Drew University

College of Liberal Arts

Protocol Development for the Synthesis and Application of Samarium Diiodide Using Schlenk Line Techniques

A Thesis in Chemistry

by

Caroline Tramontana

Submitted in Partial Fulfillment of the Requirements for the Degree of Bachelor in Sciences

With Specialized Honors in Chemistry

Examining Committee:

Dr. Kimberly Choquette, Thesis Advisor

Chemistry

Dr. Vincent Gullo, Member

Chemistry

Dr. James Supplee, Member

Physics

May 2022

Table of Contents

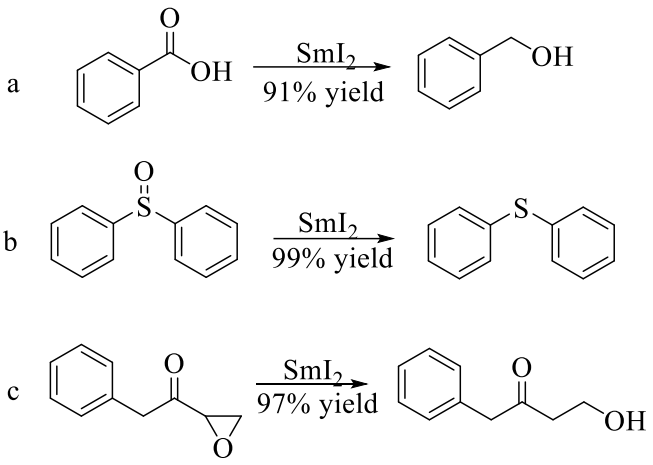
Abstract

Samarium diiodide (SmI_2) is a useful reagent used in synthetic chemistry laboratories. SmI_2 is a chemoselective single electron reductant that mediates radical reactions, redox reactions, and carbon-carbon bond-forming reactions.[1-5] Despite its versatility, SmI_2 is rarely used in undergraduate laboratories due to its sensitivity to air and water, both of which inactivate the compound. To combat these sensitivities, it is general practice that all reagents are distilled and degassed, glassware is dried in the oven, and SmI_2 is synthesized and utilized in a glove box under inert conditions; however, glove boxes are expensive and may be difficult to obtain, especially for an undergraduate laboratory. A Schlenk line is a lower-cost alternative that creates micro inert environments within the glassware by vacuuming out all of the air in the glassware and purging it with an inert gas such as argon or nitrogen. The goal of this laboratory was to develop a protocol for the synthesis and application of SmI_2 using a Schlenk line so it may be used with ease in laboratories without gloveboxes. Various steps and procedures for the synthesis of SmI_2 were investigated to develop a simple, robust protocol that yielded consistent results. Using the protocol we developed, SmI_2 was consistently synthesized as a 0.1 M solution using Kagan's method and afforded high conversions of ketones (98% conversion). This protocol will enable undergraduate laboratories to synthesize and employ SmI_2 in more reactions due to its ease of use on the Schlenk line and consistent results.

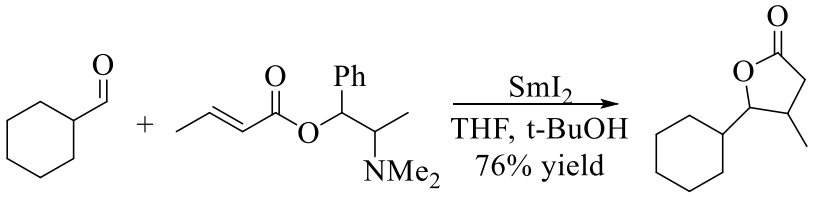
Chapter 1: Introduction

1.1 Samarium Diiodide (SmI_2)

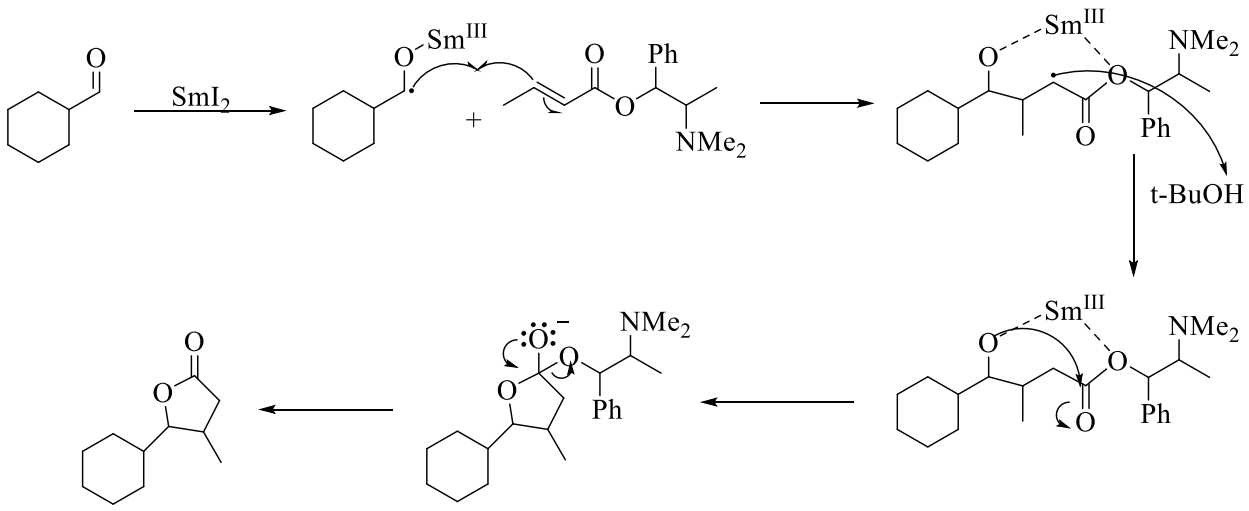
Since it was first discovered in 1977 by Henri Kagan, samarium diiodide (SmI_2) has been used in multiple chemical reactions due to its powerful reducing capabilities, versatility, and chemoselectivity.[1-5] As a single electron reductant, SmI_2 is versatile as it can mediate functional group transformations such as the reduction of ketones, alkyl halides, sulfoxides, and epoxides (Scheme 1).[2-6] Additionally, interesting and complex radical and nucleophilic addition cascades can be carried out with SmI_2 (Schemes 2 and 3). While other reagents, such as metal hydrides, can also mediate simple reductions, SmI_2 is advantageous as it is soluble in tetrahydrofuran (THF) and is available as a homogenous solution at 0.1 M (Figure 1).[1] In addition, SmI_2 is chemoselective due to its ability to reduce various functional groups at different rates which allows for control over product formation (Scheme 4).[1-7] Because of its versatility and chemoselectivity, SmI_2 has been employed in total synthesis reactions and has proven useful in complex cascade sequences and carbon-carbon bond formations and disconnections.[5,8] Some applications of SmI_2 in industry have been in the synthesis of the antibiotics platensimycin[8,9] and pleuromutilin[10] where SmI_2 was used to mediate selective reductions (Scheme 5) and complex carbon-carbon bond formations (Scheme 6), respectively. SmI_2 has also proven useful in the synthesis of strychnine, where the reagent mediates the formation of two new rings allowing for the shortest total synthesis of the insecticide (Scheme 7).[11]



Scheme 1: Functional group transformations SmI_2 mediates a) reduction of carboxylic acids b) reduction of sulfoxides c) reduction of epoxides[2]



Scheme 2: Reductive coupling of an aldehyde and crotonate mediated by SmI_2



Scheme 3: Proposed mechanism for intermolecular ketyl-olefin coupling reaction mediated by SmI_2

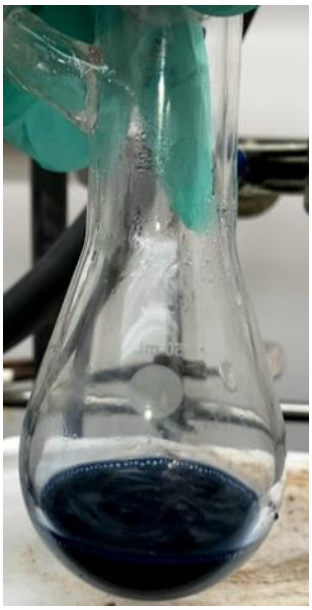
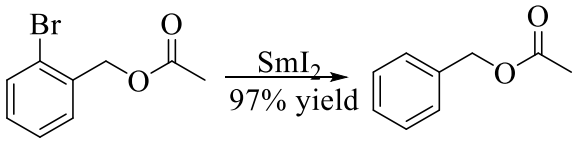
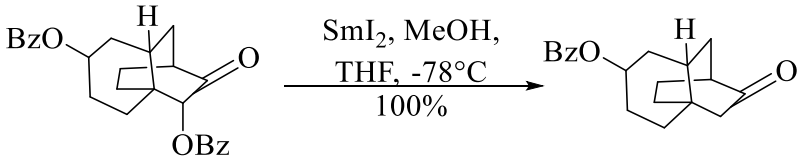


