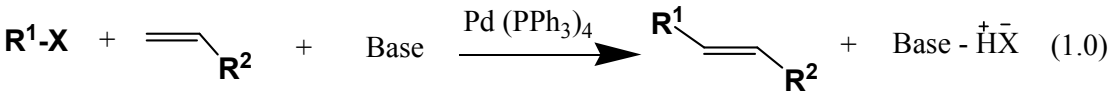
Palladium catalysts have attained a vital role in organic synthesis. Traditionally, palladium phosphine complexes have been employed as catalysts in most coupling reactions. However, in recent years it has been shown that palladium complexes containing N-heterocyclic carbene (NHC) ligands are effective catalysts for coupling reactions such as the Heck reaction,[4,5,6] Suzuki-Miyaura coupling reaction,[7,8,9] and Buchwald-Hartwig amination reaction.[10,11] The high catalytic activities found in N-heterocyclic carbene-based catalysts have been attributed to the strong σ-donor ability of the carbenes, unique steric properties[12,13] and enhanced thermal stability[14] of the N-heterocyclic carbene ligands as compared to phosphine ligands. Important synthetic applications have been achieved using N-heterocyclic carbene ligands in ruthenium-catalyzed ring–closing olefin metathesis,[14-16] palladium-catalyzed Heck reaction,[4,6] palladium-catalyzed Suzuki -Miyaura cross coupling,[7-9] nickel-catalyzed cycloaddition,[17,18] and palladium-catalyzed aerobic alcohol oxidation.[19] Although N-heterocyclic carbene ligands have advantages over phosphine ligands, limited structural variations of NHCs are available because most examples are based on imidazole. In addition, synthesis of the free carbene often results in low yields in ligand synthesis.

Chelating carbene ligands are expected to combine the favorable properties of N-heterocyclic carbenes with greater stability and possibly greater catalytic activity. Chelate ligands bind more strongly to transition metals due to the chelate effect. Nevertheless, chelating carbenes have not been widely investigated in catalysis. A few

examples of chelating palladium dicarbene complexes have been shown to be efficient catalysts in cross-coupling reactions.[4,6,20-22]

Heck Reaction

The Heck reaction is one of the basic types of palladium-catalyzed carbon-carbon bond forming reactions.[23] The palladium-catalyzed arylation of an olefin with an organic halide was discovered independently by Mizoroki and co-workers[24] in 1971 and Heck and co-workers in 1972.[25] The reaction entails bond formation between an sp^2 carbon of an olefin and an aromatic carbon of an organohalide, proceeding with formal loss of HX under basic condition.[26] This classical coupling reaction has since been known as the Heck reaction (Eq 1.0).



(1.0)

R^1 = aryl or vinyl group
X = Cl, Br, I, OTf, OTs
R^2 = electron withdrawing or releasing group

The Heck methodology has been found to be highly adaptable and applicable to a broad range of aryl species and a large array of olefins.[26] The Heck reaction works best with alkenes containing electron-withdrawing groups and in most cases gives the β-arylated products exclusively. The significance of the electron-withdrawing group is to ensure that in the catalytic cycle the insertion of the olefin takes place in a mode to give the β-arylated products.[1] The Heck reaction has attracted growing interest in synthetic

applications due to the essential role it plays in assembling larger molecules from convenient precursors.[23]

Since its discovery, the palladium-catalyzed Heck reaction has proven to be a practical synthetic method for carbon-carbon bond formation. An important aspect of the attractiveness of the Heck reaction is its outstanding *trans*-selectivity and high functional group tolerance.[27] In addition to its versatility, the Heck reaction has the advantage of using inexpensive and readily available olefins as precursors as compared to other palladium-catalyzed reactions such as the Suzuki, Stille, and Kumada coupling reactions which often employ expensive organometallic reagents.[23,27,28] Moreover, the Heck reaction has the benefit of employing inexpensive and readily available aryl bromide and chloride substrates which are convenient to synthetic chemists.[26] The Heck reaction has seen wide application in natural products synthesis,[29-31] materials science,[32,33] and bioorganic chemistry.[34,35] In addition, the Heck reaction has been practiced on an industrial scale for the production of compounds such as naproxen,[36] the antiasthma agent Singulair™,[36] and octyl methoxycinnamate (UV-B sunscreen).[36,37] The reaction is also useful in polymer chemistry allowing synthesis of conjugated polymers for specialized applications.[23]

The generally accepted mechanism for the palladium-catalyzed Heck reaction[26,38-40] is shown in Figure 1.1. The active catalytic species in this mechanism of the Heck reaction has been proposed to be a coordinatively unsaturated 14-electron palladium(0) complex. The complex is usually formed *in situ* from a Pd(II) precursor.

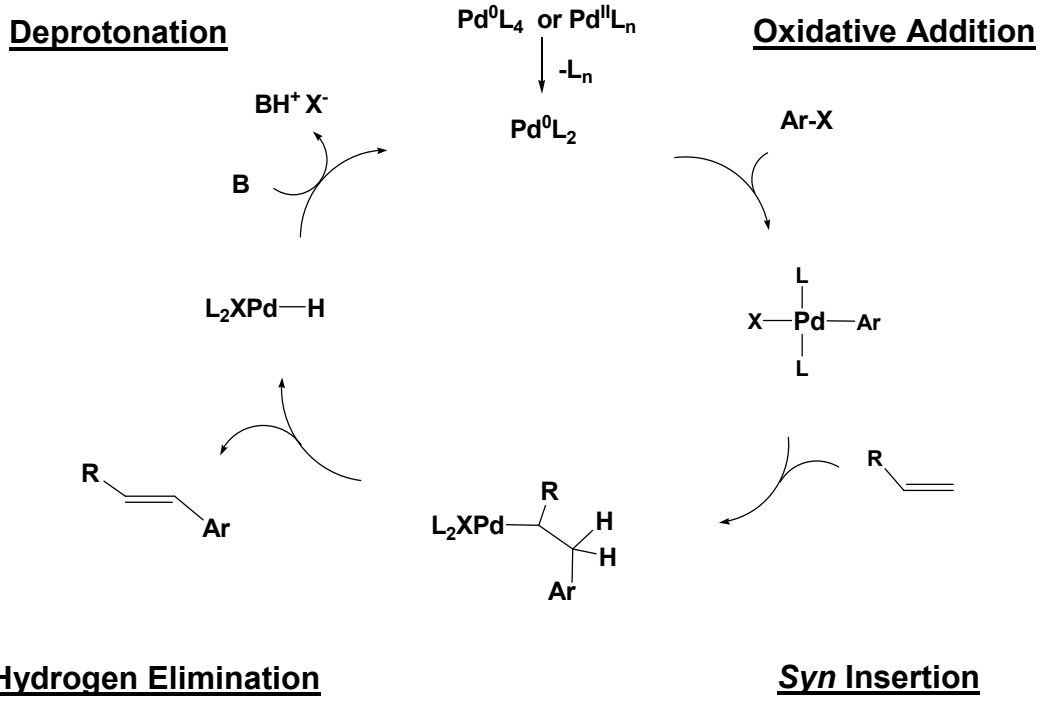


Figure 1.1 Postulated Catalytic Cycle for the Heck Reaction.

The first step of the mechanism of the Heck reaction is the oxidative addition of aryl halide RX to the coordinatively unsaturated palladium (0) complex to generate a *cis*-L_2-Pd(II)RX species which then isomerizes to a *trans* configuration that is thermodynamically more stable.[26] The electrophilicity of the complex is enhanced by the +2 oxidation state, and the olefin readily inserts into the Pd-aryl bond resulting in the formation of an unstable Pd alkyl complex.[40] The coupling product is obtained by β-hydride elimination to yield the new substituted alkene.[26,38-40] The active palladium (0) complex is regenerated by the addition of a base to eliminate hydrogen halide allowing the catalytic cycle to continue.[26,38-40] The oxidative addition step is favored when strong

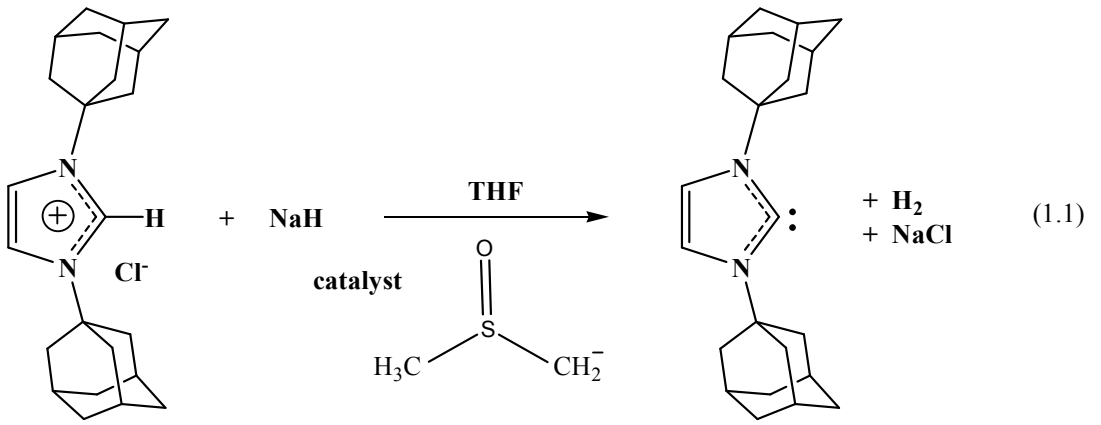
σ-donor ligands are employed, allowing the aryl halide to readily add to the palladium complex.

Various catalytic systems are known for the Heck reaction. Palladium phosphine complexes have most commonly been employed because they allow good control over the reactivity and selectivity in Heck coupling reactions.[23,26,41] One function of the ancillary phosphine ligands is to stabilize palladium in its zero oxidation state, which can initiate the catalytic cycle, while preventing the formation of inactive palladium black.[42] Fu,[27,43] Hartwig,[44] and Beller[45] have demonstrated the use of sterically bulky and electron-rich tertiary phosphines as catalyst modifiers in Heck aryl-olefin reactions. These ligands result in complexes that are able to activate less reactive aryl bromides and aryl chlorides as coupling partners in the Heck reaction due to faster rates of Ar-X oxidative addition. However, tertiary phosphine ligands and their palladium complexes are often highly water and air sensitive and prone to decomposition at the higher temperatures commonly employed under Heck conditions.[46] Consequently, about 100 times more of the phosphine ligand than the metal is required to control the activation and propagation steps in homogeneous Heck catalysis.[4] In large-scale applications, the use of excess ligand increases the running cost of production;[47] electron-rich phosphine ligands are especially expensive and toxic. Moreover, the presence of excess ligand reduces the rate of the reaction, and the removal of decomposition or oxidation byproducts from the desired product requires an involved workup and/or purification procedure. Therefore, ligands which do not need to be added in excess would be advantageous.

