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α-Arylation of cyclopentanone : palladium-catalyzed coupling of enamines and aryliodides & n-acyloxazines as novel bicyclic Weinreb amides

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α-ARYLATION OF CYCLOPENTANONE: PALLADIUM-CATALYZED COUPLING OF ENAMINES AND ARYLIODIDES

&

N-ACYLOXAZINES AS NOVEL BICYCLIC WEINREB AMIDES

By

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ABSTRACT

GEHRING, KRISTINA α-Arylation of Cyclopentanone: Palladium-catalyzed Coupling of Enamines and Aryliodides

The introduction of an aryl group α to a carbonyl is a useful step in the preparation of a variety of biologically interesting compounds. The palladium-catalyzed α-arylation of ketones and esters, through their enolates, has received a great deal of attention lately. Despite these efforts, cyclopentanones remain one of the most difficult classes of ketones to arylate. Many of these methods suffer from the limitation of the relatively basic reaction conditions needed in order to prepare the enolate nucleophiles *in-situ*. The direct palladium-catalyzed α-arylation of enamines as an alternative route to α-aryl ketones has received very little attention and might be a way to circumvent the strong base problem. In an effort to overcome this problem a method for the direct palladium-catalyzed α-arylation of unactivated enamines of cyclopentanone through the use of high-throughput screening was developed. When applied to reactions with 1-pyrollidino-1-cylcopentane and various iodobenzene derivatives we have achieved yields of above 90% for the arylated cyclopentanone in all successful cases at a one mmol scale.

ABSTRACT

KRISTINA GEHRING N-Acyloxazines as Novel Bicyclic Weinreb Amides
Department of Chemistry, June 2006

Weinreb amides, N-methoxy-N-methyl amides, act as important acylating agents when they react with organometallic nucleophiles such as Grignard reagents and/or organolithium reagents tc yield ketones upon aqueous acid work-up . With the idea that *N*-acyloxazines (**40**) are, in fact, bicyclic forms of Weinreb amides, they might reasonably be predicted to act similarly to the original Weinreb amides. We have sought to investigate the behavior of *N*-acyloxazines when subjected to organometallic nucleophiles such as Grignard reagents, followed by acid hydrolysis to afford a ketone product. The synthesis of the N-acyloxazine proved to be a bit more difficult than expected, and the starting material for the reaction, phenylhydroxamic acid (**63**), first needed to be made. We have successfully synthesized the phenylhydroxamic acid using phenyacetic acid (**64**) and hydroxylamine hydrochloride with cyanuric chloride present as a coupling reagent. Further investigation is required into the synthesis of the N-acyloxazine and its reaction upon exposure to organometallic nucleophiles.

ACKNOWLEDGEMENT

Throughout my work in the past year I have been helped along the way by many inspiring individuals. I owe to them many thanks and ample gratitude for their constant support. I would like to thank Dr. A for all of his patience, wisdom, guidance, and support throughout this past year and at all times before that. Without his continuous motivation and optimism when things didn't go as planned, my time in the lab would have been much less enjoyable. I also thank him for patiently answering the countless questions I bring to his office, for it has expanded my knowledge greatly.

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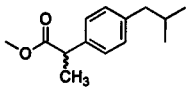
CHAPTER I.

INTRODUCTION

I.1. *Background Information*

The importance of α aryl carbonyl compounds is highlighted by their presence in biologically important molecules such as ibuprofen **(1)**, naproxen **(2)**, and other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).[1] These pharmaceuticals possess analgesic and anti-inflammatory properties that reduce inflammation and pain by playing an inhibitory role in the cyclooxygenase system.[1] There have been many attempts to synthesize these α aryl carbonyl compounds in an effort to provide an economically and chemically efficient process. The result of these endeavors has led to many catalytic methods in synthesizing the α-aryl carbonyl bonds. Following the previous work for synthesis of such bonds, I have focused my research on the scale up reactions for the synthesis of α-aryl ketones using cyclopentanone derivatives.



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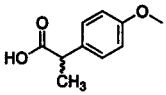

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It has been demonstrated that α-aryl carbonyl compounds can be synthesized using a palladium catalyst through the reaction of an aryl halide and an electron donor to produce an aryl radical. This radical then combines with a nucleophile, and in the case that this nucleophile is an enolate, an α aryl ketone results.[2] Buchwald and coworkers determined that this reaction is limited to electron withdrawing aryl halides, and the composition of the solvent limits the feasibility of the reaction as well.

Solvents with hydrogen atoms that can be abstracted by an aryl radical would not be useful, as they would be chemically altered and this would detract from their neutral solvent characteristics.[2] An additional challenge to this method arises if hydrogens are positioned β to an enolate, as they can be abstracted by aryl radicals and convert the aryl halide to an arene instead of the α aryl ketone (Figure 1).[2,3]

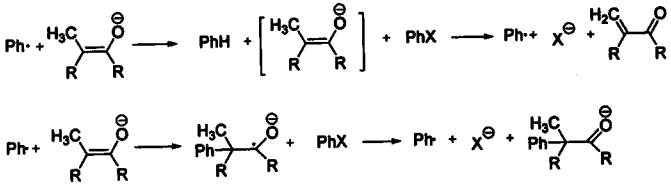


Figure 2. Abstraction of hydrogens β to an enolate and conversion of an aryl halide to an arene.

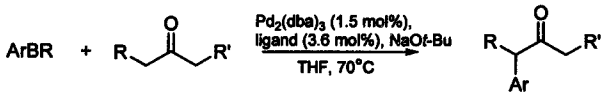
A variety of reagents have been developed strictly to facilitate the generation of α-aryl carbonyl compounds. Some of these include diaryliodonium salts, organobismuth reagents, organoboron reagents, and aryldiazonium salts, yet the feasibility is severely decreased by the time and cost required to prepare them in useful, stoichiometric amounts.[2] Therefore, although the synthesis of the α-aryl ketone has been achieved, the reaction was limited by the scope of the solvents and reactants that could be used.

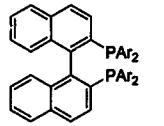
An alternative to the method used by Buchwald and coworkers is the use of Heck-like reactions. Heck reactions are comprised of palladium catalyzed cross coupling reactions that result in the arylation and akenylation of alkenes.[4] Work done by previous coworkers has demonstrated that α aryl ketone compounds can be synthesized through palladium catalyzed cross coupling reactions between enamines and aryl halides. We

have proposed a novel scale up procedure for this synthesis, as well as optimization conditions for the reaction.

