Drew University

College of Liberal Arts

Ketone and Alkyl Halide/ Aryl Halide Barbier Coupling Reactions Using Versatile SmI₂ - Ni (II) System and External Ligands

Thesis in organic Chemistry

By

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Submitted in partial fulfill of the requirements for the Degree of Bachelor of Science

with Specialized Honors in Biochemistry and Molecular Biology

May 2025

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Abstract

Samarium Diiodide (SmI₂) is a single electron reductant with the ability to couple carbonyls, aldehydes and alkyl halides. SmI₂ has been effectively used with NiI₂ to carry out Barbier reactions in the past, which has a similar mechanistic approach as the Nozaki-Hiyama-Kishi reaction which uses chromium (II) instead of SmI₂. This paper first focuses using the well-known Sm- Barbier coupling reaction to explore the product selectivity of a range of substrates. Furthermore, this paper investigates the ability for external ligands to stabilize the Ni (0) intermediate that forms in the Barbier pathway and the effect these have on product selectivity. Three phosphorus-based ligands and one nitrogen-based ligand were used in this study, as well as two different Nickel (II) sources. Three different alkyl halide- ketone Barbier coupling reactions were carried out, with one yielding high Barbier selectivity, while the other two had decent to low product ratios. Addition of ligands led to a slight increase in product selectivity with Triphenylphosphine (PPh₃), while a decrease in Barbier selectivity with all others. These results suggest that Ni (0) chemistry must be further studied with other ligands to determine how it can be stabilized to effectively and continuously carry out the Barbier cycle. This paper utilizes the Sm- Barbier coupling pathway to investigate ketone and aryl halide as well as ketone- vinyl halide couplings as we try to provide an alternative to the NHK reaction which utilizes carcinogen chromium (II) and is used in biomedical synthesis. This paper, for the first time reports successful ketone and aryl halide (SP² carbon) coupling using versatile reductant system SmI₂-Ni (II) and external ligand. Reactions with DPPP as the external ligand saw the highest selectivity for the desired ketone- aryl coupled product, although the side products were still highly favorable. In the future, other ligands should also be tested to increase ketone-aryl product selectivity and try to diminish or even eradicate the side products observed

in this reaction. Lastly, a vinyl halide was successfully synthesized in the lab and used to carry out a coupling reaction with a ketone. For the first time, we report successful vinyl halide- ketone coupling using SmI_2 - Ni (II) system as a trace amount was observed when this reaction was carried out with 4 eq DPPP. These findings are promising as a similar approach can be made for future ketone and vinyl halide (SP^2 carbon) optimization reactions aiming for single product selectivity to successfully provide an alternative to the NHK reaction.

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Chapter 1- SmI₂ Introduction

1.1 Samarium Diiodide Properties

Organic reductants to date play a huge role in pharmaceutical drug synthesis and development. In some cases, some of these pharmaceuticals such as Spirastrellolide A and Epothilone are important for treatment of current diseases (Figure 1)¹⁻³. Spirastrellolide A has gained interest for its potential role in cell cycle inhibition as a potential treatment for cancer¹. Epothilone has also been studied for use in cancer therapy as it induces cell apoptosis². Both of these molecules can be synthesized in a lab with a series of different reactions one of which involve the Nozaki-Hiyama-Kishi (NHK) reaction which is used to couple a ketone and a vinyl halide using Chromium (Cr (II)) and a nickel (Ni (II)) catalyst (Scheme 1)⁴. The NHK reaction is a well known coupling reaction in organic chemistry that has been around since 1986⁵. One flaw with this reaction is the use of Chromium (II) as the reducing agent, since this one is still a suspected carcinogen⁶. Such an issue has led to others to find an alternative to this reductant. One possible alternative can be found in Samarium Diiodide (SmI₂), which is a single electron reductant that can interact with nickel and is used in current ketone and alkyl halide coupling reactions⁷. To the best of our knowledge this alternative has not been proposed in the past, and as a result this paper explores SmI₂ as a possible alternative to Chromium.



Figure 1. (A) Spirastrellolide A synthesized partially using the NHK reaction. **(B) Epothilone B** compound synthesized using the NHK reaction.



Scheme 1. Nozaki-Hiyama-Kishi Reaction which couples a Ketone with a Vinyl Halide using Ni (II) and Chromium.

Samarium Diiodide ever since introduced in 1977 by Kagan, has been used throughout decades as a single electron reductant⁷. Focus on Samarium Diiodide has been growing throughout the recent years, as many more organic and inorganic chemists are becoming aware of the versatility this compound has on synthesis reactions and reductions. SmI₂ in its +2-oxidation state has been identified as a powerful reductant, able to interact and reduce alkyl halides, carbonyls, esters and carboxylic acids amongst some functional groups (figure 2)⁷⁻⁸. These reductions involve the formation of radicals, as SmI₂ is characterized as a single electron reductant, giving one electron to the substrates leading to a +3-oxidation state (Scheme 2). When a carbonyl is exposed to SmI₂, a radical is formed, and when it interacts with a hydrogen proton an alcohol is generated.



Figure 2. SmI₂ reducing carbonyls, alkyl halides, esters and carboxylic acids



Scheme 2. Samarium Diiodide interacting with a Ketone to form a radical.

1.2 Reductions and Couplings with SmI₂

Besides reductions, Samarium Diiodide can also be used for carbon-carbon bond formations. One way in which coupling can occur is when 2 radicals interact with each other and form a carbon-carbon bond (Scheme 3). Samarium Diiodide also has the ability to carry out reactions in the presence of catalysts and cosolvents, which are often used to obtain higher product yields⁸. All of these characteristics make this reductant very efficient, but it has certain inconveniences which makes it hard to handle.



Scheme 3. Two radical compounds being coupled and forming a radical coupled alcohol

Although SmI₂ is safer to use than other reductants such as magnesium or sodium (flammable with water), it can still be hard to handle. Samarium diiodide can lose its reactivity when exposed to moisture as it transitions into its +3-oxidation state and becomes more stable compared to its +2 state⁸. As a result, reactions using SmI₂ require a glovebox or Schenk line with noble gases like Argon to minimize possible Samarium Diiodide- moisture interactions. Additionally, SmI₂ can be obtained from reacting Samarium metal and Iodide crystals in a solvent such as freshly distilled THF (Scheme 4). A major complication is that THF is hydrophilic therefore it needs to be distilled every 21 days, as this one can take up moisture when stored in the Schenk line under argon, and affect SmI₂ reactivity¹⁰. These results have led us to anticipate a similar THF behavior when stored in the glovebox under argon. A solution to deal with the moisture THF may absorb is the addition of molecular sieves which can trap any moisture that may get into the solvent. Although molecular sieves can be effective, frequent distillation still needs to be carried out to make sure THF is not a variable in synthetic reactions¹⁰. If THF with moisture were used for SmI₂ synthesis, this one would go into its +3-oxidation state becoming highly stable⁷. Although moisture can be a problem, SmI₂'s versatility makes it very valuable to work with.

Scheme 4. Samarium Diiodide synthesis, reacting Samarium metal and I₂ crystals in freshly distilled THF

SmI₂'s reductive and coupling abilities has led to this being used in many and different carbon- carbon bond forming reactions. Including functional groups like carbonyls, nitriles, alkyl halides and lactones, while aiming to obtain high product yields¹¹⁻¹⁵. In these reactions lactones were successfully reduced by samarium diiodide, which caused the rings to open resulting in alcohols (Figure 3)¹¹. Although only 6 member rings were reduced, while 5 and 8 member rings remained unreacted, this showed SmI₂'s ability to reduce compounds other reductants could not¹¹. Although SmI₂ reduced 6-member ring lactones, it could not carry out the reduction of simple esters, in the presence of water. While SmI₂ can carry out reductions other reductants cannot, it also has its limitations with certain substrates, without an established reactivity pattern.



Figure 3. Lactone reductions with SmI₂

SmI₂'s versatility allows it to carry out alkyl halide and carbonyl coupling reactions by itself, which lead to multiple product formation. In these reactions Samarium Diiodide will produce alkyl halide and ketone radicals which will be able to interact with one another and result in multiple combinations¹². As a result, alkyl halide- ketone coupling reaction utilizing SmI₂ can yield up to five different products (Figure 4). These 5 products include alkyl halide- carbonyl, alkyl halide- alkyl halide, and carbonyl- carbonyl couplings as well as alkyl halide and carbonyl reductions¹³. These many products can be troublesome in the synthesis of pharmaceuticals due to the high demand for single product formation that is easy to isolate.



Figure 4. Side product formation when a Carbonyl and an Alkyl Halide are coupled with SmI₂. The Barbier product as well as coupled and reduced Carbonyls and Alkyl Halides are observed¹³.

1.3 SmI₂ and Nickel Chemistry

In the past the introduction of a transition metal catalyst with SmI_2 has been used to maximize product selectivity in these coupling reactions. Some of these reactions are known as Barbier coupling reactions, which involve alkyl halides, carbonyls, and a metal catalyst (Scheme 5). These Barbier reactions are very similar to Grignard reactions where the major difference is the number of steps needed. The Barbier reaction can have all substrates and solvents added at once, in a single step process. Meanwhile the Grignard reaction needs the alkyl and metal added first and the Carbonyl incorporated in a secondary step (Figure 5)¹⁴.



Scheme 5. Barbier reaction using an Alkyl Halide, Carbonyl, SmI₂ and Ni (II).



Figure 5. Barbier reaction vs Grignard reaction schemes

The most common catalyst used in Barbier reactions is nickel (Ni (II)), and although the mechanism for how they carry out reactions has not always been entirely clear, it has proven to positively impact percent yields. In the past it has been determined that coupling of alkyl halides and lactones using SmI₂ and Ni (II) led to high percent yield¹³⁻¹⁵. Meanwhile when Ni (II) was not present in the reaction, lower product yields and ratios were observed (Figure 6). This proved the importance of adding nickel to this reaction as it led to higher product yields and selectivity. At the same time, this made evident SmI₂'s ability to interact with a catalyst and which can be used to influence products in a coupling reaction.