The design of a catalytic system which is capable of activating unreactive (deactivated) aryl chlorides towards Heck coupling reactions with high turn over numbers would be of great advantage. This is currently a challenging area in Heck chemistry. Aryl chlorides are the most desirable group of substrates for coupling reactions. The advantages of aryl chlorides over other aryl halides as substrates for Heck reaction are: (1) aryl chlorides are economically cheaper than other halides; (2) aryl chlorides are more widely available commercially; and (3) aryl chlorides are more robust and can withstand a broader array of reaction conditions.[26]

N-Heterocyclic Carbene Ligands in Catalysis

Arduengo and co-workers in 1991[48] successfully isolated the first free N-heterocyclic carbene. The carbene was prepared by the deprotonation of 1,3-di-1-adamantylimidazolium chloride in tetrahydrofuran at room temperature using one equivalent of sodium hydride and catalytic dimsyl anion (Eq.1.1).[48] The crystalline free carbene was stable in the absence of oxygen and moisture.[48] Arduengo and co-workers attributed the stability of the carbene to both steric and electronic factors.[48,49] The steric factors resulted from the presence of the two adamantyl groups, which shield the carbene center from external reagents and thereby enhance kinetic stability.[48] The electronic stability of the carbene was ascribed to the electron donation of the nitrogen filled *p*-orbitals into the vacant out-of-plane *p*-orbital of the carbene combined with the σ-electronegativity effect of the nitrogen atoms.[48]

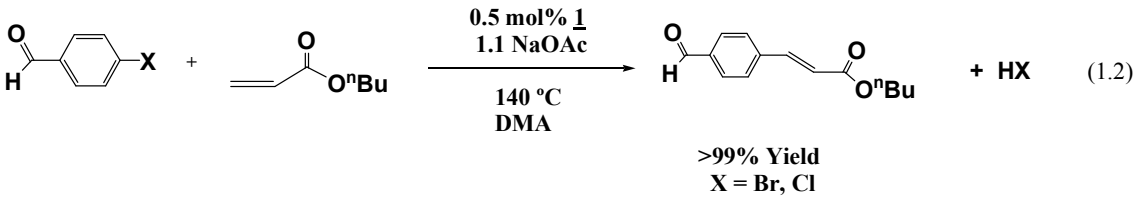


(1.1)

Since Arduengo's discovery of stable N-heterocyclic carbenes, extensive research efforts have focused on the design and application of carbenes as ligands in catalysis. These ligands are strong σ–donors with negligible π-accepting ability.[50] In this view, they resemble tertiary phosphines as electron donors. In contrast to metal phosphine complexes, N-heterocyclic carbene ligands form metal complexes that have high stability towards moisture and oxygen.[12] In addition, the carbene ligands do not easily dissociate from the metal center. Moreover, metal complexes with N-heterocyclic carbene ligands can also withstand higher temperatures in the solid state and in solution.[26] Finally, syntheses of the carbene ligands are convenient and inexpensive.[26] Significant advances in catalytic performances have been achieved with nucleophilic carbene ligands in various catalytic reactions such as palladium-mediated carbon-carbon coupling reactions,[51-54] amination of aryl chlorides,[10,11] olefin metathesis,[12,14,15,55] and olefin hydrogenation,[56,57] and opportunities exist for their application in a range of other synthetically useful reactions. The favorable steric and electronic properties exhibited by various nucleophilic carbene ligands makes them attractive candidates for mediating the Heck reaction.[58]

N-Heterocyclic Carbene Ligands in Catalytic Heck Reaction

One of the first examples of Heck catalysis using N-heterocyclic carbene ligands employed a chelating carbene ligand.[4] Using the palladium complex (**1)** shown below, Herrmann and coworkers were able to catalyze the Heck coupling of activated aryl bromides and aryl chlorides with *n*-butyl acrylate in high turnovers (Eq 1.2). High yield of the coupling product could be obtained, which Herrmann and co-workers attributed to the high thermal stability of the palladium-carbene bonds of the catalyst in solution. However the catalytic system was inefficient with electron-rich aryl halides substrates. Following Herrmann's initial report of Heck reaction with palladium N-heterocyclic carbene complexes, nucleophilic N-heterocyclic complexes attracted growing interest in other areas of catalysis.



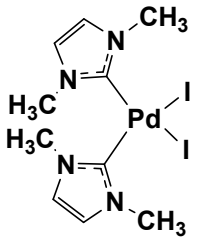
Catalyst:  **1**

Figure 1.2 Carbene Palladium Complex for Heck Reaction.

Cavell and McGuinness have shown that palladium complexes of bis-monocarbene or chelating dicarbene ligands are efficient in mediating the Heck reaction.[59,60] Cavell and McGuinness developed several palladium complexes of functionalized imidazolium-based carbenes as catalysts for practical Heck coupling of aryl halides. In their studies, they investigated the activities of the various palladium complexes in the Heck reaction using electron-poor aryl halides with *n*-butyl acrylate. Excellent yields of 90% to 92% of product were obtained for electron-neutral phenyl iodide substrate. Moderate to high yields of the coupling product, 61% to 99% were achieved when electron-deficient 4-bromoacetophenone substrate was utilized. Satisfactory conversion to the coupling product with a range of 66% to 75% was obtained for 4-chlorobenzaldehyde. A high reaction temperature of 120 ºC was used in the protocol studies. Cavell *et al.* attributed the stability and high catalytic activities observed with their selected palladium complexes to the influence of an electron-donating methyl group coordinated to the palladium center. However, the complexes were effective for only electron-poor aryl halides. The catalytic system was also efficient for Suzuki[59,60] coupling and Sonogashira[59] coupling reactions.

Nolan and coworkers have established catalytic complexes formed *in situ* from palladium precursors with sterically demanding imidazolium chlorides as active catalysts in various carbon–carbon coupling reactions.[11,52-54] The use of these ligands was successfully extended to the Heck reaction, allowing identification of a highly effective catalyst for a range of Heck reactions of aryl bromides with *n*-butyl acrylate.[58] Excellent yields close to 100% of the Heck product were obtained in less than 30 min of reaction time when electron-poor 4-bromobenzaldyde and 4-bromobenzonitrile were used as

coupling substrates in this protocol. In the reaction of electron-rich 4-bromoanisole and 3-bromoanisole, Nolan and coworkers reported that 91% and 99% yields of the coupling products could be achieved under the optimized conditions. Nonetheless, the catalytic systems developed by Nolan *et al.* were ineffective for aryl chlorides.

Chagaev-type Carbene Ligands

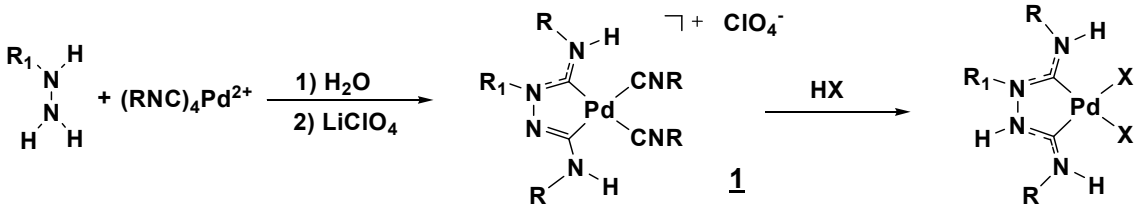
A relatively unexplored class of chelating ligand is the 'Chugaev-type' carbenes. Platinum complexes of these ligands were prepared by Chugaev and coworkers[61,62] in 1915. Nonetheless, their structures were incorrectly formulated until spectroscopic studies by Rouschias and Shaw[63] and crystallographic studies by Balch and coworkers[64] in 1970 characterized the structure. The complexes are formed by chelate addition of hydrazine to coordinated methylisocyanide. These ligands possess electronic similarities to N-heterocyclic carbenes. However, in principle chelating ligands have greater modularity than monodentate N-heterocyclic carbenes as the chelate backbone can be adapted to vary bite angle.[65-68] In addition, the ease of synthesis and modularity of chelate ligands are an advantage over N-heterocyclic carbene ligands.

Synthetic routes for a series of modular palladium Chugaev-type carbene complexes were explored in our research group. The synthesis, characterization and activities of these complexes as precatalysts in Suzuki-Miyaura cross coupling reactions have been reported by Moncada *et a*l.[69] Modular ligand variation allowed catalyst optimization. The optimized precatalyst was efficient for electron poor aryl chlorides and a range of aryl bromides.

In view of the effectiveness of these catalysts in Suzuki reactions, it was decided to investigate the activity of the novel palladium Chugaev-type carbene complexes as precatalysts in Heck coupling reactions. The following objectives were set for this project. First, the aim was to optimize substrate scope and yield in Heck reactions by varying the structure of the new carbene ligands, which possess strong donor properties similar to those of imidazole-based N-heterocyclic carbenes. The second objective was to achieve catalytic activity with aryl chlorides, the most attractive class of substrate for Heck coupling reactions. The third objective was to achieve high catalytic activity in air.

RESULTS AND DISCUSSION

A two-step procedure for the synthesis of a series of palladium Chugaev-type carbene complexes containing various alkylisocyanide substituents and halide ligands has been reported by Moncada *et a*l.[69-70] These complexes proved to be efficient precatalysts in Suzuki-Miyaura cross-coupling reactions.[69] It was a goal to investigate whether palladium Chugaev-type carbene complexes could be used as effective precatalysts in the Heck reaction. Herein are presented optimization studies probing the effect of ligand variation and selection of optimal base on the catalytic Heck reaction. Functional group tolerance of the Heck reaction catalyzed by the optimized catalyst is also presented. A general procedure[69] for the preparation of the palladium Chugaev-type dicarbene complexes used for the optimization studies is shown in Figure 1.3.



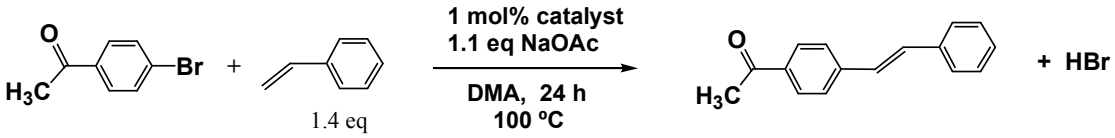
1a (R_1 = H, R = Me)
1b (R_1 = H, R = ^{i}Pr)
1c (R_1 = H, R = Cy)
1d (R_1 = H, R = ^{t}Bu)
1e (R_1 = R = Me)

Figure 1.3 Palladium Chugaev-type Dicarbene Complexes.

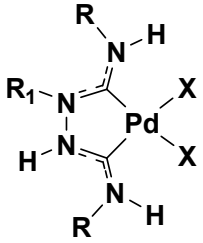
1.1 Effect of Catalyst Ligand Variation on the Heck Reaction of 4-Bromoacetophenone with Styrene.

In an effort to select the most effective precatalyst for the Heck reaction, optimization studies using several precatalysts with different substituents on the dicarbene ligand were tested (Figure 1.3) on a model reaction. 4-Bromoacetophenone (1 equiv) was treated with styrene (1.4 equiv) using 1 mol% of the precatalyst and 1.1 equiv of anhydrous sodium acetate (NaOAc) in 5 ml of N, N-dimethylacetamide (DMA). The reaction mixture was stirred at 100 ºC for 24 hours under N_2. Results for the coupling reaction are shown in Table 1.1.

Table 1.1 Effect of Catalyst Ligand Variation on the Heck Reaction of 4-Bromoacetophenone with Styrene.



Catalyst



2a - e (X = Cl)
3a - e (X = Br)

Entry	Precatalyst	R	R_1	X	Yield (%)[a]
1	2a	Me	H	Cl	16
2	3a	Me	H	Br	36
3	2b	^{i}Pr	H	Cl	69
4	3b	^{i}Pr	H	Br	93
5	2c	Cy	H	Cl	48
6	3c	Cy	H	Br	93
7	2d	^{t}Bu	H	Cl	43
8	3d	^{t}Bu	H	Br	68
9	2e	Me	Me	Cl	59
10	3e	Me	Me	Br	98

[a] Yield determined by ^{1}H NMR

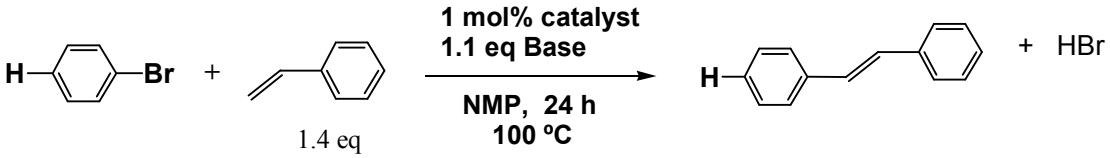
From the results in Table 1.1, the activity of the precatalysts bearing chloride ligands resulted in significantly lower yields of product (Table 1.1 entries 1, 3, 5, 7, and 9) as compared to those having bromide ligands. This could be explained as possibly due to the bromide ion being a better leaving group compared with the chloride ion. The best catalyst was found to be **3e**, the methyl hydrazine-derived complex, which gave 98% yield of *trans* 4-acetylstilbene when used in the coupling reaction (Table 1.1, entry 10). In addition, higher catalytic activity was observed with a 93% yield of the coupling product when either precatalyst **3b** or **3c** was used in the Heck reaction (Table 1.1, entries 4 and 6). The higher yields observed using palladium dicarbene complexes **3e**, **3b** and **3c** could be due to a combination of electronic and steric effects in these complexes. Recent work by Nolan[9,58] has demonstrated the use of various nucleophilic carbene ligands as suitable ligands for the Heck reaction. The strong σ-donor ability of the ligands is thought to be responsible for the high efficiency in mediating the Heck reaction by promoting Ar-X oxidative addition.[9,58] A moderate yield (68%) of *trans* 4-acetylstilbene was obtained when sterically hindered precatalyst **3d** was used. A possible explanation is weaker σ-donation of the carbene ligand as a result of the polarizability effect of the *tert*-butyl groups attached to the carbene ligand. Low catalytic activity was observed for complex **3a** (Table 1.1, entry 2). This could be due to reduced σ-donor ability of the ligand in complex **3a** due to smaller alkyl substituents making the complex less effective for Heck coupling reactions. Based on the results obtained in the catalytic Heck reaction, the best precatalyst examined was **3e**, the methylhydrazine-derived dicarbene complex. A plausible explanation for the higher activity observed with precatalyst **3e** in the Heck

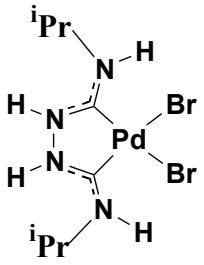
reaction could be that the three CH_3 substituents result in a more strongly electron-donating ligand compared to disubstituted dicarbene ligands.

