Mechanistic Study and Development of Catalytic Reactions of Sm(II)

Sandeepan Maity and Robert A. Flowers II*

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania-18015, USA.

ABSTRACT: Samarium diiodide (SmI$_2$) is one of the most widely used single electron reductants available to organic chemists because it is effective in reducing and coupling a wide range of functional groups. Despite the broad utility and application of SmI$_2$ in synthesis, the reagent is used in stoichiometric amounts and has a high molecular weight, resulting in a large amount of material being used for reactions requiring one or more equivalents of electrons. Although few approaches to develop catalytic reactions have been designed, they are not widely used or require specialized conditions. As a consequence, general solutions to develop catalytic reactions of Sm(II) remain elusive. Herein, we report mechanistic studies on catalytic reactions of Sm(II) employing a terminal magnesium reductant and trimethyl silyl chloride in concert with a non-coordinating proton donor source. Reactions using this approach permitted reductions with as little as 1 mol% Sm. Mechanistic studies provide strong evidence that during the reaction, SmI$_2$ transforms into SmCl$_3$ therefore broadening the scope of accessible reactions. Furthermore, this mechanistic approach enabled catalysis employing HMPA as a ligand, facilitating the development of catalytic Sm(II) 5-exo-trig ketyl olefin cyclization reactions. The initial work described herein will enable further development of both useful and user-friendly catalytic reactions; a long-standing, but elusive goal in Sm(II) chemistry.

Samarium diiodide (SmI$_2$) and related Sm(II)-based reductants are important reagents in the arsenal of synthetic chemists.$^{1-9}$ First introduced by Kagan and coworkers, SmI$_2$ is a versatile single electron reductant capable of reducing a range of functional groups under mild reaction conditions.$^{10}$ The majority of SmI$_2$-based reactions are carried out in THF since the reagent is stable in this medium and is soluble up to 0.1 M. Initially considered a “specialized” reagent, a range of studies have shown that SmI$_2$ is capable of efficiently reducing a wide range of functional groups.$^{11,12}$ The rate by which SmI$_2$ reduces different functional groups varies significantly.$^{11,12}$ As a result, SmI$_2$ can be used to selectively reduce a particular functional group in a multifunctional substrate for follow-up bond-forming reactions and is exceptionally effective in reductive couplings.$^{15-22}$ and cascade reactions.$^{25-34}$ Most importantly, its use allows for alternative and selective methods for the synthesis of multifunctional targets.$^{46}$ While numerous reactions have been developed for SmI$_2$, its scope in synthesis certainly has not been exhausted and new applications for this reagent are steadily being discovered.$^{36,37}$ As a consequence, SmI$_2$ has attained a prominence reserved only for select reagents.$^{3,6,58}$

In spite of the importance and continued use of stoichiometric Sm(II)-based reactions, economic and environmental concerns remain an issue with this chemistry, demonstrating the need for development of practical catalytic approaches as important tools for synthetic chemists. In nearly all reactions of SmI$_2$, a stoichiometric amount of the reductant is required. The high molar mass of SmI$_2$ (MW 404) poses practical problems for scale up because a great deal of metal and solvent are required to carry out these reductions. A number of approaches that employ inexpensive terminal reductants to regenerate Sm(II) have been developed.$^{39-45}$ The early work of Corey on the development of catalytic reactions of SmI$_2$ showed that Zn-Hg in combination with TMSOTf and LiI gave excellent yields in the coupling of ketones with acrylates.$^{39}$ Endo described the use of SmI$_2$-Mg-trimethylsilyl chloride in the pinacol coupling of aldehydes and ketones, but in this system, some reactions took as long as 48 hrs. whereas stoichiometric reactions are complete in minutes.$^{46}$ Greeves and coworkers carried out a more extensive study employing glymes along with Mg as an additional additive in pinacol couplings.$^{47}$ Although excellent diastereoselectivities were obtained in some of these reactions, reaction time and conditions make scale-up problematic. At the time of the Greeves report, Orsini was also successful in using SmI$_2$-Mg in Reformatsky-type reactions.$^{42}$ In studies using alternative terminal reductants, Namy and coworkers have shown that inexpensive mischmetal (50% Ce, 33% La, 12% Nd, 4% Pr, 1% other lanthanides) can reduce substoichiometric amounts of Sm(II) in some Reformatsky and Barbier reactions.$^{43,44}$ More recently, electrochemical methods have been employed to regenerate Sm(II), but a Sm electrode is required.$^{36,47}$