Lactone	Alkyl Halide	Mischmetal- SmI ₂ Yield %	SmI ₂ -NiI ₂ Yield %
Propiolactone	1-Iodoheptane		
		37	47
Butyrolactone	1-Iodoheptane		
		0	83





A similar trend was seen when nitriles and alkyl iodides were reacted in the presence of SmI_2 and Ni (II), with higher percent yields being observed when nickel was present in the reaction (Figure 7)¹⁶. Prior to these results, nitriles had been very hard to couple, or even reduce, by other common reductants including SmI_2 by itself. This suggested that SmI_2 and nickel (II) interacted with the substrates in a different fashion than SmI_2 did, potentially mediated by nickel chemistry which allowed coupling to take place and led to increased product yields¹⁶.

Nitrile	Alkyl Halide	Product yield %
PhCN	CH ₃ CH ₂ CH ₂ I	68
PhCN	Ph (CH ₂) ₃ I	67
Ph (CH ₂) ₂ CN	I (CH ₂) ₃ CH (CH ₃) ₂	



Figure 7. Nitriles and alkyl halide coupling using SmI₂ and NiI₂¹⁶

Years later, selectivity for the Barbier product was once again observed in reactions with alkyl halides and ketones being coupled by SmI_2 and Ni (II)¹⁷. When Ni (II) was present, high percent yields of the Barbier coupled product were observed, although the reaction had been carried out for a very short time (Figure 8). Meanwhile when Ni (II) was absent, lower percent yield as well as side products were observed, while the reaction took longer to proceed¹⁷.



Figure 8. Barbier reaction using Nickel Iodide and SmI₂ to couple an Alkyl Halide and a Ketone, yielding high selectivity for the Barbier product in very short reaction time¹⁷.

From these reactions it was proposed that SmI₂ reduced Ni (II), which produced Ni (0), and this one subsequently interacted with the alkyl halide through oxidative addition to form an organonickel complex (Figure 9). Transmetallation with the organonickel complex led to the formation of the organosamarium complex which coupled with the ketone while nickel (II) was released back into the catalytic cycle¹⁷. The Organosamarium complex and ketone coupling lead to a single alcohol product formation. In this process the formation of Ni (0) was fundamental to obtain the high Barbier product selectivity observed¹⁷. In this cycle the samarium interacts with nickel (II), before it can interact with the substrates, which leads to Ni (0) forming and subsequently a single couple product. This process explains why a single product is observed when Nickel is incorporated into the system. Left-over Samarium Diiodide can reduce substrates left behind, if any, and result in minimal side product formation in some cases. In this case Ni (II) catalyst is not only beneficial to reduce reaction times while increasing percent conversion, but also detrimental for single product formation. As a result, this Samarium Diiodide- Nickel chemistry discovery has been useful to avoid side products when carrying out Barbier coupling reactions.



Figure 9. SmI₂-Nickel (II) coupling mechanism proposed in which Ni (0) is formed and leads to selectivity of the Barbier coupled product¹⁷.

1.4 Ligand Addition to Coupling Reactions

While SmI₂ and nickel have led to high yields and selectivity in certain reactions, others have used ligands to accomplish similar results. In the past Nickel (II) has been synthesized with additional ligands to stabilize Ni (0). As a result, alkyl halides and cyclic reactions where coupling was mediated by Nickel (0), had high selectivity for the major product¹⁸. These results agree with previous reports where Ni (0) in the reaction is responsible for high selectivity¹⁷. Although Ni (0) is beneficial in these reactions, it has also been observed to be highly unstable and it is likely to crash out in nanoparticle¹⁷. Such low stability may lead to reactions, using nickel, to yield many different side products when reduced with SmI₂ as they would not go through the Barbier cycle (Figure 9) and instead just have the reductant interact with both substrates (Figure 4). As a result, many have turned to external ligands trying to stabilize Ni (0) particles in reactions using Ni catalysts. In the past reactions between carbonyls and alkyl bromides with different ligands have led to different product selectivity. In the majority of these reactions the percent yield of the desired product decreased with increasing ligand size while smaller ligands increased yields (Figure 10)¹⁹. Similar reactions carried out using SmI₂ and Nickel (0) saw bulkier ligand incorporation lead to a decrease in percent yield²⁰. In these reactions, although alkyl halides were coupled, using bigger ligands made it harder for an Alkyl Halide- Ni (0) complex to form, which resulted in lower percent yield and selectivity.

Entries (Aldehyde – Alkyl Bromide coupling)	Ligand	Yield % Desired product
	1,5 haxadiene	
Bn + Br CO ₂ Et		93%
	Cod	
Br Br CO ₂ Et		59%
	Вру	
Bn + Br CO ₂ Et		15%
	Terpy	
Bn + Br CO ₂ Et		0%

Figure 10. Aldehyde and Alkyl bromide coupling using Ni, NaI, Mn and different ligands¹⁹.

Furthermore, coupling of alkyl halides with different hybridized carbons, such as an Sp² carbon, have been affected by ligands in the reactions, similar to Sp³ carbons. When Ni (II) and ligands were introduced, depending on the size of the ligand, the coupled alkyl halide percent yield would decrease as the ligand size increased (Figure 11)²¹. Additionally previous studies have reported that small phosphorus-based ligands like Triphenylphosphine (PPh₃), 1,3 Bis(diphenylphosphine)propane (DPPP), 1,4 Bis(diphenylphosphine)Butane (DPPB) are highly effective in single bond and cycloaddition coupling, respectively (Figure 12)²²⁻²³. At the same time other external ligands like nitrogen based (pyridine) have been found to be great catalyst stabilizers in coupling reactions²⁴. Such properties could be used to stabilize the Ni (0) produced in Barbier reactions. These ligands can be used to stabilize nickel catalysts, therefore understanding ligand- Ni (0) relation can be fundamental for high product selectivity.

Reactants	Ligand	Yield % (Desired product)
Sp ³ and Sp ² alkyl halide coupling	L1 Me Me Ph \xrightarrow{N} Ph	85 %
Sp ³ and Sp ² alkyl halide coupling		84%
Sp ³ and Sp ² alkyl halide coupling	$Pr \xrightarrow{V} Pr$ $Pr \xrightarrow{V} Pr$ Pr Pr Pr Pr Pr Pr	75%

Figure 11. Sp³ alkyl halide coupled with Sp² alkyl halide in NI (II), NaI, TMSBR and 3 different ligands²¹.



Figure 12. Aryl Bromide coupling with Nickel and PPh₃²³.

Besides the incorporation of external sources, ligands in the solvents have also been examined before. In the past, the reduction of alkyl halides with SmI₂ – HMPA, has been examined and showed that ligands in the solvent (HMPA) were affecting the alkyl reduction. These ligands in the solvent had a higher affinity for SmI₂ than the alkyl halide, therefore the HMPA would displace the substrate and lead to lower reduction²⁵. The opposite effect was seen for ketones, which had higher affinity for SmI₂ than HMPA, thus higher reduction was observed as SmI₂- ketone interactions were favored. As a result, it was theorized that some ligands can enhance, while others diminish, the effect Nickel has on product selectivity. Is not clear if the ligands present in the nickel source itself would also have an impact on the reaction. It may be expected for bulkier nickel ligands, to generate a bigger gap between the nickel and SmI₂ molecules, so less Ni (0) will get formed. Therefore, bulkier Nickel ligands could generate lower Barbier product selectivity and lead to higher side products formation. Based on these previous observations it would be beneficial to determine the effect nickel (II) sources and external ligands would have on ketone and alkyl halide Barbier coupling reactions.

Trying to determine the effect of SmI_2 - Ni (II), this paper uses the known Sm-barbier coupling reaction to focus on product selectivity of a range of substrates (Scheme 6). Furthermore, external ligands will be explored to determine if these would help stabilize Ni (0) intermediate and promote product selectivity. Any ligand able to stabilize Ni (0) should promote its pathway and lead to single product formation. In these reactions two nickel sources (Figure 13) will be examined, as well as 4 different ligand sources. We expect reactions carried out with SmI_2 and Ni (II) to have Barbier product selectivity. We also expect to observe full Barbier selectivity with the incorporation of external ligands (Figure 19).



Scheme 6. Ketone and Alkyl Halides Barbier coupling reaction carried out in this paper using SmI₂- Ni (II) and external ligands.



Figure 13. Nickel sources used in this paper: A) Nickel Iodide (NiI₂) and B) [1,2-Bis(diphenylphosphino)ethane] dichloronickel (II) (NiDPPE).

Chapter 2- NHK Introduction

Before SmI₂- Nickel (II) were observed to interact and generate Ni (0), the Nozaki-

Hiyama- Kishi (NHK) reaction had been discovered (Scheme 7)⁵. The NHK reaction uses Ni (0)

chemistry to carry out the coupling of a vinyl halide with a carbonyl (Figure 14). This reaction

utilizes Chromium (II) and Ni (II) to generate Ni (0) which then reacts with the vinyl halide

followed by transmetalation with chromium (III) and leads to alcohol formation⁴. The NHK reaction can carry out coupling similarly to the Barbier reaction but the major difference is chromium (II) being used and the vinyl halide.



Scheme 7. Nozaki-Hiyama-Kishi Reaction which couples a Ketone with a Vinyl Halide using Ni (II) and Chromium.



Figure 14. Nozaki-Hiyama-Kishi Reaction using Chromium (II) and Nickel (II)¹⁷.

The Nozaki- Hiyama- Kishi reaction is highly important as it is used in biochemistry and biopharmaceutical synthesis, for the production of biomolecules. The NHK reaction is observed in drug synthesis, such as Spirastrellolide A and Epothilone B compounds both previously used in cancer therapy (Figure 1)¹⁻³. Additionally, an NHK like reaction is also involved in vitamin C and hepatitis B drug synthesis (Figure 15) as it's used to synthesize Homoallylic Alcohol- which is a building block for these drugs (Figure 16)²⁶. Although the NHK mechanism is used to obtain high selectivity for the desired coupled product, it has the downside that it uses Chromium.