1.2 Effect of Base on the Heck Reaction of Bromobenzene with Styrene

The reaction rate was also influenced by the type of base used in the reaction (Table 1.2). As a model reaction, bromobenzene (1 equiv) was treated with styrene (1.4 equiv) using 1 mol% of precatalyst **3b** and 1.1 equiv of the corresponding base in 5 ml of N-methyl pyrrolidone (NMP).

Table 1.2 Effect of Base on the Heck Reaction of Bromobenzene with Styrene Catalyzed by $[Pd(C_8H_{18}N_4)Br_2]$ **(3b)**.





Entry	Base	Yield (%)[a]
1	NaOAc	94
2	NEt_3	21
3	K_3PO_4	92
4	$CsCO_3$	90
5	none	11

[a] Yield determined by ^1H NMR.

An increase in activity was observed with sodium acetate (NaOAc), potassium phosphate (K_3PO_4), and cesium carbonate ($CsCO_3$) as base (Table 1.2 entries 1, 3, and 4). The use of the organic base triethylamine (Table 1.2 entry 2) gave a poor yield of the

desired Heck product as has also been demonstrated by Nolan[9] using palladium complexes formed from 1,3-disubstituted imidazolium chlorides. The low yield could be due to the ability of NEt_3 to act as a bulky ligand on palladium. Very little activity was observed when the Heck reaction was performed in the absence of a base (Table 1.2 entry 5), which indicates the significant role of the base in a Heck reaction. Based on these results NaOAc, an inexpensive and milder base, was selected as the best base for the Heck reaction using the dicarbene palladium catalysts.

1.3 Functional Group Tolerance of the Heck Reaction of Aryl Halides with Styrene Catalyzed by $Pd(C_5H_{12}N_4)Br_2$.

After optimizing the reaction conditions by selecting the best precatalysts (**3e**) and base, (anhydrous sodium acetate), Heck coupling reactions of various aryl halides with styrene were examined using 1 equiv of aryl halide with 1.4 equiv of styrene with 1 mol% of the precatalyst and 1.1 equiv of NaOAc in 5 ml of N-methyl pyrrolidone (NMP). The reaction mixtures were stirred at 120 ºC for 24 hours. Excellent yields of the coupling products were obtained from a wide range of aryl bromides when the reaction was carried out under N_2 (Table 1.3).

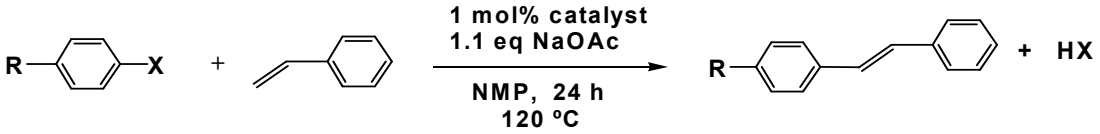
For electron-neutral aryl bromides, a nearly quantitative reaction (99%) of *trans* stilbene was obtained when bromobenzene was treated with styrene (Table 1.3 entry 1a). For electron-deficient aryl bromides 4-bromoacetophenone, 4-bromobenzonitrile and bromo-4-nitrobenzene, excellent yields of 98%, 97% and 97% of the coupling products were achieved respectively (Table 1.3 entries 2a, 3a and 4a). The precatalyst was effective for electron-rich aryl bromides as well. High yields of 93% and 92% of the

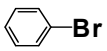
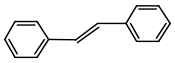
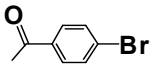
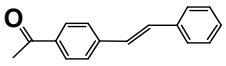
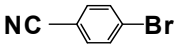
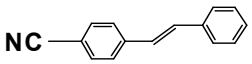
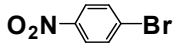
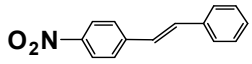
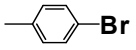
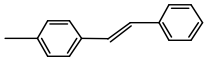
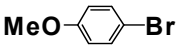
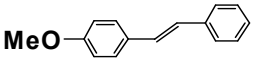
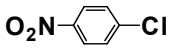
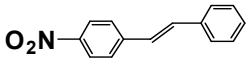
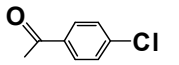
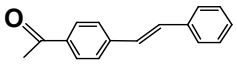
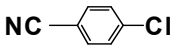
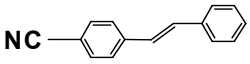
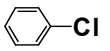
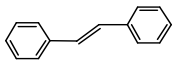
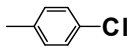
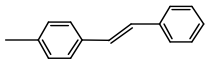
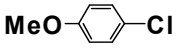
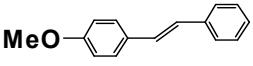
coupling product were obtained for Heck reaction of bromotoluene and bromoanisole with styrene (Table 1.3 entries 5a and 6a).

However, moderate to low yields (64% - 9%) of the coupled products were obtained for aryl bromides under aerobic conditions (Table 1.3 entries 1b, 2b, 3b, 4b, 5b, and 6b). A possible explanation could be that the catalyst has limited air stability. In addition, the lower yields obtained for electron-rich substrates (Table 1.3 entries 5b and 6b) could reflect that the substituents (-Me and –OMe) are susceptible to oxidation at higher temperature. It is unclear whether oxidative stability of the substrate or that of the catalyst is the limiting factor.

The optimized precatalyst was also examined with an array of aryl chlorides as possible coupling partners in the Heck reaction using the reaction protocol described above. Excellent to moderate yields of products (96% - 40%) were obtained for electron-poor aryl chlorides (Table 1.3 entries 7, 8 and 9). However, no coupling products were achieved for electron-rich aryl chlorides (Table 1.3 entries 10, 11 and 12). This could arise from the fact that Ar-Cl has a stronger bond compared to other aryl halides which makes the electron-rich aryl substrates less reactive toward oxidative addition to the active palladium(0) complex in the catalytic cycle. This suggests that the active Pd(0) intermediate is not reactive enough to activate aryl chlorides.

Table 1.3 Functional Group Tolerance of the Heck Reaction of Aryl Halides with Styrene Catalyzed by $Pd(C_5H_{12}N_4)Br_2$.



Entry	Ar-X	Conditions	Product	Yield (%)[a]
1a		N_2		99
b		Air		13
2a		N_2		98[b]
b		Air		64
3a		N_2		97
b		Air		57
4a		N_2		97
b		Air		58
5a		N_2		93
b		Air		18
6a		N_2		92
b		Air		9
7		N_2		96
8		N_2		40
9		N_2		45
10		N_2		-
11		N_2		-
12		N_2		-

Reaction conditions: 1.0 mmol of aryl halide, 1.4 mmol styrene, 5 ml of NMP.
[a] Yield determined by ^1H NMR.
[b] Reaction carried out at 100 °C.

SUMMARY AND CONCLUSIONS

By varying the ligand structure of Chugaev-type dicarbenes, new effective palladium precatalysts for the Heck reaction have been successfully identified. The best precatalyst selected is the methylhydrazine palladium dicarbene dibromide complex (**3e**). The best precatalyst selected (**3e**) proved to be highly effective for a range of aryl bromides and electron-poor aryl chlorides in Heck coupling reactions with styrene. Aryl bromides and chlorides are useful classes of substrates for synthetic chemists due to their low price and ready availability. This protocol gives the desired *trans* coupling product in excellent yield. The reactivity of the precatalyst did not appear efficient for electron-rich aryl chlorides, and the catalysts showed limited air stability. Future studies could be aimed at increasing activity of the catalyst by modifying the ligand structure with more electron-donating groups to allow activation of a range of aryl chlorides in the Heck reaction and also at improving Heck reactions in air.

EXPERIMENTAL SECTION

General Considerations. Palladium-catalyzed Heck reaction substrates 4-bromoacetophenone (Aldrich) and 4-bromonitrobenzene (Eastman) were recrystallized from hexanes prior to use. 4-Bromobenzene (Aldrich) was purified according to a literature procedure.[71] 4-Bromotoluene (Acros Organics); 4-bromoanisole (Acros Organics); 4-bromobenzonitrile (Aldrich); 4-chloroacetophenone (Acros Organics); 4-chlorotoluene (Acros Organics); 4-chloroanisole (Aldrich); 4-chloronitrobenzene (Eastman); 4-chlorobenzonitrile (Aldrich); styrene (Acros Organics 99%); and diethylene glycol dibutyl ether (NMR standard, Acros Organics) were used as received. Anhydrous sodium acetate (Acros Organics); potassium phosphate (Aldrich); cesium carbonate (Across Organics); triethylamine (Fisher Scientific); and magnesium sulfate (Fisher Scientific) were used as received. Anhydrous N, N-dimethylacetamide (Acros Organics, septum-sealed bottle); anhydrous N-methylpyrrolidone (Acros Organics, septum-sealed bottle), were used as received for reactions under inert atmosphere, and undried N-methylpyrrolidone (Acros Organics, 99+%) was used as received for aerobic reactions. Dichloromethane (Pharmco) was of reagent grade and was used without purification. Water was purified by an E-pure system (Barnstead) and had a resistivity of ≥ 17.6 MΩ-cm. The NMR solvent $CDCl_3$ (Cambridge Isotope Laboratories, Inc, 99.8%) was used as received.

^{1}H nuclear magnetic resonance spectra were recorded on Varian 300 MHz or Varian 400 MHz spectrometers. Reported chemical shifts were referenced to residual solvent peaks. Yields were determined by ^{1}H NMR spectroscopy.

1.1 Effect of Catalyst Ligand Variation on the Heck Reaction of 4-Bromoacetophenone with Styrene.

General Procedure: In a glove box, anhydrous sodium acetate (1.87 mmol, 154 mg), 4-bromoacetophenone (1.7 mmol, 338 mg) and styrene (2.4 mmol, 275 μL) were added to an ampule flask, followed by addition of a solution of precatalyst (0.017 mmol) in anhydrous N, N-dimethylacetamide (5 mL). The flask was sealed with a Teflon stopcock, placed in a preheated oil bath at 100 ºC, and vigorously stirred for 24 hours. The reaction mixture was allowed to cool to room temperature, and 100 μL of diethylene glycol dibutyl ether (NMR internal standard) was added to the flask. A 200-μL aliquot of the reaction mixture was then added to 10 mL of CH_2Cl_2. The organic layer was extracted four times with 10 mL portions of water and then dried ($MgSO_4$). The extraction solvent (CH_2Cl_2) was removed in vacuo. The remaining residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy. The product peak assignments were based on authentic samples. The percent yield of the coupling product was calculated by comparing ^{1}H NMR integrations with an internal standard.

1.2 Effect of the Base on the Heck Reaction of Bromobenzene with Styrene Catalyzed by [$Pd(C_8H_{18}N_4)Br_2$] (3b) .

General Procedure: In an ampule flask were placed respective amounts of base (1.87 mmol, 1.1 eqv.), bromobenzene (1.7 mmol, 179 μL), styrene (2.4 mmol, 275 μL) and a solution of precatalyst **3b** (0.017 mmol) in anhydrous N-methylpyrrolidone (5 mL) in a glove box. The flask was sealed, and the reaction mixture was vigorously stirred in a preheated oil bath at 120 ºC for 24 hours. The reaction mixture was allowed to cool, and 100 μL of diethylene glycol dibutyl ether (NMR internal standard) was added to the flask. A 200-μL aliquot of the reaction mixture was then added to 10 mL of CH_2Cl_2. The organic layer was extracted four times with 10 mL portions of water, and dried ($MgSO_4$), and filtered, and the CH_2Cl_2 was removed in vacuo. The residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR spectroscopy. The product peak assignments were based on an authentic sample. The percent yield of the coupling product was calculated by comparing ^1H NMR integrations to those of an internal standard.