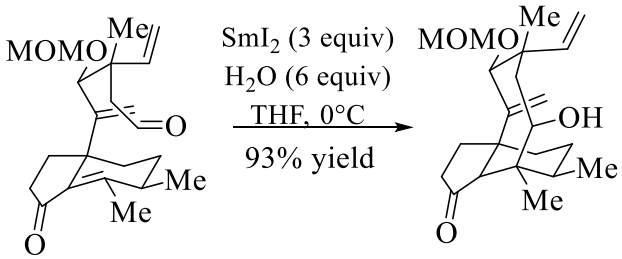
Figure 1: SmI_2 in THF



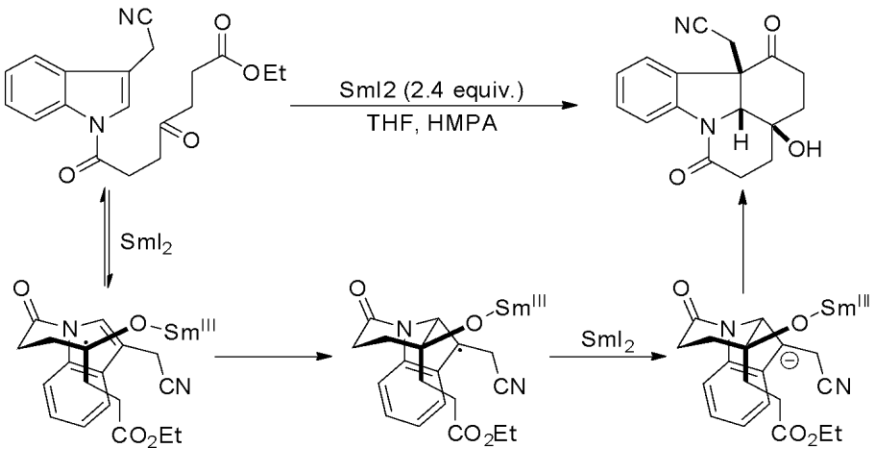
Scheme 4: Chemoselectivity of SmI_2, in the presence of a carbonyl and aryl halide the halide is selectively reduced



Scheme 5: Selective reduction of the benzoyl group in the synthesis of Platensimycin



Scheme 6: Complex carbon-carbon bond forming reaction in the synthesis of Pleuromutilin



Scheme 7: SmI_2 mediated cyclization cascade in the synthesis of Strychnine[11]

Despite its chemoselective advantages, SmI_2 is often underutilized in small laboratories as it may be viewed as a difficult reagent to work with due to its sensitivity to both air and water.[1-5] Cautionary steps must be employed when synthesizing and working with SmI_2 such as using oven dried glassware, working under air-free conditions, and distilling and purifying all reagents. When these steps are taken, SmI_2 can be synthesized in house and high conversions can be obtained using the reagent. To ease some of the apprehension surrounding the synthesis and application of SmI_2, studies such as that of Procter et al. have examined the different variables that are required for maintaining an air-free reaction. Procter et al. studied the effects samarium quality, water content in THF, iodine source, and experimental set up have on the air-free synthesis of SmI_2.[1] Using their findings and experimental methods as a guide, our lab also examined the various factors that go into maintaining an air-free and water free environment. Although Procter et al. claim that strict air-free techniques need not be used to obtain a reliable concentration of SmI_2,[1] our lab has found otherwise.

1.2 Oxidation States of SmI_2

SmI_2 is composed of the lanthanide metal, samarium, and halide iodine.[2,12] Divalent lanthanide metals naturally exist in the +3 oxidation state.[2,12] Lanthanides, such as samarium, may lose three of the outermost electrons to form the +2 oxidation state.[2] In this state, Sm(II) reagents are excellent reducing agents as they readily give up an electron through a single electron transfer to achieve the desirable Sm^{+3} state (Scheme 8). While the oxyphilic character of samarium is beneficial for reductions and reductive couplings, it is not beneficial while trying to synthesize the reagent. Therefore, steps must be taken when working with samarium to prevent premature oxidation which would result in inactivation of the reagent.

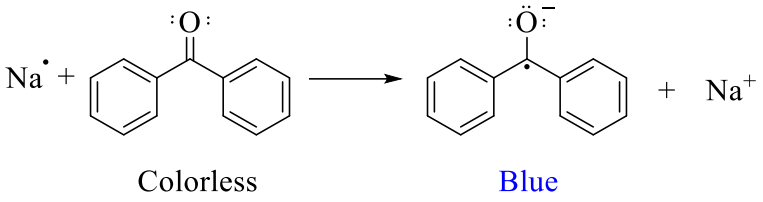
$$Sm(II) \longrightarrow Sm(III) + e^-$$

Scheme 8: Oxidation of Sm(II)

1.3 Water and SmI_2

Not only is the presence of air a concern for the synthesis and application of SmI_2, but the presence of water may also be an issue. Due to its oxyphilic nature, samarium metal and SmI_2 can be oxidized by water to the inactive Sm^{+3} state. Water may be introduced to the reaction mixture through the addition of reagents and solvents that are “wet” or by using glassware and tools that were left on the benchtop and may have atmospheric water on it. To ensure there is no water in the reaction mixture and prevent premature oxidation of the reagent, it is general practice that glassware is dried overnight in an oven and all reagents are anhydrous.[1] One of the greatest concerns for the presence of water is in the solvent, THF. The most rigorous way of drying THF is to carry out a distillation with sodium, with benzophenone as an indicator that all of the water has been removed. Fortunately, a THF still, allows researchers to distinguish when

the THF is dry due to the deep blue color of the solution which is indicative of the free radical being formed (Scheme 9) (Figure 2). Unfortunately, other reagents such as HMPA, have no indicator for the dryness so all reagents should be distilled to eliminate any water.



Scheme 9: Na and Benzophenone indicator for presence of water

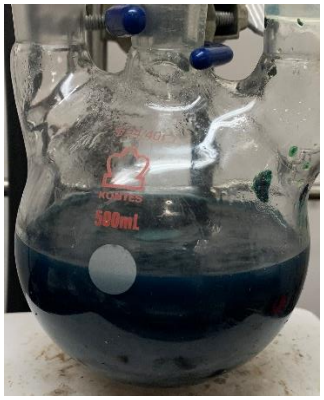


Figure 2: Dry THF as indicated by dark blue color

1.4 Synthesis of SmI_2

SmI_2 is typically synthesized in a glove box which creates an air-free environment within the box through the steady flow of an inert gas such as nitrogen or argon (Figure 3). Although gloveboxes make synthesizing and working with the reagent easy, gloveboxes are expensive and can be difficult to obtain for small laboratories. A Schlenk Line, which creates micro inert environments within the glassware, presents as a low-cost alternative to gloveboxes (Figure 4 and Figure 5). By vacuuming out the air from the glassware and replacing it with argon gas, commonly referred to as vacuum/purging the glassware, an air-free environment is obtained within the glassware. Air-free techniques are standard for working with SmI_2; however, Procter

et al. claim that an air-free environment is not necessary to synthesize SmI_2 and the reagent may be synthesized and utilized on a bench top.[1] Procter et al. proport that the quality of samarium metal is more important than the presence of air during the synthesis of SmI_2.[2] Despite their conclusions, our lab has found no success in synthesizing the reagent on the bench top under the Procter conditions.

