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

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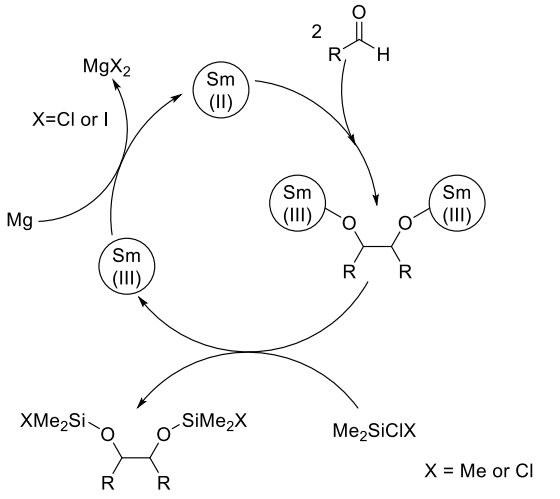
ABSTRACT: Samarium diiodide (SmI_2) is one of the most widely used single electron reductants available to organic chemists because it is effective in reducing and coupling a wide range of functional groups. Despite the broad utility and application of SmI_2 in synthesis, the reagent is used in stoichiometric 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 $SmCl_2$ 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.[1–9] 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,[13–22] and cascade reactions.[23–35] Most importantly, its use allows for alternative and selective methods for the synthesis of multifunctional targets.[4,9] 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.[3,6,38]

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.[40] Greeves and coworkers carried out a more extensive study employing glymes along with Mg as an additional additive in pinacol couplings.[41] 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.[46,47]

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,[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 capture the coordinated alkoxide 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 diastereoselectivity of the pinacol coupling.[46]



Scheme 1. Proposed Catalytic cycle by Greeves *et al*.[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.[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.[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[51,52] of lanthanides and they have been used in the catalytic Sm(II) mediated reductions studied by Greeves.[41] In Greeves original work, he proposed that the glyme was important in driving the stereoselectivity 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).

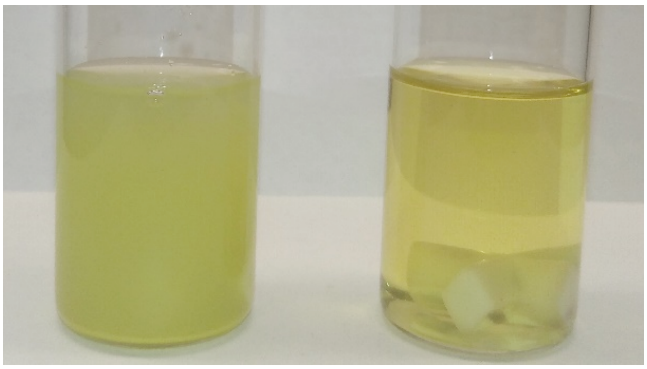


Figure 1: Photo of SmI_3 and SmI_3-tetraglyme in THF. [SmI_3] = 0.1 M and [tetraglyme] = 1 M.

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_2 (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_2. 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.

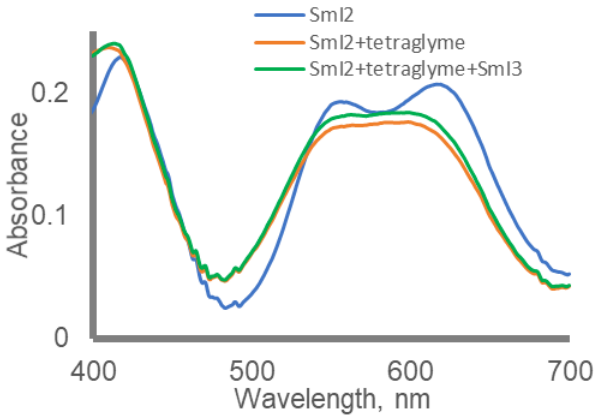


Figure 2: UV-Vis of SmI_2 (2 mM); SmI_2+tetraglyme (8 mM) and SmI_2+tetraglyme+SmI_3 (2 mM).

With this preliminary study complete, we attempted to reduce cyclohexylmethyl ketone (**1**) and 4-phenyl-2-butanone (**2**) under the following conditions: SmI_2 (0.05 mmole), tetraglyme (0.8 mmole), substrate (0.5 mmole), TMSCl (2.8 mmole) and Mg (0.1 g) in 10 mL of THF. Despite several attempts, only starting material was recovered. This could be due to unsuccessful reduction of substrate, however, in that case the color of SmI_2 should have been retained. Decolorization of reaction mixture was observed in 3-5 min and color was not regenerated even after 24 hrs of stirring. To explore the basis for the lack of reaction, we examined the reduction of SmI_3 in the absence of substrate. Treatment of SmI_3 in the presence of tetraglyme, TMSCl and Mg led to generation of Sm(II) with 2-3 min. This observation indicates that unsuccessful reduction was potentially a result of difficulty in cleaving Sm(III)-oxygen bond to liberate Sm(III).