Exposure to high Chromium concentration over time can lead to oncogenic transformation of cells, also known as cancer, making Cr not a desirable reductant to synthesize biomolecules⁶.



Figure 15. (A) Vitamin A with Homoallylic Alcohol highlighted. (B) Hepatitis B drug with Homoallylic Alcohol highlighted.



Figure 16. Homoallylic Alcohol synthesis using NHK like reaction²⁶.

Considering the mechanistic similarities between SmI₂- Nickel (II) and Chromium (II)-Nickel (II), brings about the question whether SmI₂ could replace Chromium (II) in biomolecule synthesis. It would be beneficial to determine if Samarium Diiodide and Nickel (II) can carry out the coupling of a vinyl halide with a ketone while yielding high coupled product selectivity (Scheme 8). Trying to answer this question, we had proposed to carry out a ketone- vinyl halide (an Sp² halide) coupling using SmI₂ and Ni (II); unfortunately, commercially available vinyl halides are very expensive. As a result, we decided to start by coupling a ketone and a different Sp² halide like aryl halide, since this one also has an Sp² carbon that would bind to the carbonyl alpha carbon. This can serve as a proof of concept for ketone and Sp² aryl halide (similar to the vinyl halide) coupling.



Scheme 8. Ketone and Vinyl Halide coupling with SmI₂ and NI (II).

This paper explores ketone and aryl halide coupling reactions using SmI₂ and Ni (II) in the presence of external ligands. In this case the ketone (3-pentanone) and aryl halide (4-Iodotoluene) will be coupled using SmI₂ and NiI2/ NiDPPE with 4 different external ligands (Scheme 9). We aim to use the well-known Sm-Barbier coupling mechanism and external ligands, helping to stabilize Ni (0), to obtain ketone and aryl halide coupling and potentially high product selectivity. Since commercially available vinyl halides are expensive for an undergraduate lab, we aim to synthesize a vinyl halide and use this one in a coupling reaction. In this paper, the synthesized vinyl halide will be coupled to ketone using the SmI2- Ni (II) system to further explore if SmI₂ and Ni (II) are a viable alternative to the NHK reaction (Scheme 10). External ligands will also be incorporated into this system trying to stabilize Ni (0) and increase the likelihood of the desired product being formed. If the desired product is observed from these reactions, then this can serve as a lead way to couple vinyl halides (another SP² carbon) and ketones in the future; as we try to compare Samarium Diiodide and nickel (II)'s ability to couple vinyl halides like Chromium and Nickel²⁷.



Scheme 9. Pentanone and 1-Iodotoluene coupling with SmI₂ and Ni (II) using external ligands being carried out.



Scheme 10. Pentanone and vinyl halide coupling with SmI₂ and Ni (II) system and external ligands being carried out.

Methods

THF Distillation in the Schenk line

Benzophenone (10.0 g, 0.055 mol) was added to an oven dried 3-neck round bottom flask. The round bottom flask was vacuumed/purged 3 times and kept under argon. Tetrahydrofuran (250 mL) was added to the flask and stirred to dissolve with Benzophenone and Sodium in paraffin (6.0g, 0.255 mol). The round bottom flask was placed on an oil bath and the reflux water was turned on; this went on for an hour. The reaction turned blue and persisted in this color during reflux. Reflux water was shut off and distillation water was turned on and the distillation proceeded for around 1 hour. The THF was not distilled to dryness to avoid directly heating up the Sodium. Distilled THF, clear liquid, was stored in the glovebox with activated molecular sieves and under Argon using an oven dried flask. Based on data we currently have from the Choquette lab, THF can be stored in the glovebox for up to 20 days, before it needs to be distilled again (Appendix A)²⁸. As a precaution, the THF used in these reactions has been distilled every 14 days and stored with activated molecular sieves.

SmI₂ synthesis in the glovebox

Inside the glovebox, I_2 crystals (1.01g, 0.004 mol), Samarium metal (0.902g, 0.006 mol) and distilled THF (40 mL) were added to a round bottom flask. This reaction had to be left stirring overnight to ensure full synthesis. The reaction turned a blue color indicating SmI₂ synthesis and then left stirring in the glovebox under argon until used. The SmI_2 could be left stirring in the glovebox for up to 7 days.

Acetophenone and 1-Iodooctane Coupling with SmI₂

In the glovebox, SmI_2 (5 mL) was added to a vial and left stirring. In a secondary vial, Acetophenone (29 µL, 2.5 x 10⁻⁴ mol), 1-Iodooctane (45 µL, 2.5 x 10⁻⁴ mol), N-dodecane (57 µL, 2.5 x 10⁻⁴ mol) and distilled THF (~1 mL) were mixed. Content from the secondary vial was transferred into the vial with SmI_2 and left stirring for 24 hours. The reaction was removed from glovebox and worked up with 0.1 M HCl (5 mL, 5 x 10⁻⁴ mol), Diethyl Ether (5 mL the first extraction and 3 mL the following 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and CaCl₂. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar and on a 40 degrees Celsius water bath. The organic layer was then run in the Gas Chromatography Mass Spectrum (Agilent Technologies, 7890A). This data was then used to determine product ratio.

4,4-Dimethyl Benzophenone and 1-Iodooctane Coupling with SmI₂

Working in the glovebox, SmI_2 (5 mL) was added and left stirring in a vial. In a secondary vial, 4,4-Dimethylbenzophenone (0.052g, 2.5 x 10⁻⁴ mol), 1-Iodooctane (45 µL, 2.5 x 10⁻⁴ mol), N-dodecane (57 µL, 2.5 x 10⁻⁴ mol) and distilled THF (~1 mL) were mixed. Content from the secondary vial was transferred into the vial with SmI_2 and left stirring for 24 hours. Reaction was removed from glovebox and worked up with 0.1 M HCl (5 mL, 5 x 10⁻⁴ mol), Diethyl Ether (5 mL the first extraction and 3 mL, 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and Calcium Chloride. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar and on a 40 degrees Celsius water bath; and

subsequently ran through the GCMS (Agilent Technologies, 7890A). The GCMS data was used to determine product ratio.

3-Pentanone and 1-Iodooctane Coupling with SmI₂

Working in the glovebox, SmI_2 (3 mL) was added and left stirring in a vial. In a secondary vial, 3-Pentanone (16 µL, 1.5 x 10⁻⁴ mol), 1-Iodooctane (27 µL, 1.5 x 10⁻⁴ mol), N-dodecane (34 µL, 1.5 x 10⁻⁴ mol) and distilled THF (~1 mL) were mixed. Content from the secondary vial was transferred into the vial with SmI_2 and left stirring for 24 hours. Reaction was removed from glovebox and worked up with 0.1 M HCl (5 mL, 5 x 10⁻⁴ mol), Diethyl Ether (5 mL the first extraction and 3 mL, 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and Calcium Chloride. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar, on a 40 degrees Celsius water bath and ran through the GCMS (Agilent Technologies, 7890A). The GCMS data was used to determine product ratio.

SmI₂- Nickel (II) Barbier Reaction: Coupling Acetophenone and 1-Iodooctane

In the glovebox, using a vial, SmI_2 (5 mL) and Nickel source (20 mol%, 1.0 x 10⁻⁴ mol) were combined and left stirring. In a secondary vial, Acetophenone (29 µL, 2.5 x 10⁻⁴ mol), 1-Iodooctane (45 µL, 2.5 x 10⁻⁴ mol), N-dodecane (57 µL, 2.5 x 10⁻⁴ mol) and distilled THF (~1 mL) were mixed. Content from the secondary vial was transferred into the vial with SmI_2 -Nickel and left stirring for 24 hours. Reaction was removed from glovebox and worked up with 0.1 M HCl (5 mL, 5 x 10⁻⁴ mol), Diethyl ether (5 mL the first extraction and 3 mL the following 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and CaCl₂. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar, on a 40 degrees Celsius water bath and ran through the GCMS (Agilent Technologies, 7890A). The GCMS data was used

to determine the percent conversion of the substrates and the Barbier product ratio compared to other side products obtained.

SmI₂- Nickel (II) Barbier Reaction: Coupling 4,4 Dimethyl benzophenone and 1-Iodooctane

Using the glovebox, SmI₂ (5 mL) and Nickel (II) source (20 mol%, 1.0 x 10^4 mol) were combined in a vial and left stirring. In a secondary vial, 4,4-Dimethylbenzophenone (0.052g, 2.5 x 10^4 mol), 1-Iodooctane (45 µL, 2.5 x 10^4 mol), N-dodecane (57 µL, 2.5 x 10^4 mol) and distilled THF (~1 mL) were mixed. The mixed substrates were transferred into the vial with SmI₂-Nickel and left stirring for 24 hours. Reaction was worked up with 0.1 M HCl (5 mL, 5 x 10^{-4} mol), Diethyl ether (5 mL the first extraction and 3 mL the following 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and CaCl₂. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar, on a 40 degrees Celsius water bath and ran through the GCMS (Agilent Technologies, 7890A). The GCMS data was used to determine Barbier product ratio compared to other side products obtained.

SmI₂- Nickel (II) Barbier Reaction Coupling: 3-Pentanone and 1-Iodooctane

Using the glovebox, SmI_2 (3 mL) and Nickel (II) source (20 mol%, 6 x 10⁻⁵ mol) were combined in a vial and left stirring. In a secondary vial, 3-Pentanone (16 µL, 1.5 x 10⁻⁴ mol), 1-Iodooctane (27 µL, 1.5 x 10⁻⁴ mol), N-dodecane (34 µL, 1.5 x 10⁻⁴ mol) and distilled THF (~1 mL) were mixed. The mixed substrates were transferred into the vial with SmI_2 -Nickel and left stirring for 24 hours. Reaction was worked up with 0.1 M HCl (5 mL, 5 x 10⁻⁴ mol), Diethyl ether (5 mL the first extraction and 3 mL the following 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and CaCl₂. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar, on a 40 degrees Celsius water bath and ran through the GCMS (Agilent Technologies, 7890A). The GCMS data was used to determine Barbier product ratio compared to other side products obtained.