While these catalytic systems are an excellent initial extension of the utility of this reagent, optimization of such systems has not occurred and have not been utilized extensively by synthetic chemists due to their narrow scope of application.$^{45}$ Given the overall challenges developing a catalytic system employing Sm(II), it is our supposition that if the intent is to develop a catalyst, it is best to start with a functioning catalytic system and understand the strengths and limitations of a known process instead of trying to develop a new system from first principles. Once the mechanistic role of the various additives and components in a known system are understood, it enables a rational approach to the design of a new method or system for regenerating Sm(II) from Sm(III). During the last several years, we have studied a number of reported catalytic systems and learned a great deal that is useful in enabling the development of a robust and user-friendly approach to catalytic reactions of Sm(II).$^{48,49}$ We will focus on the approaches developed by Endo and Greeves.$^{40,41}$ but note that all of the systems we have examined to date have similar challenges. An example of a typical approach is shown in Scheme 1.
In the systems developed by Endo and Greeves,\textsuperscript{40,41} substrate (typically aldehyde) is exposed to a substoichiometric amount of SmI\(_2\) containing superstoichiometric amounts of Mg as the terminal reductant. During the reaction, reduction of the aldehyde by Sm(II), leads to pinacol coupling. Since Sm(III) has a high affinity for alkoxides, the intermediate coordinates to Sm(III) preventing regeneration. In addition, the presence of a silylchloride is necessary to capture the coordinated alkoxy and cleave the Sm-O bond. During the last step, the sacrificial reductant converts Sm(III) to Sm(II). The proposed catalytic cycle for the process is shown in Scheme 1. The only difference between the two systems is the approach designed by Greeves uses a glyme which is proposed to enhance the dia stereoselectivity of the pinacol coupling.\textsuperscript{46}

![Scheme 1](image)

**Scheme 1.** Proposed Catalytic cycle by Greeves et al.\textsuperscript{41}

Before examining the systems, we saw several challenges. During the course of reactions with SmI\(_2\), iodide ligands are displaced through exchange with intermediates that have a higher affinity for Sm than the initial ligand. Additionally, Sm(III) gains a third contact anion, stemming from its increase in charge. This ligand exchange likely causes the Sm(III) species reduced in the catalytic cycle to gradually produce a reductant other than SmI\(_2\). Mechanistic studies on stoichiometric systems have shown that even a conservative replacement of iodide by bromide or chloride on Sm(II) has a dramatic impact on the reactivity of the reductant.\textsuperscript{50} In addition, formation of Sm(III) salts are highly insoluble in THF making regeneration of Sm(II) more difficult. As a consequence, reduction of insoluble Sm(III) by Mg is likely to be slow due to inefficient electron transfer. Another potential problem is the lack of a proton donor necessary to protonate substrate after electron transfer from Sm(II). Finally, many of the catalytic systems are not general and are only efficient for selective reactions.\textsuperscript{40,41,45} To develop an effective and more general catalytic system, we undertook studies to answer the following key questions: 1) What are the mechanistic roles of individual components of the catalytic system? 2) Can turnover be made more efficient? 3) Can the system be made to be much more general to accommodate a range of reactions? 4) Can important bond-forming reactions such as carbonyl-alkene reactions be made catalytic? Herein we present the results of experiments that address these fundamental questions.

**Results and Discussion**

*Approach in Designing the Catalytic System*

In the pursuit of designing an efficient catalytic system, we first focused on solubility and reversibility of the Sm(II)/Sm(III) redox couple. We have investigated several Sm(III) salts and discovered that SmI\(_3\) has highest solubility in THF. We have also found that it is relatively straightforward to reduce SmI\(_3\) to SmI\(_2\) using Mg. To further enhance the solubility of SmI\(_3\) in the reaction mixture, we proposed adding a ligand which is capable of complexing with Sm(III). Glymes are well known for coordinating with both +3 and +2 oxidation state\textsuperscript{51,52} of lanthanides and they have been used in the catalytic Sm(II) mediated reductions studied by Greeves.\textsuperscript{41} In Greeves original work, he proposed that the glyme was important in driving the stereo selectivity of pinacol coupling reactions. It was our supposition that the role of the glyme was to facilitate solubility of the Sm(III). To examine the possibility of SmI\(_3\) solubility enhancement tetraglyme was added to a turbid solution of SmI\(_3\). The addition of 10 equivalent of tetraglyme based on [SmI\(_3\)] transformed the turbid solution to a clear, homogeneous solution (Figure 1).