To counter a similar problem, Greeves et al. used Me_2SiCl_2 instead of TMSCl.[41] We have taken an alternate approach to solve this problem. To enhance the efficiency of cleaving the intermediate Sm(III)-oxygen bond by TMSCl, we envisioned that it may be possible to enhance the Lewis acidity of TMSCl by hydrogen bond (H-bond) donors. This supposition is based on previous work employing hydrogen bond donors, such as squaramides to enhance the Lewis acidity of trimethylsilyl triflate.[53] The advantage of H-bond induced Lewis acid enhancement is that one can potentially tune this weak interaction to achieve selectivity required for a reaction of interest. While squaramides have been used previously, employing them in SmI_2 mediated reductions can potentially lead to intermediate coordination compounds that can alter the reactivity of Sm(II). Alcohols which are also known for their H-bond donor capabilities can be an alternative for the present system. Apart from H-bonding to TMSCl, the presence of an alcohol might be advantageous in terms of a) availability of protons which are necessary for product formation; b) the proton source can potentially form H-bond with intermediate Sm(III)-oxygen bonds to weaken the electrostatic interaction and facilitate the cleavage of Sm(III)-oxygen bond.[54]

Mechanistic analysis of the last 40 years has enabled us to understand the role of proton donors in the SmI_2 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).[55,56] Although it has been demonstrated that coordinating proton sources are more efficient in proton transfer than the non-coordinating variants,[55] 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 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.[57] Interestingly, the reduced alkyne provided the *cis* alkene product exclusively. It is important to note that control experiments in

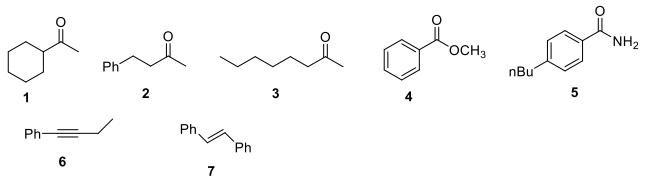


Chart 1. Substrate used for the reduction by catalytic Sm(II) system.

the absence of SmI_2 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 SmI_2 in the presence of tetraglyme-TFE

Substrate	Reaction time (hrs)	Product	Conversion (NMR Yield)[a,b]
1	3	Alcohol	99 (90)
2	3	Alcohol	99 (93)
3	3	Alcohol	99 (90)
4	5	Alcohol	99 (67)
5	5	Alcohol and amine (1:1)	99 (66)
6	15	Cis alkene	36 (30)
7	15	Alkane	57 (54)

a: SmI_2: 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 SmI_2. These reactions were performed keeping the substrate amount the same as in the previous experiment (0.5 mmole) and reducing the amount of SmI_2. 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 SmI_2 required 20 hrs.[41] 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 SmI_2. Reduction of 4-Phenyl-2-butanone (**2**) and 2-octanone (**3**) with 1 mole percent of SmI_2 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 SmI_2/tetraglyme-TFE system

Catalyst loading (SmI_2 amount, mmole)	Reaction time (hrs)	Conversion (%)[a]
5 (0.025)	5	99
2 (0.01)	15	99
1 (0.005)	24	99

a: Subs: 0.5 mmole; Tetraglyme: 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 SmI_2 has a significant impact on the selectivity, stereoselectivity, and reactivity of the reagent.[11,12,50] While the exact speciation of the intermediate reductant in solution formed upon addition of HMPA to SmI_2 is not known,[58,59] HMPA coordinates to Sm(II) displacing iodide ligands from the inner-sphere of the metal.[58,60] Additionally, HMPA coordination to SmI_2 enhances the reducing power of SmI_2 by decreasing its reduction potential and stabilizing the +3 oxidation state.[58,61,62] 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.[61] Nonetheless, given the importance of HMPA in a range of useful bond forming reactions[16,22] we thought it was prudent to examine whether a catalytic system could be developed employing the additive.

