Drew University

College of Liberal Arts

Samarium Diiodide:
Air-Free Synthesis Methods and
Some Applications in Simple Reduction and Cross Coupling Reactions

A Thesis in Chemistry
by
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Abstract

Samarium diiodide (SmI_2) is a powerful and versatile single electron reductant discovered by Henri B. Kagan in 1977. Over the years, it has found increasing applications in organic synthesis. Despite being a useful synthetic tool, it is underutilized in many synthetic chemistry laboratories due to limitations caused by its oxyphilicity that requires expensive equipment such as a glovebox to work with the reagent under inert conditions. The first part of this paper will show an easy and straightforward method for the synthesis of SmI_2 without using a glovebox. Our method employs a Schlenk line to achieve inert microenvironments within reaction glassware. Using our Schlenk line technique we successfully developed a synthesis protocol for SmI_2 that is reproducible. Simple reduction reactions with high yields well recorded in literature were carried out with freshly distilled SmI_2. Gas chromatography and mass spectrometry were used to determine the % conversions of these reduction reactions which were used to back-calculate the concentration of samarium diiodide. The second part of the paper addresses synthetic applications of the reagent in the SmI_2-mediated Barbier coupling reaction with three different Nickel (II) salts: NiI_2 and $Ni(acac)_2$ and $Ni(dppe)_2$. Ni(II) salts in catalytic amounts were tested for their efficiency in catalyzing the reaction and selectively forming the Barbier coupling product. Results were analyzed using GC-MS. We have successfully formed the Barbier product using this strategy, however, GC data showed a mixture of products. Future work in our laboratory includes refining our protocol in order to successfully synthesize the desired Barbier product in high yields. After achieving our first goal, we aim to apply this catalytic approach to the Nozaki-Hiyama-Kishi reaction which is catalyzed by Cr(II) by replacing Cr(II) with Sm(II). This will ultimately provide a novel and greener approach to the NHK reaction by effectively replacing a toxic metal reducing agent with a non-toxic one.

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Chapter 1 *Introduction*

1.1 Samarium Diiodide: Properties and Applications

Metal-based reagents are extensively employed to mediate or catalyze organic reactions. As stoichiometric reagents, metals can reduce functional groups and form intermediates which facilitate new bond forming events. As catalysts, metals interact with intermediate species lowering activation barriers to form new products and make reaction conditions milder and more efficient [1]. Some of the most common metal reagents include the Grignard reagent, lithium-based reagents[2], palladium and copper catalysts[3], and metal hydrides such as sodium borohydride and lithium aluminum hydride[4] (Figure 1.1).

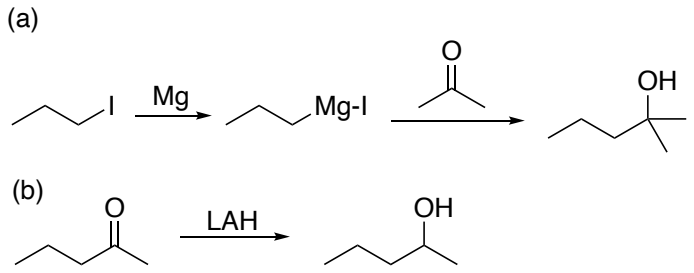


Figure 1.1: Examples of metal-mediated reactions. (a) Grignard reaction which utilizes magnesium (Mg) metal to carry out a coupling between an alkyl halide and ketone (b) Reduction of a ketone to an alcohol carried out by reducing agent lithium aluminum hydride.

Although all of these reagents and many more have been proven to be very efficient in carrying out or catalyzing organic reactions, there are certain limitations they possess that leave room for improvement. These limitations include things like the toxicity of many transition metals including palladium and copper, and the extreme flammability of metal hydrides making them dangerous reagents to work with. Another limitation is that reagents like the Grignard require that the reagent is prepared in a separate pot and then combined with the substrates limiting the development of one-pot synthesis strategies.

Henri B. Kagan introduced Samarium diiodide (SmI_2) in 1977 as a new metal-based reagent that can be employed in organic synthesis[5 6 7 8 9 10]. SmI_2 is an incredibly mild, versatile, and powerful single electron reductant[5 6 7 8 9 10] that has found increasing applications in organic synthesis since its introduction. It is a particularly useful reagent due to its ability to selectively interact with different functional groups at varying reaction rates allowing for the design of controlled and complex cascade reactions[7]. It can reduce a wide range of functional groups including but not limited to organic halides, carbonyl compounds, α-heterosubstituted carbonyl compounds, and epoxides and aziridines[11] (Figure 1.2). There is a number of possible heterosubstituents for α-substituted compounds SmI_2 can reduce (e.g. halides, and oxygen and sulfur containing substituents like -OH, -OR, and S-Ar)[12].

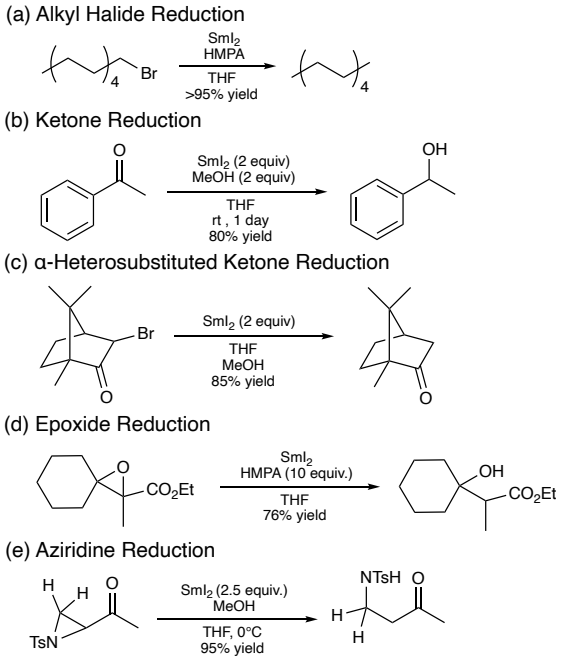


Figure 1.2: Examples of reductions carried out by SmI_2 .
(a) alkyl halide reduction[7] , (b) ketone reduction[13] , (c) α-heterosubstituted ketone reduction[12] (d) epoxide reduction[14] (e) aziridine reduction[15] (all reactions are worked up with dilute HCl upon completion)

In addition to simple reductions, SmI_2 is capable of carrying out a variety of intra- and intermolecular carbon-carbon bond forming transformations such as pinacol couplings, Barbier-Grignard type couplings, ketyl-olefin couplings, and Reformatsky-type couplings (Figure 1.3)[12].

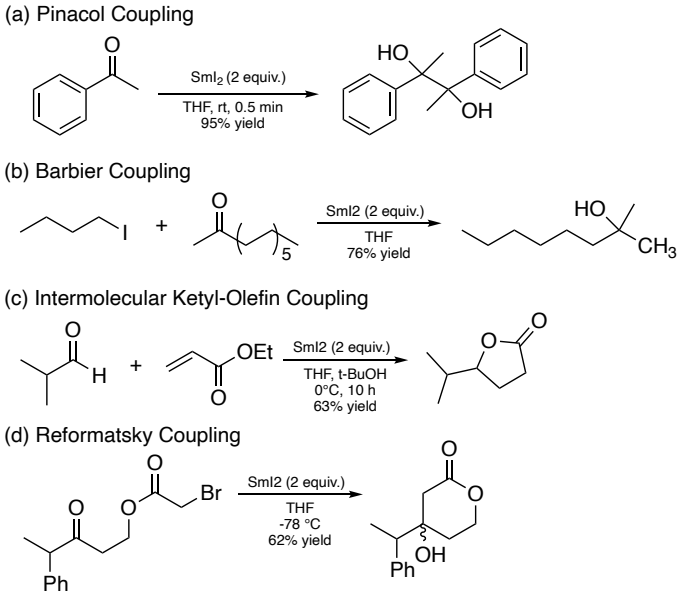


Figure 1.3: Examples of coupling reactions carried out by SmI_2
(a) pinacol coupling[12] (b) Barbier coupling[16] (c) intermolecular ketyl-olefin coupling[17]
(d) Reformatsky coupling[18]

To understand the abilities of SmI_2, we have to consider the chemical properties of Samarium (Sm). Sm is a lanthanide metal, and like all lanthanides, is most stable in its +3 oxidation state[7]. Samarium in its +2 oxidation state readily gives up its outermost shell electron and becomes Sm(III) to achieve greater thermodynamic stability[7 16 19]. Samarium's drive to exist in its +3 oxidation state makes Sm(II) reagents such as SmI_2 excellent single electron reductants. SmI_2-mediated reactions follow two main pathways (Figure 1.4). After SmI_2 gives up one electron through a single electron transfer (SET), the radical that is formed can go through a radical chemical pathway[7 9]. Alternatively, the radical can react with

another equivalent of Sm forming an organosamarium intermediate which can then proceed through an anionic pathway (Figure 3)[7 9].

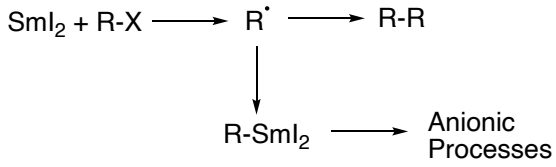


Figure 1.4: The two possible pathways of SmI_2 mediated reactions.

When reacting with carbonyl compounds, SmI_2 first forms a ketyl intermediate via a SET (1; Figure 1.5). Procter and co-workers suggested that the outcome of such reactions depend on the rate of protonation of the ketyl intermediate[7]. If rapid protonation of the intermediate occurs, the dimerized pinacol product is observed (2; Figure 1.5). If protonation is slow, the monomeric alcohol product is observed (3; Figure 1.5). The ability to control the intermediates in SmI_2 chemistry has allowed researchers to design one-pot complex cascade reactions using the reagent.

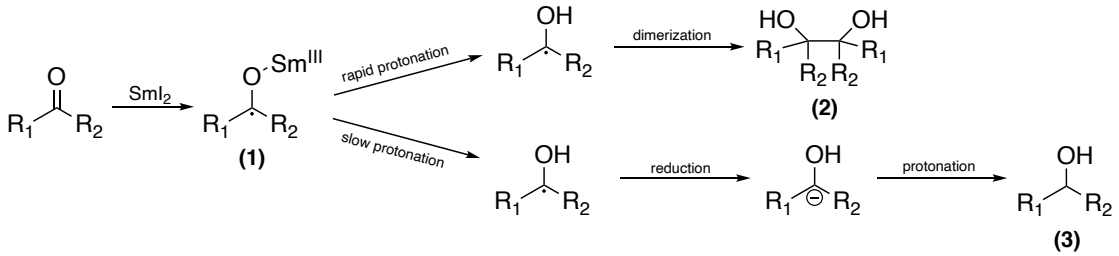


Figure 1.5: Two possible pathways for SmI_2 reactions with carbonyl compounds. (Figure adapted from Procter, Flowers, and Skrydstrup; 2010[7])

In addition to being an efficient and versatile reagent, SmI_2 is soluble in organic solvents which offers the advantage of a homogenous medium for reactions carried out with the reagent which makes it a lot easier to use compared to a reagent like the Grignard which requires solid magnesium metal. The outcome of SmI_2 reactions is highly impacted by the

solvent of choice and the optimal solvent for SmI_2-mediated reactions is tetrahydrofuran (THF)[20]. The reagent has a maximum solubility of 0.1 M in THF [20].

The reducing abilities of SmI_2 can be enhanced through the use of additives. One of the most common additives in SmI_2 chemistry is hexamethylphosphoramide (HMPA)[a]. In addition to enhancing its reducing abilities, co-solvents and additives in SmI_2-mediated reactions allow for great control of reaction intermediates by inducing selective SmI_2-substrate interactions. (Role of co-solvents and additives is further discussed in section 1.3)

There are many examples of SmI_2-mediated transformations in total synthesis. Lowe and Panek reported using SmI_2-mediated Barbier cyclization in the total synthesis of kendomycin which is an anti-cancer and anti-osteoporosis agent (3; Figure 1.6)[21].