SmI₂- Nickel (II) Barbier reaction: Coupling 3-Pentanone and 1-Iodooctane using External Ligands to Stabilize Ni (0).

Using the glovebox, SmI₂ (3 mL), Nickel (II) source (20 mol%, 6 x 10^{-5} mol) and external ligand- PPh₃, DPPP, DPPB or PCMH- ((2 eq with respect to SmI₂, 6 x 10^{-4} mol) or (4 eq with respect to SmI₂, 1.2 x 10^{-3} mol)) were combined in a vial and left stirring. In a secondary vial, 3-Pentanone (16 µL, 1.5 x 10^{-4} mol), 1-Iodooctane (27 µL, 1.5 x 10^{-4} mol), N-dodecane (34 µL, 1.5 x 10^{-4} mol) and distilled THF (~1 mL) were mixed. The mixed substrates were transferred into the vial with SmI₂-Nickel and left stirring for 24 hours. Reaction was worked up with 0.1 M HCl (5 mL, 5 x 10^{-4} mol), Diethyl ether (5 mL the first extraction and 3 mL the following 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and CaCl₂. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar, on a 40 degrees Celsius water bath and ran through the GCMS (Agilent Technologies, 7890A). The GCMS data was used to determine Barbier product ratio compared to other side products obtained.

SmI₂- Nickel (II) Coupling 3-Pentanone and 4-Iodotoluene

Using the glovebox, SmI_2 (3 mL) and Nickel (II) source (20 mol%, 6 x 10⁻⁵ mol) were combined in a vial and left stirring. In a secondary vial, 3-Pentanone (16 µL, 1.5 x 10⁻⁴ mol), 4-Iodotoluene (0.032 g, 1.5 x 10⁻⁴ mol), N-dodecane (34 µL, 1.5 x 10⁻⁴ mol) and distilled THF (~1 mL) were mixed. The mixed substrates were transferred into the vial with SmI_2 -Nickel and left stirring for 24 hours. Reaction was worked up with 0.1 M HCl (5 mL, 5 x 10⁻⁴ mol), Diethyl ether (5 mL the first extraction and 3 mL the following 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and CaCl₂. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar, on a 40 degrees Celsius water bath and ran through the GCMS (Agilent Technologies, 7890A). The GCMS data was used to determine Barbier product ratio compared to other side products obtained.

SmI₂- Nickel (II) Coupling 3-Pentanone and 4-Iodotoluene using External Ligands to Stabilize Ni (0).

Using the glovebox, SmI_2 (3 mL), Nickel (II) source (20 mol%, 6 x 10⁻⁵ mol) and external ligand- PPh₃, DPPP, DPPB or PCMH- ((2 eq with respect to SmI_2 , 6 x 10⁻⁴ mol) or (4 eq with respect to SmI_2 , 1.2 x 10⁻³ mol)) were combined in a vial and left stirring. In a secondary vial, 3-Pentanone (16 µL, 1.5 x 10⁻⁴ mol), 4-Iodotoluene (0.032 g, 1.5 x 10⁻⁴ mol), N-dodecane (34 µL, 1.5 x 10⁻⁴ mol) and distilled THF (~1 mL) were mixed. The mixed substrates were transferred into the vial with SmI_2 -Nickel and left stirring for 24 hours. Reaction was worked up with 0.1 M HCl (5 mL, 5 x 10⁻⁴ mol), Diethyl ether (5 mL the first extraction and 3 mL the following 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and CaCl₂. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar, on a 40 degrees Celsius water bath and ran through the GCMS (Agilent Technologies, 7890A). The GCMS data was used to determine Barbier product ratio compared to other side products obtained.

Vinyl Halide Synthesis

The vinyl halide was synthesized using a CEM microwave synthesizer (300 W). To a 10 mL microwave reaction tube, 4-phenyl1-butyne (0.07 g, 0.50mmol), NaI (0.21g, 1.40 mmol), cerium (III) chloride heptahydrate (0.26g, 0.70 mmol) and acetonitrile (7 mL) were added. The reaction was microwaved for 30 minutes at 180 degrees Celsius.

SmI₂- Nickel (II) Coupling 3-Pentanone and the synthesized vinyl Halide using External Ligands to Stabilize Ni (0).

Using the glovebox, SmI₂ (3 mL), Nickel (II) source (20 mol%, 6 x 10⁻⁵ mol) and external ligand- DPPP (4 eq with respect to SmI₂, 1.2 x 10⁻³ mol)) were combined in a vial and left stirring. In a secondary vial, 3-Pentanone (16 μ L, 1.5 x 10⁻⁴ mol), synthesized vinyl halide (~ 35 mL), N-dodecane (34 μ L, 1.5 x 10⁻⁴ mol) and distilled THF (~1 mL) were mixed. The mixed substrates were transferred into the vial with SmI₂-Nickel and left stirring for 24 hours. Reaction was worked up with 0.1 M HCl (5 mL, 5 x 10⁻⁴ mol), Diethyl ether (5 mL the first extraction and 3 mL the following 2 extractions), DI water (5 mL, 3 washes), NaCl solution (5 mL) and CaCl₂. The organic layer was placed in the rotary evaporator (Butchi R-300 rotavapor) at 410 mbar, on a 40 degrees Celsius water bath and ran through the GCMS (Agilent Technologies, 7890A). The GCMS data was used to determine Barbier product ratio compared to other side products obtained.

GCMS Data Analysis for Substrate Conversion

First an Rf value for each of the substrates was obtained. This was done by adding 0.1 M N-dodecane (2 x 10⁻³ moles) and 0.1 M substrate (2 x 10⁻³ moles) into a 2 mL volumetric flask, and then running this mixture in the GCMS. Using Windows' GCMS Data Analysis and Windows' MS Instrument Control and Tune, N-dodecane's and the Substrates' end areas were obtained and used to calculate the Rf value using the following formula:

Substrate Rf = (Substrate end area * concentration of N-dodecane [0.1M]) /

(N-dodecane end area * concentration of substrate [0.1M])

This Rf value was then used to determine the substrate's end concentration in reductions and coupling reactions. Trying to get substrate's end concentration the organic layer obtained from each reaction was run through the GCMS, where the substrate's end area and N-dodecane's end area were obtained and used in the following formula to obtain the substrate's end concentration:

Substrate End Conc. = (N-dodecane concentration [0.1M] * End area of substrate) /

(End are of N-dodecane * Rf value of substrate)

This end concentration was then used to obtain substrate Percent conversion by using the following formula:

Substrate % conversion = ((Substrate Starting Concentration [0.1M] – Substrate's End

Concentration)/ Substrate Starting Concentration [0.1M]) * 100

This would give the Substrate's percentage used in each reaction. These calculations were carried out twice per reaction- one to determine the Ketone's percent conversion and a second one to determine the Alkyl Halide's percent conversion. Rf Values were determined for all Ketones and the Alkyl Halide used in these reactions (Table 1).

Substrate	Rf Value (at a 0.1M)
1-Iodooctane	0.84
Acetophenone	1.01
4,4-Dimethylbenzophenone	1.87
3-Pentanone	0.43

Table 1- Rf Values Calculated for the Ketones and Alkyl Halide Used in this Paper

GCMS Data Analysis

The GCMS data for each Ketone- Alkyl Halide and Ketone- Aryl halide coupling reactions were used to obtain product ratios, and percent conversions. Gas Chromatography was used to separate products and determine abundance with respect to each other (Figure 17). Meanwhile the Mass Spectrum was used to identify the products isolated from the Gas Chromatography spectrum based on molecular weight (Figure 18). Each peak in the Gas Chromatography corresponded to a substrate or product formed during the reactions. In Figure 17-18, a reaction between Acetophenone and Iodooctane is observed, which had peaks for Octane (13.4 min), Barbier product (15.1 min) and coupled Acetophenone (4.7 min). It was important to establish what these peaks represent since future reactions were analyzed using the same method (25 minutes starting at 80 degrees Celsius and ramping up to 300 degrees Celsius). Leftover Acetophenone (4.7 min) and N-dodecane (6.6 min) were also observed as indicated by the peaks in the Gas Chromatography (Figure 17). These also served as reference for future reactions to determine what peaks to look for to determine if any Acetophenone was left over and to find the internal standard. Peaks at 11.98 and 21.12 minutes were not assigned to any possible products, as they were not consistently observed in other reactions. It is important to point out that the Mass spectrum for each of the peaks was obtained and analyzed to assign compounds to each peak present.



Figure 17. Gas Chromatography Data Indicating the different products observed in the reactions, the time they came out and their relative abundance. This data was obtained from an

Acetophenone and 1-Iodooctane Barbier reaction SmI₂ and 20 mol % NiI₂ for 24 hours. This reaction had 5 different compounds including a substrate, internal standard and 3 different products, which were all separated by Gas Chromatography based on their boiling points.



Figure 18. Mass Spectrum Data Indicating the compound and its fragment's molecular weights which are used to identify the products observed in the Gas Chromatography. This is Acetophenone Mass Spectrum, indicating the molecular weights before and after several bonds were broken as it went through the MS column.