1.3 Functional Group Tolerance of the Heck Reaction of Aryl Halides with Styrene Catalyzed by $Pd(C_5H_{12}N_4)Br_2$.

General Procedure: Sodium acetate (1.87 mmol, 154 mg), aryl halide (1.7 mmol) styrene (2.4 mmol, 275μL), and a solution of the precatalyst **3e** (0.017 mmol) in N-methyl pyrrolidone (5 mL) were added, respectively, to an ampule flask. Reactions performed under N_2 were set up in a dry box. Anhydrous N-methyl pyrrolidone (5 ml) was used, and the flask was sealed with a Teflon stopcock. For aerobic reactions, undried N-methylpyrrolidone was employed, and the flask was connected to a reflux condenser open to air. The flask was placed in a preheated oil bath at 120 ºC, and stirred for 24

hours. The reaction mixture was allowed to cool, and 100 μL of diethylene glycol dibutyl ether (NMR internal standard) was added to the flask. A 200-μL aliquot of the reaction mixture was then added to 10 mL of CH_2Cl_2. The organic layer was extracted four times with 10 mL portions of water, dried ($MgSO_4$), and filtered, and the CH_2Cl_2 was then removed in vacuo. The remaining residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR spectroscopy. The product peak assignments were based on an authentic sample. The percent yield of the coupling product was calculated by comparing ^1H NMR integrations to those of an internal standard.

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Chapter 2

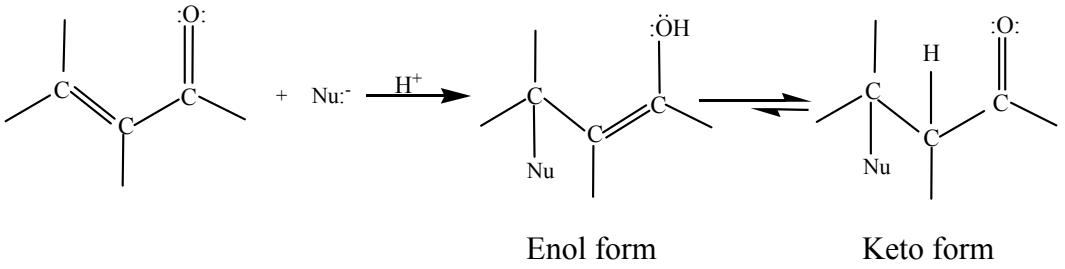
Application of Palladium and Rhodium Dicarbene Complexes as Precatalysts in 1,4-Addition Reactions of Organoboron Reagents

INTRODUCTION

Carbon-carbon bond formation plays an important role in synthetic chemistry. Growing interest has been devoted to transition-metal catalyzed reactions of organometallic reagents in modern organic chemistry. The use of organometallic reagents provides a source of nucleophilic carbon atoms that can react with an electrophilic carbon site to form a new carbon-carbon bond. These coupling reactions are widely employed in the synthesis of pharmaceuticals, fine chemicals, petrochemicals, agricultural chemicals, and polymers.[1,2,3] The advancement of these catalyzed reactions are usually powered by the nature of the catalyst and its allied ligands. On the other hand, altering the nature of the organometallic reagents for example, organozinc, organotin, and organoboron compounds, can fine-tune reactivity.

The 1,4-conjugate addition reaction is a nucleophilic addition of a carbon nucleophile to the β carbon of a carbon-carbon double bond of an α,β-unsaturated aldehyde or ketone[4,5](Eq 2.0). The reaction proceeds because the oxygen atom of the α,β-unsaturated carbonyl compound is electronegative and withdraws electrons from the β carbon, making it electron-poor and readily available for nucleophilic attack.[4] The 1,4-

conjugate addition reaction usually is preferred over 1,2-addition to the carbonyl carbon when weaker nucleophiles are utilized.



2.0

Enol form Keto form

Nu: $^-$ = nucleophile

The 1,4-conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a powerful and widely used method for the construction of carbon-carbon bonds.[6] These bond formations yield β-substituted carbonyl compounds which are useful synthetic intermediates in organic synthesis.[6] The 1,4-addition reaction proceeds in moderately polar or nonpolar solvents such as tetrahydrofouran (THF), dioxane, and cyclohexane. Also the reaction proceeds smoothly without addition of base, which is of great practical advantage. Copper-catalyzed additions of organozinc reagents are the most commonly developed catalytic systems for conjugate additions to activated alkenes.[7-11] However, the synthetic applications of these systems are limited due to the low availability of organozinc reagents and their air sensitivity.

Rhodium-catalyzed reactions of organoboranes,[12-19] organosilanes,[20-24] and organostannanes[25-27] have received growing attention as an attractive alternative to the copper catalyzed processes due to their compatibility with a wide range of functional

groups, their moisture and air stability, and the availability of a range of chiral phosphine ligands for rhodium catalysts.[28] In addition, these reactions occur with aryl nucleophiles that are mild organometallic reagents, in contrast to reactions involving copper catalysis.[29] Miyaura and co-workers[19] reported the first practical rhodium-catalyzed 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones. Using different phosphine ligands, Miyaura *et al*. were able to obtain good yields in the range of 70 to 99% for the reaction of phenylboronic acid with methyl vinyl ketone at 50 °C.

The rhodium system of Miyaura *et al*. encouraged optimization of the reaction conditions of the rhodium-catalyzed 1,4-addition to attain high enantioselectivity in asymmetric reactions. A major advancement from the research groups of Miyaura and Hayashi demonstrated that rhodium (I) complexes are excellent catalysts for chiral conjugate addition reactions of enones using aryl- and alkenylboron reagents.[6,19] The rhodium-catalyzed reaction has also been extended the addition of arylboronic acids and their like to carbon-carbon triple bonds[30] and carbon-heteroatom double bonds.[31-35] The recent application of the rhodium-catalyzed addition reaction to catalytic asymmetric carbon-carbon bond forming reactions[8,36-39] is of great synthetic value. High enantioselectivities have been reported by Hayashi *et al.* in the 1,4-conjugate addition involving a range of activated olefins catalyzed by rhodium chelating phosphine complexes.[40] The rhodium catalyst system works efficiently in the 1,4-conjugate addition under mild conditions and in reaction temperature range of 50 °C to 100 °C, typically needed to obtain high yields.[6,19]

The rhodium (I) catalyzed conjugate addition of organoboron and silicon reagents to α,β-unsaturated carbonyl compounds has been well developed since Miyaura's

discovery.[40] The design of a palladium-based catalyst capable of catalyzing the 1,4-conjugate addition of organometallic reagents in high yields is of great synthetic value. The advantages of using palladium complexes as catalyst over rhodium complexes in 1,4-conjugate addition reactions are that palladium is economical cheaper than rhodium and palladium complexes could catalyze the 1,4-conjugate addition reaction at lower temperatures in contrast to rhodium complexes that employ temperatures above 50 °C. Considerable efforts have been made to develop palladium-catalyzed conjugate addition reactions of organometallic reagents such as organomercury,[41,42] organoantimony,[43,44] organoboron,[45-47] organotin[48] organobismuth[49,50] and organosilicon.[51,52] However, most of these reactions result in the formation of the Heck-type coupling products which lack new chiral centers.

Miyaura and co-workers recently reported that cationic palladium(II) complexes catalyze conjugate addition reactions involving organoboron[46,53] and organosilicon[51,53] reagents with enones using chelating phosphines as ligands. These reactions gave the addition products in excellent yields, and most of the reactions were performed at room temperature as compared to high temperatures required for the rhodium-catalyzed systems.[6,19] Although organoboron and organosilicon reagents are inert with respect to palladium(II) halides, they readily transmetalate the organic groups to cationic palladium (II) complexes. Uemura[45] and Miyaura[53] reported that the readily occurring β-hydride elimination reaction of palladium is the main hindrance to this reaction. Eliminating this drawback will be important in further developing palladium(II)-catalyzed conjugate additions of organoboranes. The proposed mechanism for the 1,4-conjugate addition involves transmetallation, enone insertion, and protonolysis of the metal enolate

species.[46,53,54] In the catalytic cycle, the palladium catalyst forms C-bound enolates upon insertion of enones into the carbon-palladium bond in contrast to O-bound enolate formation in the insertion of enones into a carbon-rhodium bond.[46,55,56] This demands protonolysis to be faster than β-hydride elimination, which would give the Heck-type coupling products.

The general mechanism for the palladium-catalyzed 1,4-conjugate addition reactions[46,53,54] is shown in figure 2.1. Dicationic palladium(II) complexes have been demonstrated to be excellent catalysts for 1,4-conjugate addition reactions.[53] The first step is the transmetalation of an aryl group to a dicationic palladium(II) complex **1** to form an aryl palladium complex **2**. Insertion of the enone into the Pd-aryl bond of complex **2** yields C-bound palladium(II) enolate **3**, which is in equilibrium with O-enolate **4** or oxa-π-allyl species **5**. The conjugate addition product **6** is obtained by protonolysis of the C-enolate. The active palladium complex **1** is regenerated by the addition of water, and the catalytic cycle continues. A similar mechanism has been proposed for rhodium catalyzed conjugate addition reactions.[29,40,57]

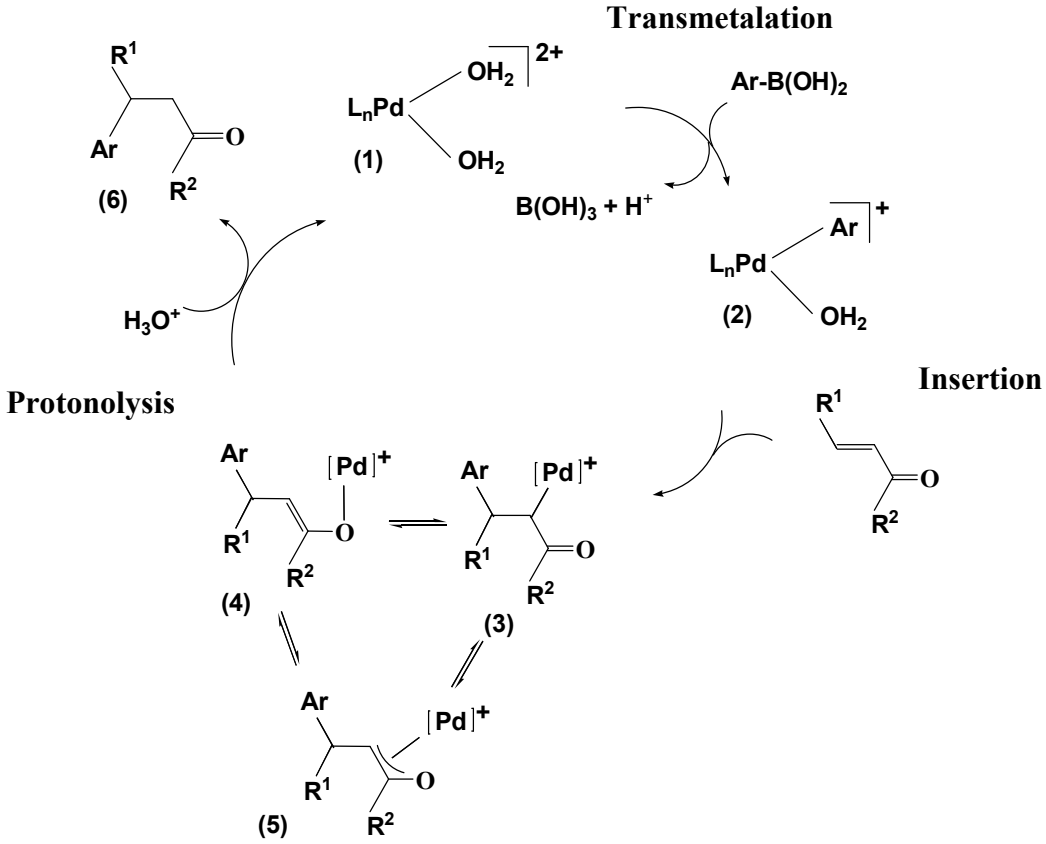


Figure 2.1 Proposed Catalytic Cycle for Palladium-Catalyzed, 1,4-Conjugate Additions.