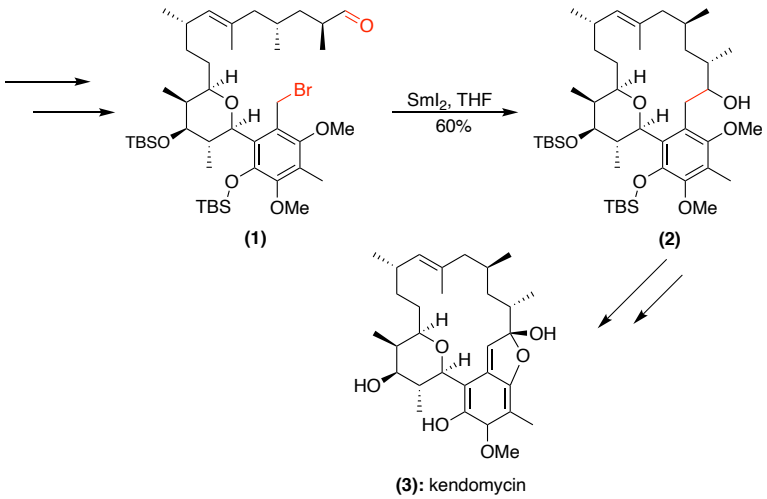


Figure 1.6: Barbier cyclization in the total synthesis of kendomycin[21]

In this example, we can see that SmI_2 successfully carried out a Barbier cyclization between the alkyl halide and ketone moieties (1;Figure 1.6, shown in red) in a

[a] SmI_2 in THF has a redox potential of -1.41 V[7]. Upon the addition of 4 equiv HMPA into a solution of SmI_2 in THF, the redox potential of the reagent has been shown to increase to -1.79 V[7] making it an even stronger single electron reductant.

chemoselective manner. This is one of the biggest advantages of using SmI_2, especially when working with large molecules containing multiple functional groups.

Tatsuta and co-workers reported the use of SmI_2-mediated ε-elimination (α and ε positions shown in red) in the final step of the synthesis of actinopyrone A[22] (2; Figure 1.7), taking advantage of the fact that SmI_2 is very efficient at chemoselectively cleaving functional groups in large and complex molecules.

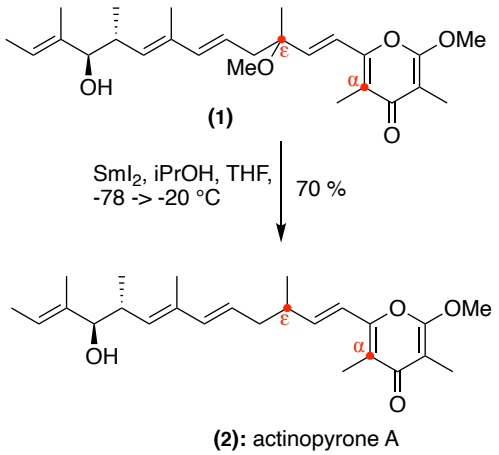
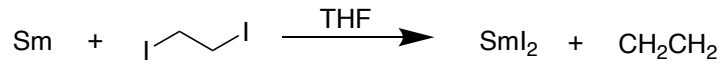


Figure 1.7: ε-elimination in the total synthesis of actinopyrone A[22]

1.2 Synthesis of SmI_2

There are two main methods of synthesizing SmI_2: Kagan's method and Imamoto's method (Figure 1.8). Kagan's method uses Samarium metal and 1,2-diiodoethane (or diiodomethane) in THF which yields SmI_2 with a side product of ethene gas [13]. Imamoto's method uses Samarium metal and I_2 to yield SmI_2 with no side products[23] making it the more atom efficient method and for this reason it tends to be the preferred method for synthesis. Using Kagan's method, the synthesis of SmI_2 can take up to two hours[12]. Flowers utilized ultrasound sonication for the synthesis of SmI_2 by Kagan's method and as a result decreased the reaction time from two hours to as little as five minutes[24].

(a) Kagan's Method



(b) Imamoto's Method

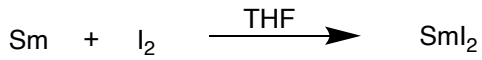


Figure 1.8: Procedures for the synthesis of SmI_2 in THF

The completion of the synthesis can be qualitatively observed by the formation of a characteristic deep blue color (Figure 1.9). As stated before, the maximum concentration of SmI_2 in THF is 0.1 M. However, the color of the reagent is not indicative of its concentration. A study done by Szostak and co-workers reports that the SmI_2 solution in THF takes on the deep blue color at concentrations between 0.005 M - 0.1 M[25]. This means that the formation of the color alone is not enough to determine the concentration of SmI_2 synthesized. The concentration of SmI_2 needs to be properly understood in order to set up efficient reactions using the reagent. It is important to mention that while SmI_2 is a commercially available reagent, in the same study done by Szostak and co-workers, concentrations of different commercially purchased batches were shown to vary despite being advertised as 0.1 M[25]. For this reason, we believe it is preferable to have a synthesis protocol that is reproducible and forms SmI_2 at a consistent concentration.

Figure 1.9: SmI_2 in THF. The completion of the synthesis is determined by the formation of the characteristic deep blue color.

1.3 Role of Additives in SmI_2-Mediated Reactions

Many SmI_2-mediated reactions employ additives to achieve greater regio- and stereochemical control and shorten reaction times[8 26 27]. Lewis bases are common additives to SmI_2-mediated reactions due to their ability to coordinate around the metal center and enhance the reducing ability of the reagent[8 26 27]. The oxidation number of Sm has an effect on its atomic radius. Sm(II) has a larger atomic radius than Sm(III) [26 27]. This allows Sm(II) to accommodate a large number of ligands[26 27]. When dissolved in THF, SmI_2 forms a complex with the solvent by taking on five THF molecules as ligands forming $[SmI_2(THF)_5]$ (Figure 1.10).

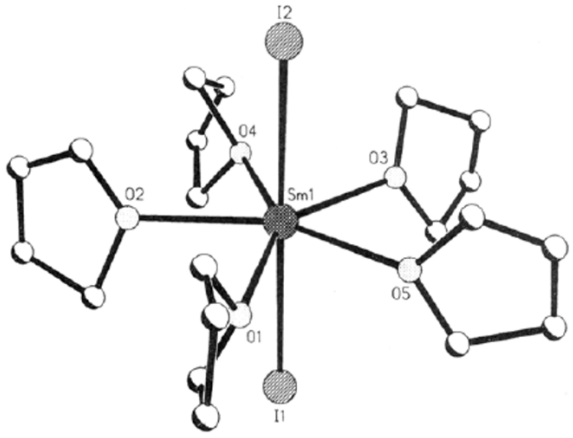


Figure 1.10: Crystal Structure of SmI_2 in THF. (Picture reprinted from Evans et al. 1995[28])

Samarium is an oxophilic metal. This means that an oxygen containing ligand is highly likely to interact with Sm. One of such oxygen containing ligands and the most common additives in SmI_2-mediated reactions is Hexamethylphosphoramide (HMPA) (Figure 1.11).

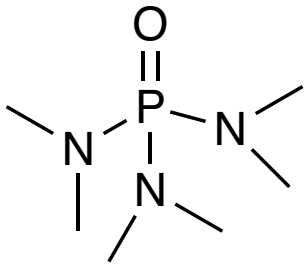
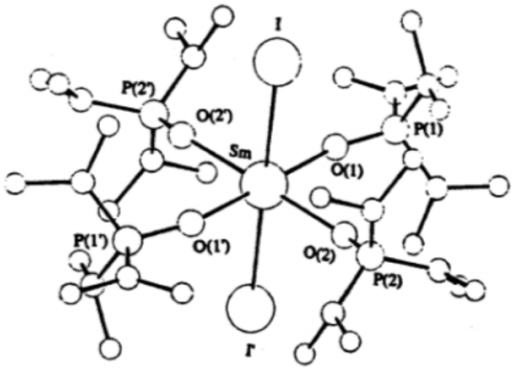


Figure 1.11: Chemical Structure of HMPA

HMPA is one of the most common additives used in SmI_2 chemistry[26]. When added into a solution of SmI_2 in THF, it replaces the THF ligands coordinated around the metal center forming complexes with SmI_2. At low concentrations of HMPA, the complex that is formed is $[SmI_2(HMPA)_4]$ [26 29 30 27] (A; Figure 1.12) . At high concentrations of HMPA (~10 equiv), six HMPA ligands coordinate around the metal center pushing the iodide atoms out forming the complex $[Sm(HMPA)_6]I_2$ [26 29 30 27] (B; Figure 1.12). Both complexes have increased reduction potential[26 29 30 27]. Ligand binding studies report that the bond length between

samarium and the oxygen of the electron donating ligand HMPA is short (2.5 Å) which explains the enhanced reduction potential of the reagent in the presence of HMPA[31].

A)



B)

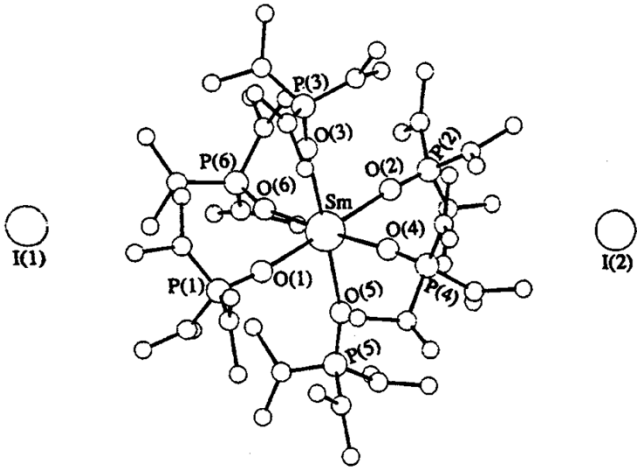


Figure 1.12: Crystal Structures of (A) $[SmI_2(HMPA)_4]$ and (B) $[Sm(HMPA)_6]I_2$ (Structures reprinted from Choquette, 2013[27]; and Hou et al. 1998[32] respectively)

Kinetic studies have shown that adding about 4 equiv of HMPA into a ketone or alkyl halide reduction of SmI_2 increases reaction rate dramatically[30]. Adding more HMPA (up to 10 equiv), has been shown to further increase the rate of reduction of alkyl halides, although,

the same was not observed for the rate of ketone reductions[30]. Additionally, the iodide atoms that are pushed out of the metal center vacate coordination sites for substrates resulting in increased reaction rates[26 27].

The ability of HMPA to enhance the reactivity and selectivity of SmI_2 makes HMPA a very popular additive in SmI_2 chemistry. However it is important to mention that HMPA is a suspected human carcinogen which raises safety concerns about the use of the compound especially in larger amounts. Safer and greener alternatives to HMPA in SmI_2-Mediated reactions is discussed in Chapter 3.

Chapter 2 *Samarium Diiodide: Synthesis and Applications Using a Schlenk Line*

2.1 Introduction

2.1.1 Limitations of SmI_2 and Purpose of Project

Despite being a powerful, mild, and versatile reagent, SmI_2 is often underutilized in synthetic chemistry laboratories due to its limitations. SmI_2 is highly oxyphilic which requires inert conditions when working with the reagent. This oxyphilicity of SmI_2 is caused by the instability of Sm metal in its +2 oxidation state. This results in Sm(II) readily oxidizing to its most stable state, Sm(III), when exposed to air forming Sm_2O_3 and losing all reactivity. For this reason, SmI_2 is seen as an intimidating reagent to work with, especially for small laboratories, since achieving inert conditions requires expensive and possibly inaccessible laboratory equipment such as a glovebox or a solvent system. This chapter addresses this issue and proposes a protocol for synthesizing and utilizing SmI_2 without the use of such sophisticated laboratory equipment.

The proposed protocol described in this chapter employs a dual-manifold Schlenk line to carry out the synthesis of the reagent (Figure 2.1). One line is connected to a vacuum and the other line is connected to an argon tank. This oxygen-free technique consists of vacuuming out the gases in sealed, air-tight reaction glassware and purging with argon to create inert microenvironments in which the synthesis of the reagent can be carried out.