![Figure 1](image)

**Figure 1:** Photo of SmI\(_3\) and SmI\(_2\)-tetraglyme in THF. [SmI\(_3\)] = 0.1 M and [tetraglyme] = 1 M.

Since the goal of the work is the development of a catalytic reduction system based on Sm(II)/Sm(III) redox couple, it is very important to understand the relative affinity of tetraglyme for both oxidation states of Sm. To examine this the UV-Vis spectrum of SmI\(_3\) (2 mM) and SmI\(_2\) with tetraglyme (8 mM) were obtained. Next, 2 mM of SmI\(_3\) was added to SmI\(_2\)-tetraglyme. If tetraglyme has an affinity towards SmI\(_3\) and SmI\(_2\), this will lead to rapid ligand exchange generating free SmI\(_2\) which can easily be detected from its characteristic UV-Vis. Analysis of Figure 2 suggests that indeed addition of SmI\(_3\) leads to generation of free SmI\(_2\) to some extent, however the affinity of tetraglyme is probably slightly higher for SmI\(_3\). Nonetheless, the fact that tetraglyme has higher affinity towards Sm(II) than Sm(III) has less importance since solubilization of the relatively insoluble Sm(III), likely facilitates the reduction of Sm(III) to Sm(II) by the Mg terminal reductant.
Mechanistic analysis of the last 40 years has enabled us to understand the role of proton donors in the SmI₂ mediated reductions and classify them under two major categories; a) coordinating proton donors (such as MeOH, water and glycols) and b) non-coordinating proton donors (ethanol, trifluoroethanol and t-BuOH). Although it has been demonstrated that coordinating proton sources are more efficient in proton transfer than the non-coordinating variants, the latter scenario is preferred since they will not alter the reactivity of Sm. The rationale behind this supposition comes from the fact that coordinating proton donors generate a very strong Sm(III)-O bond as a result of proton transfer and it is rather difficult to cleave this bond to liberate Sm(III) for subsequent reduction to regenerate Sm(II). With this background in mind, trifluoroethanol (TFE) was chosen as a proton source because it does not coordinate to Sm and is an excellent H-bond donor.

**Tetraglyme-TFE System**

To test the efficiency of the tetraglyme-TFE system, we carried out reduction of a range of substrates displayed in Chart 1. All reactions employed 10 mole percent Sm using tetraglyme as a ligand and TFE as the proton donor. Reductions of carbonyl compounds were completed with 2-3 hrs and reactions with alkyne 6 and alkene 7 were continued for 15 hrs. Substrates 1-4 provided the corresponding alcohol as product. Reduction of amide 5 resulted mixture of alcohol and amine in almost 1:1 mixture. Interestingly, the reduced alkyne provided the cis alkene product exclusively. It is important to note that control experiments in the absence of SmI₂ do not yield reduction products even for 24 hrs. Reactions performed in the absence of proton donors or TMSCl also led to recovery of starting material. These findings confirm that all the reaction components present were necessary for the reaction to proceed.

**Table 1: Reduction of substrates with 10 mol % of SmI₂ in the presence of tetraglyme-TFE**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction time (hrs)</th>
<th>Product</th>
<th>Conversion (NMR Yield)³⁵⁻⁶⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Alcohol</td>
<td>99 (90)</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Alcohol</td>
<td>99 (93)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Alcohol</td>
<td>99 (90)</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>Alcohol</td>
<td>99 (67)</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>Alcohol and amine (1:1)</td>
<td>99 (66)</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>Cis alkene</td>
<td>36 (30)</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>Alkane</td>
<td>57 (54)</td>
</tr>
</tbody>
</table>

a: SmI₂: 0.05 mmole; Subs: 0.5 mmole; Tetraglyme: 0.8 mmole; TFE: 2 mmole; TMSCl: 2.8 mmole and Mg: 0.1 g. b: NMR Yields are based on internal standard.

To examine the limit of catalyst loading for the system, we performed the reduction of cyclohexylmethyl ketone (1) employing 5, 2 and 1 mole percent of SmI₂. These reactions were performed keeping the substrate amount the same as in the previous experiment (0.5 mmole) and reducing the amount of SmI₂. All loadings of 5, 2 and 1 mole percent Sm resulted in...
99% conversion to corresponding alcohol. Keeping in mind that conversion of a ketone to an alcohol requires 2 electrons, up to 200 turnovers were achieved for this system. It is worth mentioning that in a previous report, the reduction of cyclohexylmethyl ketone to the corresponding pinacol using 20 mole percent SmI2 required 20 hrs.\textsuperscript{31} In light of the present results, the impact of proton donor is remarkable and clearly facilitates the catalytic turn over. Table 2 represents the results of reduction of 1 by 5, 2 and 1 mole percent of SmI2. Reduction of 4-Phenyl-2-butanoic (2) and 2-octanone (3) with 1 mole percent of SmI2 resulted 85 and 99 % of corresponding alcohol respectively under similar condition (see SI, Table S1).