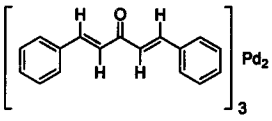
The most common method of generating α aryl carbonyl compounds is a palladium catalyzed coupling reaction involving ketone enolates and aryl halides. Buchwald and his coworkers continued their investigation into the methods of α aryl ketone preparation. They have acknowledged the reaction of an enolate with a benzyne derivative as being an alternative to the nucleophilic aromatic substitution reaction, which requires one or more electron withdrawing groups as substituents on the arene.[2] These intermolecular reactions, however, are not usually regioselective and can result in intramolecular rearrangement of the α ketone product instead of protonolysis.[2] Frustrated by these challenges and those posed by previous coupling reactions between aryl halides and ketones, Buchwald devised a novel palladium catalyzed reaction for the direct cross coupling of aryl halides with ketones.[5] While studying the reaction of aryl bromides with sodium alkoxides and observing the reduced arene product, the group serendipitously found that small amounts of α-aryl ketone were produced based on GC data.[6] In an effort to optimize this apparent side reaction, the combination of $Pd_2(dba)_3$ **(3)** and Tol-BINAP**(4)** or BINAP **(5)** in the presence of sodium tert-butoxide catalyzed the coupling reaction between an aryl bromide and various ketones in yields ranging from 63-93% (Scheme 2).[6] The mild reaction conditions afforded product within 4-12 hours and seemed suitable for other functional groups including nitriles, ethers, imines, amides, aryl chlorides, and acetals.

Scheme 2



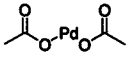


4: Ar = 4-MeC_6H_4
5: Ar = Ph



3

Further investigation into this reaction system lead to optimization of the α aryl ketone production through the use of different ligands, bases, aryl halides, and ketones. Specifically, it was found that $Pd(OAc)_2$ **(6)** in combination with a tricyclohexylphosphine derived ligand **(7)** effectively catalyzed reactions involving a large variety of these substrates and ketones. The differences in the effectiveness of the catalysts are explained by their electronically rich and sterically hindered nature that drives oxidative addition and reductive elimination steps in the catalytic cycle, respectively (Scheme 3).[2]



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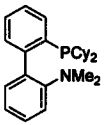

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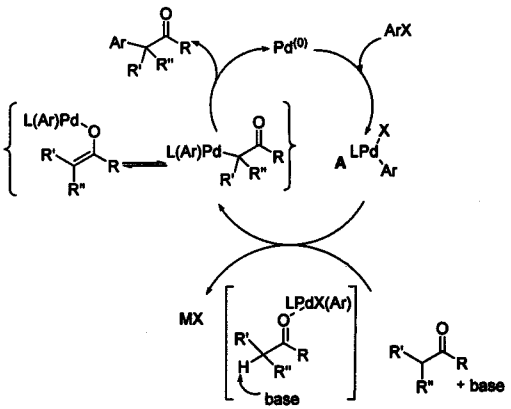
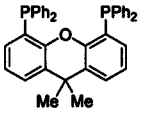
Scheme 3



In addition, the use of Xantphos **(8)** and BINAP **(5)** allows aryl halides with electron withdrawing substituents to couple with aliphatic ketones to produce α aryl ketones with a yield of approximately 70%.[2] Buchwald has further shown that a weak base, K_3PO_4, can be used in palladium catalyzed ketone arylation reactions when the substrate is base sensitive. [2]

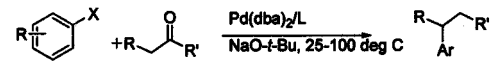


8

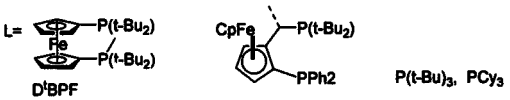
Another group that focused their research on the development of α aryl ketone synthesis was Hartwig and coworkers. This group devised a palladium catalyzed reaction which employed 1,1'- bis(di-*tert*-butylphosphino)ferrocene (D^{t}BPF) **(9)** as the ligand

(Scheme 4). This resulted in the arylation of ketones and malonates with aryl halides at 60-99% yields.[6] In one specific reaction, 4-methyl-3-pentanone reacted with 3-bromoanisole to provide the product from a single α arylation in 84% yield with a 89:11 ratio of isomers in the crude reaction.[5]

Scheme 4



X=Br, Cl, OTs R, R'=alkyl, aryl
R= C(O)OR, R'=OR



D'BPF also produced clean reactions with chloroalkenes at 70°C.[5] Additionally, bromoalkenes were used in combination with $P(t\text{-}Bu)_3$ **(11)** and PCy_3 **(12)** to produce arylated ketones in high yields.[5] Ketones, conversely, did not react with aryl tosylates when using DBPF as a ligand, but good yields occurred when PPF-t-But_2 **(10)** was utilized.[5]

The Hartwig group also addressed the mechanism of these reactions. Their work suggested that the phosphine ligands' ability to chelate the palladium catalyst was not the key factor in reductive elimination being favored over β-hydrogen elimination.[5] Instead, they concluded it was the steric hindrance of the monophosphines that drove the preference for reductive elimination.[5] The chelating properties of such phosphine ligands may, however, play an integral role in the regioselectivity for such reactions, while the monophosphines and bidentate phosphines serve as the complementary catalysts.[5] They

concluded that chelation was not necessary for chloroalkene activiation under mild conditions and that simple malonates can be arylated with sterically hindered alkylphosphines integrated into the catalyst system.[5]

The methods proposed by Hartwig and Buchwald were successful, yet yielded a variety of drawbacks that threaten the success of the reaction. Substrates with a nitro, cyano, carboxyl, or keto group react with strong bases and nucleophiles to result in products of a low yield.[7] The basic conditions limit the asymmetric induction due to the greater acidity of the product. After oxidation insertion of the palladium, followed by reductive elimination, the α carbon is deprotonated by the strong base needed to propagate the enolate, resulting in a loss of chirality.[7]

I.2. *Enamines as Nucleophiles*

In order to circumvent the strong base problem encountered with enolate intermediates in the formation of α aryl carbonyl compounds through the use of strong bases, Tian Tian of Union College suggested the use of enamines as a route around the problem. This suggestion was based on their similar resonance and structural characteristics, allowing them to act similarly in reactions in which they are used as nucleophiles (Figure 2).

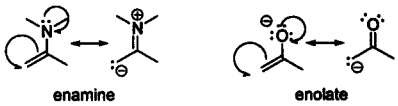
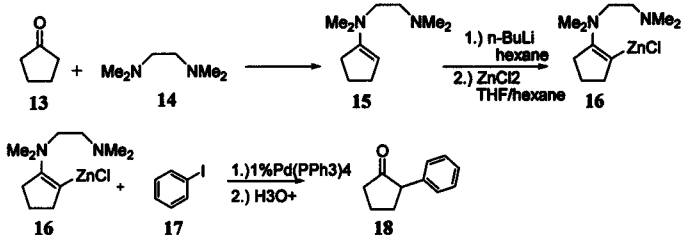


Figure 2. Comparison of enamine and enolate resonance structures.