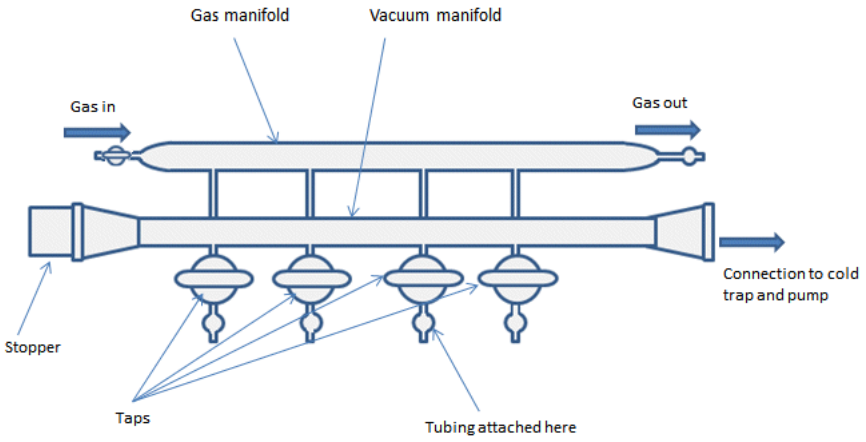


Figure 2.1: Diagram of a dual-manifold Schlenk line. (Picture reprinted from Millar, 2013[33])

In addition, all of the glassware used in the synthesis must be oven dried for at least 12 hours and all of the solvents must be distilled to make sure there is no water or peroxide content present during the reactions. All solids (samarium metal and 1,2-diiodoethane or I_2) are added into the reaction flask before sealing it with a rubber septum and connecting the flask to the Schlenk line. Although Sm metal is also air-sensitive, we found that it does not oxidize quickly enough to become "inactive" when exposed to air for short periods of time as long as it is stored under argon[25]. Upon vacuuming out the air and purging the sealed reaction flask containing the Sm metal and iodine source with argon, THF is added into it via a syringe to carry out the synthesis. The formation of the characteristic blue color indicates that SmI_2 has been successfully formed. After the synthesis is completed, to carry out any

reactions with the reagent, all substrates and additives should be transferred into the flask containing SmI_2 via a syringe as to not expose the reagent to air. The contents of the flask can be exposed to air once a reaction is carried out to completion since all of the SmI_2 is used up and no air sensitive substance remains in the reaction flask.

When SmI_2 is formed as a soluble reagent in THF, it has a characteristic blue color. While the formation of the blue color allows the confirmation of the presence of Sm(II), the concentration of the reagent must be quantified. Working with the Schlenk line method requires that SmI_2 is contained in fully sealed glassware which poses limitations when working to determine the concentration of the reagent. Traditional methods of assessing the concentration of SmI_2 include iodometric titration and UV-Vis Beer's Plot studies. However, for both of these methods. Titrations could not be carried out on the Schlenk line because in order to titrate SmI_2 , the reagent has to be removed from the flask it is synthesized in which, in the absence of a glovebox, exposes it to air. Attempts were made to use capped/airtight UV-Vis cuvettes, but during the dilution of SmI_2, the solution was consistently oxidized[34]. Therefore, we had to take an alternative route to determine our reagent's concentration while working with the Schlenk line. In order to determine the concentration, the synthesized SmI_2 is used in subsequent ketone and alkyl halide reduction reactions. The alkyl halide and ketone reported in this paper are 1-iodooctane and acetophenone respectively. These simple reduction reactions have been reported numerous times in literature to afford nearly quantitative yields when carried out in a 1:1 molar ratio[5 6 7 8 9 10]. By determining the % conversions of the starting material of these simple reductions, we are able to back calculate the concentration of the Schlenk line synthesized SmI_2. The details of this protocol and the

method development/data analysis process will be addressed in the methods (2.2) and results/discussion (2.3) sections respectively.

2.2 Methods

Distillation of THF To an oven-dried two or three-necked round bottom flask was added benzophenone (10 g, 0.055 mol), sodium in paraffin (4 g, 0.17 mol). Distillation set-up was vacuumed and purged with argon three times. Tetrahydrofuran (300 mL) was added into the round bottom flask. The solution was stirred until it turned blue and was refluxed for an hour. The refluxed solution was distilled into an oven-dried round bottom flask with a side arm and molecular sieves and was stored under argon. Distilled THF is a clear colorless liquid and has a storage life of 10 days before it needs to be redistilled.

Distillation of Acetophenone Acetophenone was added to an oven-dried round bottom flask. The distillation set-up was vacuumed and purged with argon three times. The substrate was distilled under vacuum into an oven-dried round bottom flask with molecular sieves. Distilled acetophenone was stored under argon.

Distillation of 1-iodooctane 1-iodooctane was added to an oven-dried round bottom flask. The distillation set-up was vacuumed and purged with argon three times. The substrate was distilled under vacuum into an oven-dried round bottom flask with molecular sieves. Distilled 1-iodooctane was stored under argon.

Distillation of Hexamethylphosphoramide To an oven-dried flask was added HMPA (50 mL) and calcium oxide (~4g). The distillation set-up was vacuumed and purged with argon three times. The solution was stirred for an hour and refluxed for an hour. HMPA was distilled into an oven-dried round bottom flask with molecular sieves and stored under argon.

Purification of 1,2-diiodoethane In a separatory funnel was combined 1,2-diiodoethane (10 g , 0.035 mol) and diethyl ether (500 mL). Contents were washed with saturated sodium thiosulfate solution five times and with water once. The organic layer was dried with magnesium sulfate and the solvent was evaporated (Rotavapor at ~200 vacuum) to yield fluffy, white crystals. The final product was covered with tin foil and stored in 4 ℃.

Synthesis of SmI_2 in the Schlenk Line (Kagan's Method) In an oven-dried round bottom flask with a side arm hooked to the argon line was combined Samarium (0.30 g, 0.002 mol) and 1,2-diiodoethane (0.25 g, 0.001 mol). The glassware was vacuumed and purged with argon three times. Into the flask was added 10 mL of THF. The solution was sonicated for 10 minutes. The final product (SmI_2, 0.1 M*) is a deep blue color.

Reduction of 0.1 M Acetophenone in the Schlenk Line Assuming 0.1 M SmI_2 A small pear-shaped round bottom flask with a side arm was vacuumed and purged with argon three times. Into the flask was added acetophenone (0.12 mL, 0.001 mol), dodecane (0.23 mL, 0.001 mol), and THF (2 mL). Into the flask containing SmI_2 (0.1 M, 10 mL) was added 1.74 mL of HMPA (10 eq with respect to SmI_2). The contents of the pear-shaped flask were transferred to the flask containing the SmI_2/HMPA mixture via syringe. The reaction was left to stir for at least two hours.

Reduction of 0.02 M Acetophenone in the Schlenk Line Assuming 0.02 M SmI_2 A small pear-shaped round bottom flask was vacuumed and purged with argon three times. Into the flask was added acetophenone (0.023 mL, 0.0002 mol), dodecane (0.045 mL, 0.0002 mol), and THF (2 mL). Into the flask containing SmI_2 (0.02 M, 10 mL) was added 0.34 mL of HMPA (10 eq with respect to SmI_2). The contents of the pear-shaped flask were transferred

to the flask containing the SmI_2/HMPA mixture via syringe. The reaction was left to stir overnight.

Reduced Acetophenone Work-up Into the flask containing now reduced acetophenone was added HCl (5 mL, 0.1 M). The contents of the flask were transferred to a separatory funnel. The solution was washed with diethyl ether and water three times, and with brine once. The isolated solution was dried with magnesium sulfate and filtered through vacuum filtration. The final product is a clear, yellow oil.

Reduction of 0.1 M 1-Iodooctane in the Schlenk Line Assuming 0.1 M SmI_2 A small pear-shaped round bottom flask was vacuumed and purged with argon three times. Into the flask was added 1-iodooctane (0.18 mL, 0.001 mol), dodecane (0.23 mL, 0.001 mol), and THF (2 mL). Into the flask containing SmI_2 (0.1 M, 10 mL) was added 1.74 mL of HMPA (10 eq with respect to SmI_2). The contents of the pear-shaped flask were transferred to the flask containing the SmI_2/HMPA mixture via syringe. The reaction was left to stir for at least two hours.

Reduction of 0.02 M 1-Iodooctane in the Schlenk Line Assuming 0.02 M SmI_2 A small pear-shaped round bottom flask was vacuumed and purged with argon three times. Into the flask was added 1-iodooctane (0.036 mL, 0.0002 mol), dodecane (0.045 mL, 0.0002 mol), and THF (2 mL). Into the flask containing SmI_2 (0.02 M, 10 mL) was added 0.34 mL of HMPA (10 eq with respect to SmI_2). The contents of the pear-shaped flask were transferred to the flask containing the SmI_2/HMPA mixture via syringe. The reaction was left to stir overnight.

Reduced 1-Iodooctane Work-up Into the flask containing now reduced 1-iodooctane was added HCl (5 mL, 0.1 M). The contents of the flask were transferred to a separatory funnel.

The solution was washed with diethyl ether and water three times, and with brine once. The isolated solution was dried with magnesium sulfate and filtered through vacuum filtration. The final product is a clear, yellow oil.

2.3 Results and Discussion

We have successfully developed a reproducible protocol to carry out the synthesis of SmI_2 in THF using a Schlenk line (Figure 2.2). Based on previous findings by the Flowers group, we used ultrasound sonication to mix the contents of the reaction flask with the expectation that it would decrease the reaction time[24]. As mentioned previously, the formation of SmI_2 can be qualitatively assessed by the formation of its characteristic deep blue color[25]. Consistent with the findings of the Flowers group, we were able to regularly observe the formation of the blue color on average in 5 minutes upon sonication[24].

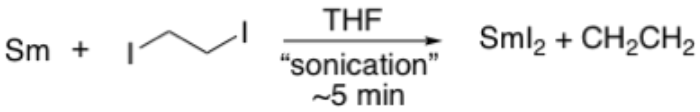


Figure 2.2: Kagan's method facilitated by sonication

During our experiments, we noticed that one of the most crucial factors in order to successfully carry out the synthesis of SmI_2 is the dryness of the solvent THF. Previous research in our lab suggested that distilled THF has a shelf life of 10 days when stored under argon in the Schlenk line before it needs to be redistilled. In order to further test the importance of the dryness of THF, we attempted to carry out the synthesis using a commercially available sure-sealed bottle of dry THF. All of our experiments with the commercial THF either failed to form any product or were not nearly as efficient as the syntheses carried out using THF distilled in our laboratory. For these reasons, we recommend that the solvent is freshly distilled and stored under argon prior to its use in synthesis.

Our next goal was to determine the concentration of the SmI_2 we synthesized. We could not directly analyze the concentration of our reagent using traditional methods such as a titration or a UV-Vis Beer's plot due to its air-sensitivity since removing it from the sealed reaction flask would expose it to air. Therefore, we had to take a different route. A 0.1 M solution of SmI_2 should carry out simple alkyl halide and ketone reductions with nearly quantitative yields[5 6 7 8 9 10] given that the reagent and the substrate have a 1:1 molar ratio. Our strategy was to subject the freshly synthesized SmI_2 to a simple alkyl halide or ketone reduction and determine the % conversion assuming the SmI_2 concentration to be 0.1 M. We hypothesized that with consistent results, we could work backwards to quantitatively determine the concentration of the SmI_2 using the % conversion values obtained. The alkyl halide and ketone used in our laboratory were 1-iodooctane and acetophenone respectively (Figure 2.3). Prior to the addition of the substrate, HMPA was added to the reaction flask containing SmI_2 to enhance its reducing [35 26 29 30 27]. Similarly to THF, we recommend that HMPA is distilled prior to its use in reactions.

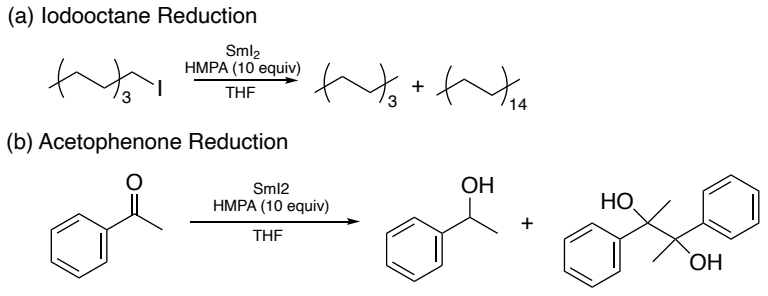


Figure 2.3: Simple reduction reactions of the selected substrates carried out with SmI_2 in THF.