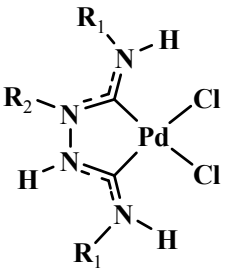
Miyaura and co-workers reported the first example of 1,4-addition of arylboronic acids and arylsiloxanes to α,β-unsaturated carbonyl compounds.[53] By varying the palladium precursor, they obtained moderate to excellent yields ranging from 61% to 98% for the addition of phenylboronic acid to 2-cyclohexenone at room temperature.[53] For the addition of phenylsiloxanes to 2-cyclohexenone moderate to good yields of 33% to 80% of the addition product was obtained when the reaction was carried out at 75 °C.[53] Miyaura explained that the cationic nature of the palladium(II) complexes promoted

smooth transmetalation of phenylboronic acid and phenylsiloxanes. In addition, the cationic palladium enolate intermediate readily hydrolyzed to the desired product, avoiding the possible formation of the Heck-type coupling product in the catalytic cycle.

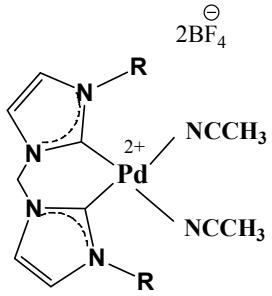
N-Heterocyclic carbenes have substantial similarities to tertiary phosphines as electron donors. However, reports of N-heterocyclic carbenes as ligands in the design of metal complexes for the conjugate addition are rare. A series of modular palladium Chugaev-type carbene and palladium/rhodium complexes of a chelating imidazole-based dicarbene has been prepared in our research group. The complexes have electronic and steric properties that could be suitable for effective catalysis of organoboron additions to α,β-unsaturated aldehydes and ketones. Since N-heterocyclic carbene ligands have not received much attention as ligands in catalyst design for conjugate addition and also that palladium complexes can catalyze conjugate additions at lower temperatures than rhodium systems, it was decided to investigate the activity of palladium Chugaev-type carbene complexes and palladium/rhodium complexes of a chelating imidazole-based dicarbene as precatalysts for 1,4-conjugate addition. The following objectives were proposed. The first was to optimize substrate scope and yield in 1,4-conjugate additions with organoboron reagent by utilizing various carbene ligands which have strong donor abilities similar to those of phosphine based ligands but are more easily modified. The second objective was to extend the activity of the conjugate addition to unactivated olefins, which are of synthetic interest due to their ready availability.

RESULTS AND DISCUSSION

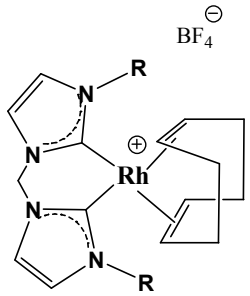
In Chapter 1, a series of palladium Chugaev-type carbene complexes containing various alkylisocyanide substituents and halide ligands[58] were investigated in the Heck reaction. The optimized precatalyst was highly efficient for a range of aryl bromides and deactivated aryl chlorides in Heck coupling reactions. The synthesis of the palladium Chugaev-type carbene complexes is a simple, two-step procedure, and the ease of modification of the carbene complexes should also allow optimization of a 1,4-conjugate addition catalyst, similar to that observed with the Heck and Suzuki[58] reactions. In related work, the synthesis and characterization of a sterically hindered rhodium bis (N-heterocyclic carbene) complex has been reported by Wanniarachchi *et al*.[59] Moreover, a sterically palladium complex of the same ligand has been developed in our research group. These complexes are useful for comparison due to the similarity expected in ligand donor ability. Due to the similarity of the chelating N-heterocyclic carbene to Chugaev-type carbenes, it was of interest to compare the activities of these complexes to the Chugaev carbenes as precatalysts in 1,4-conjugate addition reactions. Herein are presented optimization studies probing the effect of various silver salts as additives in 1,4-addition reaction as well as the effect of varying the carbene ligand attached to palladium. Functional group tolerance of the 1,4-addition reaction catalyzed by the optimized precatalyst is also presented. The various complexes used in these studies are shown in Figure 2.2.



2a (R_1, R_2 = Me)
2b (R_1 = ^{i}Pr, R_2 = H)
2c (R_1 = Cy, R_2 = H)
2d (R_1 = ^{t}Bu, R_2 = H)
2e (R_1 = Me, R_2 = H)



2f (R = 2, 4, 6-Trimethylphenyl)



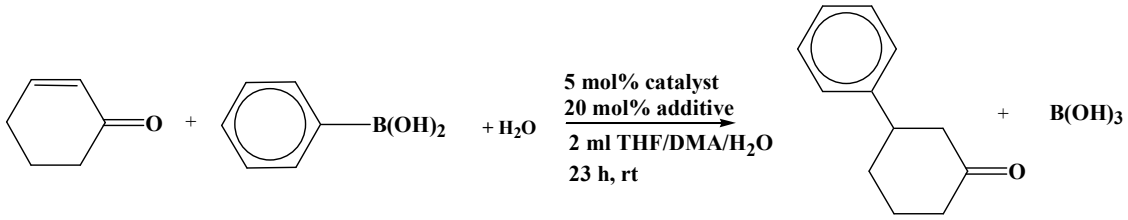
2g (R = 2, 4, 6-Trimethylphenyl)

Figure 2.2 Dicarbene Complexes of Palladium and Rhodium.

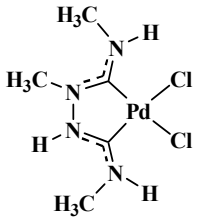
2.1 Effect of Additives on the 1,4-Addition Reaction of Phenylboronic Acid to 2-Cyclohexenone.

In preliminary studies, a 1,4-addition reaction of phenylboronic acid with 2-cyclohexenone was used to investigate the effect of different silver salts on activity of dicationic palladium catalysts. The salts used in the test reaction were silver tetrafluoroborate ($AgBF_4$), silver hexafluoroantimonate ($AgSbF_6$), silver trifluoromethanesulfonate (AgO_3SCF_3), and silver tetrakis[(3,5-trifluoromethyl)phenyl]borate ($AgBAr^F{}_4$). A mixture of 2-cyclohexenone (1 equiv) and phenylboronic acid (1.5 equiv) in THF-H_2O-DMA (6:1:1 ratio) was stirred at room temperature for 23 h in the presence of 5 mol% of palladium precatalyst **2a** and 20 mol% of a silver salt as additive. Addition of water to the mixture was necessary to hydrolyze the Pd-enolate and regenerate the activate dicationic palladium complex in the catalytic cycle. Table 2.1 summarizes results of the 1,4-addition reactions.

Table 2.1 Effect of Additives on the 1,4-Addition Reaction of Phenylboronic Acid to 2-Cyclohexenone.



catalyst



Entry	Additive	Yield (%)[a]
1	$AgBF_4$	21
2	$AgSbF_6$	19
3	AgO_3SCF_3	8
4	$AgBAr^F{}_4$	1.2
5	none	-

[a] Yield determined by GC using an internal standard,diethylene glycol dibutyl ether.

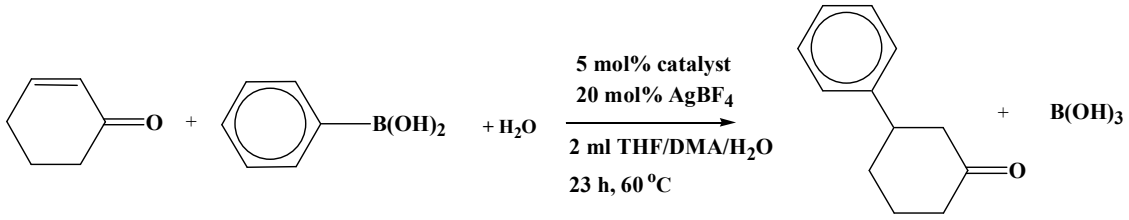
From the results obtained, $AgBF_4$, and $AgSbF_6$ were found to give appreciable yields of product (Table 2.1, entries 1 and 2). AgO_3SCF_3 and $AgBAr^F{}_4$ failed to give the desired product in good yields (Table 2.1 entries 3 and 4). The ineffectiveness of AgO_3SCF_3 could be that the counter anion formed in solution coordinate to the vacant site on the active catalyst in the catalytic cycle. The low yield observed with $AgBAr^F{}_4$ additive could be explained as a result of an ion pairing effect of the non-coordinating anion of the $AgBAr^F{}_4$. The use of silver additive was found to be essential in the 1,4-addition reaction as no product was formed when the reaction was carried out in the absence of silver salt (Table 2.1, entries 3 and 4). This probably reflects the need to generate a cationic active catalyst. The $AgBF_4$ was therefore selected as reagent of choice. The experimental procedure for the 1,4-conjugate addition reaction was modified for the subsequent optimization studies.

2.2 Effect of Ligand and Metal Variation on the 1,4-Addition Reactions of Phenylboronic Acid to 2-Cyclohexenone.

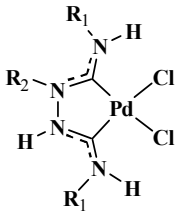
In an attempt to optimize the catalytic system for the 1,4-addition reaction, a number of different dicarbene complexes were used as precatalysts (Figure 2.1) for a model reaction. 2-Cyclohexenone (1 equiv) was treated with phenylboronic acid (1.5 equiv) in the presence of 5 mol% of the precatalyst and 20 mol% of silver tetrafluoroborate ($AgBF_4$) in a solvent mixture of THF-H_2O-DMA (6:1:1 ratio). In some instances, a solvent mixture of THF-H_2O (6:1) was used. The reaction mixture was degassed and then stirred at room temperature for 23 hours under argon. In some cases, the reaction mixture was stirred at 60 ºC. Results for the 1,4-addition reactions are shown in Table 2.2.

The cationic rhodium complex **2g** was found to be an excellent precatalyst, giving 98% yield at 60 ºC (Table 2.2 entry 9). Palladium Chugaev carbene complexes **2a** and **2c** gave moderate yields of 43% and 37%, respectively (Table 2.2 entries 1 and 4). The use of excess phenylboronic acid with precatalyst **2a** did not improve the yield (Table 2.2 entry 2). Interestingly, Chugaev carbene complexes **2d** and **2e** were ineffective, resulting in low yields (Table 2.2 entries 5 and 6). The dicationic palladium complex **2f** also gave a low yield of product (Table 2.2 entry 7). In all cases, biphenyl was formed in less than 1% yield as a side product. The higher yield attained with the rhodium catalyst **2g** probably reflects the different reactivity of rhodium versus palladium. In addition, the stability at the high temperature of 60 ºC could be a factor in the high catalytic activity observed with the rhodium complex **2g**. Complexes **2a** and **2g** were selected as the most promising catalysts for further optimization studies.

Table 2.2 Effect of Different Catalysts on the 1,4-Addition Reaction of Phenylboronic Acid to 2-Cyclohexenone.



Catalyst



2a – 2e

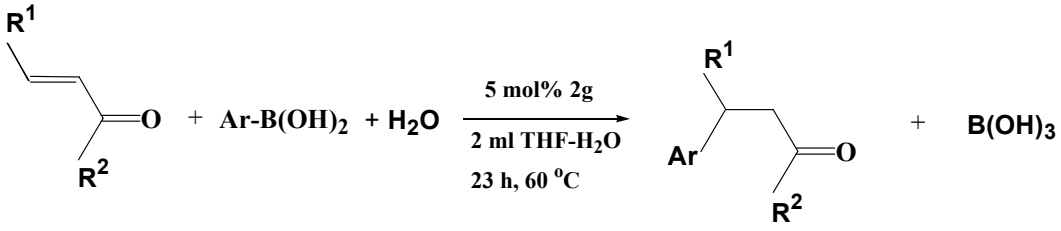
Entry	Precatalyst	Yield (%)[a]
1	**2a** (R_1, R_2 = Me)	43[b]
2	**2a**	25[d]
3	**2b** (R_1 = ^{i}Pr, R_2 = H)	12[b]
4	**2c** (R_1 = Cy, R_2 = H)	37[c]
5	**2d** (R_1 = ^{t}Bu, R_2 = H)	3.3[b]
6	**2e** (R_1 = Me, R_2 = H)	2.4[b]
7	**2f** [Pd(Mesityl dicarbene)($NCCH_3$)]$^{2+}$$BF_4^{2-}$	20[b]
8	**2g** [Rh(Mesityl dicarbene)(COD)]$^{+}$$BF_4^{-}$	16[b]
9	**2g** [Rh(Mesityl dicarbene)(COD)]$^{+}$$BF_4^{-}$	98[c]

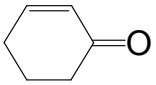
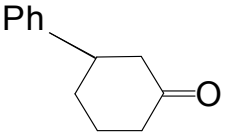
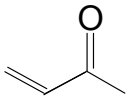
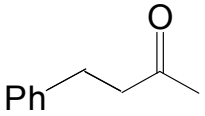
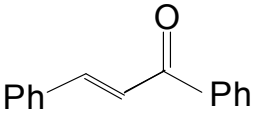
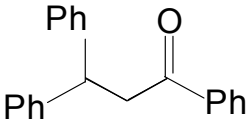
[a]Yield determined by GC using internal standard, diethylene glycol dibutyl ether.
[b]Reaction performed at room temperature.
[c]Reaction performed at T= 60 ºC.
[d] Use of excess phenylboronic acid.
Reaction carried out with complexes **2a** to **2e**, solvent mixture of THF-H_2O-DMA (6:1ratio) was used.
Reaction carried out with complexes **2f** and **2g**, solvent mixture of THF-H_2O (6:1:1 ratio) was used.