Previously, there have only been two published reactions in which enamines are used to make an α aryl ketone. In 1987, Negishi and Akyoshi described the only method in which a palladium catalyst is used to couple an activated organozinc enamine with various aryl halides.[8] Scheme 5 illustrates the coupling of an organozinc halide cyclopentanone enamine derivative(**16**) and *p*-tolyl iodide (**17**). This was then quenched with 2 M HCl to afford the desired 2-(*p*-tolyl) cyclopentanone (**18**). Although this process did afford an α aryl ketone in appreciable yield, complete regio-control could not be achieved, and it was therefore not an entirely useful method.

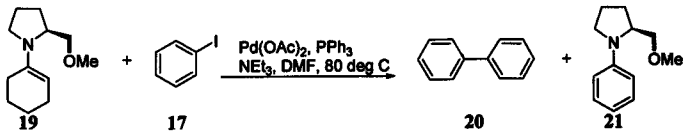
Scheme 5



13 **14** **15** **16** **16** **17** **18**

Following Negishi's work, in 1999 Meijere and Bräse reported, as unpublished results in a review, the attempt to perform a Heck coupling of chiral enamine (**19**) with iodobenzene (Scheme 6).[4] However, only biphenyl and the N-phenylpyrolidine were obtained, resulting from the oxidation of the cyclohexene ring to benzene.

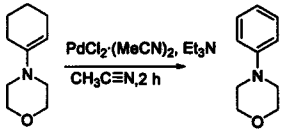
Scheme 6



19 17 20 21

Ishikawa and coworkers later confirmed this result when cyclohexanone derivatives were aromatized when treated with a stoichiometric amount of $PdCl_2(MeCN)_2$ and Et_3N/CH_3CN for 2 hours (Scheme 7).[9]

Scheme 7

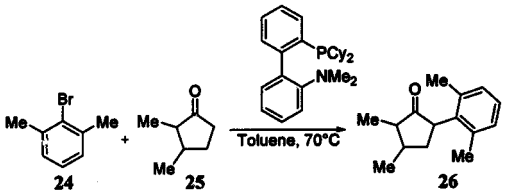


22 23

The mechanism for this aromatization was suggested to begin with electrophilic attack of a palladium salt on the β carbon of an enamine to produce a palladium substituted iminium ion intermediate which then undergoes β-hydride elimination to afford an α, β-unsaturated iminium ion. A second enamine intermediate is then formed, followed by attack of the palladium salt and β-hydride elimination to produce the aromatized enamine.[10] It is thought that cyclohexanone derivatives are more likely to undergo this aromatization because of the preferred stability, making cyclopentanone derivatives a feasible possibility. Cyclopentanone derivatives have been used by Hartwig and Buchwald in an attempt to couple ketones with aryl halides with the undesired enolate intermediate. Using an electron rich phosphine ligand, Buchwald coupled 2,6-

dimethylphenyl bromide (**24**) with 2-dimethyl cylcopentanone (**25**) to produce the α-arylated ketone (**26**) in a 64% yield (Scheme 8).[2] Although the yield is fairly low, it demonstrates the feasibility of using a cyclopentanone derivative and supports the idea that this would also work when using an enamine as well.

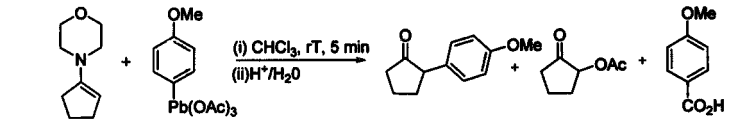
Scheme 8



24 **25** **26**

In 1982 May and Pinhey performed the C-arylation of an enamine using 1-morpholinocyclopentene (**27**) and p-methoxyphenyllead triacetate (**28**). The mixture of these in chloroform resulted in 2-(4-methoxyphenyl)cyclopentanone (**29**) (82% yield), 2-acetoxycyclopentanone (**30**), and anisic acid (**31**) production (Scheme 9). The mixture of products and the affordability of the aryl lead acetate compounds were the discouraging factors in the reactions, and a more suitable synthesis would be desired.[10]

Scheme 9

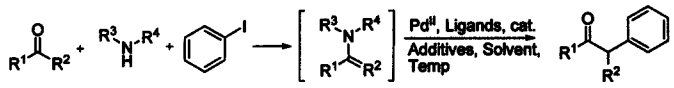


27 **28** **29** **30** **31**

I.3. *Small Scale Optimization*

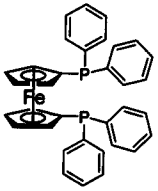
In an attempt to demonstrate that cyclopentanone derivative enamines could indeed produce the desired α aryl ketones, Tian Tian (Union College '05) began a project that sought to find and optimize the conditions for such a reaction. The reaction system was classified as a double catalytic coupling system with asymmetrical catalysis potential (Scheme 10).[11]

Scheme 10



A high throughput screening system was employed in which an aluminum block served as an 18 holed reaction vessel. This allowed for the systematic "directed random walk" reaction method used in which once a hit was found, further optimization was carried out by changing another component of the reaction system, but using the previous successful conditions.

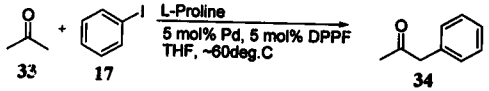
The optimization of the α arylation began by screening systems using a variety of phosphino, pyridyl, and ferrocene ligands, while also varying the catalyst palladium source. The results from these screenings showed that DPPF **(32)** and $Pd(OAc)_2$ **(6)** was the best ligand/palladium combination.



32

Concurrent optimization of the enamine, however, proved to be a drawback, and it was found that the acid group of proline was potentially causing problems in the generation of the arylated cyclopentanone. Therefore, a search for different secondary amines was started, as well as various ferrocene ligands and aryl halides. Results from these experiments demonstrated that pyrrolidine, DPPF, and aryl iodide were the most optimal reaction conditions. Further optimization led to the conclusion that a sacrificial amine would prevent the protonation of pyrrolidine by the coupling product, HI acid, and that DMF was actually a better solvent system than THF. After many optimizations a functional double catalytic system for generation of phenyl-2-propanone was found (Scheme 11).

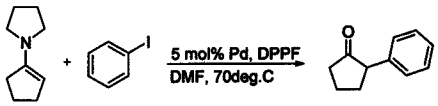
Scheme 11



33 17 34

A double component α arylation system requires the in-situ generation of enamine and then the subsequent palladium coupling of enamine with ketone. Therefore, optimization of just the coupling reaction seemed a reasonable route to a more successful conversion rate. This led to a reaction with different reaction conditions with a 100.00% conversion and yields ranging from 50 to 60% (Scheme 12).