Figure 3: A Glovebox which creates an inert environment through the steady flow of argon gas

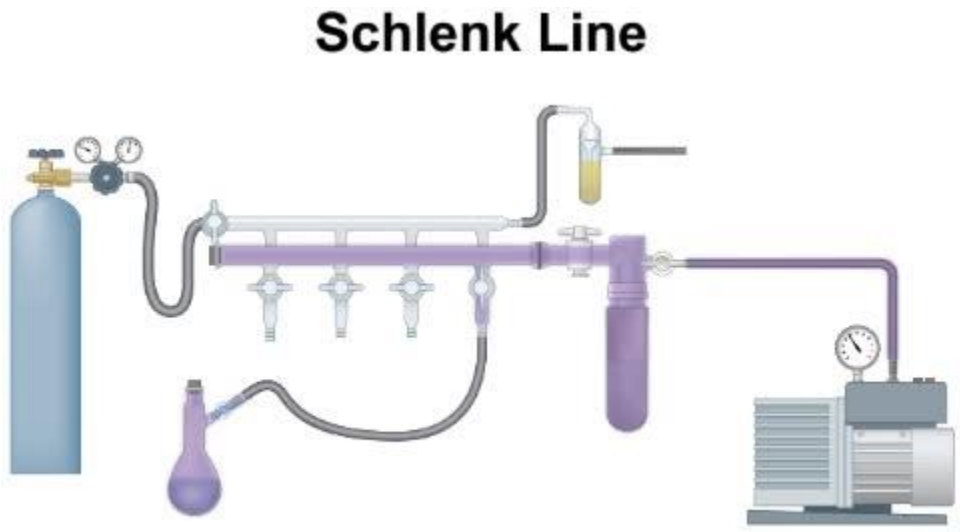


Figure 4: Graphic of a Schlenk line: glassware is attached via a hose and the flow of an inert gas or a vacuum is controlled by a valve

Figure 5: A Schlenk line which creates inert environments within the glassware through the steady flow of argon gas

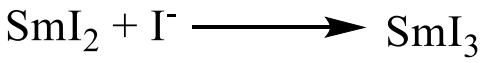
Since its discovery by Henri Kagan, multiple methods have been employed to synthesize SmI_2, but the most studied and reliable are Kagan's method and Imamoto's method. Kagan's method uses samarium metal and 1,2-diiodoethane in the solvent THF (Scheme 10).[1,12,13] Imamoto's method also uses samarium metal and THF as the solvent but utilizes iodine crystals as the iodine source (Scheme 11).[1] While both synthesis methods have proven reliable in the literature, this study utilizes Kagan's method for the synthesis of SmI_2.

Scheme 10: Kagan's method for synthesis of SmI_2

Scheme 11: Imamoto's method for synthesis of SmI_2

Once SmI_2 is synthesized, the concentration of the reagent must be determined in order to successfully work with the reagent. Commonly used techniques to determine concentration include UV-vis spectroscopy and iodometric titration.[4,14-16] UV-vis spectroscopy can be used to

determine the concentration of a solution using the transmittance and absorption of UV light by a substance. Iodometric titration involves titrating an unknown concentration of SmI_2 with a solution of I^- in order to determine the concentration (Scheme 12). However, both of these analytical techniques are difficult to conduct while maintaining an air-free environment using a Schlenk line. One goal of our project was to assess the concentration of SmI_2 without compromising the quality of the reagent. We have found that concentration can be determined while maintaining air-free conditions using conversion data of commonly studied reduction reactions.



Scheme 12: Titration of unknown concentration of SmI_2 using a known concentration of I^- solution to determine the concentration of SmI_2

1.5 Commercial SmI_2

An alternative option to synthesizing SmI_2 in house is purchasing it from a commercial supplier. SmI_2 can be purchased as a nominal 0.1 M solution in THF from suppliers such as Sigma Aldrich. Though the reagent is advertised as a "0.1 M" solution, studies have identified the variability of the concentration once the bottle is obtained.[1] The maximum soluble concentration of SmI_2 is 0.1 M and is a deep, navy blue solution (Figure 1).[13] However, there is no distinguishable difference in color between a 0.1 M solution of SmI_2 and a 0.05 M solution.[1] In fact, Szostak et al. found that there was no visual difference in color between solutions that were less than 0.005 M and those that were 0.1 M.[1] Further, commercially available SmI_2 that was advertised as a 0.1 M solution ranged in concentrations from 0.02 M to 0.05 M (Table 1).[1] This uncertainty in commercial SmI_2 has lead to an increase in the desire to synthesize the

reagent in house and use it in subsequent reactions immediately. For these reasons, SmI_2 should be synthesized in house to avoid the variability of purchasing an unknown concentration of SmI_2.

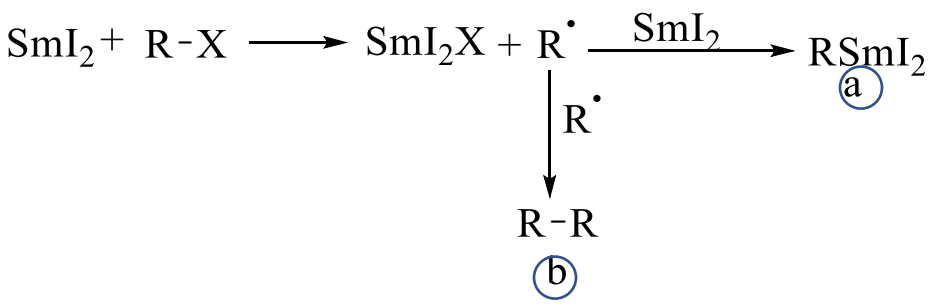
Table 1: Concentration of SmI_2 from commercial suppliers[1]

Entry	Supplier	Advertised Concentration (M)	[SmI_2]
1	ABCR	0.1	0.049 M
2	Aldrich		0.026-0.030 M
3	Alfa-Aesar		0.041 M
4	Strem		0.044 M

Note: Concentration was determined by iodometric titration within a glovebox

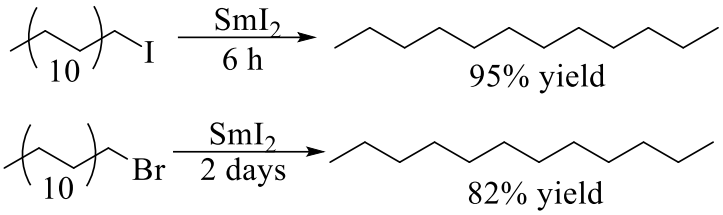
1.6 SmI_2 Reaction Mechanism

As a single electron reductant, SmI_2 reduces functional groups through a single electron transfer (SET) mechanism.[3,4,7,8] Upon addition of one equivalent of SmI_2, a radical anion is produced which can then undergo two mechanistic pathways (Scheme 13): (a) formation of an organosamarium with another equivalent of SmI_2 or (b) pinacol coupling with another free radical.[2,3,8] The former product can be selected for through the addition of a proton source, such as methanol, which protonates the radical, thereby preventing dimerization.[19]



Scheme 13: Single electron transfer mechanism possible product pathways

One of the many types of reactions SmI_2 can mediate is the reduction of various functional groups including ketones, alkyl halides, and alkenes.[2,3,8,12] These reductions are carried out under mild reaction conditions and result in high yields (Scheme 14).



Scheme 14: Reaction conditions and product yields for the reduction of organic halides by SmI_2[12]

1.7 SmI_2 and Additives

Additives and cosolvents can be added to the reaction mixture to increase the reaction rate and control product formation.[13] A commonly used additive is the Lewis base hexamethylphosphoramide (HMPA) which makes SmI_2 a more powerful reducing agent by coordinating to the samarium center thereby displacing the iodine and solvent to the outer sphere, which creates coordination sites for the substrate to interact with more easily.[4] Upon three additions of HMPA, the redox potential of SmI_2 is increased from -1.33 V to -1.95 V.[13,16] The reducing potential was further increased to -2.05 V upon the addition of four equivalents of HMPA.[5,13,16] Further equivalents of HMPA had no additional effect on the redox potential of SmI_2, as a maximum of four HMPA ligands can coordinate to each samarium atom due to steric bulk (Figure 6).[14]

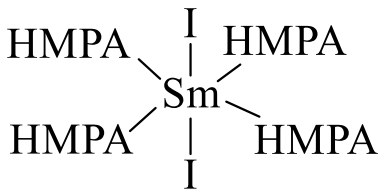


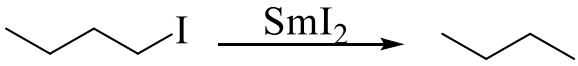
Figure 6: Four equivalents of HMPA coordinating to SmI_2[13]

Currently, HMPA is the additive of choice as it increases the reducing power of SmI_2, allows for control over product formation, increases the rate of reaction, and can be used to afford mild reaction conditions.[4,5,13,16] However, HMPA is a suspected human carcinogen so users may be hesitant to use the reagent. Other additives such as transition metal salts and proton sources may be used; however, they aren't as powerful or versatile as HMPA and require excessive amounts to achieve the same effect.[4] For these reasons, HMPA is the additive of choice. Since HMPA accelerates the rate of reaction for different functional groups, the addition of HMPA to the reaction mixture is imperative for coupling reactions as it allows for selective reduction of functional groups which drives product formation.