### Table 2: Reduction of cyclohexylmethyl ketone (1) under 5, 2 and 1 mole % of SmI2/tetraglyme-TFE system

<table>
<thead>
<tr>
<th>Catalyst (SmI2 mmole)</th>
<th>loading amount (mmole)</th>
<th>Reaction time (hrs)</th>
<th>Conversion (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (0.025)</td>
<td>5</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>2 (0.01)</td>
<td>15</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>1 (0.005)</td>
<td>24</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}: Subs: 0.5 mmole; Tetr: 0.8 mmole; TFE: 2 mmole; TMSCl: 2.8 mmole and Mg: 0.1 g

**Development of catalytic reactions employing HMPA as a ligand**

The use of HMPA as a ligand for SmI2 has a significant impact on the selectivity, stereoselectivity, and reactivity of the reagent.\textsuperscript{1,12,50} While the exact speciation of the intermediate reductant in solution formed upon addition of HMPA to SmI2 is not known,\textsuperscript{58,59} HMPA coordinates to Sm(II) displacing iodide ligands from the inner-sphere of the metal.\textsuperscript{58,60}\textsuperscript{i} Additionally, HMPA coordination to SmI2 enhances the reducing power of SmI2 by decreasing its reduction potential and stabilizing the +3 oxidation state.\textsuperscript{58,60,62}\textsuperscript{i} Based on these findings, it is reasonable to assume that it would be rather difficult to use HMPA to carry out efficient catalytic turn over since reduction of Sm(III)-HMPA by a terminal reductant is more difficult than reduction of Sm(III) alone.\textsuperscript{61}\textsuperscript{i} Nonetheless, given the importance of HMPA in a range of useful bond forming reactions\textsuperscript{9,22} we thought it prudent to examine whether a catalytic system could be developed employing the additive.

To our surprise, despite the irreversibility of the SmI2-HMPA redox couple, catalytic reductions proceeded well using Mg as a terminal reductant. In initial reactions, 10 mol% Sm was employed in reactions. One noticeable difference in the reactions with respect to the use of tetraglyme as a ligand is the ratio of HMPA:Sm was found to be critical. For example, if 0.8 mmole of HMPA was employed in 10 mole percent reactions (16:1 ratio HMPA:Sm), 0.4 mmol HMPA was required in reactions using 5 mole percent Sm, otherwise complete conversion of substrate to product was not observed. The results of initial catalytic reductions using HMPA as ligand are summarized in Table 3. Ketone substrates 1-3 and activated ester 4 provide excellent to very good yields whereas benzamide 5 leads to recovery of starting material. Alkynie 6 provides very modest yield of the cis-alkene and activated alkene 7 provides a good yield of reduced product. The lack of reaction of substrate 5 was initially surprising and will be discussed **vide infra**.

### Table 3: Reduction of substrates with 10 mole %SmI2 in the presence of HMPA-TFE

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction time (hrs)</th>
<th>Product</th>
<th>Conversion (NMR Yield)\textsuperscript{ab}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Alcohol</td>
<td>99 (80)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Alcohol</td>
<td>99 (83)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Alcohol</td>
<td>99 (89)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Alcohol</td>
<td>76 (69)</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>Cis alkene</td>
<td>15 (12)</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>Alkane</td>
<td>62 (55)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}: SmI2: 0.05 mmole; Subs: 0.5 mmole; HMPA: 0.8 mmole; TFE: 2 mmole; TMSCl: 2.8 mmole and Mg: 0.1 g; b: NMR Yields are based on internal standard.

**Identity of the active catalyst**

It is surprising that although some of the substrates used in this study fall outside of the range of reduction by SmI2/tetraglyme/TFE under stoichiometric conditions, successful reduction occurred under catalytic conditions. This finding suggests that the identity of the active Sm(II) reductant likely changes during catalytic turn over. In nearly all of the catalytic Sm(II) mediated reductions designed including the present study, TMSCl or Me2SiCl2 were employed as Lewis acids to cleave the ion-pair between Sm(III) and negatively charged products or intermediates.\textsuperscript{50,60,62}\textsuperscript{i} The capture of oxygen by the silyl chloride generates chloride which is known to have a higher affinity for Sm(II) than iodide.\textsuperscript{50} As a consequence, it is likely that SmI2 is converted to SmCl3, which known to be a more powerful reductant, during the course of the reaction.\textsuperscript{66}\textsuperscript{i} To examine this supposition, the UV-Vis spectra for the reduction of 4-phenyl-2-butanoic under a series of conditions was measured after completion of the reaction.