Percent conversion: Once the peaks were assigned, the end area for the substrates, if any present,

and the internal standard were obtained. These were used in a following formula to obtain End

Substrate Concentration:

((Concentration of Internal Std * End area substrate) / (End Area Internal Std * RF value for

substrate))

The end substrate concentration was then used to obtain the percent conversion for the substrate

by using the following formula:

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((Starting concentration – End concentration) / Starting concentration) * 100
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Product Ratios: The products' end areas were obtained from the GCMS and used in the following formula:

(1/ Side Product End Concentration = X/ Desired Product End Concentration)

This allowed us to compare the desired product obtained in the reactions with respect to side products observed. In reactions where multiple side products were observed, their end concentrations were added and used in the previous formula to obtain a single Desired product to Side products ratio. This calculation was done with every reaction carried out throughout this paper.

Results

This paper explores a range of substrates and ligands in the known Sm- Barbier coupling pathway to stabilize Ni (0) and promote single product selectivity; furthermore, it focuses on examining Sm-Ni (II) as a possible alternative to the NHK reaction. First, to optimize Ni (0) chemistry with SmI₂ coupling reactions, the Barbier reaction was examined with a variety of coupling ketone partners and different nickels. Investigating the Sm-mediated pathway Acetophenone (1) and Iodooctane (4) coupling using SmI₂ and the SmI₂-Ni (II) system was explored. Acetophenone (1) and Iodooctane (4) were coupled only using SmI₂ for 24 hours (Scheme 11). This reaction between Acetophenone and Iodooctane yielded 100 % (1) and 87.3 % (4) conversions as observed in Table 2, entry 1. This reaction also had a 1: 1.5 product ratio between the Barbier product (5) and the side product (8) (GCMS data in Appendix B). In this case the coupling of the radical ketone with another radical ketone was slightly favored over the Barbier product (5). These results were expected as Samarium Diiodide can interact with both the ketone and alkyl halide, at the same time, leading to multiple radical ketones being around and able to couple with one another which can explain the higher ratio for the Radical Coupled Acetophenone.



Scheme 11. Ketone (1-3) and Iodooctane (4) coupling reactions using SmI₂ and Ni (II) leading to Barbier product (5-7) and side product formation (8-10).

		0 4				
				(1) % conv	(2) %	Barbier
Entry	Nickel	R_1	R_2	(STDV)	conv	product:
	Source				(STDV)	Dimer
1*		Ph	CH ₃	100	87.2	1: 1.5
2-	NiI ₂	Ph	CH ₃	79.4 (6.7)	100 (0)	1.4: 1(0.3)
3-	NiDPPE	Ph	CH ₃	89.2 (7.6)	92.9	1.6: 1 (0.7)
4*		4-CH ₃ -Ph	4-CH ₃ -Ph	68.0	87.3	1.9: 1
5+	NiI ₂	4-CH ₃ -Ph	4-CH ₃ -Ph	78.1 (15)	100(0)	3.3: 1 (1.0)
6**	NiDPPE	4-CH ₃ -Ph	4-CH ₃ -Ph	66.7 (6.1)	100 (0)	10: 1 (3.4)
7*		Et	Et	100	78	10.6: 1
8+	NiI ₂	Et	Et	97.9 (4.1)	100 (0)	16: 1 (4.8)
8a*	NiI ₂	Et	Et	100	100	100: 0
9+	NiDPPE	Et	Et	88.5 (19)	98.1 (3.8)	17.1: 1 (3.7)
9a*	NiDPPE	Et	Et	100	100	100: 0

Table 2. Average percent conversions and product ratio for ketone and alkyl halide coupling reactions using SmI₂ and Nickel (II), compared to the controls.

* Reactions were only carried out once.
+ Reactions were carried out three times.
- Reactions were carried out four times.
(STDV)- Standard Deviation.
8a- Single NiI₂ reaction with full Barbier Selectivity
9a- Single NiDPPE reaction with full Barbier selectivity.

Next, Acetophenone (1) and Iodooctane (4) were coupled with nickel sources at 20% mol with respect to the SmI₂, for 24 hours (Scheme 11). First, SmI₂ and NiI₂ were used to Couple Acetophenone and Iodooctane four different times, observed in Table 2, entry 2. These four reactions had average percent conversions of 79.4 % (1) and 100 % (4) and a product ratio of 1.4: 1, where the Barbier product (5) was slightly favored over dimer Acetophenone (8) (GCMS data in Appendix B). Next, NiDPPE was used with SmI₂ to couple Acetophenone and Iodooctane, as observed in entry 3, Table 2. This reaction was also carried out four different times and yielded percent conversions of 89.2 (1) and 92.9 (4), with low standard deviations. The product ratio observed in these reactions was 1.6: 1, where the Barbier product (5) was slightly favored once again. This coupling reaction had higher Barbier product selectivity when a nickel source was used compared to only SmI₂ being used. It is important to point out that the only side product observed in this reaction was the dimer Acetophenone, the dimer alkyl halide was not observed as it is likely it came out with the solvents in the GCMS. Additionally, very little

reduced octane was observed in 3 of the 8 reactions carried out, thus not included in the final ratio. Although slight Barbier product (5) selectivity is observed with nickel, it was not close to the full selectivity we were expecting, based on previous reports.

A second ketone was examined, this new substrate was 4,4- Dimethyl benzophenone (2). Like the previous reaction, 4,4- Dimethyl benzophenone (2) was coupled with Iodooctane (4) only using SmI_2 for 24 hours (Scheme 11). As observed in Table 2, entry 4, this reaction led to 68.0 % (2) and 87.3 % (4) conversions and a 1.9: 1 product ratio (GCMS data in Appendix C). In this reaction the Barbier Product (6) was slightly favored over the side product (9) while only using SmI_2 , possibly proving that (2) may be a better coupling partner than (1).

Next, SmI_2 and nickel were used to couple 4,4 Dimethyl benzophenone and Iodooctane (Scheme 11). Three different reactions between 4,4 Dimethyl benzophenone (**2**) and Iodooctane (**4**) were carried using SmI_2 and NiI_2 . As observed in entry 5, Table 2, this led to a 78.1 % (**2**) and 100 % (**4**) conversion and a 3.3: 1 product ratio (GCMS data in Appendix C). In this case a higher Barbier (**6**) selectivity was observed when using nickel, compared to the control reaction which only had SmI_2 . Next, NiDPPE was used along with SmI_2 to couple 4,4- Dimethyl benzophenone (**2**) and 1-Iodooctane (**4**). As observed in Table 2, entry 6, this reaction yielded a 66.7 % (**2**) and 100 % (**4**) conversion and a 10: 1 product ratio, with the Barbier product (**6**) having higher selectivity, over the side product (**9**). The standard deviation for the product ratio was 3.4, yet this reaction using nickel still had higher product selectivity than the control. Although full Barbier product selectivity was not observed when coupling 4,4- Dimethyl benzophenone with Iodooctane, the desired product's (**6**) selectivity was still higher compared to the side product (**9**). This is significant since 4,4- Dimethyl benzophenone (**2**) is bulkier than Acetophenone (**1**), yet it was easier to couple it to Iodooctane (**4**).

Since, replacing Acetophenone with 4,4- Dimethyl benzophenone led to higher Barbier selectivity when using SmI_2 , we decided to test a third ketone. 3-Pentanone (**3**) was chosen to carry out the third coupling reaction. Just like the previous reactions, a control was carried out coupling 3-Pentanone and Iodooctane only using SmI_2 (Scheme 11). As observed in Table 2, entry 7, this control reaction led to 100 % (**3**) and 78.0 % (**4**) conversions as well as a 10.6: 1 product ratio with the Barbier product (**7**) being favored (GCMS data in Appendix D). Although only SmI_2 was used, the Barbier product (**7**) was more selective than the side product (**10**) in this reaction.

Following the control reaction, 3-Pentanone (3) and 1-Iodooctane (4) were coupled with SmI₂ and nickel for 24 hours (Scheme 11). First, SmI₂ and NiI₂ were used to couple Pentanone and Iodooctane 3 different times. As observed in Table 2, entry 8, these reactions led to a 97.9 % (3) and 100 % (4) conversions and a 16: 1 product ratio, with the Barbier product (7) being highly selected over the side product (10) (GCMS data in Appendix D). A fourth reaction, still using SmI₂ and NiI₂ had 100 percent conversions for both substrates (3 and 4) as well as full selectivity for the Barbier product (7). This was the first coupling reaction between a ketone and alkyl halide using SmI₂ and nickel that yielded full Barbier selectivity from all the reactions done in this paper (Table 2, entry 8a). Next SmI_2 and NiDPPE were used to couple 3-Pentanone (3) and 1-Iodooctane (4) three different times. As observed in Table 2, entry 9, this reaction averaged 88.5 (3) and 98.1 (4) percent conversions as well as a 17.1: 1 product ratio. This reaction, using NiDPPE and SmI₂, was carried a fourth time and led to full substrate conversion as well as full Barbier selectivity (Table 2, entry 9a). Coupling 3-Pentanone (3) and 1-Iodooctane (4) using Ni as a catalyst led to high Barbier product selectivity with both nickel sources and as well as full Barbier selectivity for the first time among all the reactions that were carried in this

paper. It is important to note that this third reaction did not have dimerized ketone but did have the reduced Iodooctane. No dimerized Iodooctane was observed, which if produced might have been lost during the solvent vaporization phase in the GCMS.

Although full Barbier selectivity was only observed once in these reactions, this proved that the Barbier cycle is indeed working as expected, but Ni (0) might be deactivating sooner than we thought leading to side product formation. As a result, we focused on trying to stabilize Ni (0) by incorporating external ligands into the reaction. The ligands used to try to stabilize Ni (0) and avoid its premature deactivation include PPh₃, DPPP, DPPB and PCMH (Figure 19).