1.8 SmI_2 Mediated Barbier Reactions

As a single electron reductant, SmI_2 reduces carbonyls and alkyl halides quickly, under mild conditions, and at similar reaction rates (Schemes 15 and 16; Tables 2 and 3).[2,13] Therefore, when attempting a Barbier reaction, which forms new carbon-carbon bonds between an alkyl halide and carbonyl group, HMPA must be added in order to obtain the desired product.[2,13] The addition of HMPA increases the reducing potential of SmI_2 which reduces the alkyl halide faster compared to the ketone[2,4,14] (Tables 2 and 3). By reducing the alkyl halide over the ketone, an organosamarium complex is formed, which is a key intermediate in the coupling of alkyl halides and ketones.[2,5,13,14] The organosamarium then couples with the ketone through a nucleophilic attack mechanism (Scheme 17). Without the addition of HMPA, a mixture of side products

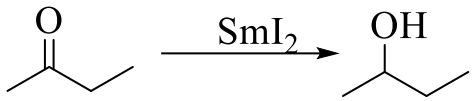
would form as SmI_2 reduces alkyl halides and ketones at a similar rate which can derail the coupling reaction (Scheme 18).



Scheme 15: Reduction of 1-Iodobutane by SmI_2 with and without HMPA

Table 2: Reaction scheme and reaction rate for the reduction of 1-iodobutane with and without HMPA[14]

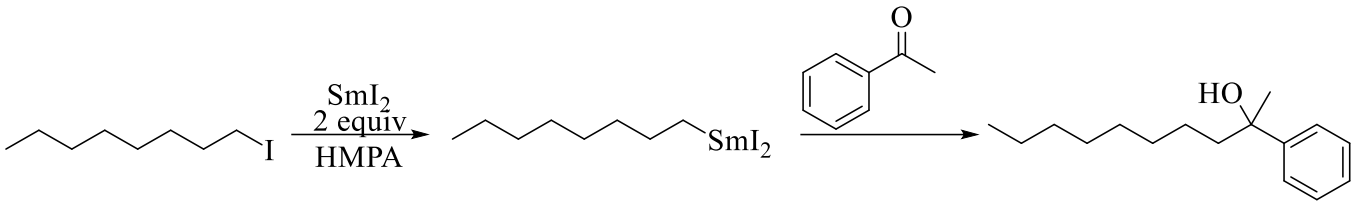
System	Rate ($M^{-1}s^{-1}$)
SmI_2-1-iodobutane	$(8\pm2) \times 10^{-4}$
$[Sm(THF)_2(HMPA)_4]I_2$-1-iodobutane	1.0 ± 0.1



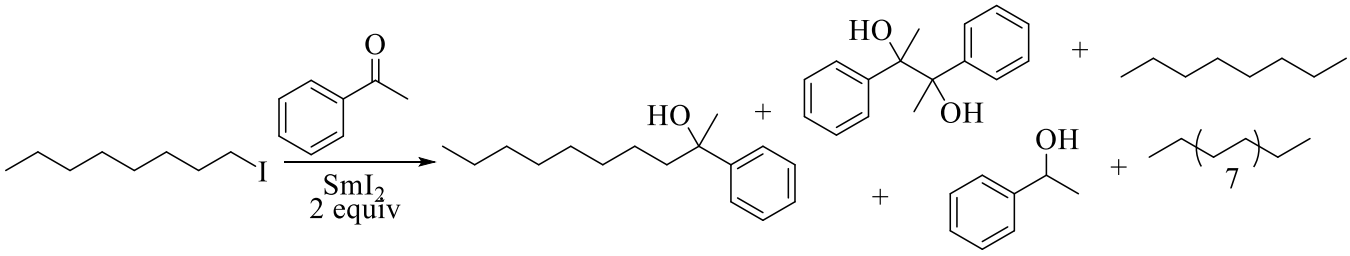
Scheme 16: Reduction of 2-Butanone by SmI_2 with and without HMPA

Table 3: Reaction scheme and reaction rate for the reduction of 2-butanone with and without HMPA[14]

System	Rate ($M^{-1}s^{-1}$)
SmI_2-2-butanone	$(7\pm3) \times 10^{-4}$
$[Sm(THF)_2(HMPA)_4]I_2$-2-butanone	$(8 \pm 1) \times 10^{-3}$



Scheme 17: Barbier coupling reaction between 1-iodooctane and acetophenone



Scheme 18: Barbier reaction resulting in mixture of undesired side products due to the absence of HMPA

Herein we provide evidence for the facile synthesis of SmI_2 using Kagan's Method on the Schlenk line. Questions regarding the need to distill substrates, the quality of commercial SmI_2, and the role HMPA plays were investigated in this study. Further, SmI_2 was synthesized at a consistent concentration. This confirms that our protocol is successful and may be used to synthesize SmI_2 (0.1 M) and be used to afford high conversions and yields for the reductions of ketones.

Chapter 2: Methods

2.1 Acetophenone Distillation

The distillation apparatus was set up using oven-dried glassware. To an oven-dried round-bottom flask, acetophenone was added (100 mL, 0.86 mol). The entire distillation set up was vacuumed and purged with argon three times. Acetophenone was distilled, collected over molecular sieves, and stored under argon on the Schlenk line.

2.2 HMPA Distillation

The distillation apparatus was set up using oven-dried glassware. To an oven-dried round-bottom flask, HMPA (50 mL, 0.29 mol) and calcium oxide (4.5 g, 0.08 mol) were added. The entire distillation apparatus was vacuumed and purged with argon three times and allowed to stir for 1 h. HMPA was refluxed under vacuum for 1h then distilled under vacuum, collected over molecular sieves, and stored under argon on the Schlenk line

2.3 THF Distillation

The distillation apparatus was set up using oven-dried glassware. To an oven-dried three neck round-bottom flask, benzophenone (10 g, 0.055 mol) was added. The flask was vacuumed and purged with argon three times. To the flask, distilled THF (250 mL) and sodium in paraffin (6 g, 0.26 mol) were added. The solution was refluxed for 1h and the solution turned a deep blue color indicating that the benzophenone radical reaction occurred. The solution was distilled until a small amount of solution was left (~5 mL). Additional sodium and THF were added based on the color of solution: if the solution was yellow or orange the solution was removed from heat and additional sodium was added; if the solution was green additional benzophenone and sodium were added. THF was collected over molecular sieves and stored under argon on the Schlenk line. After ten days, THF needed to be redistilled.

2.4 1,2-Diiodoethane Purification

To a separatory flask, 1,2-diiodoethane (10 g, 0.035 mol) and diethyl ether (200 mL) were added. The ether solution was washed with saturated sodium thiosulfate (50 mL) five times, and the aqueous layer was drained. The ether solution was washed with water (50 mL), and the aqueous layer was drained. The ether solution was dried with magnesium sulfate and then filtered using a filter funnel into a small round-bottom flask. The solvent was removed by rotary

evaporation until white crystals formed, and the crystals were stored at 4℃ in an aluminum foil covered flask.

2.5 SmI_2 Synthesis-Kagan's Method

To an oven-dried round-bottom flask with neck attachment, samarium metal (0.30 g, 0.002 mol, 2 eq Sm) and purified 1,2-diiodoethane (0.28 g, 0.001 mol, 1 eq 1,2-diiodoethane) were added. The flask was vacuumed and purged three times with argon and was kept under a steady flow of argon. Using an oven-dried syringe, distilled THF (10 mL) was added to the flask. The solution stirred for 6 min and then sonicated for 10 min and a dark blue solution was formed. The solution was kept under argon until it was used within 1h.

2.6 Acetophenone Reduction (Assuming 0.1 M, 1:1 SmI_2: Substrate)

Using a needle attachment, an oven-dried pear-shaped flask was vacuumed and purged with argon three times. To the glass, distilled acetophenone (0.12 mL, 0.001 mol), dodecane (0.23 mL, 0.001 mol), methanol (0.1 mL, 0.002 mol) and distilled THF (2 mL) were added using syringes. To the synthesized SmI_2, (10 mL, assuming 0.1 M) HMPA (1.74 mL, 0.01 mol) was added. Using a syringe, the contents of the pear-shaped flask was added to the SmI_2 flask, and the solution stirred overnight. The solution was transferred to a separatory funnel and extracted with diethyl ether (5 mL) and washed with water (5 mL). The aqueous layer was drained, and the wash was repeated three times. The ether solution was washed once with a saturated sodium chloride solution, and the aqueous layer was removed. The solution was transferred to an Erlenmeyer flask and dried with magnesium sulfate. The magnesium sulfate was removed by vacuum filtration and the product was collected in a round-bottom flask. The solvent was removed by rotary evaporation to yield an oil. The product was analyzed by gas chromatography

mass spectrometry (GCMS). **Note**: Methanol was omitted from the protocol halfway through the study.