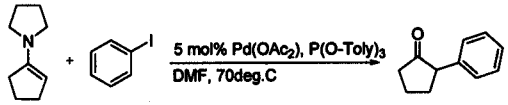
Scheme 12



35 **17** **18**

Further optimization research resulted again in different reaction conditions that led to a more successful reaction (Scheme 13).[12]

Scheme 13



35 **17** **18**

I.4. *Scale-Up Methodology*

Based on previous research, it is obvious that the α arylation of cylcopentanone derivatives is a feasible process that required a large amount of optimization. With the successful end reaction, the next logical step in the process is performing these reactions on a larger scale. All reactions done previously were performed on a 0.01 mmol scale, a size that demonstrates the success of the reaction but is not entirely useful for many applications. Therefore, we have proposed the scale up of the two component catalytic system to generate α aryl ketones to a 1.00 mmol scale.

Chapter II.

EXPERIMENTAL- GENERAL PROCEDURE

II.1. *2-(4-methoxyphenyl) cyclopentanone*

The preparation of 2-(4-methoxypehneyl) cyclopentanone is representative of all cases. A solution of 4-iodoanisole (1.0 mmol, 246 mg) was weighed and added into a 25 mL 3 neck round bottom flask. 1-pyrollidino-1-cylcopentane (1.5 mmol, 274 μl), diisopropylethylamine (1.2 mmol, 209 μL), tri-o-toluylphosphine (0.1 mmol, 37.3 mg), and palladium (II) acetate (0.05 mmol, 12.3 mg) were then added to 10 mL of butanol and stirred for 24 hours at 80 °C under nitrogen. To the resulting dark red solution (usual color), was added 10 mL of 0.1M HCl. The phase were separated and the organic layer was washed sequentially with three 10 mL portions of water, a 10 mL portion of brine, dried ($MgSO_4$) and concentrated in vacuo. The resulting dark brownish oil was purified by flash chromatography (75/25% ether/hexane.)

^{1}H NMR ($CDCl_3$) δ 1.9-2.8 (m, 6H), 3.28 (m, 1H), 3.79 (s, 3H), 6.88 (d, J = 9 Hz, 2 H), 7.12 (d, J = 9 Hz, 2H); ^{13}C NMR δ, 20.716, 31.733, 38.220, 54.526, 55.201, 113.989, 129.027, 130.355, 158.436, 218.476; IR 1739 cm^{-1}; HRMS *m/e* calcd for $C_{12}H_{14}O_2$ 190.0993 (M^+), measured 190.0989

II.2. *Methyl 4-(2-oxocyclopentyl)benzoate*

^{1}H N NMR δ 2.1-2.9 (m, 6H), 3.63 (m, 1H), 4.16 (s, 3H), 7.53 (d, J=7, 2H), 8.26 (d, J=8, 2H); ^{13}C NMR δ, 20.777, 31.407, 38.319, 52.007, 55.178, 128.132, 129.771, 143.550, 166.858, 216.943; IR 1722 cm^{-1}; HRMS *m/e* calcd for $C_{13}H_{14}O_3$ 218.0943 (M^+), measured 218.0938

II.3. *2-p-tolycyclopentanone*

^{1}H NMR ($CDCl_3$) δ 1.9-2.5 (m, 6H),2.32 (s, 3H), 3.29 (m, 1H), 7.07 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H) ; ^{13}C NMR δ, 20.785, 29.674,31.726, 38.312, 54.974, 127.935, 129.247, 135.332, 136.433, 218.855.; IR 1738 cm^{-1}; HRMS *m/e* calcd for $C_{12}H_{14}O$ 174.1045 (m^+), measured 174.1050

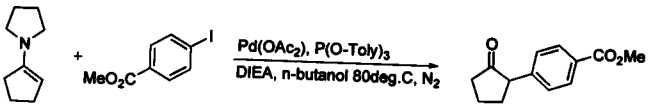
CHAPTER III.

RESULTS AND DISCUSSION

III.1 *Optimizing Reaction and Chromatography System*

The initial scale up reaction (Scheme 14) was monitored with pentadecane as an internal standard and analyzed using the GC/MS instrument. The reaction was run for 24 hours and both the GC/MS and ^{1}H-NMR data demonstrated that the reaction had not gone to completion and that starting material was still present in solution. In hopes of driving the reaction forward we increased the concentration of the reaction by decreasing the amount of solvent present from 10 mL of butanol to 5 mL. This, however, did not change the results, as starting material was still present after the reaction had run for 24 hours.

Scheme 14



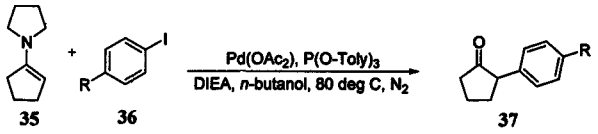
35 **36a** **37a**

In an attempt to rid the product of any undesired contaminants, flash chromatography was performed multiple times with a 75%/25% ether/hexane mixture. This solvent system, however, was not effectively separating the product components and I then sought out a more efficient system in hopes of recovering the product with a greater yield. After many combinations of ether, hexane, and methylene chloride, I found the best solvent system to be a 50/50 mixture of methylene chloride/ether. Running the reaction again (Scheme 14), and performing flash chromatography on the dark red

product resulted in the separation of the resulting products to some extent. There was, however, a greater overlap in fractions than desired, and this was most likely due to the solvent system used, of which both solvents were polar. The solvent system was then changed again to pure $MeCl_2$ and the reaction was run once more using the same procedure as shown in scheme 14. Thin layer chromatography was then employed and a potassium permanganate solution was used to detect fraction movement up the plate. When dipped into this solvent and then heated, the fraction spot oxidized and changed from a dark purple to white color. The appropriate fraction was analyzed using ^{1}H-NMR and ^{13}C-NMR spectroscopy and it was found that the desired product had been formed but in low yield and with obvious contaminants. It was again necessary to optimize the chromatography system.

In an effort to separate the components of the product more thoroughly, the use of a fritted disk column was used with a 100% $MeCl_2$ solvent system prior to using the longer and more effective flash chromatography column. The solvent system found to work best for the flash chromatography after an initial separation was a 75%/25% ether/hexane system, the exact system that had been used from the start. Upon analysis with ^{1}H-NMR and ^{13}C-NMR it was found that our product had indeed been recovered and separated with a 100% yield before separation and with a 73% yield after. High resolution Mass Spectroscopy again confirmed the results. It was then obvious that a crude chromatography column needed to be run prior to the flash chromatography to remove additional contaminants. Following this success, various iodobenzene derivatives were used and their resulting yields are reported (Table 1).