First, the tetraglyme system was examined by measuring the UV-Vis spectrum before ([SmI2] = 6.25 mM + 16 eq of tetraglyme) and after the reaction. UV-Vis spectrum obtained after the completion of reaction matches very well with previously reported spectrum of SmCl3 in THF.\textsuperscript{50,63}\textsuperscript{i} To verify that the change in Sm(II) speciation occurs indeed due to generation of chloride ion during the course of reaction, 2 eq (with respect to Sm) of tetrabutylammonium chloride was added to SmI2-tetraglyme complex. The resultant spectrum matches very well with spectrum of Sm(II) obtained at the end of the catalytic reaction. Thus, Figure 3 unequivocally establishes that SmCl3, a more powerful reductant than SmI2, was generated during course of catalytic turnover and hence explains the successful reduction of substrates which are recalcitrant towards electron transfer from SmI2.
In light of these findings, it is our supposition that SmCl$_2$, which is formed in HMPA reaction is very weakly bound to HMPA which is not sufficient to induce the double hump nature in the Sm(II) spectrum, rather it alters the peak maximum. It is possible that SmCl$_2$ is bound with only 1-2 molecule of HMPA and hence electronic structure of Sm(II) is governed by chloride ion rather than HMPA.

The fact that the spectrum obtained at the end of HMPA mediated reactions is hardly perturbed by HMPA suggests that the concentration of HMPA decreases as the reaction proceeds towards completion. A possible mechanistic pathway in which concentration of HMPA could decrease as reaction proceeds is catalyst deactivation. In other words, in each catalytic cycle a fraction of Sm(III)-HMPA was not reduced back to Sm(II)-HMPA and as a result of that concentration of HMPA decreases as reaction proceed. However, since 16 eq of HMPA per Sm was used in these reactions, even with catalyst deactivation, some amount of HMPA should remain in solution. Another possible pathway responsible for the apparent disappearance of HMPA from the Sm(II) metal center could be ligand exchange reaction by of Mg$^{2+}$ ion as reaction proceeds. Since it is known that HMPA forms coordination complex with Mg$^{2+}$,$^{64,65}$ and that there is a high concentration of Mg relative to Sm, we believe this is a likely pathway for the decomplexation of HMPA from Sm.

**Role of Proton Donors and H-bonding in Sm$_2$ Catalysis**

Initial studies foreshadow an important role for proton donors, but don't provide a great deal of mechanistic insight into their capacity as H-bond donors to enhance the Lewis acidity of TMSCl or how mechanistic differences between tetraglyme and HMPA mediated Sm(II) catalysis can be influenced by different types of H-bond donors. To elucidate these details, reduction of cyclohexylmethyl ketone (I) was conducted with several other H-bond donors (isopropanol, methanol, pinacol and 1,3-diphenylurea) using tetraglyme and HMPA as ligands and 10 mol% Sm$_2$. Isopropanol is similar to TFE in terms of its non-coordinating nature towards Sm$_2$. However, it is less acidic and more sterically encumbered than TFE and as a consequence is expected to form a weak H-bond with TMSCl. Methanol and pinacol are known for their ability to coordinate to Sm$_2$ and hence employing them as H-bond donors may result in ligand (tetraglyme or HMPA) displacement, that may have a deleterious impact on the Sm(II) catalysis.$^{35,62}$ 1,3-diphenylurea was employed to provide insight that Sm(II) catalysis is not only specific with alcohol based H-bond donor, but rather a more general phenomenon.

Results of these experiments are summarized in Table 4. There are several interesting features of these results: 1) With the exception of TFE, Sm(II) catalysis does not work very well with other H-bond additives when HMPA was used as ligand. 2) Despite the coordinating nature of MeOH, Sm(II) catalysis works well when tetraglyme is employed as a ligand. However, the reaction yield significantly decreases with pinacol suggesting that MeOH is the limit of employing coordinating additives. 3) Successful Sm(II) catalysis was observed with 1,3-diphenylurea using tetraglyme as ligand. This supports our supposition that activation of TMSCl through H-bonding is critical for Sm(II) catalysis. Surprisingly, this is not the case with HMPA as ligand.

Given the differences among H-bond donors in catalytic reactions using tetraglyme and HMPA, some discussion is war-

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**Figure 3:** UV-vis spectra of Sm$_2$-tetraglyme complex, Sm$_2$-tetraglyme with 2 eq. of chloride ion and Sm$_2$-tetraglyme mediated reaction mixture. [SmI$_2$] = 6.25 mM.