2.7 Acetophenone Reduction (Assuming 0.02 M, 1:1 SmI_2: Substrate)

Using a needle attachment, an oven-dried pear-shaped flask was vacuumed and purged with argon three times. To the glass, distilled acetophenone (0.023 mL, 0.0002 mol), dodecane (0.045 mL, 0.0002 mol), methanol (0.016 mL, 0.0004 mol) and distilled THF (2 mL) were added using syringes. To the synthesized SmI_2, (10 mL, assuming 0.02 M) HMPA (0.36 mL, 0.002 mol) was added. Using a syringe, the contents of the pear-shaped flask was added to the SmI_2 flask, and the solution stirred overnight. The solution was transferred to a separatory funnel and extracted with diethyl ether (5 mL) and washed with water (5 mL). The aqueous layer was drained, and the wash was repeated three times. The ether solution was washed once with a saturated sodium chloride solution, and the aqueous layer was removed. The solution was transferred to an Erlenmeyer flask and dried with magnesium sulfate. The magnesium sulfate was removed by vacuum filtration and the product was collected in a round-bottom flask. The solvent was removed by rotary evaporation to yield an oil. The product was analyzed by gas chromatography mass spectrometry (GCMS). **Note**: Methanol was omitted from the protocol halfway through the study.

2.8 RF Calculation

A retention factor (Rf) was calculated for each substrate and the reduced product using the molecular weights of the compound (Table 4). To a 10 mL volumetric flask, 1-phenylethanol (0.12 mL, 0.001 mol) and dodecane (0.23 mL, 0.001 mol) was added, then the flask was filled with ether. The Rf was calculated by integrating the area under each peak (Figure 7) and using the formula below (Figure 8).

Table 4: Rf values used for conversion calculations

Compound	Rf
Acetophenone	1.18
1-phenylethanol	1.66

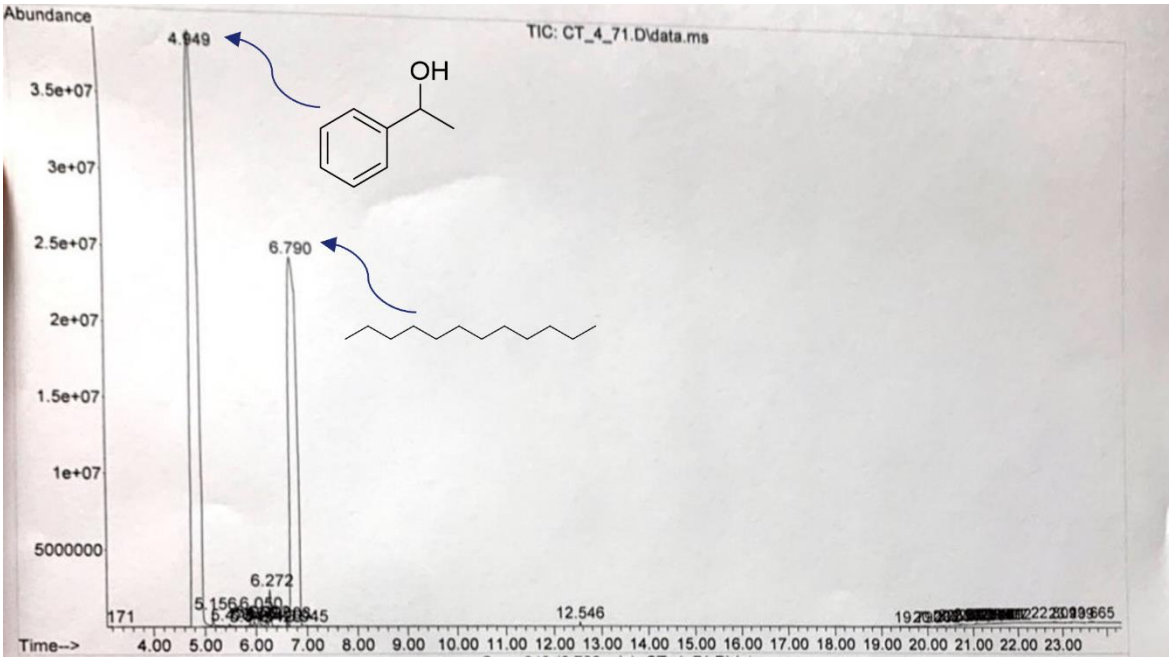


Figure 7: GC chromatogram for the Rf of the reduced product 1-phenylethanol

$$R_f = \frac{C_{is}A_x}{A_{is}C_x}$$

Figure 8: Formula for determining the Rf for each substrate using the concentration of the internal standard dodecane (C_{is}), the concentration of the starting material (C_x), and the areas under the curve (A_x and A_{is}).

2.9 Percent Conversion Calculations

Percent conversion was determined by gas chromatography mass spectrometry (GCMS) with dodecane as an internal standard. The concentration of starting material (C_x) was determined by integrating the area under each peak (Figure 9) and using the formula below (Figure 10).

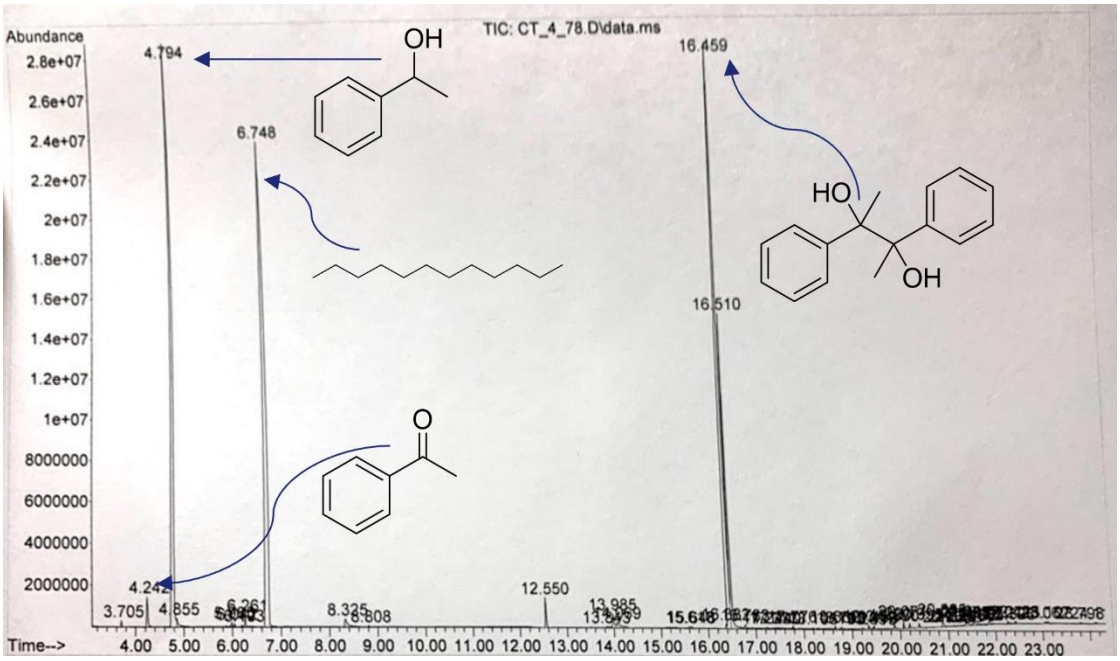


Figure 9: GC chromatogram for the reduction of acetophenone by SmI_2. From left to right the labeled peaks represent acetophenone (4.2 min), 1-phenylethanol (4.7 min), dodecane (6.7 min), and 2,3-diphenyl-2,3-butanediol (16.4 min).

$$C_x = \frac{C_{is}A_x}{A_{is}R_f}$$

Figure 10: Formula for determining percent conversion of starting material. C_{is} represents the concentration of the internal standard (dodecane), Rf is the calculated retention factor, A_{is} represents the area of the internal standard (dodecane), and A_x represents the area of the starting material.

2.10 Iodometric Titration (in glovebox)

SmI_2 was synthesized using Kagan's method (Section 2.5) on the Schlenk line and taken into the glovebox to be titrated. To make a solution of I^-, to a 10 mL volumetric flask, iodine crystals (0.250 g, 0.001 mol) were added then the flask was filled with THF. To a small oven dried vial with a stir bar, SmI_2 (500 µL, 0.001 mol) was added. The solution was diluted with

THF (~2 mL). Using an oven dried syringe, the SmI_2 solution was titrated dropwise with the I^- solution while stirring. The starting and final volume of I^- solution was recorded to calculate the concentration of SmI_2.