Table 1



37a: R = $MeCO_2$
37b: R = CH_3
37c: R = OCF_3
37d: R = $COCH_3$
37e: R = OCH_3

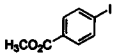
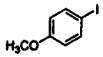
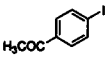
Ar	α-ArylKetone GC %-Yield (0.01 mmol scale	α-Aryl Ketone %-Yield at 1 mmol scale (isolated)
	98	100 (51)
	90	100 (73)
	96	100 (56)
	98	0
	69	0

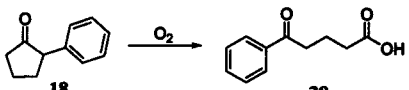
Table 1. Results for production of α-Aryl Ketone at a 0.01 and 1 mmol scale.

III. 2. *Oxidation of Product*

Although the reaction shown above (Scheme 14) was successful with three different iodobenzene derivatives at a scale of 1 mmol, we found interesting results in the ^{1}H-NMR and ^{13}C-NMR analysis. If the spectra were taken immediately following the work up, the resulting spectra looked as they should, with fairly pure results. However, upon exposure to the air for even a short period of time, a contaminant was present as

indicated by additional peaks in the ^{1}H-NMR spectra. This was found to be the oxidation product of the arylated cyclopentanone, and was confirmed by Mislow and Lazarus who reported that 2-phenylcyclopentanone (18) was oxidized by air to γ-benzoylbutyric acid **(38)** (Scheme 15).[13] Therefore, it was imperative to store the product under nitrogen at all times to preserve its desired structure.

Scheme 15



18 **38**

γ -benzoylbutyric acid

CHAPTER IV.

FUTURE WORK

In this section of my thesis, we have presented our studies of the palladium catalyzed α-arylation of cyclopentanone at a 1 mmol scale. We have shown that such a process can occur for three different ketones in fairly high yields. In the future, it would be advantageous to optimize the reactions of the ketones that did not react particularly well in order to expand the scope of starting materials one can use.

The biggest problem in the arylation of cyclopentanone is the instability of the product, as it is very susceptible to oxidation upon exposure to the air. Although this can be minimized by keeping the product sample under a nitrogen atmosphere at all times, it is inconvenient and not 100% accurate. Therefore, future work should be focused on stopping this oxidation. It has been hypothesized that the oxidation is occurring because of an aryl radical reaction, and it is therefore necessary to find a reagent that would prohibit this radical from forming.

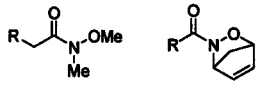
Section 2. *N-Acyloxazines as Novel Bicyclic Weinreb Amides*

CHAPTER I.

INTRODUCTION

I.1. *Weinreb Amides*

The discovery of N-methoxy-N-methyl (Weinreb) amides **(39)** by Stephen Weinreb in 1981 created a class of molecules that have proved useful in various reactions. Weinreb amides are commonly used as carboxylic acid protecting groups, as well as acylating agents. Their ability to chelate a metal ion between the oxygen of the carbonyl and that of the methoxy group gives this compound an interesting functionality. Literature has reported the synthesis and reactivity of a molecule that also possesses this dioxygen structure, with the difference being the substituents of the nitrogen and oxygen molecules. Instead of the methoxy and methyl groups, a double ring, or bicyclic structure is formed, creating a class of molecules none as N-acyloxazines **(40)**. We have set out to determine whether these "bicyclic Weinreb amides" are able to undergo the same reactions as Weinreb amides do, while creating an asymmetric environment and potentially controlling the stereochemistry of the resulting product.

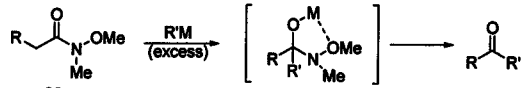


39 **40**

The most common use of Weinreb amides is their ability to act as an acylating agent through addition of an acyl group to another molecule.[14] The synthesis of ketones from compounds in the carboxylic acid oxidation state by coupling with organometallics has generally been viewed as a difficult procedure. This is due to the reactivity of

Grignard and organolithium reagents, causing the production of a tertiary alcohol.[14] In 1981, it was found that N-methoxy-N-methyl amide (39) combines with Grignard and organolithium agents in THF to form the desired ketones, thus acylating an R group (Scheme 16). The reaction is thought to be controlled by a metal-chelated tetrahedral intermediate that does not collapse until aqueous acidic workup, preventing further addition.[15] In addition to this, it was found that these compounds can be reduced to aldehydes in the presence of $LiAlH_4$.

Scheme 16



39

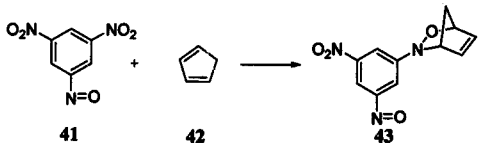
I.2. *N-Acyloxazines: "Bicyclic Weinreb Amides"*

With the knowledge that Weinreb amides could undergo reactions such as that in Scheme 16, it was interesting to consider what the result of controlling the stereochemistry of such a reaction would be. One way to do this would be to start with an asymmetric derivative of the Weinreb amide, found to be a class of compounds called N-acyloxazines. Several reports in literature describe the synthesis of these "bicyclic Weinreb amides," each with their advantages and disadvantages. In almost all cases the reaction involves the use of cyclopentadiene as the dienophile in the Diels-Alder reaction, and it is the diene, catalysts, and oxidation methods used that differ.

One of the earliest reported syntheses of the "bicyclic Weinreb amide" was published by Just and Cutrone, where they used a nitroso compound such as 2,4-dinitrosobenzene (**41**) as their diene. They found that the reaction of this with

cyclopentadiene **(42)** afforded the expected product **(43)** in 82% yield (Scheme 17).[16] They discovered that electron withdrawing groups on the nitroso compound produced higher yields of the adduct than those with electron donating groups, and through additional experiments they concluded that the electron withdrawing group was essential for the stabilization of the bicyclic product.

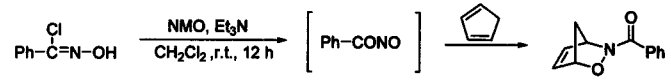
Scheme 17



41 **42** **43**

Quadrelli and coworkers have used another method for the synthesis of the acyl nitroso compounds, focusing on the oxidation of nitrile oxides with a tertiary amine N-oxide and then this product's subsequent reaction with cyclopentadiene. The reaction can be performed using hydroximoyl halides **(44)** while generating the nitrile oxides *in situ* **(45)**. Adding triethylamine (Et_3N) to a solution of hydroximoyl halide and N-Methylmorpholine-N-Oxide (NMO) in the presence of cyclopentadiene afforded the nitroso carbonyl cycloadduct **(46)** in 68% yield (Scheme 18).[17] A yield this low, however, leads one to believe a more effective process is available.