Figure 19. External ligands used: A). Triphenylphosphine (PPh₃) B). 1,3-bis (Diphenylphosphine) propane (DPPP) C). 1,4-bis (Diphenylphosphine) Butane (DPPB) D). Pyrimidine-2-carboximidamide hydrochloride (PCMH)

First 3-Pentanone (3) and 1-Iodooctane (4) were coupled with SmI_2 and NiI_2 in the presence of 2 eq PPh₃ with respect to Nickel (Scheme 12). This led to a product ratio of 17.9: 1 with the Barbier product (7) being favored over the side product (Table 3, entry 1) (raw data in

appendix E). Next the same reaction was carried out with SmI_2 - NiDPPE and 2 eq PPh₃ (with respect to nickel) which yielded a 14.7: 1 product ratio, with the Barbier product (7) being favored. The product ratios observed in these reactions using 2 eq PPh₃ are similar to the ones observed in Table 2, entries 8-9, without external ligands. In this case PPh₃ did not impact Barbier product selectivity. Next DPPP was added to the reaction at 2 equivalents with respect to the nickel source. In Table 3, entry 3, SmI₂-NiI₂ and DPPP were used to couple Pentanone and Iodooctane which led to a 17.9: 1 product ratio (raw data in appendix E). Then, the nickel source was replaced with NiDPPE (entry 4, Table 3) and led to a 2.3: 1 product ratio. In this case using NiDPPE and DPPP led to a significant decrease in single product selectivity. A similar trend was observed when DPPB was incorporated into this reaction (Scheme 9). NiI₂ and DPPB combination led to a 10.5: 1 product ratio (Entry 5, Table 3) (raw data in appendix E); meanwhile using NiDPPE with DPPB yielded a 5.6: 1 product ratio (Entry 6, Table 3). Adding DPPB as an external ligand to this reaction (Scheme 12) led to a reduction in Barbier product selectivity compared to the reactions using PPh₃ (Entry 1 & 2, Table 3) and those without ligands (Entries 8 & 9, Table 2).

Considering phosphorus-based ligands did not increase selectivity as theorized, a nitrogen-based ligand, PCMH, was utilized (Scheme 12). First, PCMH was used with SmI₂ and NiI₂ were used to couple Pentanone and Iodooctane, producing a 1.4: 1 product ratio (Table 3, entry 7) (raw data in Appendix E). Next, NiDPPE was incorporated into the reaction using SmI₂ and PCMH, which resulted in a 1.5: 1 product ratio (Table 3, entry 8). The incorporation of PCMH as an internal ligand further hindered Barbier product selectivity, compared to other external ligands previously used (Entries 1-6, Table 3).

Based on the external ligands tested in Table 3, PPh₃ seemed to slightly increase Barbier product selectivity or remain about the same compared to entries 8 and 9 in Table 2, which did not have an external ligand. As a result, a higher PPh₃ equivalent with respect to the nickel was used. In entry 9, Table 3, 4 eq PPh₃ was incorporated with SmI₂ and NiI₂ to couple Pentanone and Iodooctane, which yield a 3.5: 1 product ratio. Incrementing the PPh₃ eq from 2 to 4 led to a significant decrease in Barbier selectivity as observed in Entries 1 and 9, Table 3. In conclusion, 2 eq PPh₃ seemed to slightly increase Barbier selectivity, while all other external ligands tested significantly hindered single product selectivity.



Scheme 12. 3-Pentanone (3) and 1-Iodooctane (4) Barbier coupling reaction with SmI2, 20 mol % Ni (II) and external ligands for 24 hours, producing the Barbier product (7) and side product, Octane (10). The external ligands were tested at a 2 and 4 equivalent with respect to the Ni (II).

Ξ.		()		
	Entry (#)	Nickel Source	External ligand and Equivalent	Barbier Product (9): Octane (10)
	1*	NiI ₂	PPH_3 (2 eq)	17.9: 1 (4.6)
	2*	NiDPPE	PPH_3 (2 eq)	14.7: 1 (7.5)
	3	NiI ₂	DPPP (2 eq)	17.9: 1
	4	NiDPPE	DPPP (2 eq)	2.3: 1
	5	NiI ₂	DPPB (2 eq)	10.5: 1
	6	NiDPPE	DPPB (2 eq)	5.6: 1
	7	NiI ₂	PCMH (2 eq)	1.4: 1
	8	NiDPPE	PCMH (2 eq)	1.5: 1
	9	NiI ₂	PPh_3 (4 eq)	3.5: 1

Table 3. Product ratio for 3-Pentanone (**3**) and 1-Iodooctane (**4**) Barbier coupling reactions using SmI₂, 20 mol% Ni (II) and external ligands at 2 and 4 equivalent for 24 hours.

*= These reactions were carried out twice.

All other reactions were carried out once.

Working towards SmI_2 and Ni (II) possibly being used as an alternative to the NHK reaction (Scheme 7), this paper focused on coupling a carbonyl and an Sp² halide with SmI₂-Nickel and an external ligand (Scheme 13). The Sp² halide used for this reaction is an aryl halide, because a pure vinyl halide could not be acquired. Although the Aryl halide may be affected by the benzene ring, if successfully coupled, it could serve as a guide for vinyl halide coupling. At the same time if a bulky Sp² aryl halide can be coupled to a ketone, then it is likely for the vinyl halide to also be coupled using SmI₂ and Ni (II) since it's a smaller molecule and has less steric hindrance. First 3-Pentanone (3) and 4-Iodotoluene (11) were coupled using SmI_2 and Nickel. In these reactions, observed in Table 4, when NiI_2 and NiDPPE were used, the desired product (12) was not observed (raw data in appendix F). As a result, external ligands were incorporated into this reaction to try to determine if the desired product (12) could be observed (Scheme 13). Pentanone (3) and 4-Iodotoluene (11) were coupled with SmI_2 -NiI₂ and 2 eq PPh₃ with respect to nickel, which led to 1: 43.2 product ratio (Table 5, entry 1) (raw data in Appendix F). This reaction had high selectivity for side product (14 and 15) formation, but for the first time we report carbonyl and Sp² halide coupling (12) using SmI₂- nickel and an external ligand. To our knowledge this is the first time an Sp² halide and a ketone have been coupled using Sm (II) and Ni (II). This is an important and critical step towards finding an alternative to vinyl halide and ketone coupling using Chromium, and all other reactions that utilize the NHK pathway. Next, this reaction (Scheme 13) was carried out with SmI₂- NiDPPE and 2 eq PPh₃ (Table 5, entry 2), leading to a 1: 29.4 product ratio and the desired product (12) being formed. This reinforces the findings in Table 5, entry 1 as a different nickel source was also able to yield the desired coupled product.

This reaction was also tested with other external ligands, trying to determine if higher desired product selectivity could be observed compared to PPh₃. When DPPP was used at a 2-molar equivalent with respect to NiI₂, a 1: 27.2 product ratio was observed (Entry 3, Table 5) (raw data in appendix F). Using 2 eq DPPP led to slightly higher desired product selectivity (**12**), compared to entries 1 and 2 which had PPh₃. Next, 2 eq DPPB was used, with respect to the nickel, with SmI₂- NiI₂ which led to a1: 15.3 product ratio (Entry 4, Table 5) (raw data in Appendix F). DPPB led to the lowest product ratio, and highest desired product (**12**) selectivity observed when coupling Pentanone and Iodotoluene. When 2 eq PCMH was used with NiDPPE and SmI₂, a 1: 29.2 product ratio was observed, where the desired product was not as favored compared to the reactions using DPPP and DPPB (Entries 3 and 4). Based on the product ratios observed in Table 5, entries 1-5, using 2 eq DPPP, with NiI₂ and SmI₂ appears to result in the highest desired product selectivity when coupling a ketone with an Sp² aryl halide.



Scheme 13. 3-Pentanone (3) and 4-Iodotoluene (11) coupling reaction with SmI_2 , 20 mol % Ni (II) and external ligands for 24 hours, producing the desired product (12) and two side products (14 and 15). The external ligands were tested at a 2 and 4 equivalent with respect to the Ni (II).

Table 4. Product ratio for 3-Pentanone (3) and 4-Iodotoluene (11) coupling reactions using SmI2and 20 mol% Ni (II) for 24 hours.

Nickel	Ligand?	Desired product (12): Sides Products
		(14 & 15)
NiI ₂	None	No Desired product
NiDPPE	None	No Desired product

Entry (#)	Nickel Source	External ligand and Equivalent	Desired product (12): Sides Products (14 & 15)
1	NiI ₂	PPH_3 (2 eq)	1: 43.2 (3.6)
2	NiDPPE	PPH_3 (2 eq)	1: 29.4 (17.7)
3	NiI ₂	DPPP (2 eq)	1: 27.2
4	NiI ₂	DPPB (2 eq)	1: 15.3
5	NiDPPE	PCMH (2 eq)	1: 29.2

 Table 5. Product ratio for 3-Pentanone (3) and 4-Iodotoluene (11) coupling reactions using SmI₂,

 20 mol% Ni (II) and external ligands at 2 equivalent for 24 hours.

Following the successful ketone- aryl halide coupling observed with the SmI2-Ni(II) system, we wanted to take it a step further and try to couple a vinyl halide. Now vinyl halides are very expensive substrates to source from an external company, as a result we decided to synthesize one in the lab. A vinyl halide was synthesized using 4-phenyl-butyne and acetonitrile in a microwave reaction for 30 mins at 180 degrees Celsius (Scheme 14). Successful Vinyl halide synthesis was confirmed using the GCMS (Appendix G). This vinyl halide was then used to couple with 3-Pentanone using SmI₂- NiI₂ and 4 eq DPPP (Scheme 15). This coupling reaction yielded a trace amount of the desired coupled product as observed in table 6 (appendix H). Based on these results we report, for the first time, successful ketone- vinyl halide coupling using the SmI2- NiI₂ system, and proving to be a potential alternative to Chromium used in NHK reactions.



Scheme 14. Vinyl Halide synthesis using 4-phenyl1-butyne and acetonitrile. Sodium Iodide, Cerium (III) Chloride and heptahydrate were used to carry out this CEW microwave reaction at 180 degrees Celsius for 30 minutes.



Scheme 15. Vinyl Halide- ketone coupling using SmI₂- Ni (II) system and 4 eq DPPP for 24 hrs.