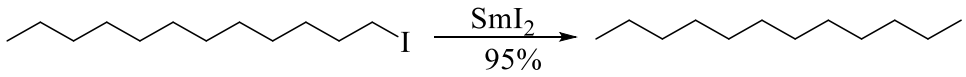
Chapter 3: Results and Discussion

The goal of this laboratory was to develop and optimize a protocol for the synthesis of the versatile, yet air sensitive, reagent samarium diiodide (SmI_2). To be successful in our goal, we had various questions that we sought to answer. The most important aspect of the experiment was determining the concentration of SmI_2 when using the Schlenk line. In addition, we investigated various steps that are commonly employed in the literature to determine whether they were beneficial or unnecessary. Some questions we sought to answer were: What is the concentration of SmI_2? Is methanol beneficial in controlling product formation? Is it necessary to distill all reagents and substrates? Is HMPA necessary for all reactions? How many equivalents of samarium are necessary in the synthesis of SmI_2? Is commercially purchased SmI_2 a reliable alternative to synthesizing the reagent? In answering these questions, we developed a protocol for the facile synthesis of SmI_2 using a Schlenk line.

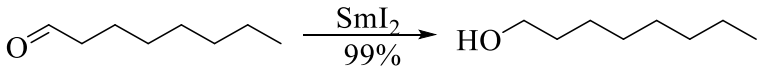
3.1 Concentration of SmI_2

One of the drawbacks of synthesizing SmI_2 on the Schlenk line is the inability to analyze the concentration using standard techniques such as iodometric titration and UV-vis spectroscopy. Iodometric titration is not possible on a Schlenk line as the solution would have to be exposed to air on the bench top in order to titrate it. In the past, our laboratory attempted to use UV-vis to determine the concentration of SmI_2, but the blue solution was too dark to obtain an absorbance value and an appropriate dilution factor could not be determined.[19] Therefore, the concentration of SmI_2 must be determined in an alternative way. According to multiple studies in

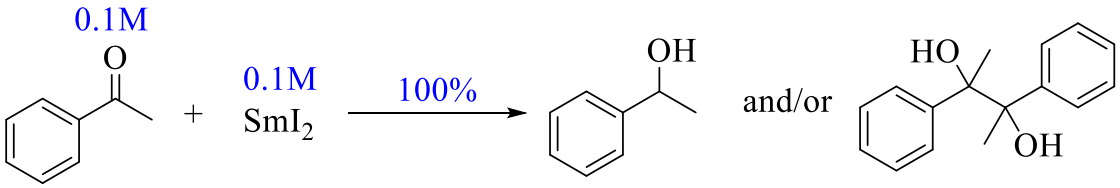
the literature, as a 0.1 M solution, SmI_2 reduces carbonyls and alkyl halides with 90-100% yield (Schemes 19 and 20).[2,13,17] Knowing this, if we are synthesizing a 0.1 M solution, we reasonably assume to also achieve nearly quantitative conversions of our carbonyl source, acetophenone. Further, if we don't see full conversion, we then propose that the concentration of SmI_2 is not actually 0.1 M but rather a lower concentration as the literature conversion values are a reliable comparison. We can verify the concentration of SmI_2 using the conversion of starting material to product based on the fact that a 0.1 M solution of SmI_2 will reduce 100% of a 0.1 M of substrate (Scheme 21).



Scheme 19: Reduction of 1-Iodododecane by SmI_2



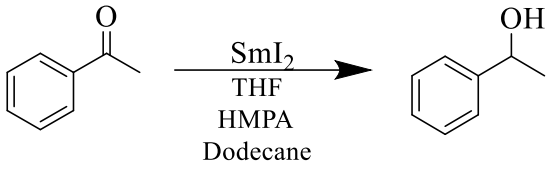
Scheme 20: Reduction of Octanal by SmI_2



Scheme 21: 0.1M SmI_2 Conversion of Starting Material to Product

Following our protocol for the synthesis of SmI_2 (0.1 M), we consistently obtained low conversions of the starting ketone, acetophenone, to the reduced product 1-phenylethanol and/or 2,3-diphenyl-2,3-butanediol (Scheme 22) (Table 5). Following work done checking air leaks in our system, we hypothesized that the concentration of SmI_2 synthesized was not 0.1 M. Based on

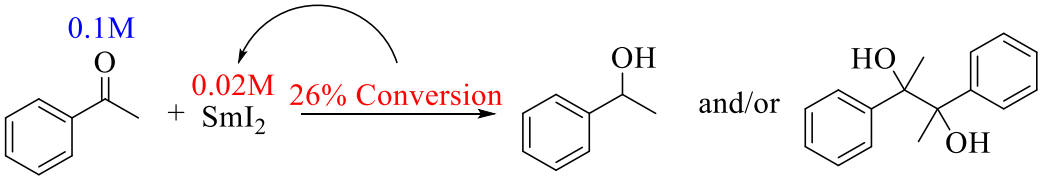
our conversion data and the underlying assumption that a 0.1 M solution will convert 100% of starting material to product, we determined that the concentration of SmI_2 that was synthesized using our protocol was 0.02 M (Scheme 23). With the concentration determined, we were able to adjust the stoichiometric ratios for the reduction of acetophenone in order to obtain consistently high conversions (Table 6).



Scheme 22: Reduction of acetophenone by SmI_2

Table 5: Percent Conversion values for the reduction of acetophenone using SmI_2 synthesized (Assuming 0.1 M SmI_2, HMPA used)

Entry	Percent Conversion
1	33.93%
2	22%
3	17%
4	20.9%
5	32.6%
6	30%
Average	**26.07%**



Scheme 23: Calculation to determine the concentration of SmI_2 using conversion values

Table 6: Percent conversion values for the reduction of acetophenone using SmI_2 synthesized in house (Assuming 0.02 M SmI_2, HMPA used)

Entry	Percent Conversion
1	97.8%
2	97.2%
3	97%
Average	**97.3%**

3.2 Is commercial SmI_2 reliable?

Since the synthesis of SmI_2 requires specific conditions such as dry glassware, degassed and dried solvents, and an inert environment, some laboratories might seek alternative options to synthesizing the reagent. An alternative to synthesizing SmI_2 in house is purchasing the reagent from a commercial supplier. SmI_2 can be purchased as a nominal 0.1 M solution in THF from various suppliers such as Sigma Aldrich and Alfa Aesar. However, Procter et al. found that SmI_2 that was advertised as a 0.1 M solution was not the promised concentration.[1] In fact, they found that the concentration ranged anywhere between 0.02 M and 0.05 M (Table 1).[1] Because of this, laboratories should take caution when ordering SmI_2 and using it in reactions. Like Procter, our lab wanted to see if commercial SmI_2 is reliable. Using our protocol and commercially purchased SmI_2, we reduced acetophenone. Commercial SmI_2 resulted in poor conversions of starting material to product, most likely due to the varying concentration of the reagent (Table 7). Further, some trials were a complete failure as the SmI_2 turned yellow as soon as it was drawn into a needle, which was most likely due to air exposure which resulted in formation of Sm(III) (Figure 11).

Table 7: Conversion results for the reduction of acetophenone using commercial SmI_2 (Assuming 0.1 M as labeled on bottles, HMPA used)

Entry	Conversion
1	37%
2	36%
Average	**36.5%**

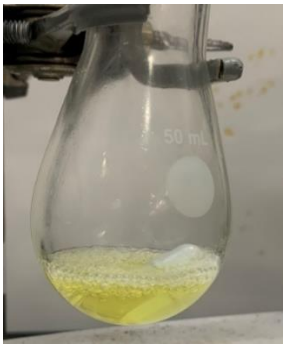


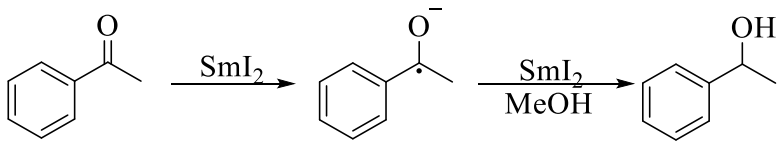
Figure 11: Commercially purchased SmI_2 that has been oxidized as soon as it was added to the flask

Another drawback of commercial SmI_2 is that the opened SmI_2 bottle cannot be adequately stored on the Schlenk line under argon overnight. Doing so resulted in a failed trial as the SmI_2 was oxidized before it could be used even though it was in a sure seal bottle (Figure 11). In sum, commercial SmI_2 is unreliable and should not be purchased for multiple reasons. Its varying concentration makes it difficult to obtain consistent results and the inability to store the reagent means it must be used up as soon as it is opened. For these reasons, SmI_2 should always be synthesized in house.