Dodecane (1 equivalent with respect to substrate) was added as an internal standard to the reaction mixture along with the reactants. Gas chromatography and mass spectrometry (GC-MS) analysis of the reduced products were used to calculate the % conversion of the starting

materials. In order to calculate the % conversion, we first needed to calculate retention factor (Rf) values for the reactants with respect to the internal standard. To determine Rf values, a mixture of equal concentrations of our internal standard and substrate in diethyl ether was run on the GC. The relation shown in Figure 2.4 was used to calculate Rf.

$$\frac{C_{IS}}{A_{IS}} = Rf\,\frac{C_x}{A_x}$$

Figure 2.4: Internal Standard equation to calculate Rf from GC data where C_{IS}, A_{IS}, C_X and A_X are the concentration and area of the GC peak of the internal standard and the concentration and area of the GC peak of the substrate respectively.

Because SmI_2 reactions can proceed through both anionic and radical processes, these reduction reactions have two possible products. One product forms when the radical formed by the single electron transfer gets protonated by a proton source producing a monomeric alcohol and the second product forms via a radical coupling producing a dimerized product (Figure 2.5).

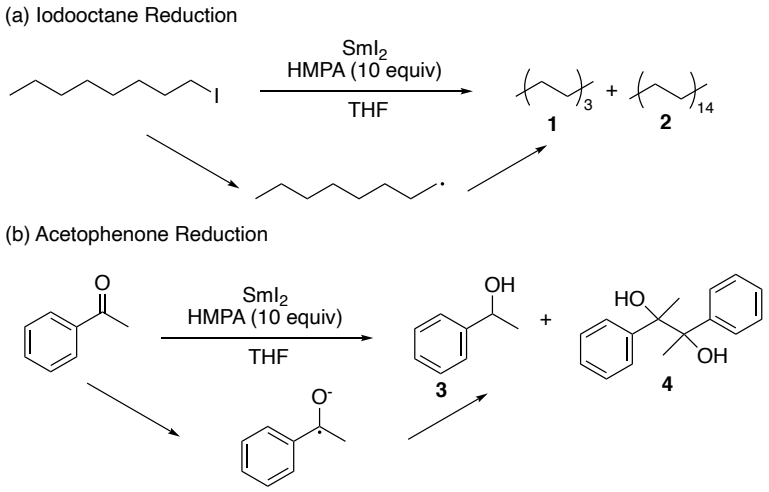


Figure 2.5: Possible products of (a) 1-iodooctane and (b) acetophenone reduction reactions carried out by SmI_2: (1) octane, (2) hexadecane, (3) 1-phenylethanol (4) 2,3-Diphenyl-2,3-butanediol

The purpose of running these reactions was to calculate the concentration of SmI_2 therefore we were not concerned about the type of products formed. Since calculating the % yield requires additional steps due to multiple possible products, we decided to calculate % conversions instead. This meant that while analyzing the GC data, the two most important peaks to identify were the internal standard peak and the substrate (acetophenone or 1-iodooctane) peak. Dodecane is used as the internal standard meaning it does not react with any of the reagents during the course of the reaction thus, we could expect that the dodecane peaks observed in the GC have the same concentration as the dodecane that was added to our reactions (1 equivalent with respect to substrate). The reason that we look for the substrate peak is to determine the amount of substrate that still remains in solution after the reduction reaction is complete. That way, we can determine the concentration of the substrate that actually reacted and calculate % conversion. Acetophenone and 1-iodooctane reductions were carried out with a 1:1 molar ratio with SmI_2. Since we conducted these reactions with the assumption that the SmI_2 we synthesized was 0.1 M, our substrates (acetophenone and 1-iodooctane) were also 0.1 M. A sample GC spectrum of reduced acetophenone is given in Figure 2.6. To calculate % conversion for acetophenone, we used the relationship given in Figure 2.4. With the Rf factor for acetophenone and dodecane, we solved the equation for the concentration of acetophenone (C_x). This concentration is the concentration of leftover acetophenone that was unreacted during the course of the SmI_2 reduction. We subtracted the leftover concentration from the initial concentration (0.1 M) which provided the concentration that actually reacted. The concentration of the substrate that reacted was used to determine % conversion.

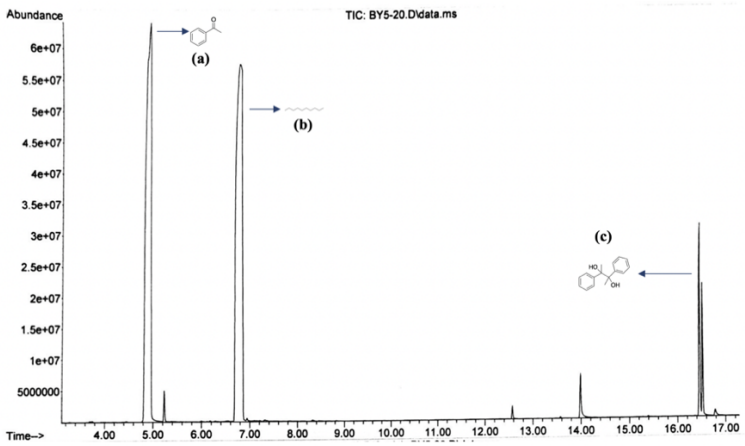


Figure 2.6: Sample GC Spectrum of Reduced Acetophenone (0.1 M). Peaks were identified by mass spectrometry. Peaks identified are (a) leftover acetophenone, (b) the internal standard dodecane, (c) 2,3-Diphenyl-2,3-butanediol which forms during the pinacol coupling of acetophenone. Rest of the peaks are small impurities that have not yet been identified.

A sample GC spectrum of reduced 1-iodooctane is given in Figure 2.7. To calculate % conversion for the reduction of 1-iodooctane, we once again used the relation given in Figure 2.4 and solved for the concentration of unreacted 1-iodooctane (C_X) and calculated % conversion for each trial.

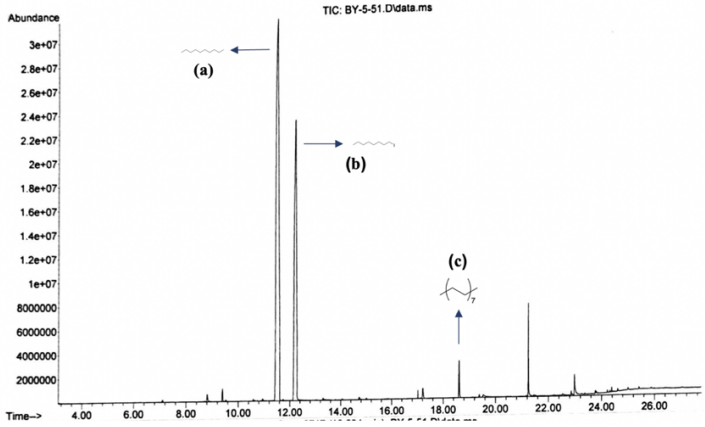


Figure 2.7: Sample GC Spectrum of Reduced 1-Iodooctane (0.1 M). Peaks were identified by mass spectrometry. Peaks identified are (a) the internal standard dodecane, (b) leftover 1-iodooctane, (c) hexadecane which forms during the radical coupling of 1-iodooctane. Rest of the peaks are small impurities that have not yet been identified.

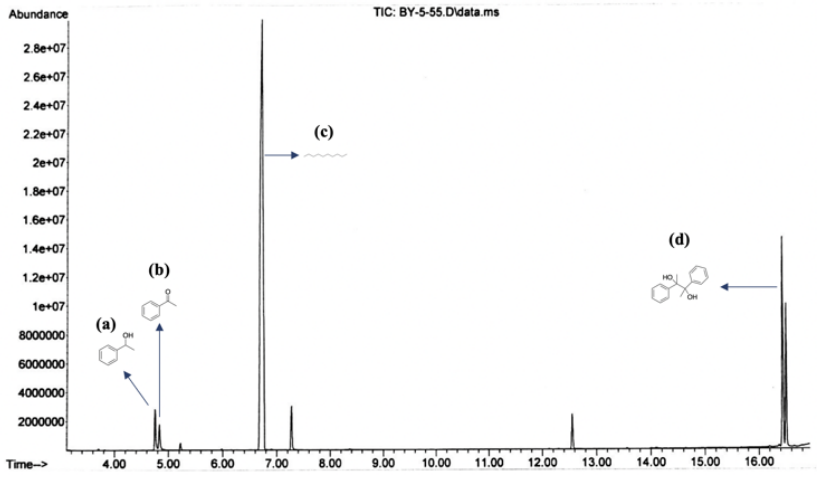
Table 2.1: % Conversion Values for the Reduction of 0.1 M Acetophenone and 1-Iodooctane

Entry	Assumed Concentration of SmI2 (M)	% Conversion	
		Acetophenone	1-iodooctane
1	0.1	32.6	25.2
2	0.1	33.9	30
3	0.1	17	29
4	0.1	20.9	28
5	0.1	22	18
Average		**25.3**	**26.0**
Standard Dev.		**7.52**	**4.84**

Table 2.1 shows % conversion values for the reduction of acetophenone and 1-iodooctane. The average of all trials for each substrate is also reported. We know that these reductions carried out by 0.1 M SmI_2 with HMPA should have >90% conversion[5 6 7 8 9 10]. However, our % conversion values were much lower. Even after attempts of optimizing our synthesis method such as using freshly distilled substrates and making sure the glassware is adequately oven-dried, we continued to observe low % conversion values, however, they were consistent. This consistency suggested that the concentration of SmI_2 we synthesize is much lower than we assumed. We concluded that it was not a matter of optimizing reaction conditions, rather it was simply that our reactions were not being carried out in a 1:1 ratio. In order to work backwards and determine the concentration of SmI_2, we averaged the % conversion values we obtained from both substrates and got values of 25.3% and 26.0% from acetophenone and 1-iodooctane reactions respectively (Table 1). The consistency of these results allowed us to deduce the concentration of SmI_2 synthesized in our lab. If our SmI_2 was 0.1 M, we would have been seeing nearly quantitative conversions. However, since our average % conversion is in between 25-27%, we hypothesized that the SmI_2 we synthesized is ~0.02M-0.025M. In order to test this hypothesis, we adjusted the amount of

substrate used in our reactions this time assuming our SmI_2 to be 0.025M. We ran an acetophenone and a 1-iodooctane reaction with this adjusted ratio which resulted in % conversions of 74.5% and 80.8% respectively. We wanted to see if we could maximize our % conversion values even further so we ran reactions assuming that the SmI_2 is 0.02M. The results of these reactions are given in Table 2.2. The results obtained from repeated trials of reduction reactions with adjusted ratios supported our hypothesis by affording nearly quantitative yields as expected. Sample GC spectra of acetophenone and 1-iodooctane reduction products carried out with the adjusted substrate concentration are shown in Figure 2.8.

A) Acetophenone (0.02 M) Reduction



B) 1-Iodooctane (0.02 M) Reduction

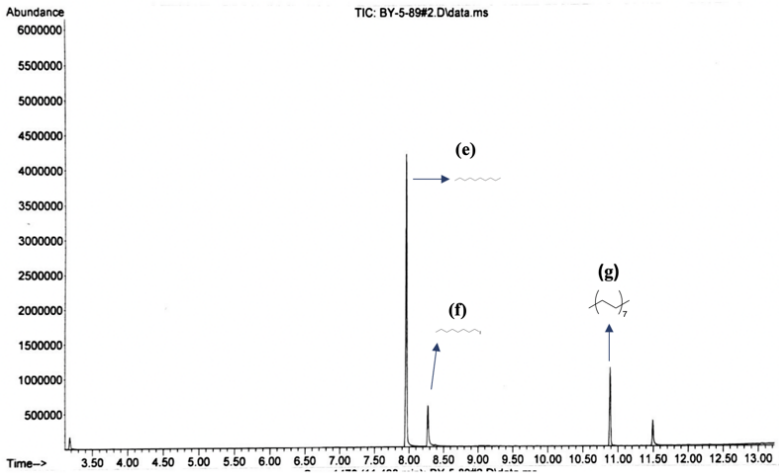


Figure 2.8: Sample GC Spectra of **A)** Acetophenone (0.02 M) Reduction and **B)** 1-Iodooctane (0.02 M) Reduction. Peaks were identified by mass spectrometry. Compounds observed in the first spectrum are **(a)** 1-phenylethanol which forms from the reduction of acetophenone, **(b)** leftover acetophenone, **(c)** the internal standard dodecane, and **(d)** 2,3-Diphenyl-2,3-butanediol which forms during the radical coupling of acetophenone. Compounds observed in the second spectrum are **(e)** the internal standard dodecane, **(f)** the leftover 1-iodooctane, and **(g)** hexadecane which forms during the radical coupling of 1-iodooctane Unreported peaks are small impurities that have not yet been identified.