2.3 Functional Group Tolerance of the 1,4-Addition of Phenylboronic acid to α,β-unsaturated Ketones Catalyzed by Rhodium Complex 2g.

The functional group tolerance of the rhodium complex **2g** was investigated in 1,4-additions of organoboron reagents to cyclic and acyclic enones. Good to excellent yields were obtained at temperatures of 60 ºC using 5 mol % of catalyst and 80 ºC with 2 mol % of catalyst. Results are summarized in Table 2.3.

Table 2.3 Functional Group Tolerance of the 1,4-Addition of Phenylboronic Acid to α,β-Unsaturated Ketones Catalyzed by Rhodium complex **2g.**



Entry	Enone	Condition	Product	Yield (%)[a]
1a 1b		N_2		81 86[b]
2		N_2		73
3		N_2		97

[a] Yield determined by GC and GC-MS using diethylene glycol dibutyl ether as internal standard.
[b] Reaction carried out at 80 °C using 2 mol % of **2g.**

The addition of phenylboronic acid to 2-cyclohexenone gave 81% and 86% yields of 3-phenylcyclohexanone using 5 mol % of **2g** at 60 ºC and 2 mol % of **2g** at 80 ºC, respectively (Table 2.3 entries 1a and 1b). A 73% yield of the desired product, 4-phenyl-2-butanone, was obtained when 3-buten-2-one was treated with phenylboronic acid in THF-H_2O (Table 2.3 entry 2). Nearly complete conversion to 3,3-diphenyl-

propiophenone was achieved in the 1,4-addition reaction between chalcone and phenylboronic acid (Table 2.3 entry 3). The activity of the precatalyst **2g** was also investigated in phenylboronic acid addition to unactivated olefins such as cyclohexene, styrene, and norbornene but all attempts at the addition were unsuccessful.

The 1,4-addition reactions of phenylboronic acid with 2-cyclohexenone, 3-buten-2-one and chalcone were monitored over time (Figures 2.3 to 2.6). The 1,4-addition of 2-cyclohexenone occurred over 21 hours of reaction time with 81% product formation (Figure 2.3). However, the yield of the desired product was slightly improved to 86% when the catalyst loading was reduced to 2 mol% and reaction temperature increased to 80 ºC for 23 hours of stirring (Figure 2.4). For the addition reaction between 3-buten-2-one and phenylboronic acid, a maximum yield (73%) of the desired product formed in 5 hours with stirring (Figure 2.5). A maximum yield (97%) in the chalcone reaction occurred in 6 hours of reaction time (Figure 2.6). In monitoring the reaction, it was observed in many cases that the yield of the product formation dropped as the reaction time increased. This may be due to decomposition of the product over time. Therefore it was essential to optimize the reaction times.

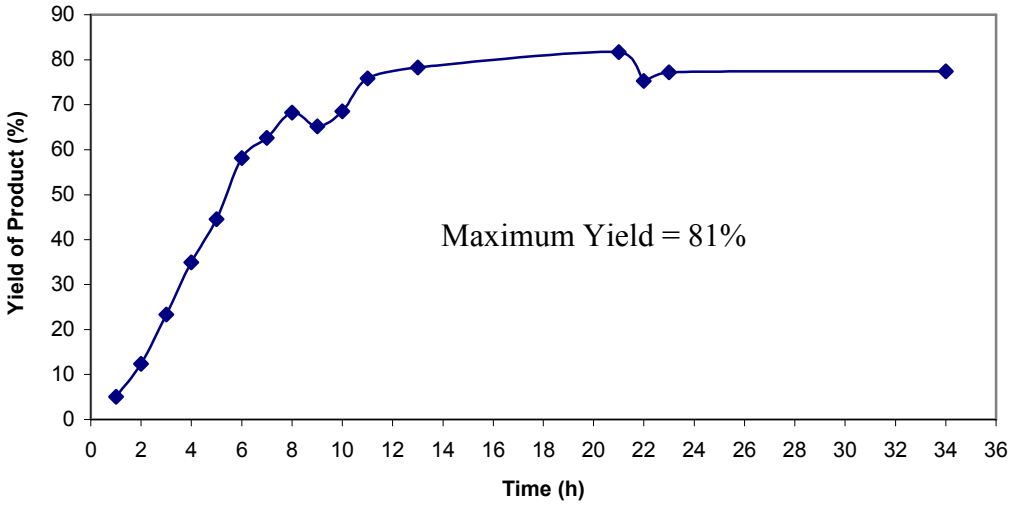


Figure 2.3 Addition to 2-Cyclohexenone using 5 mol% of Precatalyst **2g** at 60 ºC.

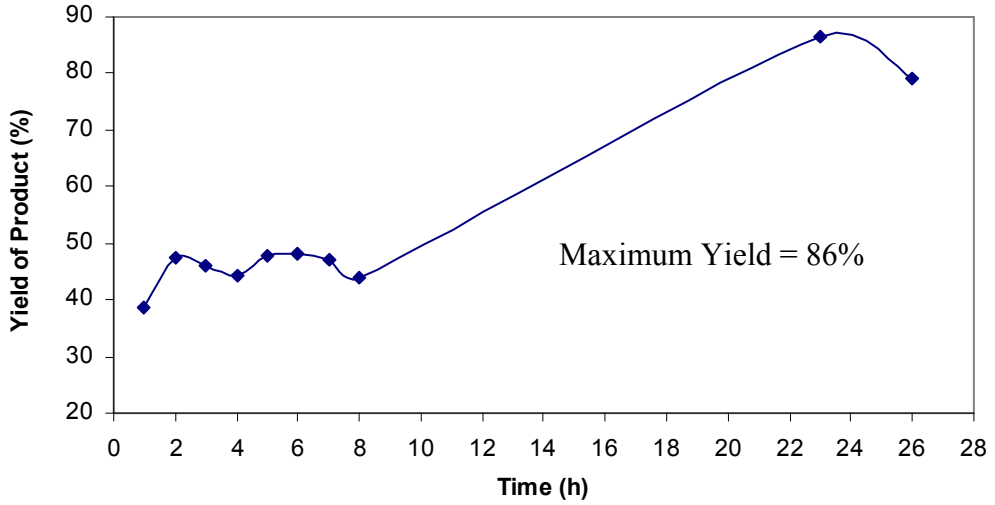


Figure 2.4 Addition to 2-Cyclhexenone using 2 mol% of Precatalyst **2g** at 80 ºC.

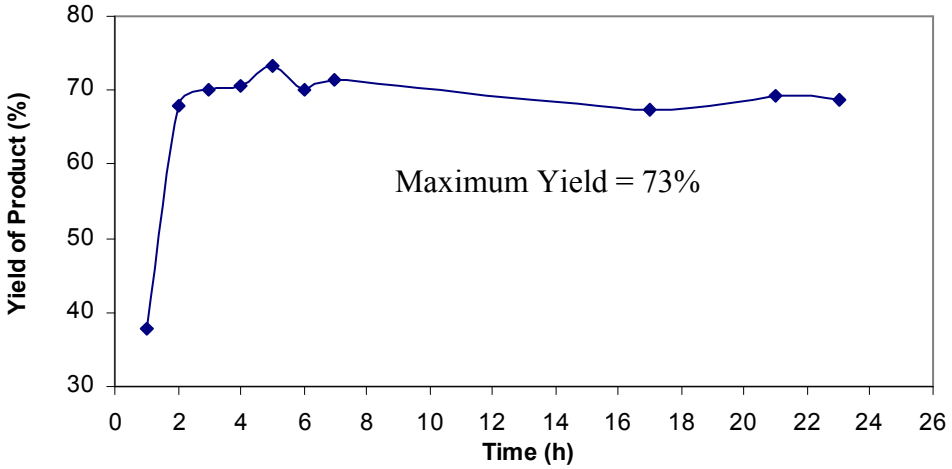


Figure 2.5 Addition to 3-Buten-2-one using 5 mol% of Precatalyst **2g** at 60 ºC.

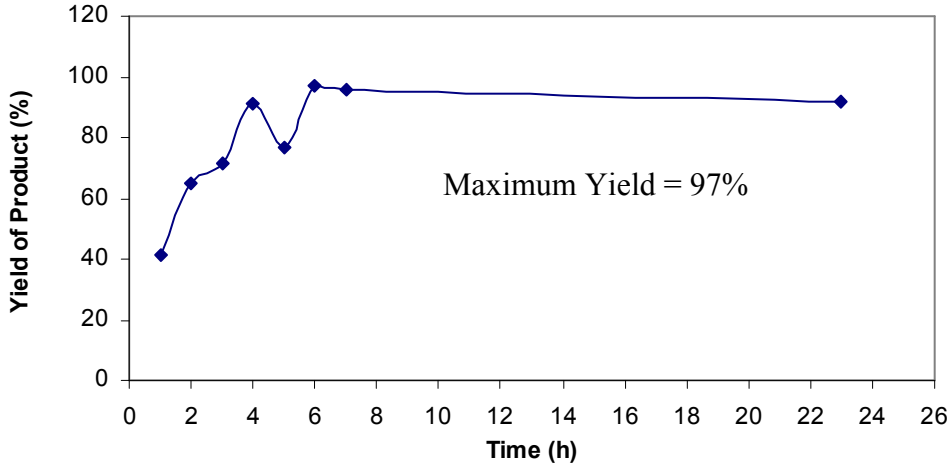


Figure 2.6 Addition to Chalcone using 5 mol% of Precatalyst **2g** at 60 ºC.

2.4 Functional Group Tolerance of the 1,4-Addition of Phenylboronic Acid to α,β-Unsaturated Ketones Catalyzed by Palladium Carbene Complex 2a

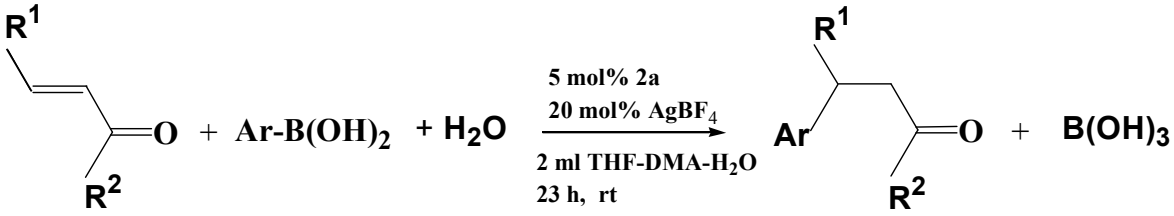
Although the rhodium dicarbene complex **2g** displayed the highest catalytic activity among the various precatalysts tested, it was of interest to further investigate the activity of the methylhydrazine-derived palladium dicarbene complex **2a**. Palladium is cheaper than rhodium, and it would be economically advantageous to use palladium complexes as precatalysts in 1,4-conjugate addition reactions. Also, palladium complexes could possibly catalyze the 1,4- conjugate addition effectively at room temperature as demonstrated by Miyaura *et al*.[46,53] using palladium chelating phosphine complexes.