3.3 Is Methanol Beneficial?

After obtaining consistently high conversions of starting material to product using our protocol, we wanted to determine if all the steps that were employed were necessary. Oftentimes, a proton source such as water or an alcohol is used to control product formation by quickly protonating the free radical that is formed when one equivalent of SmI_2 reacts with the substrate,

favoring the reduced radical over the dimer product (seen in Scheme 21) (Scheme 24).[17] For this study, methanol was used as the proton source. Since the presence of water is a concern in each reagent we add to the reaction mixture, we wanted to investigate whether omitting methanol would have a drastic effect on our results. Upon removing methanol, our conversion results improved and product distribution did not change drastically, with both the reduced product and dimer product still being produced (Table 8). Therefore, we omitted the addition of a proton source as it may be another source of water contamination and its presence did not drastically favor the reduced product over the dimer.



Scheme 24: Role of methanol as a proton donor in the reduction of acetophenone

Table 8: Percent conversion of acetophenone with and without the proton source methanol using SmI_2 synthesized in house (Assuming 0.1 M SmI_2, HMPA used)

Methanol	Entry	Percent Conversion
Yes	1	33.93%
	2	32.6%
	3	40%
	Average	**35.51%**
No	4	43%
	5	85%
	Average	**64%**

3.4 Is it necessary to distill substrates?

The next question we wanted to address was whether distilling the substrates was necessary. As previously stated, the synthesis of SmI_2 is a sensitive reaction as Sm(II) is converted to Sm(III) and therefore inactivated, by the presence of water and air. To avoid

inactivation of the compound, the synthesis is conducted under an inert environment and all reagents and substrates are distilled to ensure there is no water present. We wanted to investigate whether distilling our substrates was an unnecessary precaution we were taking. Using SmI_2 synthesized in house, we reduced distilled, anhydrous acetophenone and non-distilled, anhydrous acetophenone. We found that there was no significant difference in conversion values between distilled acetophenone and non-distilled acetophenone (Table 9). Therefore, we deemed distilling substrates unnecessary and omitted it from our protocol.

Table 9: Comparison of percent conversion for distilled and non-distilled acetophenone using SmI_2 (Assuming 0.02 M SmI_2, HMPA used)

Distilled Acetophenone	Entry	Percent Conversion
Yes	1	97.8%
	2	97.2%
	3	97%
	Average	**97.3%**
No	4	98.5%
	5	98.82%
	6	97.2%
	Average	**98.17%**

3.5 Is HMPA necessary?

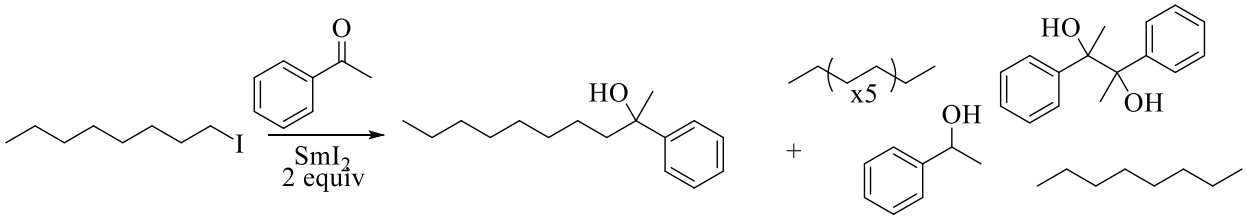
Hexamethylphosphoramide (HMPA), a lewis base, is a commonly used additive in SmI_2 reactions as it increases the reducing potential of SmI_2, accelerates reactions, and aids in control over product formation.[4,5,13,16] Although HMPA is beneficial, it is a suspected carcinogen so precautions must be taken when using the reagent. Further, the addition of HMPA is another opportunity for water to be introduced to the reaction mixture, for this reason, we omitted adding it in reductions mediated by SmI_2 as it is unnecessary in simple reductions . In doing so, we

found that there was no significant difference in product formation or conversion values (Table 10).

Table 10: Comparison of percent conversion of acetophenone with and without the addition of HMPA using SmI_2 synthesized (Assuming 0.02 M SmI_2)

Added HMPA	Entry	Percent Conversion
Yes	1	97%
	2	98.5%
	3	98.82%
	Average	**98.11%**
No	4	96.6%
	5	99.15%
	6	99%
	Average	**98.25%**

Based on our results, we omitted adding HMPA to the reaction mixture for common reductions such as that of a ketone or alkyl halide for all future reactions. However, HMPA must still be added when running Barbier reactions because undesired side products can form as a result of SmI_2 reducing both the ketone and the alkyl halide (Scheme 25). The addition of HMPA is necessary as it increases the reduction rate of alkyl halides but not that of ketones. So, the alkyl halide is selectively reduced and the ketone is left alone. In sum, HMPA is not necessary in common reductions mediated by SmI_2, but it is necessary for coupling reactions such as Barbier reactions to control product formation.



Scheme 25: Potential products for the Barbier reaction between acetophenone and 1-iodooctane

3.6 Verifying the Concentration Via Iodometric Titration

During our study we were able to obtain a glovebox in the laboratory. While our synthesis protocol remained unchanged, we were able to verify the concentration of SmI_2, which was previously determined using conversion values, via iodometric titration. After synthesizing SmI_2 using our protocol on the Schlenk line, the solution was taken into the glovebox to be titrated using a solution of I^- to yield SmI_3 (Scheme12). The titration was carried out three times on the same batch of SmI_2 and the concentration was determined to be 0.091 M (Table 11).

Table 11: Determining the concentration of SmI_2 via Iodometric titration in a glovebox (Assuming 0.1 M SmI_2)

Entry	Concentration (M)
1	0.106
2	0.085
3	0.087
Average	**0.091**

These results were unexpected. Previously, when we synthesized SmI_2 and ran the reduction using our 0.1 M protocol, we consistently obtained low conversion rates (Table 5); however, after titrating our solution we found that we were actually synthesizing 0.1 M SmI_2 from the start . This led us to believe that HMPA was causing issues in the reduction of acetophenone leading to low conversion values. We hypothesized that even after distilling HMPA, there was still water present in the reagent which was corrupting the reaction. Therefore, we ran a 0.1 M reduction of acetophenone using SmI_2 synthesized in house, without HMPA and obtained nearly quantitative results (Table 12).

Table 12: Reduction of acetophenone without HMPA using our 0.1 M protocol (Assuming 0.1 M SmI_2)

Entry	Percent Conversion of Acetophenone
1	98.08%
2	97.7%
3	98.4%

All in all, the iodometric titration verified two things for us: that we were synthesizing 0.1 M SmI_2 on the Schlenk line and the concentration can be determined using conversion values.

3.7 Is it Necessary to Distill THF

Another experimental aspect we investigated was whether distilling THF was necessary. Procter et al. found that the presence of water in THF had no significant effect on the synthesis of SmI_2.[1] Based on this statement, a small amount of water in the solvent should not have an effect on the synthesis of SmI_2; unfortunately, this was not the case in our hands. On multiple occasions, there were issues with the distillation of THF. When these batches of distilled THF was used SmI_2 could not be synthesized, this was indicated by the lack of blue color. To avoid distilling the solvent, we purchased THF to determine whether commercial anhydrous THF was a reliable option. Again, SmI_2 could not be synthesized using commercial THF as the solution never turned blue even after stirring for two days (Table 13). Further, previous studies in our laboratory showed that distilled THF has a shelf life of 10 days. After 10 days, the solvent was deemed unreliable due to the presence of water and efforts to synthesize SmI_2 were unsuccessful (Table 13).[19] Therefore, we concluded that degassed, anhydrous THF is a necessary component of the synthesis of SmI_2.