Table 2.2: % Conversion Values for the Reduction of 0.02 M Acetophenone and 1-Iodooctane

Entry	Assumed Concentration of SmI2 (M)	% Conversion	
		Acetophenone	1-iodooctane
1	0.02	97.8	90
2	0.02	97.2	97.9
3	0.02	97	91.1
Average		**97.3**	**93**
Standard Dev.		**0.416**	**4.28**

2.4 Conclusions, Collaborative and Future Studies

We successfully developed a method for the synthesis of SmI_2 using a dual-manifold Schlenk line. Throughout our experimentation, we have identified some crucial reaction

conditions that must be met for our protocol to be efficiently employed. We found that the most important factor in order to successfully synthesize SmI_2 in the Schlenk line is the dryness of the solvent THF. As mentioned before, we report that THF has a shelf life of 10 days when it is stored under argon on the Schlenk line before it needs to be redistilled. In addition to the dryness of the solvent, all glassware that will be used to synthesize and carry out a reaction with SmI_2 needs to have been dried in the oven for at least ~12 hours. We have also seen that, although Sm metal is also air-sensitive, exposing it to air for a few minutes while weighing out and transferring it into the reaction flask does not notably affect the synthesis.

Based on the data we obtained, we determined the concentration of the reagent synthesized with our protocol to be approximately 0.02 M. Moreover, we confirmed the concentration of our reagent by observing nearly quantitative yields by carrying out simple reduction reactions in a 1:1 molar ratio using the hypothesized concentration of SmI_2 we synthesized. We knew that further improvement was necessary because we struggled to synthesize SmI_2 in high concentrations in the absence of a glovebox or solvent system. This project was continued by other students in our laboratory who were working to find the source of air or water contamination that was causing the low concentrations. They ran experiments to test each component to identify the source of this contamination. One of such experiments removed HMPA from the reaction mixture. They discovered that in the absence of HMPA, their % conversion values for simple reductions that assumed the concentration of the reagent to be 0.1M were dramatically higher (average conversion: 92.3%[36]) and closely matched the expected values found in literature. Although we were using HMPA as a means to make SmI_2 a better and faster reductant, SmI_2 is fully capable of carrying out simple

reductions without co-solvents given enough time. This provided us with insight that the co-solvent HMPA which we used to increase the reduction abilities of SmI_2 was the factor that was introducing water into our reduction reactions and "deactivating" our SmI_2. Although the removal of HMPA from the reaction matrix is an effective way of achieving high yields in simple reduction reactions, co-solvents are necessary for chemoselectively carrying out SmI_2-mediated coupling reactions (as will be discussed in Chapter 3). Future studies in our lab include investigating how to properly dry and store HMPA in order to be able to carry out coupling reactions with SmI_2 in the Schlenk line.

At the end of my time with this project, Drew University purchased a glovebox. As other members of our lab continued the Schlenk line method development project, I transitioned to working in the glovebox for a project that investigates applications of SmI_2 in synthesis with catalytic metals the details of which are discussed in the following chapter.

Chapter 3 *Applications: SmI_2-Mediated Reactions with Ni(II) Catalysts*

3.1 Introduction

3.1.1 SmI_2-Mediated Barbier and Grignard Reactions

The Barbier and Grignard reactions are carbon-carbon bond forming reactions that involve the coupling of alkyl halides and a carbonyl group which results in the formation of an alcohol. Alternatively, using esters in the reaction as the electrophile forms a ketone product[7]. Although both reactions serve the same purpose, what differentiates them is the method with which the reaction is carried out. In a Grignard reaction, the alkyl halide is formed into the nucleophile before adding the ketone or ester into the reaction pot, whereas in a Barbier reaction, both substrates are present in the reaction pot from the beginning[7].

The SmI_2-mediated Barbier reaction proceeds by the reduction of the alkyl halide into a radical via a single electron transfer[29]. Another equivalent of SmI_2 reacts with the radical forming an organosamarium species which acts as the nucleophile in the reaction[29] (Figure 3.1).

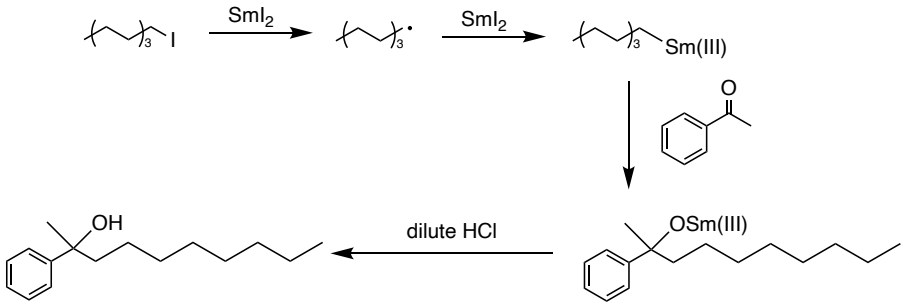


Figure 3.1: Reaction Scheme of the SmI_2 Barbier Coupling of 1-Iodooctane and Acetophenone with HMPA

The presence of both a ketone and an alkyl halide in the reaction mixture raises some questions about the effectiveness of the SmI_2-mediated Barbier reaction considering that SmI_2 is able to effectively reduce both functional groups. Therefore, it would be true to assume that SmI_2 alone would not be able to afford the desired Barbier product in good yields, rather, it would yield a mixture of reduction and coupling products. In order to ensure that the coupling is carried out in a chemoselective fashion, SmI_2 is often used with additives.

3.1.1.1 SmI_2-Mediated Barbier Reaction with HMPA

HMPA is one of the most common and additives in the SmI_2-mediated Barbier reaction (Figure 3.2). Flowers reports that in the absence of HMPA, the reaction is inefficient as it yields a mixture of products[37]. The addition of HMPA induces the chemoselective reduction of alkyl halides over ketones[26 29 30 27].

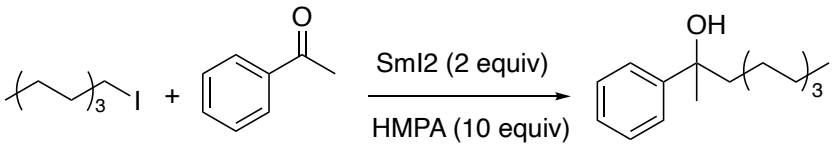


Figure 3.2: SmI_2 Barbier Coupling of 1-Iodooctane and Acetophenone with HMPA

As previously mentioned, rate studies on the impact of HMPA on the reduction of alkyl halides show HMPA increases the rate of alkyl halide reductions by 4 orders of magnitude[26] [29] [30] [27]. Whereas kinetic studies on the reduction of ketones show that the increase in the reduction rate for ketones is less significant[26] [29] [30] [27]. In addition to enhancing the reduction potential of SmI_2 by coordinating around the metal center, HMPA interacts with the alkyl halide resulting in an elongation of the carbon-halide bond which plays a role in its selective reduction[26] [29] [30] [27]. Thus, SmI_2 is able to selectively interact with the alkyl halide to form the organosamarium nucleophile which then goes through coupling with the ketone yielding the desired alcohol product (Figure 3.1).

Mechanistic studies assessing the effect of HMPA on the rate and the yield of the Barbier reaction found that high yields were obtained in the presence of HMPA, whereas when HMPA was not added, the yields were as low as 15%[6]. Despite being a very effective additive, HMPA has a few limitations that are making chemists look for alternatives. One of the biggest limitations is the fact that HMPA is a suspected human carcinogen. Another reason why chemists are looking for replacements is because stoichiometric amounts of HMPA are needed to be effective in having an impact on reaction rates which results in SmI_2/HMPA reactions with high process mass intensity (PMI) values. As a less toxic and wasteful alternative, transition metal salts can be used in catalyzing SmI_2 reactions. There are numerous studies reporting that various transition salts such as NiI_2, $FeCl_3$, and CuI, in catalytic amounts increase reaction rates and efficiency of SmI_2-mediated reactions[27] [38] [37].

Ni(II) salts have been shown to be effective catalysts in the Samarium Barbier Reaction. Research on the effect of Ni(II) salts on the Samarium Barbier reaction has shown that Ni(II) salts such as NiI_2, Ni(acetylacetonate)$_2$, and Ni(diphenylphosphinoethane)Cl_2 in catalytic amounts decrease the reaction time and increase yield [37].

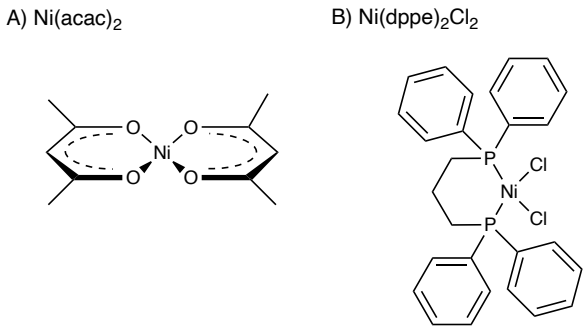


Figure 3.3: Structures of (A) Ni(acetylacetonate)$_2$ and (B) Ni(diphenylphosphinoethane)Cl_2

3.1.2 Ni(II) Catalysis in Cross Coupling Reactions

Nickel is a group 10 metal and like palladium , platinum and other transition metals has been studied extensively in the field of organometallic synthesis. Being in the same group as palladium and platinum provides nickel with similar reactivity patterns to its group 10 counterparts allowing it to facilitate many of the same reactions[39]. One glaring advantage of nickel over palladium or platinum is its cost-efficiency[39], however, it is not fair to write nickel off as a cheaper alternative to more costly transition metals as it possesses some unique properties making it more preferable to other metals in numerous reaction pathways. Nickel is a relatively electropositive transition metal[39]. This is a very useful property of nickel as it is able to react with “less reactive” electrophiles such as aryl, alkenyl, allyl halides, aryl fluorides, and phenol derivatives [39 40]. Unlike other metals such as palladium, platinum, and magnesium, nickel is capable of going through oxidative addition with such “less reactive” electrophiles under mild reaction conditions [40] (Figure 3.4).

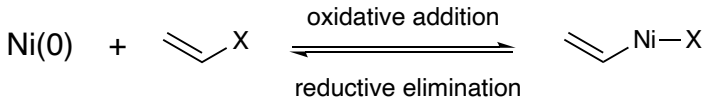


Figure 3.4: Oxidative addition (forward) and reductive elimination (reverse) of Ni(0) with alkenyl halides. (X: I, Br, Cl, F) (figure adapted from Tamaru, 2005[40])

Nickel has a total of five oxidation states (0, 1+, 2+, 3+, 4+) although 0 and 2+ are the most frequently observed and commonly used in nickel catalysis[40]. Nickel catalyzed cross coupling reactions go through a standard organometallic pathway which includes oxidative addition, transmetallation, and reductive elimination[b 40]. The rate of oxidative addition of nickel to carbon-halide bonds decreases as the following: C-I > C-Br > C-Cl > C-F [40]. Nickel is particularly advantageous in the case of oxidative addition to carbon-fluorine bonds due to the difficulty of cleaving a bond as strong as C-F. When accompanied by electron-donating ligands, Ni(0) species are able to undergo mild oxidative addition with alkyl and aryl fluorides[40].

3.1.2.1 SmI_2-Mediated Barbier Reaction with Ni(II) Salts

Ni(II) salts are effective at replacing HMPA in the SmI_2-mediated Barbier coupling reaction. Although the combination of SmI_2 and Ni(II) salts were shown to be effective in the selective coupling of alkyl halides and ketones, the mechanism of the reaction had not always been well understood. Kinetic studies show that the rate of reduction of Ni(II) by SmI_2 is 5 orders of magnitude faster than those of alkyl halides and ketones[37]. Additionally, stopped-flow spectroscopy experiments revealed that in the SmI_2/Ni(II) Barbier reaction, the reduction of Ni(II) to Ni(0) is the rate determining step[37]. Based on their kinetic findings, the researchers proposed the following mechanism (Figure 3.5). (1) SmI_2 reduces Ni(II) to Ni(0)

[b] Non-exhaustive list. Other processes such as insertion after oxidative addition, and β-hydrogen and β-carbon elimination following reductive elimination are also commonly observed[*cite].