	Table 6. Vinv	l halide- ke	tone couplin	g using SmI	2 - Ni (II	and 4 ec	1 DPPP
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Nickel	External ligand	Desired product
NiI ₂	DPPP (eq)	Trace amount

Conclusion

Based on previous reports on ketone and alkyl halide coupling with SmI₂ and nickel leading to single product selectivity, this paper first focused on using the known Sm-Barbier coupling cycle to explore single product selectivity of a range of substrates and the impact of ligands. Additionally, two different nickel (II) sources were tested to determine the impact on product selectivity. First, Acetophenone (1) and 1-Iodooctane (4) were coupled with SmI₂, which led to lower selectivity for the Barbier product (5) compared to the side product (8), 1: 1.5, as observed in Table 2, entry 1. This control was compared to two reactions using SmI₂ and Nickel (II). When SmI₂-NiI₂ was used, a slightly higher Barbier product (5) selectivity was observed compared to the side product (8). A similar result was observed when SmI₂-NiDPPE were used to couple ketone and alkyl halide, which yielded slightly higher selectivity for the Barbier product (5) over the side product (Table 2, entries 2 & 3). In this case, similar results were observed when both nickels were used indicating no significant difference between them. Now, although higher Barbier product selectivity was observed when nickel was used to couple (1) and (4), it is not consistent with previous reports indicating single product formation¹⁷.

These results raised concerns on the Barbier cycle not working as expected since when Nickel was added, a side product was formed which contradicts the single product selectivity previously reported. A possible problem in the Barbier cycle, leading to multiple products being observed is Ni (0) deactivating and crashing out as nanoparticles early on in the reaction (Figure 20), which would allow SmI₂ to directly interact with the substrates and lead to multiple product formation²⁹. One way to stabilize Ni (0) would be by adding an external ligand that could interact with the Ni (0) leading to stabilization and avoid its deactivation. Before we fully turned our attention to Ni (0) stabilization, different ketone sources had to be tested using the similar conditions as Acetophenone and Iodooctane coupling.



Figure 20. SmI₂-Nickel (II) coupling mechanism with Ni (0) crashing out and deactivating as the cycle progresses.

Exploring how our ketones would react in this coupling reaction, 4,4

Dimethylbenzophenone (2) was coupled with 1-Iodooctane (4) and product selectivity was analyzed. When SmI_2 was used to couple (2) and (4), slightly Barbier product (6) selectivity was observed over the side product (9), as observed in Table 2, entry 4. Once NiI₂ was incorporated into the reaction, higher Barbier product (6) selectivity was observed with the product ratio being 3.3: 1 (Table 2, entry 5). Using NiDPPE also led to higher Barbier product selectivity, with a 10:1 product ratio being observed. In this reaction higher Barbier selectivity was observed compared to Acetophenone (1) and 1-Iodooctane (4) coupling, possibly indicating some ketones may be hard to work with for these reactions. Next a third ketone, 3-Pentanone (3) was coupled to 1-Iodooctane (4). The control reaction, only using SmI_2 led to Barbier product (7) selectivity with a 10.6: 1 product ratio (Table 2, entry 7). This was compared to 3-Pentanone (3) and 1-Iodooctane (4) being coupled with SmI₂ and NiI₂ which had two different outcomes, first, high Barbier selectivity (7) was observed with a 16: 1 product ratio compared to the side product (Table 2, entry 8). This reaction also yielded full Barbier product selectivity, for the first time in all the reactions that were carried in this paper (Table 2, entry 8a). When SmI_2 and NiDPPE were used, a similar outcome was observed, with high Barbier product selectivity (Table 2, entry 9) as well as full Barbier selectivity, for the second time in this coupling reaction (Table 2, entry 9a). Observing full Barbier product selectivity in this reaction with two different nickel sources reinforced the idea of Acetophenone (1) being the problem in this first reaction which had very low Barbier selectivity compared to 4,4 dimethyl benzophenone (2) and 3-Pentanone (3). The full Barbier selectivity observed in entries 8a and 9a also concur with previous studies reporting single product formation when SmI_2 and Nickel were utilized¹⁷.

Substrates	Nickel/ Ligands	Product ratio	Original Table	
Acetophenone + Iodooctane	NiI2	1.4 : 1	Table 2, Entry 2	
4,4-DBP + Iodooctane	NiI2	3.3 : 1	Table 2, Entry 5	
Pentanone + Iodooctane	NiI2	16 : 1	6 : 1 Table 2, Entry 8	
Pentanone + Iodooctane	NiI2	100 : 0	Table 2, Entry 8a	
Pentanone + Iodooctane	NiDPPE	17.1 : 1	Table 2, Entry 9	
Pentanone + Iodooctane	NiDPPE	100 : 0	Table 2, Entry 9a	
Pentanone + Iodooctane	NiI2 + PPh3	17.9 : 1	Table 3, Entry 1	
Pentanone + Iodooctane	NiI2 + DPPP	17.9 : 1	Table 3, Entry 3	
Pentanone + Iodooctane	NiI2 + DPPB	10.5 : 1	Table 3, Entry 5	
Pentanone + Iodooctane	NiI2 + PCMH	1.4 : 1	Table 3, Entry 7	

 Table 7. Data table with best reactions taken from the results section

Although full Barbier selectivity was observed twice when coupling 3-Pentanone (**3**) and 1-Iodooctane (**4**), some side product was still present in some of the replicates that were carried out. As a result, we decided to introduce an external ligand, hoping to stabilize Ni (0) in the Barbier cycle and obtain consistent single product formation (Figure 20). The first external ligand used to try to stabilize Ni (0) in the 3-Pentanone (**3**) and 1-Iodooctane (**4**) coupling reaction was PPh₃ (at 2 eq wrt Nickel), which had a 17.9: 1 product ratio when used alongside SmI₂ and NiI₂(Table 3, entry 1). The addition of 2 eq PPh₃ led to a slightly higher Barbier

selectivity compared to when only SmI₂ and NiI₂ were used with a 16: 1 product ratio (Table 2, entry 8). When 2 eq PPh₃ was used alongside SmI₂ and NiDPPE, a 14.7: 1 product ratio was observed (Table 3, entry 2). Incorporating 2 eq PPh₃ to this reaction led to a slight Barbier selectivity decrease, compared to the reactions carried out with just SmI₂ and NiDPPE which had a 17.1:1 ratio (Table 2, entry 9). Next DPPP was utilized as an external ligand, which led to a 17.9:1 product ratio when utilized with SmI₂ and NiI₂ (Table 3, Entry 3). This Barbier product selectivity was highly compromised when DPPP was used alongside SmI₂ and NiDPPE, with a 2.3:1 ratio (Table 3, entry 4). Next, DPPB was explored in this coupling reaction. A decrease in Barbier product selectivity was observed in both reactions with SmI₂- NiI₂ and SmI₂-NiDPPE when DPPB was used, compared to the reaction without an external ligand (Table 2, entries 8 and 9). Lastly a nitrous based ligand was explored based on its previously reported stabilizing abilities²⁴. When PCMH was used to stabilize the Ni (0) in the reactions using NiI₂ and NiDPPE, a devastating decrease in Barbier selectivity was noted, with both product ratios being around 1.5: 1. Based on these results, PPh₃ seems to be the best ligand to stabilize the Ni (0) in the Pentanone- Iodooctane since a slight increase in selectivity was observed when used with SmI₂-NiI₂. At the same time, DPPP and DPPB were not successful in single bond coupling as previously reported²². PCMH also failed to stabilize the catalysts which also contradicts previous reports²⁴. Although Barbier selectivity was slightly increased with 2 eq PPh₃, SmI₂ and NiI₂, we were not able to obtain full Barbier product selectivity as we had intended.

Since 2 eq PPh₃ with respect to Nickel did not result in full Barbier product selectivity in NiI₂ and NiDPPE reactions, we decided to try to increase the external ligand added to stabilize Ni (0) for a longer period. PPh₃ was increased from 2 eq to 4 eq with respect to nickel to couple 3-Pentanone (**3**) and 1-Iodooctane (**4**). When 4 eq PPh₃ with SmI₂ and NiI₂ were used, a

significant decrease in Barbier product selectivity was observed with a 3.5: 1 product ratio (Table 3, entry 9) compared to the 17.9: 1 ratio observed with 2 eq PPh₃ (Table 3, entry 1). This finding is significant as it shows that adding a high amount of the external ligand can affect the Barbier cycle's selectivity. A potential explanation for such behavior could be the hindrance of Ni (0) – alkyl halide or SmI₂ and Ni (II) interactions due to ligand saturation in the reaction.

Following the Barbier product selectivity observed when coupling 3-Pentanone (**3**) and 1-Iodooctane (**4**) with SmI₂ and nickel (II) source, it would be beneficial to continue to test out different external ligands to stabilize Ni (0). Different external ligands should be tested while trying to obtain consistent full Barbier selectivity when coupling 3-Pentanone (**3**) and 1-Iodooctane (**4**); as well as reexamining product selectivity observed in 4,4 Dimethylbenzophenone (**2**) and Acetophenone (**1**) coupling reactions. The full Barbier selectivity (Table 2, entries 8a and 9a) findings observed in this paper are consistent with previous reports showing single product formation when utilizing SmI₂ and Nickel system¹⁷. At the same time, adding ligand to the system did not increase single product selectivity as it had been previously reported²¹⁻²⁴. This could be either because the ligands were able to stabilize Ni (0) to a point where some molecules were no longer reactive or the ligand created a gap between the Ni (0) molecule and the alkyl halide, as a result they could not interact as efficiently.