Table 13: Testing whether commercial or "expired" THF is reliable in the reduction of Acetophenone (Assuming 0.1 M SmI_2, No HMPA)

THF Notes	Percent Conversion
New THF (freshly distilled)	98%
Expired THF (13 days old)	44.2%
Commercially purchased anhydrous THF	Fail

Note: Trial was labeled a "Fail" as the solution never turned blue which is characteristic of SmI_2 being formed

3.8 How many equivalents of Samarium are necessary?

The last question we sought to answer was how many equivalents of samarium metal are necessary for the synthesis of SmI_2? Typically, when synthesizing SmI_2 an excess of samarium metal is used to ensure that the solution will remain stable in the Sm^{+2} state so that it may be stored for a few days under argon gas.[12] Studies such as that of Procter et al. and Kagan et al. employ a ratio of two equivalents of samarium metal to one equivalent of 1,2-diiodoethane when synthesizing SmI_2.[2,12] The work in this study also employs a 2:1 ratio for samarium to 1,2-diiodoethane. While this ratio ensures that there is plenty of excess samarium metal in solution which is beneficial for storing SmI_2, this ratio also wastes a substantial amount of metal. To combat this unnecessary waste, SmI_2 can be synthesized using lower ratios of samarium metal to 1,2-diiodoethane including a 1.5:1 ratio and 1.2:1 ratio. We investigated whether SmI_2 could be successfully synthesized and afford high, consistent conversions using lower ratios of samarium metal to 1,2-diiodoethane. To investigate this, we synthesized SmI_2 using different equivalents of samarium metal and ran our 0.1 M reduction of acetophenone. We found that SmI_2 can be synthesized and used in reductions using 1.5 equivalents of samarium metal but not

1.2 equivalents (Table 14). More trials need to be conducted to confidently rule out 1.2 equivalents of samarium as an option.

Table 14: The effect different ratios of samarium metal to 1,2-diiodoethane has on the conversion of acetophenone (Assuming 0.1 M SmI_2, No HMPA)

Samarium:1.2-diiodoethane	Entry	Percent Conversion of Acetophenone
2.0:1	1	98.08%
	2	97.7%
1.5:1	3	98.4%
	4	73.5%
1.2:1	5	Fail

Note: Entry 5 was labeled as a failed because conversion was not able to be calculated due to the inability to integrate the peak. Percent yield was calculated for the reduced product and was 0.000025% yield

Chapter 4: Conclusion

4.1 Goal of Study

The goal of this study was to synthesize SmI_2, a versatile, chemoselective reagent that is commonly used in complex total synthesis reactions, using a Schlenk line. As part of the process, we investigated various variables that are commonly seen in the literature to determine whether they were helpful, hurtful, or unnecessary to the reaction.

4.2 Concentration of SmI_2

First, we determined the concentration of SmI_2 using conversion values of well-studied simple reductions, such as that of ketones. We found that in our hands, SmI_2 could be synthesized on the Schlenk line as a 0.1 M solution. By determining the concentration of SmI_2, we were able to adjust our stoichiometric ratios to afford high conversions of ketones (Table 12). After consistently synthesizing SmI_2, we investigated other variables in the reduction of acetophenone.

4.3 Commercial SmI_2

In addition, we investigated whether commercial SmI_2 was a reliable alternative to synthesizing the reagent. Commercial SmI_2 afforded low conversions, was quickly oxidized when transferring the reagent to a flask and could not be adequately stored overnight on an argon line (Table 1; Figure 11). Therefore, we deemed commercial SmI_2 unreliable and only synthesized the reagent in house. However, after discovering that HMPA was corrupting SmI_2, most likely due to the presence of water in HMPA, commercial SmI_2 needs to be further investigated to determine whether higher conversions can be obtained in the absence of HMPA.

4.4 Proton Source

In the literature, proton sources such as methanol are often employed to gain control over product formation and prevent the formation of dimer products; however, we found no major difference in product formation and our conversion values improved when methanol was removed (Table 8). Based on these observations, we deemed the addition of a proton source an unnecessary step in common reduction reactions.

4.5 Distilling Substrates

Next, we investigated whether it was necessary to distill our substrates and found no significant difference in conversion values when the substrate was not distilled (Table 9). Therefore, we omitted distilling substrates from our protocol. Nonetheless, the solvent, THF, must always be distilled as large aliquots of water in the solvent can oxidize Sm(II) to Sm(III) rendering the reagent inactive. Further, THF must be used within 10 days of distilling it as water content becomes an issue and conversion values worsen.

4.6 Role of HMPA

Another variable we investigated was the addition of HMPA to the reaction mixture. HMPA is a Lewis base additive that makes SmI_2 a more powerful reducing agent. HMPA is an integral part of Barbier reactions as it selectively reduces the alkyl halide allowing for the generation of an organosamarium intermediate which can then undergo nucleophilic addition to form the coupled product (Scheme 17). Without the addition of HMPA to a Barbier reaction, a mixture of side products would form derailing product formation (Scheme 18). While HMPA is necessary for Barbier reactions, it has no drastic effects on common reductions so it may be excluded from the reaction mixture (Table 10). Further, after removing HMPA from the reaction mixture high conversions were obtained and through iodometric titration we realized the maximum soluble concentration of SmI_2 could be synthesized in our hands. Based on these results, we hypothesize that we were synthesizing 0.1 M SmI_2 using our protocol but were obtaining low conversions due to the addition of HMPA which might have still been "wet". Therefore, more studies regarding the dryness and shelf life of HMPA need to be done to determine why it was corrupting our SmI_2.

4.7 Equivalents of Samarium

Finally, we investigated the equivalents of samarium metal to 1,2-diiodoethane in the synthesis of SmI_2. When synthesizing SmI_2 an excess of samarium metal is used to stabilize the Sm^{+2} state. A ratio of 2:1 samarium to 1,2-diiodoethane is commonly used in the literature but this excess amount of samarium is wasteful. While we had no success in 1.2:1 equivalents, we had success in 1.5:1 equivalents (Table 14).

4.8 Summary

In sum, SmI_2 can be successfully and consistently synthesized on the Schlenk line using air-free techniques, oven dried glassware, and degassed and dried solvents. High conversions of

the reduction of acetophenone can be obtained by determining the concentration using conversion values and optimizing the stoichiometric ratios for the reaction. While synthesizing the reagent may be seen as difficult and time consuming to some, our study shows that extra precautions, such as distilling all substrates and adding a proton source, need not be taken to afford great results.

4.9 Future Directions

In order to improve upon this study, more substrates should be tested to compare conversion values of other ketones and alkyl halides and a Barbier coupling reaction should be run using SmI_2 synthesized in house to determine if high yields can be obtained. Further studies regarding the shelf life and dryness of HMPA need to be conducted to prevent water contamination as the reagent will be necessary for Barbier reactions.

Literature Cited

1. Szostak, M.; Spain, M.; Procter D.J. *J. Org. Chem.* **2012,** *77*, 3049-3059.
2. Procter, D. J.; Flowers, R. A.; Skrydstrup, T. *RSC Publc*.: Cambridge, **2010**.
3. Molander, G. A.; Harris, C. R. *Organic Reactions*. **1994**. *46*, 211-256.
4. Flowers, R. A. *Synlett*. **2008,** *10*, 1427-1439.
5. Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem. Int. Ed.* **2009.** *48*, 7140-7165.
6. Choquette, K. A. **2013.** 3-121.
7. Volz, E. O.; O'Neil, G. W. *J. Org. Chem.* **2011**, *76*, 8428-8432.
8. Szostak, M.; Fazakerley, N.J.; Parmar, D.; Procter, D. *J. Chem. Rev.* **2014**, *114*, 5959-6039.
9. Austin, K. A.B.; Banwell, M. G.; William, A. C. *J. Am. Chem. Soc*. **2008**. *20*, 4465-4468.
10. Farney, E. P.; Feng, S. S.; Schafers, F.; Resiman, S. E. *J. Am. Chem. Soc.* **2018**. *140*, 1267-1270.
11. Beemelmanns, C.; Reissig, H.U. *Angew. Chem. Int. Ed.* **2010**. *49*, 8021-8025.
12. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc*. **1980**. *8*, 2693-2698
13. Kagan, H. B.; Namy, J.L. *J. Organomet. Chem.* **1999**, *2*, 155-F5.
14. Prasad, E.; Flowers, R.A. *J. Am. Chem. Soc*., **2002**. *124*, 6895-6899.
15. Chopade, P. R.; Davis, T. A.; Prasad, E.; Flowers, R. A. *Org. Lett.* **2004**, *6*, 2685-2688.
16. Shabangi, M.; Flowers, R. *Tetrahedron Letters,* **1997,** *7*,1137-1140.
17. Chopade, P.R.; Prasad, E.; Flowers, R.A.II. *J. Am. Chem. Soc.* **2004**, *126*, 44–45.
18. Chopade, P.R.; Prasad, E.; Flowers, R.A. *J. Am. Chem. Soc.* **2004**. *126*, 44-45.
19. Rojas, Gisselle. Choquette Lab Research. Unpublished data, 2019.
20. Yilmaz, Beyza. Choquette Lab Research. Unpublished data, 2021.