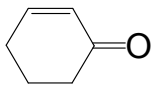
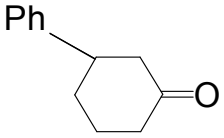
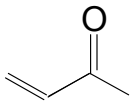
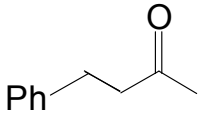
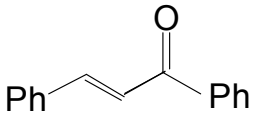
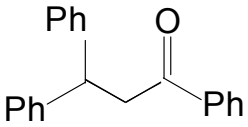
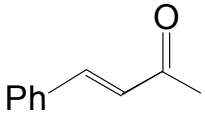
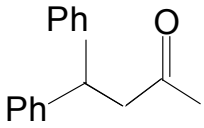
The results of the 1,4-conjugate addition reactions using 5 mol% of precatalyst **2a** with a range of enones are presented in Table 2.4. The results show that a moderate yield of 43% was obtained with 2-cyclohexenone (Table 2.4 entry 1). This precatalyst was efficient for 1,4-conjugate addition to 3-buten-2-one, providing yields of 78% and 92% when the reaction was carried out at room temperature and at 40 ºC, respectively (Table 2.4 entries 2a and 2b). However, **2a** did not show effective catalytic activity for 1,4-conjugate addition to chalcone (Table 2.4 entries 3a and 3b). Precatalyst **2a** was also ineffective for 1,4-conjugate addition reactions to 4-phenyl-3-buten-2-one (Table 2.4 entry 4).

Moreover, the 1,4-conjugate addition of phenylboronic acid to 3-buten-2-one using precatalyst **2a** was monitored over time (Figures 2.7 and 2.8). The 1,4-addition to 3-buten-2-one occurred over 48 hours at room temperature (Figures 2.7). However, the yield increased from 78% to 92% when the reaction was carried out at 40 ºC (Figures 2.8). In addition, it was observed in Figure 2.8 that the maximum yield achieved

decreased with time. This could be due to possible decomposition of the product over time.

Table 2.4 Functional Group Tolerance of the 1,4-Addition of Phenylboronic Acid to α,β-Unsaturated Ketones Catalyzed by Palladium Complex **2a.**



Entry	Enone	Conditions	Product	Yield (%)[a]
1a 1b		N_2		43
2a b		N_2		78 92[b]
3a b		N_2		2 5[b]
4		N_2		-

[a] Yield determined by GC and GC-MS using internal standard diethylene glycol dibutyl ether.
[b] Reaction carried at 40°C.

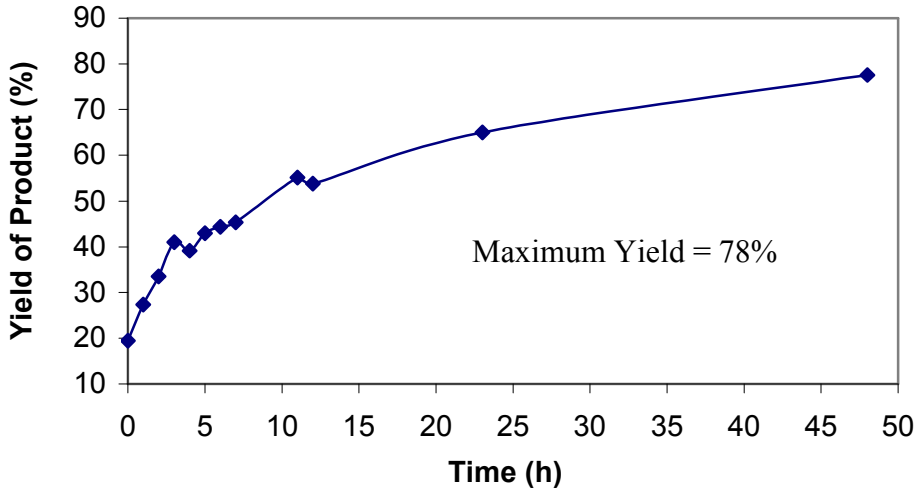


Figure 2.7 Addition to 3-Buten-2-one using 5 mol% of Precatalyst **2a** at RT.

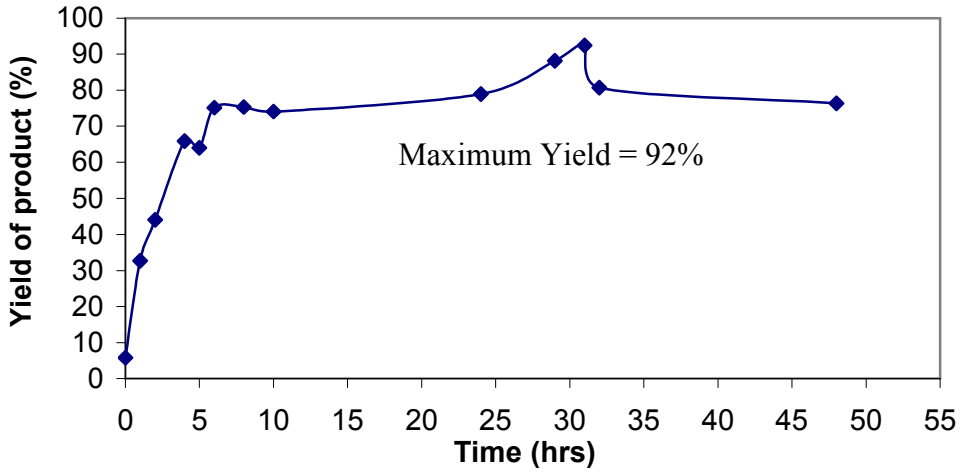


Figure 2.8 Addition to 3-Buten-2-one using 5 mol% Precatalyst **2a** at 40 ºC.

SUMMARY AND CONCLUSIONS

A series of chelating dicarbene complexes of palladium and rhodium have been investigated in 1,4-addition reactions of phenylboronic acid to enones. Optimization studies helped to identify the cationic rhodium(I) dicarbene complex as the most effective precatalyst for 1,4-addition reactions of phenylboronic acid. The activity of the rhodium complex compared to that demonstrated by Miyaura *et al.* using phosphine as ligands.[19] The rhodium dicarbene complex displayed high activity for a range of enones in 1,4-addition reactions. Palladium dicarbene complex **2a** was identified as the most promising palladium catalyst for the 1,4-addition reactions of phenylboronic acid to 2-cyclohexenone and 3-buten-2-one. Although the palladium dicarbene complexes do not demonstrate the high catalytic activities in the 1,4-addition for a range of enones that have been achieved by catalysts containing phosphine ligands,[46,53] the optimization studies of palladium carbene precatalyst have shown that variation in ligand electronic properties can positively influence catalytic activity. Future studies will focus at tuning the catalytic system through modification of the electronic and steric properties of the palladium dicarbene complexes to effectively catalyze a range of 1,4-addition reactions.

EXPERIMENTAL SECTION

General Considerations. For 1,4-addition substrates, reagents were purchased as follows and used as received: 2-cyclohexenone (Aldrich 95%); 3-buten-2-one (Aldrich 99%); 1,3-diphenyl-2-propenone (Aldrich 97%); 4-phenyl-3-buten-2-one (Aldrich); phenylboronic acid (Acros Organics 98+%). Silver tetrafluoroborate (Acros Organics 99%); silver trifluoromethanesulfonate (Acros Organics 99+%, nitrogen flushed); and silver hexafluoroantimonate (V) (Strem chemicals 98%) were used as received. Silver tetrakis[(3,5-trifluoromethyl)phenyl]borate was prepared by a literature procedure.[60] Magnesium sulfate (Fisher Scientific) was used as received. For standards used for GC calibration plots: 3-phenyl cyclohexanone (98% pure by GC) was extracted from a catalytic reaction mixture with diethyl ether and purified by silica flash chromatography (19:1 hexanes/acetone); 4-phenyl-2-butanone (Acros Organics); 3,3-diphenylpropiophenone (Aldrich); and diethylene glycol dibutyl ether (internal standard, Acros Organics) were used as received. Dichloromethane (Pharmco) was of reagent grade and was used without further purification. Tetrahydrofuran was purified by distillation from sodium benzophenone ketyl. Water was purified by an E-pure system (Barnstead) and had a resistivity of ≥ 17.6 MΩ-cm.

Gas chromatography employed a Hewlett-Packard 6850 gas chromatograph with a 100% dimethylpolysiloxane capillary column (HP-1, Agilent Technologies, 0.25mm i.d. x 30m) and a flame ionization detector. For calculations of concentration by GC,

multilevel calibration plots were carried out with stock solutions of analytes and an internal standard (diethylene glycol dibutyl ether). The concentrations were in the expected range of experimental concentrations.

2.1 Effect of Additives on the 1,4-Addition Reactions of Phenylboronic Acid to 2-Cyclohexenone.

General Procedure: In a glove box, anhydrous phenylboronic acid (0.5 mmol, 61 mg), precatalyst **2a** (0.017 mmol, 5.2 mg) and additive (0.067 mmol) were added to a 25-mL, round bottomed flask equipped with a rubber septum. Argon gas was bubbled through the solution for about 5 minutes. Tetrahydrofuran (dried, 1.5 mL), 2-cyclohexenone (0.33 mmol, 32 μL), anhydrous N,N-dimethylacetamide (250 μL), water (250 μL), and diethylene glycol dibutyl ether (GC internal standard, 0.204 mmol, 50 μL) were added sequentially to the flask through the rubber septum. The mixture was vigorously stirred at room temperature for 23 hours. A 5 μL aliquot of the reaction mixture was extracted and added to 50 μL of CH_2Cl_2, and the mixture was filtered through a filter pipet plugged with a glass micro fiber filter. The organic extract was analyzed by GC to determine the yield of product formed. The product retention times were identified based on authentic samples.

2.2 Effect of Ligand and Metal Variation on the 1,4-Addition Reaction of Phenylboronic Acid with 2-Cyclohexenone.

General Procedure: Into an ampule flask were placed respective amounts of anhydrous phenylboronic acid (0.5 mmol, 61 mg), precatalyst (0.017 mmol), and $AgBF_4$ (if used, 0.067 mmol, 13 mg) in a glove box. Tetrahydrofuran (dried, 1.5 mL), 2-cyclohexenone (0.33 mmol, 32 μL), anhydrous N,N-dimethylacetamide (if used, 250

μL), water (250 μL), and diethylene glycol dibutyl ether (GC internal standard, 0.204 mmol, 50 μL) were added successively to the flask. The ampule flask was sealed with a Teflon stopcock. The entire mixture was degassed thrice and then back-filled with argon gas. The solution mixture was vigorously stirred at room temperature for 23 hours. In some instances, the mixture was vigorously stirred at 60 ºC for 23 hours. A 5 μL aliquot of the reaction mixture was extracted and added to 50 μL of CH_2Cl_2, and the mixture was filtered through a filter pipet plugged with a glass micro fiber filter. The organic extract was analyzed by GC to determine the yield of product formed. The product retention times were identified based on authentic samples.

2.3 Functional Group Tolerance of the 1,4-Addition of Phenylboronic Acid to α,β-Unsaturated Ketones Catalyzed by Rhodium Complex 2g.

General Procedure: In a glove box, anhydrous phenylboronic acid (0.5 mmol, 61mg), enone (0.33 mmol), diethylene glycol dibutyl ether (GC internal standard, 0.204 mmol, 50 μL) and a solution of the precatalyst **2g** (0.017 mmol, 11.6 mg) in tetrahydrofuran (dried, 1.7 mL) were added successively into a 5 mL vial. The vial was sealed with a cap equipped with rubber septum. Degassed water (300 μL) was then added to the mixture through the rubber septum. The solution mixture was vigorously stirred at 60 ºC for 23 hours. A 5 μL aliquot of the reaction mixture was extracted and added to 50 μL of CH_2Cl_2, and the mixture was filtered through a filter pipet plugged with a glass micro fiber filter. The organic extract was analyzed by GC to determine the yield of product formed. The product retention times were identified based on authentic samples. During the monitoring of reactions, 5 μL aliquots of the reaction mixture were analyzed at hourly intervals.

2.4 Functional Group Tolerance of the 1,4-Addition of Phenylboronic Acid to α,β-Unsaturated Ketones Catalyzed by Palladium Complex 2a.

General Procedure: In a glove box, was placed anhydrous phenylboronic acid (0.5 mmol, 61 mg), enone (0.33 mmol) and $AgBF_4$ (0.067 mmol, 13 mg) in a 5 mL screw-capped vial. A solution of the precatalyst **2a** (0.017 mmol, 5.2 mg) in anhydrous N,N-dimethylacetamide (250 μL), diethylene glycol dibutyl ether (GC internal standard, 0.204 mmol, 50 μL) and tetrahydrofuran (dried, 1.5 mL) were added in succession to the vial. The vial was then sealed with a cap secured with a rubber septum. Degassed water (250 μL) was added to the mixture through the rubber septum. The mixture was vigorously stirred at the desired temperature for 23 hours. A 5-μL aliquot of the reaction mixture was extracted and added to 50 μL of CH_2Cl_2, and the mixture was filtered through a filter pipet plugged with a glass micro fiber filter. The organic extract was analyzed by GC to determine the yield of product formed. The product retention times were identified based on authentic samples. During the monitoring of the reaction, 5-μL aliquots of the reaction mixture were analyzed at hourly intervals.