(2) a portion of the Ni(0) crashes out of solution as Ni(0) nanoparticles and exits the catalytic cycle (3) remaining Ni(0) inserts into the alkyl halide bond via oxidative addition (4) due to the instability of this organonickel species, the intermediate goes through transmetallation to produce an organosamarium (5) the nucleophilic carbon of the organosamarium species carries out the coupling by attacking the electrophilic carbon of the ketone [37].

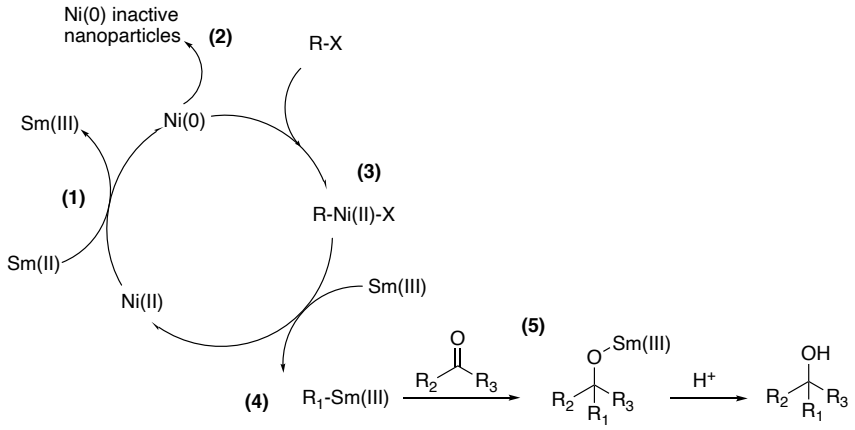


Figure 3.5: Proposed mechanism of the Sm(II)/Ni(II) Barbier Coupling Reaction[37]

3.1.3 Sm(II)/Ni(II) System in the Nozaki-Hiyama-Kishi (NHK) Reaction

The Nozaki-Hiyama-Kishi (NHK) Reaction is a cross-coupling reaction between vinyl halides and ketones/aldehydes. The NHK reaction is traditionally catalyzed by a Cr(II)/Ni(II) system in which Cr(II) works as a reductant to reduce Ni(II) to Ni(0) *in situ* and the reaction is carried out by Ni(0) as the active catalyst [41] (Figure 3.6).

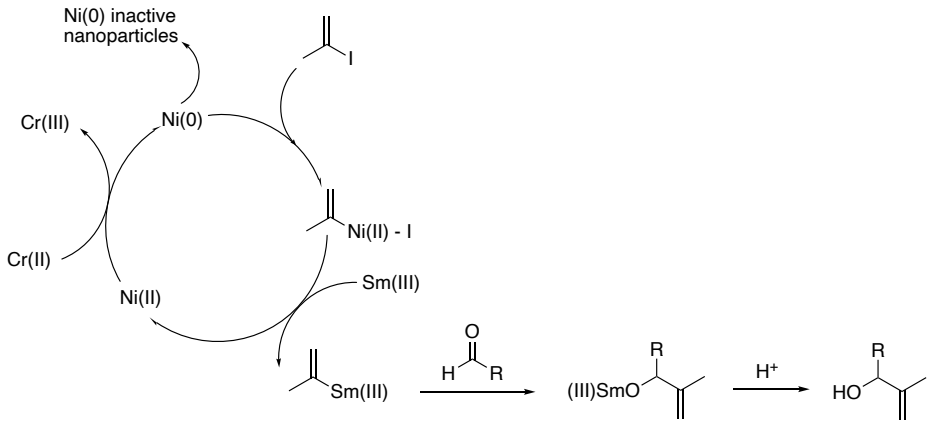


Figure 3.6: Reaction mechanism of the Cr(II)/Ni(II) catalyzed NHK Coupling Reaction

Although Cr is effective at reducing Ni to catalyze this reaction, there are concerns with the metal's toxicity and the harsh reaction conditions that it requires. We propose that Sm(II) can be a better alternative to Cr(II) (Figure 3.7). As previously discussed, Sm(II) is highly effective and fast at reducing Ni(II) to Ni(0). Once Ni(0) is generated in the reaction solution, the rest of the reaction is catalyzed by Ni(0) which gets regenerated as Ni(II) during the transmetallation step (4) of the catalysis.

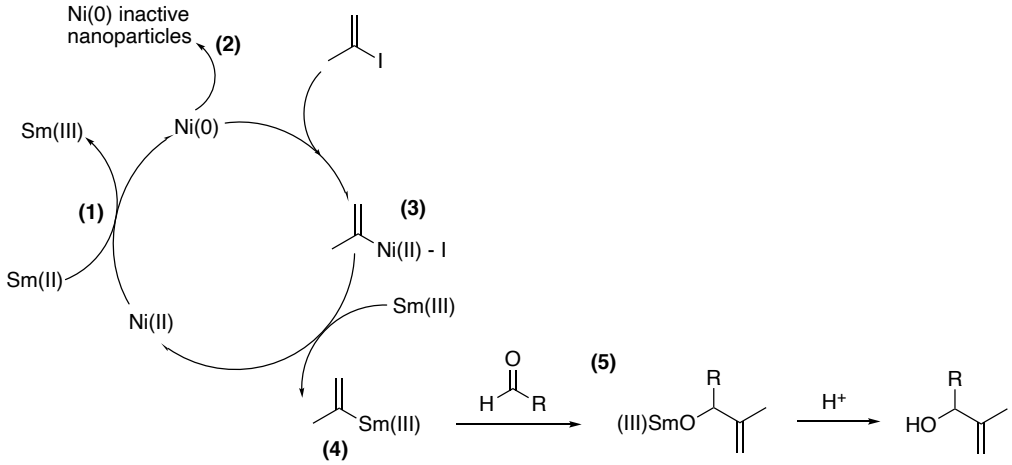


Figure 3.7: Proposed reaction mechanism of the Sm(II)/Ni(II) catalyzed NHK Coupling Reaction

3.1.4 Project Overview

This project aims to assess the effectiveness of different Ni(II) salts on catalyzing the SmI_2-mediated Barbier coupling reaction. The synthesis of SmI_2 and all reactions were performed in the glovebox. Two different sets of substrates were chosen for the Barbier coupling: acetophenone/1-iodooctane and benzophenone/iodobenzene. Three different Ni(II) salts were selected as catalysts: NiI_2, $Ni(acac)_2$, and $Ni(DPPE)_2$. The details and findings of this project are discussed herein.

3.2 Methods

Synthesis of SmI_2 in the Glovebox (Kagan's Method) In an oven-dried round bottom flask was combined Samarium (0.30 g, 0.002 mol) and 1,2-diiodoethane (0.25 g, 0.001 mol). Into the flask was added 10 mL of THF. The solution was stirred in the glovebox overnight. The final product (SmI_2, 0.1 M*) is a deep blue color.

Synthesis of SmI_2 in the Glovebox (Imamoto's Method) In an oven-dried round bottom flask was combined Samarium (0.30 g, 0.002 mol) and I_2 crystals (0.25 g, 0.001 mol). Into the flask was added 10 mL of THF. The solution was stirred in the glovebox overnight. The final product (SmI_2, 0.1 M*) is a deep blue color.

Iodometric Titration of SmI_2 Into a small vial was added 500 μL of newly synthesized SmI_2 in THF. The SmI_2 solution was diluted with an additional 4mL of dry THF. The titrant (0.2 M I_2) was prepared by combining I_2 crystals (0.255 g) and dry THF in a 10 mL volumetric flask. The endpoint of the titration is a cloudy green color. The analyte turns yellow past the endpoint.

Sm(II)/Ni(II) Catalyzed Barbier Reaction **with Acetophenone and 1-Iodooctane** Into the flask containing SmI_2 (0.1 M, 10 mL) was added Ni(II) (1 mol%). Acetophenone (0.0005

mol), 1-iodooctane (0.0005 mol), dodecane (0.0005 mol), and dry THF (2 mL) were combined in a small pear-shaped flask. The contents of the pear-shaped flask were transferred to the flask containing SmI_2 and Ni(II). The reaction mixture was stirred overnight. Final product is a clear and colorless oil.

***Sm(II)/Ni(II) Catalyzed Barbier Reaction* with Benzophenone and Iodobenzene** Into the flask containing SmI_2 (0.1 M, 10 mL) was added Ni(II) (1 mol%). Benzophenone (0.0005 mol), iodobenzene (0.0005 mol), dodecane (0.0005 mol), and dry THF (2 mL) were combined in a small pear-shaped flask. The contents of the pear-shaped flask were transferred to the flask containing SmI_2 and Ni(II). The reaction mixture was stirred overnight. Final product is a clear and colorless oil.

3.3 Results and Discussion

3.3.1 Concentration Assessment of SmI_2 via Iodometric Titration

SmI_2 was successfully synthesized in a glovebox by using the methods of Kagan and Imamoto. Its concentration was determined by iodometric titration. Iodometric titration of SmI_2 takes advantage of the color change that occurs when the reagent is oxidized by the addition of I_2 to become SmI_3 (Figure 3.8). The characteristic deep blue color of SmI_2 in THF disappears as it is titrated with a solution of I_2 in THF. The endpoint of the titration is a dirty, pale green color. When the titration passes the endpoint, the solution turns pale yellow which is the color of SmI_3.

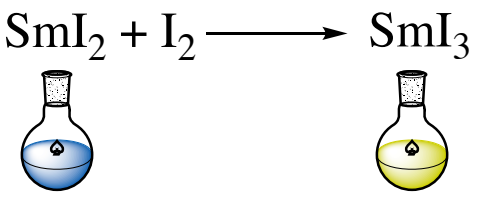


Figure 3.8: Iodometric titration of SmI_2. When titrated with I_2, SmI_2 oxidizes to form SmI_3 which changes its characteristic deep blue color to a pale yellow.

We titrated multiple batches of SmI_2 synthesized in the glovebox and determined that the concentration of SmI_2 is nearly 0.1 M (Table 3.1). This is consistent with the concentration expected based on the stoichiometry of our starting materials.

Table 3.1: Iodometric Titration Results of Five Different Batches of SmI_2 in THF

Entry	Concentration by Titration (M)
1	0.097
2	0.095
3	0.085
4	0.096
5	0.085
Average	0.0916

3.3.2 Comparing Ni(II) Sources in the SmI_2-Mediated Barbier Reaction

The catalytic abilities of two different Ni(II) salts, NiI_2 and $Ni(acac)_2$, were investigated in the SmI_2-mediated Barbier coupling reaction between 1-iodooctane and acetophenone (Figure 3.9). The SmI_2/Ni(II) system works due to the fact that SmI_2 is very efficient at reducing Ni(II) to Ni(0) and the formation of Ni(0) *in situ* initiates the rest of the chemical transformation. The amount of Ni(II) salts that were added to the reaction was 3 mol% based on previous reports in literature[37].

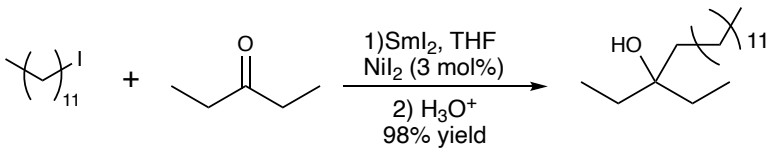
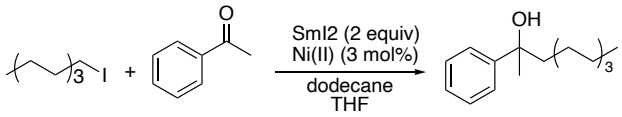


Figure 3.9: Example of a Barbier coupling reaction catalyzed by NiI_2.