Next, a similar analysis of the reaction containing HMPA was performed (Figure 4). Similar to the tetraglyme reaction, formation of SmCl$_2$ was clearly evident in this case as well. In this case, addition of 2 eq (with respect to Sm) of tetrabutylammonium chloride to Sm$_2$-HMPA complex changes the shape of spectrum suggesting that Sm$_2$-HMPA converts to SmCl$_2$-HMPA complex. Unlike tetraglyme case, the UV-vis obtained at the end of the reaction is very different from the UV-Vis spectrum of SmCl$_2$-HMPA and is similar to SmCl$_2$ (Sm$_2$ + 2 eq of tetrabutylammonium chloride). However, it is also observed that absorption maximum for the spectrum of the reaction mixture with HMPA is red shifted by 10 nm compare to SmCl$_2$.

**Figure 4:** UV-vis spectra of Sm$_2$-HMPA complex, Sm$_2$-HMPA with 2 eq. of chloride ion, Sm$_2$ with 2 eq. of chloride ion and Sm$_2$-HMPA mediated reaction mixture. [SmI$_2$] = 6.25 mM.

While examining the effect of tetraglyme and HMPA on the SmCl$_2$ (Sm$_2$ + 2 eq of tetrabutylammonium chloride) spectrum, we have observed significant differences. Tetraglyme being a weak ligand, cannot alter the spectrum of SmCl$_2$, whereas the effect of HMPA coordination is clearly visible in the spectrum of SmCl$_2$. Addition of 16 eq (with respect to Sm) of HMPA to SmCl$_2$ solution (Sm$_2$ + 2 eq of tetrabutylammonium chloride) lead to form a single hump SmCl$_2$ spectrum to a double hump (see SI, Figure S1). Addition of excess of chloride (16 eq with respect to Sm) ion to SmCl$_2$-HMPA complex was found to have a very modest impact on its UV-vis spectrum (see SI, Figure S2). Overall, these UV-vis spectra analyses strongly suggests that the presence of HMPA could easily be discerned from characteristic double hump spectrum of Sm(II) absorption irrespective of chloride ion concentration.
ranted. It is our supposition that these differences are a consequence of the fact that HMPA is stripped from Sm metal center during the catalytic turnover whereas tetraglyme remains coordinated. Although MeOH and pinacol are weaker complexing ligands for Sm(II) in comparison to HMPA, as HMPS is displaced from the coordination sphere of Sm(II) by increasing concentrations of Mg as the reactions progresses, these additives (MeOH and pinacol) are likely to compete with HMPA. Their coordination to Sm(II) will lead to a very efficient unimolecular proton transfer to organic intermediates generating a strong Sm(III)-O bond thus prohibiting Sm(II) regeneration. It is likely that the basis for the failure of the combination of HMPA and 1,3-diphenyl urea is similar to that for MeOH and pinacol. We have recently demonstrated that coordination of amides to SmI2 reduces substrates through a formal hydrogen atom transfer mechanism generating a strong Sm(III)-N bond. It is likely that the urea is behaving in a similar fashion. Furthermore, in addition to this potential deactivating pathway, 1,3-diphenylurea is also expected to form an H-bond with HMPA. To test this supposition, isothermal titration calorimetry (ITC) of 0.09 M of 1,3-diphenylurea with 1 M of HMPA in THF shows a strong interaction as shown in Figure S3 (see SI). This H-bond interaction likely inhibits coordination of HMPA to Sm(II). With this mechanistic insight one can rationalize the unsuccessful reduction of 4butylbenzamide (5) with Sm(II)-HMPA system (Table 3).

It is interesting that the differences between TFE and isopropanol in activating TMSCI through H-bond interactions is reflected only in the case of HMPA. Although, this observation is very similar to the outcome when MeOH is used, the mechanism should be different since isopropanol does not coordinate to Sm(II). A more likely scenario would be as HMPA dissociates from the Sm(II) coordination sphere, the electrostatic interaction between Sm(III) and negatively charged intermediates is enhanced. Since TFE is more acidic and less sterically crowded than isopropanol, it is more efficient in activating TMSCI and hence Sm(II) catalysis is more efficient with TFE than isopropanol when HMPA is used as a ligand. This difference is not reflected in the tetraglyme reaction, as tetraglyme likely remains coordinated with Sm(II)/Sm(III) during the course of reaction.