The second part of this paper focused on trying to bring forth a potential alternative to the NHK reaction, which uses Chromium (II) and Nickel to couple a carbonyl and vinyl halide (Figure 21). The vinyl halide used in this reaction has an Sp² carbon which gets coupled to the carbonyl's alpha carbon. These vinyl halides are highly expensive substrates hard to obtain, as a result we first focused on coupling a carbonyl with a different Sp² halide, Aryl Halide (11). Although the aryl halide is part of a benzene ring, making it hard to couple due to hindrance, it

has the double bonded carbon attached to the halogen motif of interest that vinyl halides have. As a result, we conclude that coupling a carbonyl with an Sp^2 halide could serve as a proof of concept for a possible NHK reaction using SmI_2 instead of Chromium. Furthermore, it can serve to optimize ketone- Sp^2 halide coupling reactions with different nickels and ligands if proven effective.



Figure 21. Nozaki-Hiyama-Kishi Reaction which couples a Ketone with a Vinyl Halide using Ni (II) and Chromium.

Trying to determine if SmI₂ can effectively couple carbonyls and Sp² halides, 3-Pentanone (**3**) and 4- Iodotoluene (**11**) were coupled using SmI₂ and NiI₂. This reaction did not yield the desired coupled product (Table 4). Pentanone (**3**) and 4-Iodotoluene (**11**) were then coupled using SmI₂ and NiDPPE, and similar to the previous reaction, no desired product (**12**) was observed (Table 4). These results led to the incorporation of external ligands while mainly using SmI₂ and NiI₂ (Figure 22). The first external ligand examined was 2 eq PPh₃ with respect to the nickel, and to the best of our knowledge, for the first time we report successful carbonyl-Sp² halide coupling using SmI₂-NiI₂ and an external ligand. Although the side products were highly favored in this reaction, we successfully saw the desired coupled product we were looking for. Next, we carried out this same reaction using 2 eq PPh₂, SmI₂ and NiDPPE which also led to the desired product (**12**) being formed. This reinforced the previous results we had obtained indicating that carbonyls and Sp² halides can be coupled using SmI₂-Ni (II) and an external ligand mimicking the NHK reaction²⁷. Following successful ketone- Sp² halide coupling using SmI₂- NiI₂ with PPh₃, other ligands were tested trying to obtain higher desired product (**12**) selectivity. First 2 eq DPPP was utilized, which led to a 1: 27.2 ratio (Table 5, entry 3). Replacing PPh₃ with DPPP led to a slightly higher desired product selectivity. Next 2 eq DPPB was used, and led to a 1: 15.3 product ratio between the desired product and all the side products (Table 5, entry 4). In this case DPPB had the highest desired product selectivity compared to all the other ligands that were tested in the reaction. Lastly, 2 eq PCMH yielded a 1: 29.2 product ratio, similar to the ratio observed with PPh₃. Based on these results DPPB seems to favor the formation of the desired product compared to all the other ligands tested.



Figure 22. 3-Pentanone (8) and 4-Iodotoluene (11) coupling reaction with SmI₂, 20 mol % Ni (II) and external ligands producing the desired product (12)

As our best ketone was coupled with the aryl halide using the SmI2- Nickel system, we decided to synthesize a vinyl halide in the lab and used this one in a coupling reaction (Scheme 14). Following the synthesis of a vinyl halide, this one was coupled with 3-pentanone using SmI2- NiI2 and e 4q DPPP, which led to a trace amount of the desired coupled product being observed (Figure 23). Hereby, this paper reports the first successful ketone- vinyl halide coupling using SmI2 and Nickel system, posing a viable alternative to the NHK reaction.





This paper opens the door to SmI₂'s potential to carry out the NHK reaction based on the first reports of ketone- aryl halide and ketone- vinyl halide coupling mediated by SmI₂ and Nickel system which have been observed in this paper. Going forward it is necessary to try to couple a carbonyl with a pure vinyl halide using SmI₂-Ni (II) and an external ligand to determine if higher desired product selectivity can be obtained (Appendix B). Furthermore, different ligands should be examined in both carbonyl-aryl halide and carbonyl-vinyl halide coupling reactions aiming to increase the desired product's selectivity and minimize side product formation. Additional other nickels, besides NiI₂ and NiDPPE, should be used to determine if they can impact single product selectivity similarly to the external ligands³⁰. Finally, SmI₂ and Chromium mediated carbonyl-vinyl halide coupling product ratio should be compared with Sm-mediated reaction to determine if SmI₂ is a reliable alternative to the NHK reaction.

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Figure 24. THF storage in the glovebox based on SmI₂ Molarity (0.1M). Data previously obtained in the Choquette lab by Aaron Yengbie and Gyedi Appiah-pipim²⁴.

It was found that 3 coupling reactions between Acetophenone and 1-Iodooctane using SmI₂-Ni(acac)₂ (20 mol %) had different THF distillation ages and were not replicable. For these reactions, as observed in Table 6, when the THF was 7 days old, the percent conversion for Acetophenone and 1-Iodooctane was 35.1 and 49.8, respectively. Seven -day old THF also had a 1.8: 1 product ratio with the Barbier product being favored. When THF was 11 days old the percent conversions were, 84.6 (1) and 100 (4) while the reaction yielded a 2.1: 1 product ratio; the Barbier product being favored. When THF was 20 days old, the percent conversions were 15.2 (1) and 18.4 (4). 20-day old THF yielded a 1: 1 product ratio. In this case it appears that THF affected the results in each of the reactions, since these were all carried out under the same conditions and time. Previous data from the Choquette lab indicates that THF can be stored in the glovebox for up to 21 days, before it affects the molarity of SmI₂ (Figure 24)²⁸. The molarity of SmI, with THF 20-21 days old, remains between 0.1M and 0.08M, which is the desired one

for Samarium Diiodide when carrying out reactions. This to some extent can explain why the percent conversion for 20-day old THF was low since it's close to the threshold, but it does not explain why there is such a difference between 7- and 11-day old THF. It is also questionable why a reaction with close to full percent conversions (entry 2), had a 2:1 product ratio, but entry 1 with less than 50 percent conversions had a 1.8: 1 product ratio. It appears that SmI_2 or Ni (0) are not behaving as expected and THF might be the one responsible for it. Moving Forward it was decided that all the THF used in the reactions had activated molecular sieves and was distilled every 14 days to ensure the solvent was not a variable affecting reactions.

Ni(acac) ₂ and Sin ₂ , for 1 nour							
	Nickel	Acetophenone	1-Iodooctane	2-phenyldecan-2-ol	THF Age		
Entry (#)	source	(1)	(2)	(3): Radical coupled			
		% conversion	% conversion	Acetophenone (4)			
1	$Ni(acac)_2$	35.1	49.8	1.8:1	7 days		
					_		
2	$Ni(acac)_2$	84.6	100	2.1:1	11 days		
3	$Ni(acac)_2$	15.2	18.4	1.0:0	20 days		
					-		

 Table 6. THF age used in Barbier coupling of Acetophenone and 1-Iodooctane with 20 mol %

 Ni(acac)₂ and SmI₂, for 1 hour



Appendix B- Acetophenone- Iodooctane Coupling GCMS Data





KAC_2019_LowTemp_Acetophenone Method. All Unlabeled peaks were solvents or contaminants from the GCMS.



Appendix C- 4,4- Dimethylbenzophenone- Iodooctane Coupling GCMS Data

Figure 27- 4,4- Dimethylbenzophenone- Iodooctane Coupling with Sm(II) using KAC_2019_LowTemp_Acetophenone Method. All Unlabeled peaks were solvents or contaminants from the GCMS.



Figure 28- 4,4- Dimethylbenzophenone- Iodooctane Coupling with Sm(II)- Nickel using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Appendix D- Pentanone- Iodooctane Coupling GCMS Data





Figure 30- Pentanone- Iodooctane Coupling with Sm(II)- Nickel using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Appendix E- Pentanone- Iodooctane Coupling with External Ligands GCMS Data





Figure 32- Pentanone- Iodooctane Coupling with Sm(II)- Nickel and DPPP using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Figure 33- Pentanone- Iodooctane Coupling with Sm(II)- Nickel and DPPB using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Figure 34- Pentanone- Iodooctane Coupling with Sm(II)- Nickel and PCMH using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Appendix F- Pentanone- Iodotoluene (Aryl Halide) Couplings and External Ligands GCMS Data.

Figure 35- Pentanone- Iodotoluene Coupling with Sm(II)- Nickel using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Figure 36- Pentanone- Iodotoluene Coupling with Sm(II)- Nickel and PPh3 using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Figure 37- Pentanone- Iodotoluene Coupling with Sm(II)- Nickel and DPPP using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Figure 38- Pentanone- Iodotoluene Coupling with Sm(II)- Nickel and DPPB using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Figure 39- Pentanone- Iodotoluene Coupling with Sm(II)- Nickel and PCMH using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.

Appendix G- Vinyl Synthesis Confirmed by GCMS data

Vinyl Halide Synthesis:



Scheme 14. Vinyl Halide synthesis using 4-phenyl1-butyne and acetonitrile.



Figure 40- Vinyl Halide synthesis reaction using KAC_2024_Lowtemp_pentanone_solvdelay2. All Unlabeled peaks were solvents or contaminants from the GCMS.



Figure 41- Vinyl Halide Mass Spectrum (MS) with the fragments' molecular weight matching the MS.

Appendix H- Ketone and vinyl Halide coupling with SmI₂- NiI₂ and External Ligands leading to trace amounts of the desired product being observed, confirmed by GCMS data.



Figure 42. Vinyl Halide- ketone coupling using SmI₂- Ni (II) system.



Figure 43. 3-Pentanone- Vinyl Halide Coupling reaction using SmI₂- Ni(II) and 4 eq DPPP. Peak at 18.6 mins potentially representing the coupled vinyl- ketone product. using KAC_2024_Lowtemp_pentanone_solvdelay2.



Figure 44. Mass Spectrum data for peak at 18.59 min- Desired coupled product from 3-Pentanone- Vinyl Halide Coupling reaction using SmI₂- Ni(II) and 4 eq DPPP.



Figure 45. Vinyl-ketone Coupled product Mass Spectrum analysis based on fragmentation pattern. These Fragmentation patterns match the MW observed in the MS from Figure 43.