For the analysis of the efficiency of different Ni(II) salts, one of the parameters we considered was the % conversion rates of the starting materials (Table 3.2). In general, we observed that a larger amount of acetophenone was being used up as compared to 1-iodooctane (entries 2,3,4,5). We observed that both substrates were used up in high amounts

using NiI_2 in entry 1, however, in entries 2 and 3 NiI_2 did a poor job of converting 1-iodooctane compared to the conversion value of acetophenone. $Ni(acac)_2$ was excellent at using up high amounts of both substrates in entry 4, however, in entry 5 we observed that 1-iodooctane was converted at a much lower amount than expected. Based on the data given in Table 3.2, no conclusive trend was observed to determine which Ni(II) source was more efficient. More repetitions of this reaction with both Ni(II) sources are necessary to have a concrete conclusion.

Table 3.2: % Conversion Values for SmI_2-mediated Barbier Reaction with Ni(II)



Entry	Nickel Source	%Conversion Acetophenone	%Conversion Iodooctane
1	NiI2	83.70%	97%
2	NiI2	89.24%	40%
3	NiI2	90.40%	60%
4	Ni(acac)2	97%	93.50%
5	Ni(acac)2	90%	60%

Although looking at % conversion values can give us some insight about the efficiency of the reaction, it is not enough. This is because of the possibility of side product formation. That means, even if we see nearly quantitative % conversion values, we cannot be certain that we successfully formed the Barbier product (a; Figure 3.10) as the high conversion values may also be result of reduction and/or radical coupling reactions (Figure 3.10).

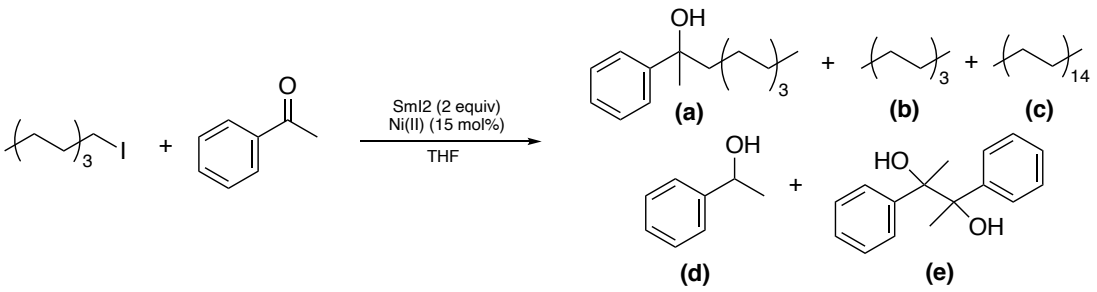
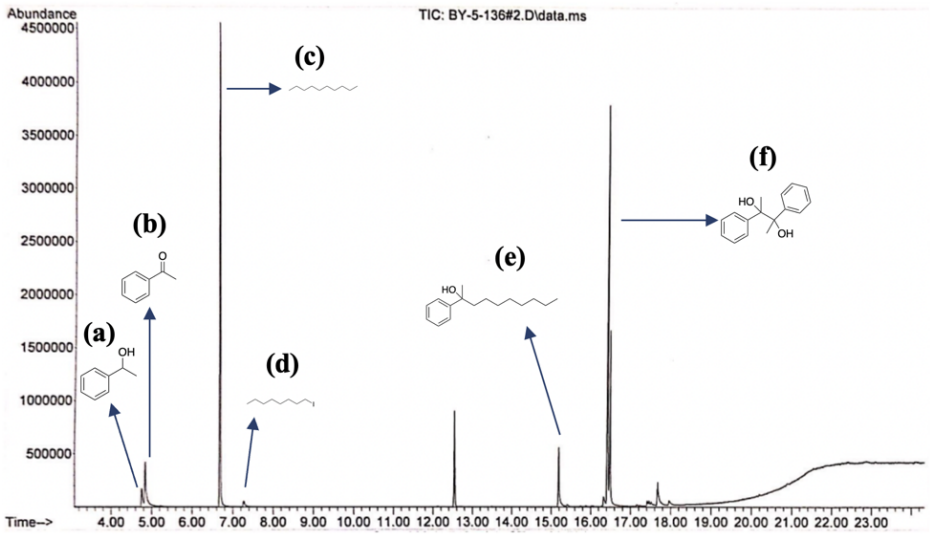


Figure 3.10: All possible products of the Barbier reaction between 1-iodooctane and acetophenone including **(a)** the Barbier coupling product α-Methyl-α-octylbenzenemethanol and all possible side products **(b)** octane **(c)** hexadecane **(d)** 1-phenylethanol **(e)** 2,3-Diphenyl-2,3-butanediol

Therefore, another – and more important – parameter we considered was product formation. A mixture of products including the Barbier product were observed in the GC analysis (Figure 3.11). Theoretically, SmI_2 should reduce Ni(II) to Ni(0) at a much higher rate than it reduces acetophenone and 1-iodooctane. The formation of both the reduction and pinacol products derived from acetophenone suggests that SmI_2 is reducing the substrate faster than it is reducing Ni. This could be due to a couple reasons. One reason could be that the metal catalyst is not soluble enough in the SmI_2/THF solution making it harder for SmI_2 to reduce nickel effectively. Another reason could be that more nickel is being formed into Ni(0) nanoparticles and exiting the catalytic cycle than we assumed. These findings require that we work to optimize reaction conditions, and experiment with different amounts and types of the nickel source.

A) Barbier Reaction with SmI_2 and NiI_2



B) Barbier Reaction with SmI_2 and $Ni(acac)_2$

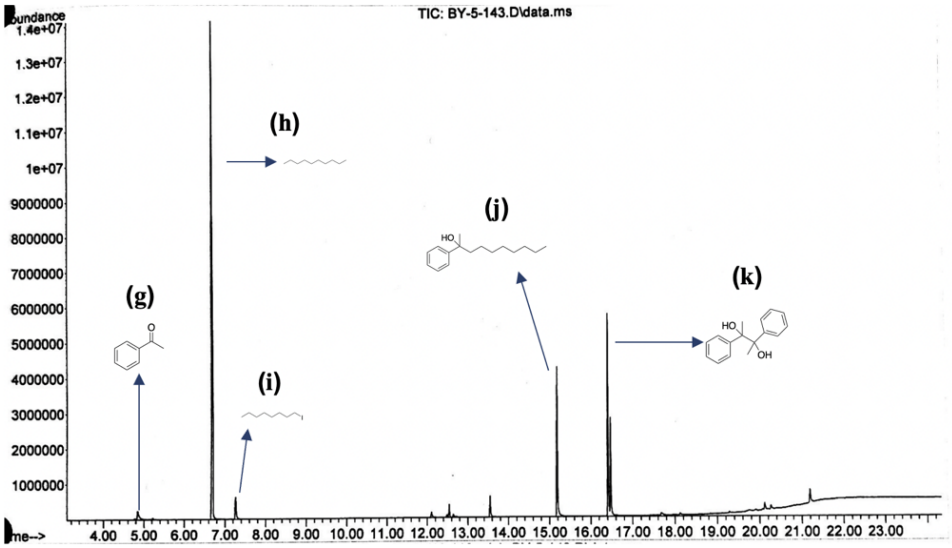


Figure 3.11: Sample GC Spectra of **A)** Barbier reaction between acetophenone and 1-iodooctane with NiI_2 and **B)** with $Ni(acac)_2$. Peaks were identified by mass spectrometry. Compounds observed in the first spectrum are **(a)** 1-phenylethanol which forms from the reduction of acetophenone, **(b)** leftover acetophenone, **(c)** the internal standard dodecane, **(d)** leftover 1-iodooctane, **(e)** α-Methyl-α-octylbenzenemethanol which is the Barbier coupling product, and **(f)** 2,3-Diphenyl-2,3-butanediol which forms during the radical coupling of acetophenone. Compounds observed in the second spectrum are **(g)** leftover acetophenone, **(h)** the internal standard dodecane, **(i)** leftover 1-iodooctane, **(j)** α-Methyl-α-octylbenzenemethanol which is the Barbier coupling product, and **(k)** 2,3-Diphenyl-2,3-butanediol which forms during the radical coupling of acetophenone. The peak at around ~12.5 min in the upper spectrum is the stabilizer butylated hydroxytoluene (BHT) that is found in the solvent ether which was used for the extraction of the products.

In order to assess which Ni(II) source was more effective, we needed to calculate % yield. To calculate % yield, we first need to obtain an Rf value of our desired Barbier product (a; Figure 3.10) with respect to the internal standard, however, we did not have our pure Barbier product at hand to be able to run an Rf experiment with it. An alternative way we can compare the amount of product formation from reactions catalyzed by different Ni(II) sources is to look at the ratio between the internal standard and the Barbier product (Table 3.3).

Table 3.3: Barbier Product to Internal Standard Ratios Obtained from Four Different Experiments Using Two Different Nickel Sources

Entry	Ni(II) Source	Barbier Product / Internal Standard Ratio of Relative Peak Areas
1	Ni(acac)2	0.262
2	Ni(acac)2	0.255
3	NiI2	0.153
4	NiI2	0.155

Based on the ratios shown in Table 5, we can come to the conclusion that using $Ni(acac)_2$ is more efficient at forming the desired Barbier product. We know this because the ratio between the integration of the Barbier product peak and the integration of the internal standard peak is greater for reactions carried out with $Ni(acac)_2$ suggesting that there is greater product formation.

Although we were able to get an idea about which Ni(II) salt leads to better product formation by comparing product to internal standard ratios, we needed to find a way to obtain % yield values to come to a concrete conclusion. For this reason, we picked out two new substrates and purchased the resulting alcohol product in order to determine an Rf value for it which will allow us to calculate % yield. The new ketone and alkyl halide we chose were

benzophenone and iodobenzene respectively which yield triphenylmethanol as their coupling product (Figure 3.12). In addition to changing the substrates, we also increased the amount of our catalyst from 3 mol% to 15 mol% with the expectation that it would improve the efficiency of the catalyst.

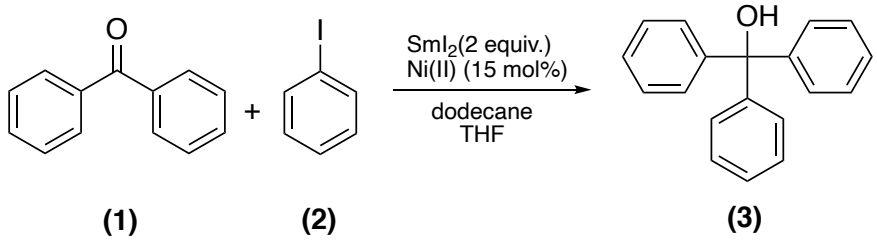
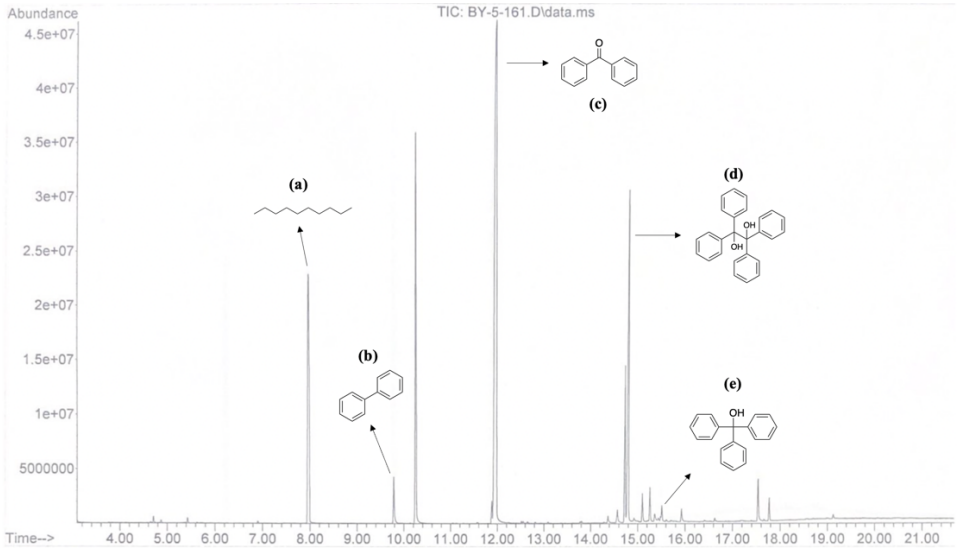