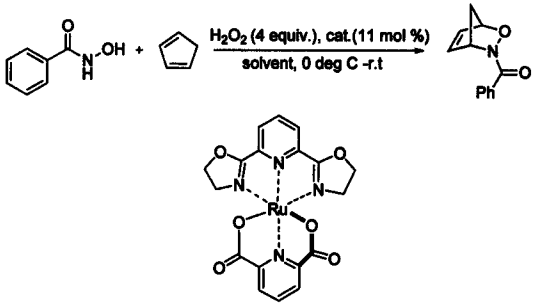
Scheme 18



44 **45** **46**

The most common starting materials for these reactions in recent years have been hydroxamic acids. In combination with cyclopentadiene and a variety of oxidation methods, various researchers have developed successful syntheses for the N-acyl`oxazines. The Iwasa group has focused their research around the use of metal catalysts, one being the ruthenium complex, Ru(II)(pybox-dh)(pydic). Iwasa and coworkers synthesized the desired compound via the ruthenium-catalyzed hydrogen peroxide oxidation of benzohydroxamic acid (47) followed by its Diels-Alder reaction with cyclopentadiene (42). Hydrogen peroxide was used in this case because water ends up being its only side product after oxidation. The reaction was successful in THF/ methanol-water mixture and cycloadduct 46 was afforded with a 97% yield (Scheme 19).[18]

Scheme 19

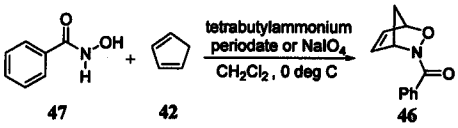


cat.: Ru(II)(pybox-dh)(pydic)

Iwasa continued to search for different catalysts for this reaction, specifically testing metallic systems. Those tested included $Co(acac)_2$, $[Rh(OAc)_2]_2$, CuI, and

$[Ir(cod)Cl]_2$ (cod = cyclooctadiene).[19] It was found that only the iridium and copper catalyst were successful, but copper was only moderately so. With the iridium catalyst in the presence of catalytic or stoichiometric amounts of some bases, a slight increase in cycloadduct was observed. The greatest yield in cycloadduct without any additives, however, was $[Ir(coe)_2Cl]_2$ (coe = cyclooctene), specifically when using benzohydroxamic acid (**47**) and THF at 0°C (Scheme 20). Once again, this method may not be convenient due to the complexity of the catalyst and the time needed to make it.

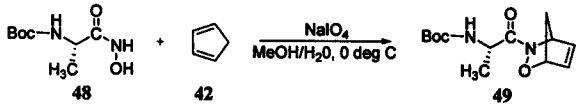
Scheme 20



47 **42** **46**

Perhaps the group that has worked most extensively with these compounds is Miller and coworkers, who have succeeded in synthesizing the cycloadducts using a Diels-Alder reaction between hydroxamates (**48**) and cyclopentadiene (42) in the presence of sodium periodate. This resulted in a 3:1 mixture of separable diastereomers (**49**) in 70% combined yield (Scheme 21).[20]

Scheme 21

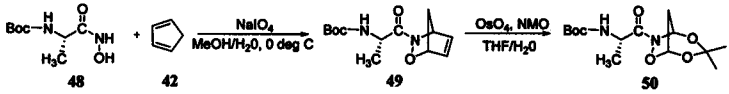


48 **42** **49**

In another attempt to synthesize these acylnitroso compounds, Miller utilized Swern-Moffet conditions, a process that calls for oxalyl chloride/dimethyl sulfoxide in

dichloromethane at -78°C.[21] Using this method to oxidize the diene component hydroxamic acid (48) and cyclopentadiene (42), the resulting cycloadduct (49) was generated in a 5:9:1 mixture of diastereomers in a 78% combined yield.[20] The double bond of the nitroso ring was subsequently removed with osmium tetroxide and N-methyl morpholine in THF to afford compound **50** (Scheme 22).[20,22] This step of the process indicated the necessity of removing the double bond of the nitroso ring before further addition, a course of action important in my future research.

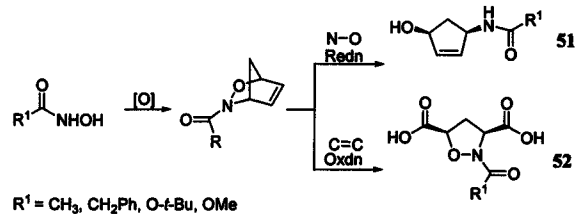
Scheme 22



48 42 49 50

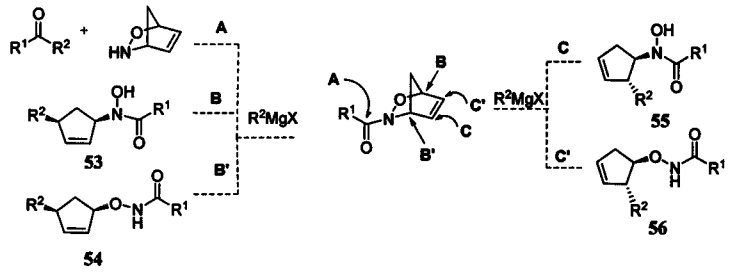
Our interest in these nitroso bicyclic compounds was specifically in whether or not they could be used as acylating agents to afford the resulting ketones and aldehydes such as the Weinreb amides have shown to do. Miller was also interested in this work and tried to do something much like this. Starting with a hydroxamic acid and cylcopentadiene in the presence of an oxidizing agent, a nitroso cycloadduct with varying R groups was afforded. Usually, this product undergoes cleavage of the N-O bond to form 1,4-aminocyclopentenols **(51)**, very important intermediates in the synthesis of carbocyclic nucleosides, prostaglandins, and other natural products (Scheme 24).[23] These cycloadducts can also be opened through oxidative cleavage of the olefin to form diacids **(52)**, precursors to various amino acids (Scheme 24).[23]