Table 4: Comparison of TFE, isopropanol, MeOH, Pinacol and 1,3-diphenylurea

<table>
<thead>
<tr>
<th>H-bond donors</th>
<th>Tetracylum2</th>
<th>HMPA2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(10 mol% Sm)</td>
<td>(10 mol% Sm)</td>
</tr>
<tr>
<td>TFE</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>99</td>
<td>50</td>
</tr>
<tr>
<td>MeOH</td>
<td>99</td>
<td>56</td>
</tr>
<tr>
<td>Pinacol</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>1,3-diphenylurea</td>
<td>97</td>
<td>4</td>
</tr>
</tbody>
</table>

a: SmI2: 0.05 mmole; Subs: 0.5 mmole; Ligand: 0.8 mmole; H-bond donor: 2 mmole, TMSCI: 2.8 mmole and Mg: 0.1 g. Reaction time: 4 hrs.

Ketyl-Olefin cyclization

With a mechanistic basis for the development of a catalytic system in hand, we wanted to focus on an important bond-forming reaction. In this regard, ketyl-olefin cyclization is arguably one of the most important reactions initiated by SmI2 and is a key step in the synthesis of several natural products. Despite significant advances in carrying out ketyl-olefin cyclizations with Sm(II), in all cases stoichiometric or super stoichiometric amounts of Sm(II) are required limiting the practical utility of the reagent. In light of the importance and utility of this reaction class, employing catalytic amounts of Sm(II) to carry out ketyl-olefin cyclization will likely broaden the practical application of Sm(II) mediated bond-forming reactions. To explore whether this approach will work, we examined a range of substrates capable of undergoing 5-exo-trig cyclization to explore the development of catalytic reactions. Substrates used to study the cyclization reactions are displayed in Chart 2.

Chart 2: Substrates for cyclization study.

Initial experiments with 8 were designed to examine the use of tetraglyme and HMPA in the cyclization. Interestingly, it was found that HMPA was the most useful in obtaining cyclized product over simple reduction. The results of the study are summarized in Table 5.

Table 5: Reduction vs cyclization for 8 with tetraglyme and HMPA

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Proton donors</th>
<th>8a (%)</th>
<th>8b (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracylum</td>
<td>TFE</td>
<td>33</td>
<td>66</td>
<td>99</td>
</tr>
<tr>
<td>HMPA</td>
<td>TFE</td>
<td>54</td>
<td>45</td>
<td>99</td>
</tr>
</tbody>
</table>

a: SmI2: 0.05 mmole; Subs: 0.5 mmole; Ligand: 0.8 mmole; HMPA: 0.8 mmole; TFE: 2 mmole; TMSCI: 2.8 mmole and Mg: 0.1 g. Reaction time: 4 hrs. Yields are determined by NMR study.

It is our supposition that difference between HMPA and tetraglyme in the yield of cyclization product stems from their ability to coordinate with Sm(II) vs Sm(III) metal ion. In the case of HMPA, it has been demonstrated that the ligand forms a stronger complex with SmI3 compared to SmI2. Additionally, previous studies from our lab proposed that HMPA was required to cleave the Sm(III)-ketyl radical ion pair to facilitate 5-exo-trig cyclization. Unlike HMPA, tetraglyme shows higher affinity towards SmI2 rather than SmI3 and hence cannot efficiently assist the dissociation of ion pair that is critical for cyclization. Taken together these findings demonstrate the suitability of HMPA as the best additive to employ in the cyclization.

Next, reactions were carried out for all the substrates using HMPA as the ligand along with 5 or 10 mole percent Sm and results are summarized in Table 6.
Table 6: Results of cyclization vs reduction for substrate 8-11.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>10 mole percent reaction</th>
<th>5 mole percent reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyclization</td>
<td>Total conversion</td>
</tr>
<tr>
<td>8</td>
<td>54 (1:1)</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>60 (2:1)</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>95 (12:1)</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>66 (2:1)</td>
<td>99</td>
</tr>
</tbody>
</table>

a: SmI₂: 0.05/0.025 mmole; Subs: 0.5 mmole; HMPA: 0.8 mmole; TFE: 2 mmole; TMSCl: 2.8 mmole and Mg: 0.1 g. Reaction time: 4 hrs for 10 mole percent and 15 hrs for 5 mole percent. Yields are determined by NMR study.

Results presented in Table 6 shows that the present system can be utilized in synthetically relevant bond forming reactions. To examine the suitability of the present method for larger scale reactions, we scaled up the catalytic reduction of 10 to 1 g using 10 mole percent Sm. Analysis of the gram scale reactions suggests that amount of cyclized product formed is comparable to that with results described in Table 6. The gram scale reaction proceeds with a high yield of 97% (see SI, Table S2 for details).