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APPENDIX

1.0 Calculation of Yield (%) of Coupling Product in Heck Reaction.

1.A. Estimation of Mole Ratio

Density of Internal Standard, (g/mL) = ρ_I

Formula Weight of Internal Standard, (g/mol) = FW_I

Volume of Internal Standard only, (μL) = V_I

Moles of Standard $= \frac{V_I * \rho_I}{FW_I}$, mmol

For Internal Standard, Diethylene Glycol Dibutyl Ether,

ρ_I = 0.885 g/ml

FW_I = 213.38 g/mol

V_I = 100 μL

Moles of internal Standard = (100 * 0.885) / (213.38)

= 0.405 mmol

For Substrate, 4-Bromoacetophenone,

Starting moles of substrate = 1.7 mmol

Therefore,

Mole ratio = starting mmol of substrate / mmol of internal standard

= 1.7 / 0.405

= 4.2

1.B. Estimation of ^{1}H NMR Integration Ratio using Figure A.1.

[(Spectral integration of product / number of hydrogens) ÷ (Spectral integration of internal standard / number of hydrogens)]

= [(50 .65 / 3H) ÷ (49.35 / 12H]

= 4.10

Hence,

% yield of coupling product = (^{1}H NMR integration ratio / mole ratio) * 100%

= (4.10 / 4.2) * 100%

= 98%

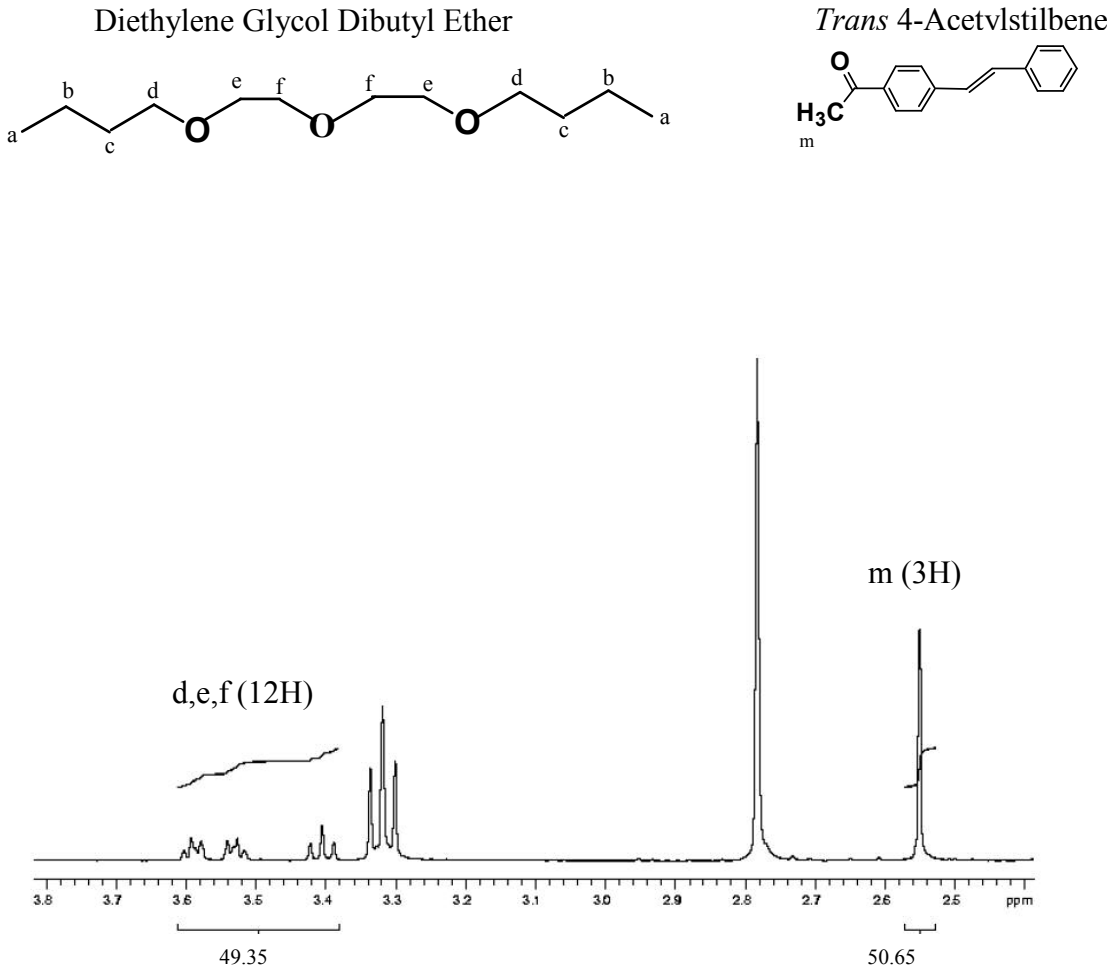

Figure A.1 Heck Reaction of 4-Bromoacetophenone using Precatalyst **3e** at 100 ºC.

2.0 Determination of Product Formation for 1,4 Addition Reactions

2.A Calibration Curve for GC Analysis of Concentrations

Internal Standard (Diethylene glycol dibutyl ether, DGDE)

Density of Internal Standard, (g/ml) = ρ_I

Formula Weight of Internal Standard, (g/mol) = FW_I

Volume of Internal Standard only, (μL) = V_I

Volume of Internal Standard Solution, (mL) = V_{IS}

Concentration of Internal Standard, = C_I

Moles of Standard $= \frac{V_I * \rho_I}{FW_I}$, mmol

$$C_I = \frac{\left(\frac{V_I * \rho_I}{FW_I}\right)}{V_{IS}} = \frac{V_I * \rho_I}{FW_I * V_{IS}}, \text{ mM}$$

Solute

Formula Weight of Solute, (g/mol) = FW_s

Mass of Solute, (mg) = M_s

Volume of Solute Solution, (mL) = V_{ss}

Concentration of Standard, = C_s

Moles of Solute $= \frac{M_s}{FW_s}$, mmol

$$C_s = \frac{M_s}{V_{ss}} = \frac{M_s}{FW_s * V_{ss}}, \text{ mM}$$

For Typical Calculation of DGDE,

FW_I = 213.38 g/mol

ρ_I = 0.885 g/ml

V_I = 220 μL

V_{IS} = 100 mL

C_I = (220 * 0.885) / (218.34 * 100)

= 8.92 mM

For Typical Calculation of Solute, 3-phenyl cyclohexanone

FW_s = 174.24 g/mol

M_S = 3.5 mg

V_{ss} = 5 mL

C_s = 3.5 / (174.24 * 5)

= 4.02 mM

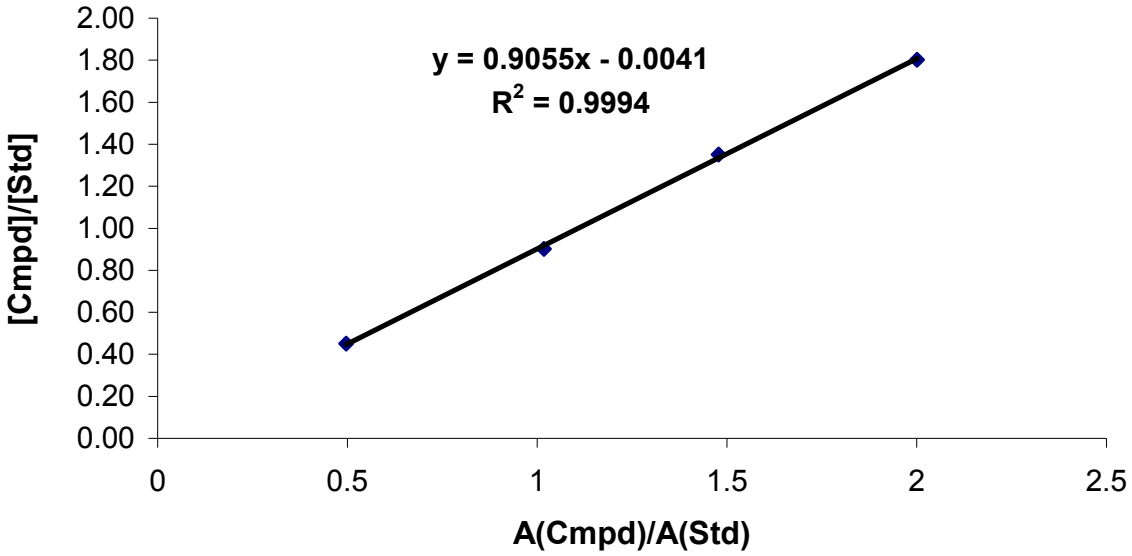

Figure A.2 Calibration Curve of 3-Phenylcyclohexanone.

2.B Percent Yield

Product Concentration, mM = y_p

Initial Substrate Concentration, mM = y_s

Yield, % = Z

Volume of Substrate, (μL) = V_{sb}

Volume of Substrate Solution, (mL) = V_{sbs}

Density of Substrate, g/ml = ρ_{sb}

Response factor of Product = Slope of Calibration Plot = R_p

Concentration of Internal Standard, = C_I

Integrated GC Peak Area of Compound, sq. units = A_{cpd}

Integrated GC Peak Area of Internal Standard, sq. units = A_I

$$yield = \frac{y_p}{y_s} * 100\%$$

Where, $y_p = R_p \left(\frac{A_{cpd}}{A_I} \right) C_I$

$$y_s = \left(\frac{V_{sb} \rho_{sb}}{FW_{sb} V_{sbs}} \right)$$

Calculation of % Yield of Product for Addition of 2-Cyclohexenone to Phenylboronic Acid using Precatalyst 2f at 60 ºC

R_p (Slope of calibration curve, Figure A.2) = 0.9055

A_{cpd} (GC analysis of reaction mixture) = 2362.56 sq. units

A_I (GC analysis of reaction mixture) = 1509.94 sq. units

ρ_I = 0.885 g/ml

FW_I = 213.38 g/mol

V_I = 50 μL

Volume of entire mixture V_E = 2.082 mL

Therefore,

C_I = (50 * 0.885) / (218.34 * 2.082)

= 96.76 mM

y_p = 0.9055 * (2362.56299) / (1509.942) * 96.76

= 137.136 mM

y_s = (32 * 0.993) / (96.13 * 2.082)

= 158.77 mM

Hence,

Yield = (137.136 * 158.77) * 100 %

=86%

VITA

MILLICENT ODEI OWUSU

Candidate for the Degree of Master of Science Chemistry

Thesis: PALLADIUM COMPLEXES OF CHELATING CARBENES FOR CATALYTIC HECK REACTIONS AND 1,4-CONJUGATE ADDITION REACTIONS

Major Field: Chemistry

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Institution: Oklahoma State University Location: Stillwater, Oklahoma

Title of Study: PALLADIUM COMPLEXES OF CHELATING CARBENES FOR CATALYTIC HECK REACTIONS AND 1,4-CONJUGATE ADDITION REACTIONS

Pages in Study: 65 Candidate for the Degree of Master of Science

Major Field: Chemistry

Scope and Method of Study: Investigating Activity of Palladium Chelating Carbene Catalysts in Heck and 1,4-Conjugate Addition Reactions

Findings and Conclusions:

Activities of a series of modular palladium Chugaev-type carbene complexes were investigated in catalytic Heck and 1,4-conjugate addition reactions. Significant variations of catalytic activity with ligand structure were observed in the Heck reaction. A methyl hydrazine-derived palladium dicarbene dibromide complex was recognized as the most effective precatalyst for the Heck reaction. The best precatalyst selected mediated the Heck reaction of electron-poor aryl chlorides and a range of aryl bromides with styrene in high yields at 120 ºC. Heck reactions performed under air showed limited air tolerance.

The modular nature of the palladium Chugaev-type carbene complexes also allowed optimization of the catalytic 1,4-conjugate addition reaction of organoboranes. A methyl hydrazine-derived palladium dicarbene dichloride complex was identified as the most promising precatalyst for the addition of phenylboronic acid to acyclic and cyclic enones at 40 ºC. Monitoring the 1,4-conjugate addition reactions revealed the need to optimize the reaction time, because the yield of the product decreased in most cases as the reaction was allowed to proceed for longer durations.

ADVISER'S APPROVAL: **Dr. LeGrande M. Slaughter**