Scheme 24



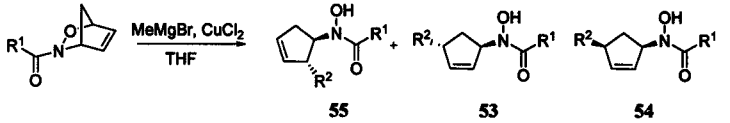
Miller, however, was interested in the less common reaction of C-O bond cleavage to generate a hydroxamic acid, and specifically in the ring opening in combination with C-C bond formation. This would prove that the carbon framework could increase directly from the cycloadduct, giving them an even greater role in synthesis. Because of the molecule's similar functionality to a Weinreb amide, one would assume that upon reaction with an organometallic compound, a ketone (path A) would be afforded. As Miller points out, however, there are many other electrophilic sites on the cycloadduct. Potential proposed reactions include direct nucleophilic displacement of the oxygen or nitrogen to generate anti-1,4-disubstituted hydroxamic acids **(53)** or hydroxamates **(54)**(path B) and an S_N2' attack that would indirectly displace the oxygen or nitrogen to give the corresponding anti-1,2-products **(55, 56)** (path B') (Scheme 25) .[23]

Scheme 25



Miller began his work by treatment of the N-acetyl cycloadduct with vinylmagnesium bromide. Although the yield was only 11%, he found the products to be a 1:1 mixture of anti-1,2:anti-1,4-hydroxamic acid (55,53,54), indicating that both nucleophilic displacement and S_N2' attack occurred (Scheme 26).[23] He noted that none of the products were generated from attack at the carbonyl carbon, meaning no ketone has been produced upon reaction with an organometallic.

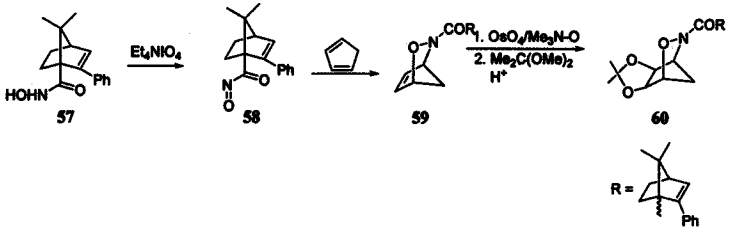
Scheme 26



With optimization leading to the addition of a catalytic amount of copper(II) chloride, the product yields of compounds 55, 53, and 54 were significantly increased, and still no ketone production was observed. Although this was the result he desired, it was not advantageous to the goals of our specific research, as it seemed that the Diels-Alder cycloadducts that one would assume to mimic Weinreb amides, in fact did not.

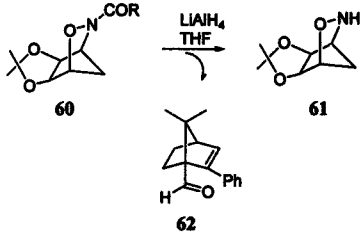
Further investigation into the project led to the discovery of similar work with the bicyclic Weinreb amides by Lin and coworkers.[24] Their research was focused on asymmetric additions to the acylnitroso compounds, and it began with the hydroxamic acid **57** oxidized to acylnitroso **58**. In the presence of cyclopentadiene this intermediate was converted to adduct **59**. The double bond of this adduct was then removed by reaction with a catalytic amount of osmium tetroxide in the presence of trimethylamine N-oxide at 25°C for 20 hours to subsequently produce the diol (**60**)(Scheme 27).[24]

Scheme 27



This was then reacted with the strong reducing agent, Lithium Alumumin Hydride and in addition the cleavage of the nitrosoamide to afford the amine, **61**, the aldehyde, **62**, was also formed (Scheme 28).[24]

Scheme 28



This result serves as a proof of concept for our research, demonstrating that the bicyclic cycloadduct could indeed act as an acylating agent such as a Weinreb amide. The difference between Lin and Miller's work was based on the removal of the double bond of the acyl nitroso compound, which prevented the opportunity for addition at these two carbons.

Previous research has shown that there are multiple ways to synthesize the acyl nitroso compounds that we are interested in treating as bicyclic Weinreb amides. It is the goal of our research to make these molecules and then set out to demonstrate their ability to react with an organometallic compound to afford the resulting ketone. Although Miller reported that such a reaction was not feasible, we are anticipating different results with the removal of the double bond in the ring. From here, it may be possible to separate an enantiomeric mixture and create a molecule capable of asymmetric induction.

CHAPTER II.

EXPERIMENTAL – GENERAL PROCEDURE

II.1. *Phenylhydroxamic acid*

To a solution of 15 mL methylene chloride in a 50 mL round bottom flask was added cyanuric chloride (3.0 mmol, 0.5 g) and the solution was allowed to stir. Phenylacetic acid (9.0 mmol, 1.09 g), N-methyl morpholine (9.9 mmol, 1.1 mL), and 4-dimethylamino pyridine (0.1 mmol, 0.01 g) were added to the mixture and allowed to stir at 0 °C. After stirring, a solution of hydroxylamine hydrochloride (9.8 mmol, 0.68 g) in 5 mL methylene chloride was added dropwise to the solution and the reaction stirred for 12 hours at room temperature. The resulting mixture was filtered on celite, and the organic phase washed three times with 15 mL of 1 M HCl, 20 mL of brine, dried ($MgSO_4$) and concentrated in vacuo to afford a light yellow solid. ^1H NMR ($CDCl_3$) δ 3.65 (s, 2H), 7.27-7.33 (m, 5H)

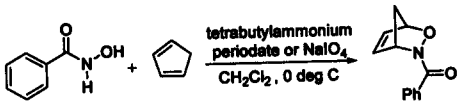
CHAPTER III.

RESULTS AND DISCUSSION

III.1. *N-Acyloxazines synthesis*

The investigation of this project began by attempting to synthesize cycloadduct 46 from the reaction between benzohydroxamic acid and cyclopentadiene using Lin's method of oxidation. The procedure, however, called for tetraethylammonium periodate, a compound not sold in the United States. Unable to use this, we substituted with tetrabutylammonium periodate in hopes of achieving the same end product (Scheme 29). Upon analysis with a 200 Mz H-NMR, it was clear that the reaction had not gone as planned, and that a majority of the material left was actually tetrabutylammonium periodate.

Scheme 29



47 42 46

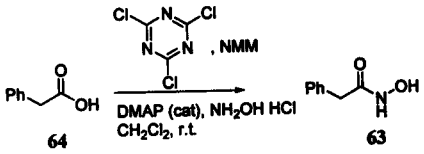
We then tried to follow Miller's synthesis of these N-acyl oxazines using Sodium periodate to oxidize the hydroxamic acid and then proceed with the subsequent reaction with cyclopentadiene (Scheme 21). Although this was cited to work in the literature with compound 49, it was apparent after NMR analysis that it did not work with benzohydroxamic acid.