While 10 provides cyclized product almost exclusively, a distribution of cyclized vs reduced products were observed for substrates 8, 9, and 11. In addition, the diastereoselectivity observed in the catalytic reactions are different than that obtained in stoichiometric reactions. It is likely that the difference in the outcome of catalytic vs. stoichiometric reactions are twofold: a) studies on the identity of the catalyst described vide infra show that HMPA is being displaced from Sm during the course of the reaction and there is a strong evidence that the sterically encumbered Sm-HMPA complex is responsible for high diastereoselectivity observed in stoichiometric reactions. b) the silyl ketyl intermediate which was generated by the cleavage of Sm(III)-O bond by TMSCl is also likely more prone towards reduction since the sterically demanding trimethyl silyl inhibits cyclization (Scheme 2).

Scheme 2: Proposed mechanism of Si-O intermediate in cyclization vs reduction outcome.

To reduce the concentration of the Si-O bond formed as an intermediate and enhance the cyclization yield, we reasoned that adding TMSCl slowly over a period of time may lower the intermediate concentration of II shown above in scheme 2. To examine this supposition, reduction of 8 was carried out using 10 mol% Sm by slowly added TMSCl over a 5 hour time period. Slow addition of TMSCl increased the yield of 8a from 54 % to 80 %. Similar results were also obtained for 9 and 11. One caveat with this approach is that we discovered for complete conversion of starting material to products, a small amount of TMSCI was required to initiate the reaction and reduce the concentration of 9 and 11. Results of these reactions and distribution of TMSCI are summarized in Table 7.

Table 7: Results with slow addition for 8, 9 and 11

<table>
<thead>
<tr>
<th>Substrate</th>
<th>TMSCI (mmole) in reaction mixture</th>
<th>TMSCI (mmole) added slowly</th>
<th>Cyclization/Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>0</td>
<td>2.8</td>
<td>80 (2:1)/99</td>
</tr>
<tr>
<td>9</td>
<td>1.4</td>
<td>1.4</td>
<td>75 (2:1)/99</td>
</tr>
<tr>
<td>11</td>
<td>1.8</td>
<td>1.8</td>
<td>82 (2:1)/99</td>
</tr>
</tbody>
</table>

a: SmI₂: 0.05 mmole; Subs: 0.5 mmole; HMPA: 0.8 mmole; TFE: 2 mmole; total TMSCI: 2.8 mmole and Mg: 0.1 g. Slow addition time: 5hrs; Reaction time: 15 hrs.

Although the aforementioned hypotheses are reasonable, we are currently studying several other substrates to determine the scope of this approach. Regardless of the mechanistic basis, the initial data clearly demonstrates that high yields can be obtained for the catalytic ketyl-olefin cyclization.

Conclusion and Future Studies

We have demonstrated that it is possible to significantly enhance the catalytic efficiency of Sm(II) in concert with terminal Mg reductant by activating the system with TMSCI in concert with an H-bond donor. This approach has also provided an opportunity to develop Sm(II) catalysis employing HMPA as a ligand, which was unsuccessful in previous studies. Mechanistic studies provided compelling evidence that during the course of Sm(II) catalysis, SmI₂ transforms into the more reactive SmCl₂. The conversion of SmI₂ into SmCl₂ during the course of reaction broadens the scope of reactions that can be carried out via Sm(II) catalysis. Mechanistic studies have also revealed that HMPA is displaced from Sm by Mg²⁺ produced during the course of the reaction. Based on these findings, we propose the following catalytic cycle (Scheme 3).

Scheme 3: Proposed Sm(II) catalytic cycle.

Beyond simple reductions, the mechanistic approach described herein was critical for developing catalytic 5-exo-trig ketyl-olefin cyclization reactions. The slow addition of TMSCI was critical for cyclization in this class of reactions. Although the
work provides important proof of principle for the present
approach, there are several challenges that remain: 1) silanes
are critical for reaction, but impede catalytic efficiency. 2) Mg
provides an inexpensive and accessible terminal reductant, but
byproduct MgCl₂ provides a deactivating pathway for reac-
tions requiring HMPA by displacing the ligand from Sm. We
are currently working on the development of systems that can
overcome these challenges and the results of this work will be
presented in due course.

ASSOCIATED CONTENT
Supporting Information
General experimental methods, spectral data, and iso-
thermal titration calorimetry data. This material is available free of charge
via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION
Corresponding Author
*rof2@lehigh.edu

Author Contributions
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