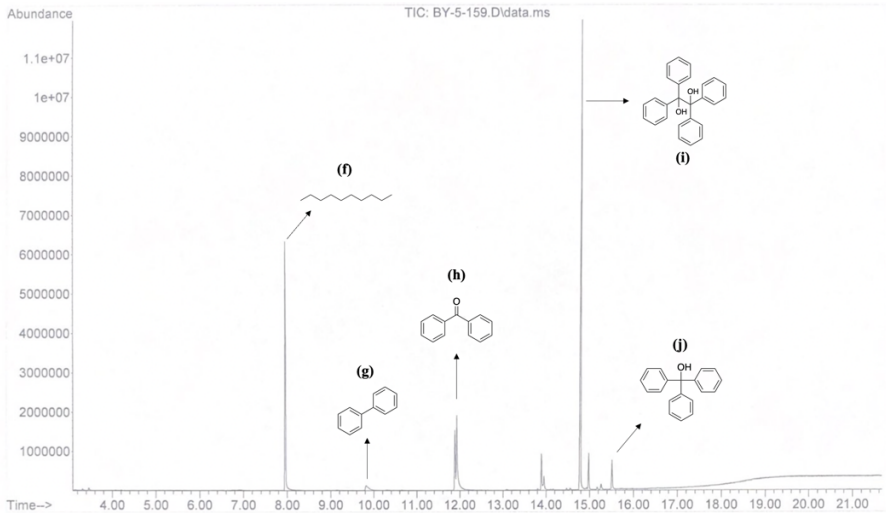
Figure 3.12: Barbier Coupling of benzophenone and iodobenzene carried out by SmI_2 and Ni(II) **(1)** benzophenone and **(2)** iodobenzene **(3)** triphenylmethanol

Sample spectra of the Barbier reaction between benzophenone and iodobenzene with NiI_2 (A; Figure 3.13) , $Ni(acac)_2$ (B; Figure 3.13), and $Ni(dppe)_2$ (C; Figure 3.13) are shown below.

A)



B)



C)

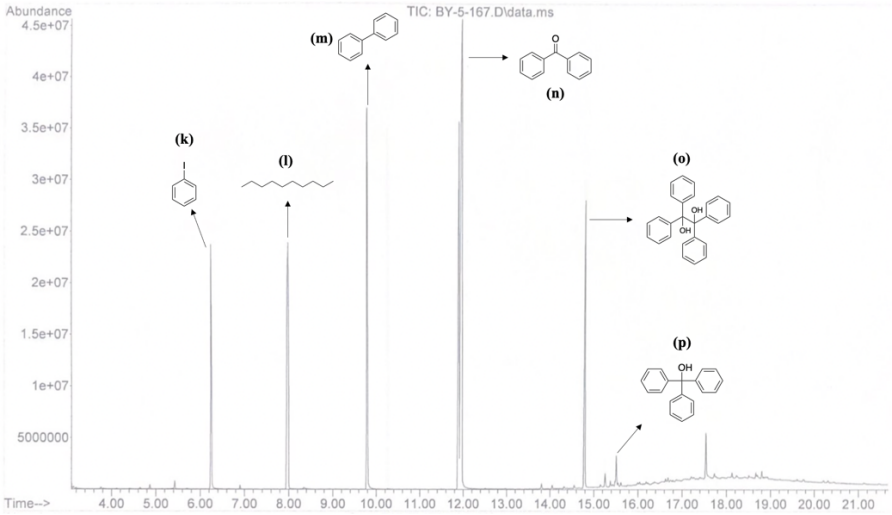
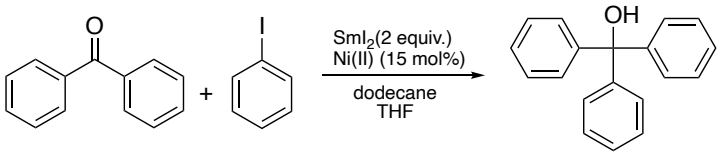


Figure 3.13: Sample GC Spectra of **A)** Barbier reaction between benzophenone and iodobenzene with NiI_2 and **B)** with $Ni(acac)_2$, and **C)** with $Ni(dppe)_2$. Peaks were identified by mass spectrometry. Compounds observed in the first spectrum are **(a)** the internal standard dodecane, **(b)** biphenyl which forms during the radical coupling of iodobenzene, **(c)** leftover benzophenone, **(d)** benzopinacol which forms during the pinacol coupling of benzophenone, **(e)** triphenylmethanol which is the Barbier coupling product. Compounds observed in the second spectrum are **(f)** the internal standard dodecane, **(g)** biphenyl which forms during the radical coupling of iodobenzene, **(h)** leftover benzophenone, **(i)** benzopinacol which forms during the pinacol coupling of benzophenone, **(j)** triphenylmethanol which is the Barbier coupling product. Compounds observed in the third spectrum are **(k)** leftover iodobenzene, **(l)** the internal standard dodecane, **(m)** biphenyl which forms during the radical coupling of iodobenzene, **(n)** leftover benzophenone, **(o)** benzopinacol which forms during the pinacol coupling of benzophenone, **(p)** triphenylmethanol which is the Barbier coupling product.

As can be seen from the GC-MS data, we were able to successfully form some of the desired Barbier product, although, a mixture of products was observed in the data collected from all experiments. Moreover, % yields of our Barbier product did not match the % conversions of our starting materials suggesting that side product formation was being favored over the Barbier product (Table 3.4). The highest yield of Barbier product we achieved was 4% (Entry 1; Table 3.4).

Table 3.4: % Conversion and % Yield Values for SmI_2-mediated Barbier Reaction with Ni(II)

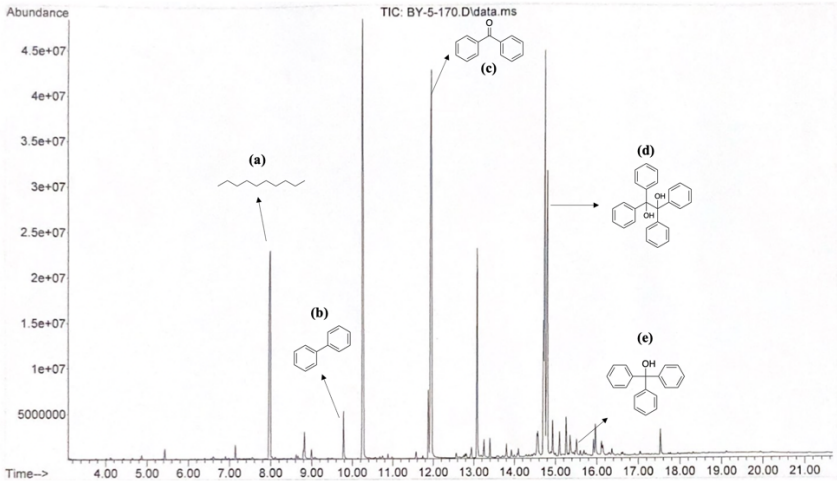


Entry	Assumed Concentration of SmI2 (M)	Ni(II) Source	% Conversion		%Yield Triphenylmethanol
			Benzophenone	Iodobenzene	
1	0.1	Ni(acac)2	91	100	4
2	0.1	Ni(acac)2	92	100	1.4
3	0.1	NiI2	67	100	1.4
4	0.1	Ni(DPPE)2	50.8	67.5	1.9
Average			**16.3**	**91.9**	**2.18**
Standard Dev.			**75.2**	**91.9**	**1.24**

There can be a couple reasons as to why we were not successful at achieving high yields of our desired product. The fact that we see reduced and dimerized products in our GC data suggests that SmI_2 is reducing the substrates at a higher rate than it is reducing Ni(II) to Ni(0). This could be because the Ni(II) sources we were using in our experiments were old and the quality of the catalyst might have diminished over time. If our nickel sources are inactive in the reaction, the SmI_2 can directly interact with the ketone and alkyl halide which

would explain side product formation that we observe in our GC data. In order to test the quality of our Ni(II) sources, we ran an experiment where we performed the same reaction twice: one with a Ni(II) catalyst and one with no catalyst. The results of the experiment are shown below in Figure 3.14.

A)



B)

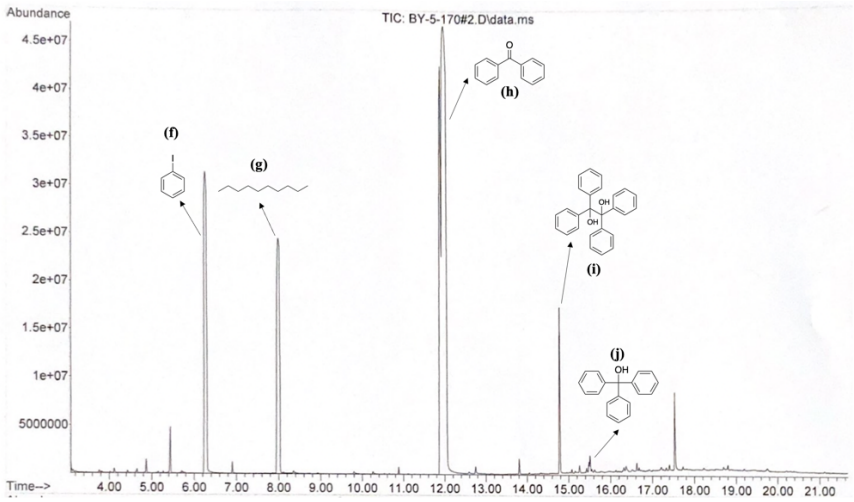


Figure 3.14: GC Results of Barbier coupling reaction A) with a Ni(II) catalyst and B) without a Ni(II) catalyst. Peaks were identified by mass spectrometry. Compounds observed in the first spectrum are **(a)** the internal standard dodecane, **(b)** biphenyl which forms during the radical coupling of iodobenzene, **(c)** leftover benzophenone, (d) benzopinacol which forms during the pinacol coupling of benzophenone, **(e)** triphenylmethanol which is the Barbier coupling product. Compounds observed in the second spectrum are **(f)** leftover iodobenzene, **(g)** the internal

standard dodecane, **(h)** leftover benzophenone, **(i)** benzopinacol which forms during the pinacol coupling of benzophenone, **(j)** triphenylmethanol which is the Barbier coupling product. The rest of the peaks have not yet been identified.

The results of this experiment revealed that the Ni(II) catalyst did not have a significant impact on the outcome of the reaction. These results indicate that, the Ni(II) salts that were used in our reactions were not acting as catalysts. This could be because our Ni(II) salts were a few years old which could have affected their quality. In order to confirm that this is the case, the same experiment should be repeated with newly purchased Ni(II) salts.

Another parameter as the potential cause of this issue is the dryness of the solvent THF. While developing the synthesis method of SmI_2 in the Schlenk line, we discovered that the dryness of the THF is one of the biggest contributors to the success of our reactions which is why we determined that THF has a shelf-life of 10 days. Since we started working in the glovebox, we have not been paying attention to the dryness of our solvent as closely as we have done while working in the Schlenk line. It could be possible that THF has a shelf-life even when stored in the glovebox. If the solvent we are using is not dry enough, it could quench the Ni(0) atoms that are generated by the reduction of Ni(II) by SmI_2 as Ni(0) is an extremely unstable and air/moisture-sensitive form of nickel.

3.4 Conclusion and Future Studies

We have confirmed that the SmI_2-mediated Barbier reaction with Ni(II) salts yields the Barbier coupling product. However, based on the data we collected so far; we are unable to confidently determine the efficiency of our Ni(II) sources. Additionally, we were unable to synthesize the desired Barbier products at high yields suggesting that there is a lot of room for improvement. Future work in our laboratory includes repeating our previous experiments with newly purchased Ni(II) sources to determine whether or not it was the quality of the

Ni(II) source that was causing the low % yields. In addition, we will be performing a series of experiments to determine whether or not THF has a shelf-life upon distillation even when it is stored in an environment as inert as the glovebox.

Once we have successfully determined the ideal Ni(II) source for the SmI_2/Ni(II) catalytic system and achieved the desired high yields of the Barbier product, we will apply our findings to the NHK coupling reaction in order to replace the use of Cr(II) with Sm(II) which is a less toxic alternative to the traditional catalysis of the reaction. Our ultimate aim is to establish SmI_2 as a more powerful, versatile, and greener alternative to traditionally used transition metals that come with an array of environmental and health concerns.

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