III.2. *Hydroxamic Acid Synthesis*

The only literature sources found that utilized benzohydroxamic acid called for expensive and somewhat complex metal catalysts, namely the rhuthenium and iridium catalyst compounds seen in Scheme 19 and Scheme 20, respectively. Therefore, it seemed feasible to use a different starting material more widely used in previous research, namely phenylacetohydroxamic acid **(63)**. However, this compound was not commercially available and needed to be synthesized. There were several methods of hydroxamic acid synthesis available, only of which a few were possible at this time. Some experiments called for solid phase chemistry, a fairly complex process that would take much more time than available, and we therefore tried more basic procedures.[25]

Giacomelli and coworkers had previously demonstrated the success of the synthesis of this N-acyloxazine with the phenylacetohydroxamic acid starting material.[26] The procedure called for the reaction of phenyl acetic acid **(64)** in the presence of cyanuric chloride (TCT), N-methyl morpholine, and hydroxylamine hydrochloride in methylene chloride (Scheme 30). The reaction was started at 0°C and warmed to room temperature upon addition of TCT and was run for 24 hours. In our first attempts at this reaction, there was very little hydroxamic acid produced, mostly below a 40% yield. The literature values were reporting yields of 90 % and it was troubling to obtain such different results.

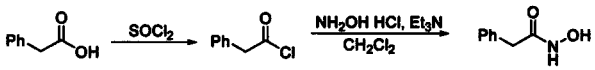
Scheme 30



64 **63**

In another attempt to synthesize the starting materials needed for this reaction, we used acid halides in combination with hydroxylamine hydrochloride and triethylamine. The acid halide (65) was derived from the reaction of its corresoponding carboxylic acid, phenylacetic acid (64), with thionyl chloride ($SOCl_2$). Upon addition of hydroxylamine hydrochloride in Et_3N, an exothermic reaction should have taken place in which the acid halide was converted to the hydroxamic acid 63 (Scheme 31). However, through ^1H- NMR analysis, it was found that only Et_3N was left, indicating that somewhere in the work up process all other reagents had been lost.

Scheme 31



64 **65** **63**

After several attempts at the reactions shown above, I contacted Giacomelli regarding the low yields produced in the reaction he reported as being very successful. A response from him provided a different experimental procedure as listed in the paper and also advised the purchase of new cyanuric chloride.[27] Making this purchase, as well as following the new experimental procedure, led to the successful synthesis of phenyl hydroxamic acid.

CHAPTER IV.

FUTURE WORK

With unexpected difficulties in the synthesis of the N-acyloxazines and then again with the hydroxamic acids, there is a great deal of work to be done on this project in the future. With the phenylhydroxamic acid now available, the next step in the process is to perform the Diels-Alder reaction with cyclopentadiene to afford the cycloadduct N-acyloxazine. Common methods for this synthesis include using sodium periodate as an oxidizing agent.[28] Once this is made, it is then necessary to remove the double bond that we believe hindered Miller from being able to convert the cycloadduct to a ketone. This procedure has been utilized by both Miller and Lin.[22,24] Upon removal of the double bond, the new "bicyclic Weinreb amide" should then be exposed to an organometallic species in hopes of converting the original structure to a ketone, as shown in Path A of Scheme 25. This would then demonstrate the N-acyloxazine's ability to act similarly to a Weinreb amide.

Once it can be shown that the N-acyloxazine does indeed act like a Weinreb amide, the next step would be to separate out the enantiomers of the product. In doing so, one could create an asymmetric molecule capable of controlling the stereochemistry of any further reactions. A chiral auxilliary would be created, making the bicyclic Weinreb amides an advantageous starting material in subsequent processes.

REFERENCES

1.) Moradi, W. and Buchwald, S. *J. Am. Chem. Soc.* **2001**, *123*, 7996-8002

2.) Fox, J. Xiaohua, H., Chieffi, A. and Buchwald, S. *J. Am. Chem. Soc.* **2000**, *122*, 1360-1370

3.) Semmelhack, M. and Bargar, T. *J .Am. Chem. Soc.* **1980**, *102*, 7765-7774

4.) Meijere, A., Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88-110

5.) Palucki, M. and Buchwald, S. *J. Am. Chem. Soc.* **1997**, *119*, 11108-11109

6.) Kawatsura, M., and Hartwig, J. *J. Am. Chem. Soc,* **1999**, *121*, 1473-1478

7.) Hama, T., Liu, X., Culkin, D., and Hartwig, J. *J. Am. Chem. Soc.* **2003**, *125*, 11176-11177

8.) Negishi, D., Akiyoshi, K., *Chem. Lett.* **1987**, 1007-1010

9.) Ishikawa, T., Uedo, E., Tani, R., and Saito, S. J. Org. Chem. **2001**, *66*, 186-191

10.)May, G. and Pinhey, J. *Aust. J. Chem.* **1982**, *35*, 1859-1861

11.) Tian, T. B.S, thesis, Union College, Schenectady, NY, 2005

12.)D'Silva, E., Shea, S. Unpublished results. **2005**, Union College

13.) Mislow, K. and Lazarus, A. *Notes.* **1955**, *77*, 6383-6384

14.)Nahm S. and Weinreb S. *Tetrahedron Lett.* **1981**, *22*, 3815-3818

15.) Singh, J., Satyamurthi N., and Aidhem I. *J. Prakt. Chem.* **2000**, *342*, 340-347

16.) Just, G., Cutrone, L. *Can. J. Chem.* **1976**, *54*, 867-870

17.) Quadrelli, P. Gamba, I., Caramella, P. *Tetrahedron Lett.* **1996**, *37*, 1909-1912

18.) Iwasa, S., Tajima, K. Tsushima, S. and Nishiyama, H. *Tetrahedron Lett.* **2001**, 5897-5899

19.) Iwasa, S. et al. *Tetrahedron Lett.* **2002**, *43*, 6159-6161

20.) Kim, K., and Miller, M. *Tetrahedron Lett.* **2003**, *44*, 4571-4573

21.) Martin, St. F., Hartmann, M., Josey, J.A. *Tetrahedron Lett.* **1992**, *33*, 3583

22.) Shireman, B., Miller, M. *Tetrahedron Lett.* **2001**, *41*, 9537-9540

23.) Surman, M., Mulvihill, M., and Miller, M. *J. C ·g. Chem.* **2002**, *67*, 4115-4121

24.) Lin et al. *J. Org. Chem.* **1997**, *62*, 3806-3807

25.)Ho, C. et al. *J. Org. Chem.* **2005**, *70*, 4873-4875

26.) Giacomelli, G., Porcheddu, A., and Salaris, M. Org. Lett. **2003**, *5*, 2715-2717

27.) Electronic Mail Correspondence with Giampaolo Giacomelli, April 19, 2006.

28.)Mulvihill, M., Surman, M., and Miller, M. *J. Org. Chem.* **1998**, *63*, 4874-4875