To our surprise, despite the irreversibility of the SmI_2-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. Alkyne **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 %SmI_2 in the presence of HMPA-TFE

Substrate	Reaction time (hrs)	Product	Conversion (NMR Yield)[a,b]
1	4	Alcohol	99 (80)
2	4	Alcohol	99 (83)
3	4	Alcohol	99 (89)
4	4	Alcohol	76 (69)
5	4		<5
6	15	Cis alkene	15 (12)
7	15	Alkane	62 (55)

a: SmI_2: 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 SmI_2/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 Me_2SiCl_2 were employed as Lewis acids to cleave the ion-pair between Sm(III) and negatively charged products or intermediates.[40,41,46,47] The capture of oxygen by the silyl chloride generates chloride which is known to have a higher affinity for Sm(II) than iodide.[50] As a consequence, it is likely that SmI_2 is converted to $SmCl_2$, which known to be a more powerful reductant, during the course of the reaction.[46] To examine this supposition, the UV-Vis spectra for the reduction of 4-phenyl-2-butanone 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 ([SmI_2] = 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 $SmCl_2$ in THF.[50,63] 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 SmI_2-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 $SmCl_2$, a more powerful reductant than SmI_2, was generated during course of catalytic turnover and hence explains the successful reduction of substrates which are recalcitrant towards electron transfer from SmI_2.

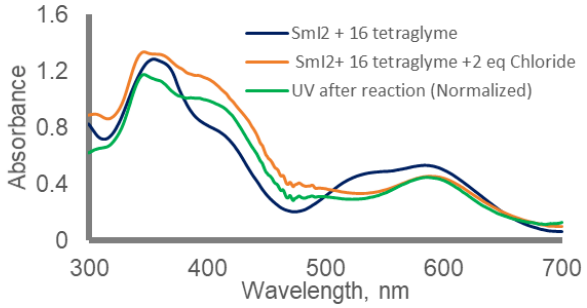


Figure 3: UV-vis spectra of SmI_2-tetraglyme complex, SmI_2-tetraglyme with 2 eq. of chloride ion and SmI_2-tetraglyme mediated reaction mixture. [SmI_2] = 6.25 mM.

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 SmI_2-HMPA complex changes the shape of spectrum suggesting that SmI_2-HMPA converts to $SmCl_2$-HMPA complex. Unlike tetraglyme case, the UV-vis obtained at the end the reaction is very different from the UV-Vis spectrum of $SmCl_2$-HMPA and is similar to $SmCl_2$ (SmI_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 $SmCl_2$.

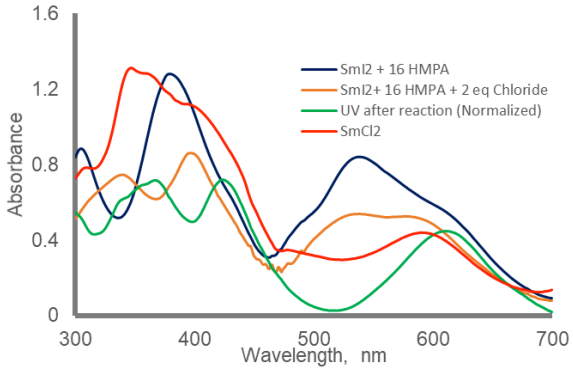


Figure 4: UV-vis spectra of SmI_2-HMPA complex, SmI_2-HMPA with 2 eq. of chloride ion, SmI_2 with 2 eq. of chloride ion and SmI_2-HMPA mediated reaction mixture. [SmI_2] = 6.25 mM.

While examining the effect of tetraglyme and HMPA on the $SmCl_2$ (SmI_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 (SmI_2 + 2 eq of tetrabutylammonium chloride) leads to transform 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.

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 SmI_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 (**1**) was conducted with several other H-bond donors (isopropanol, methanol, pinacol and 1,3-diphenylurea) using tetraglyme and HMPA as ligands and 10 mol% SmI_2. Isopropanol is similar to TFE in terms of its non-coordinating nature towards SmI_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 SmI_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.[55,62] 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-

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,[60,62] as HMPA 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 SmI_2 reduce substrates through a formal hydrogen atom transfer mechanism generating a strong Sm(III)-N bond.[66] 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 4-butylbenzamide (**5**) with Sm(II)-HMPA system (Table 3).

It is interesting that the differences between TFE and isopropanol in activating TMSCl 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 likelihood scenario would be as HMPA dissociates from the Sm(II) coordination sphere, the electrostatic interaction between Sm(III) and negatively charged intermediates is enhanced.[54,67] Since TFE is more acidic and less sterically crowded than isopropanol, it is more efficient in activating TMSCl 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

H-bond donors	Tetraglyme[a] (10 mol% Sm)	HMPA[a] (10 mol% Sm)
TFE	99	99
Isopropanol	99	50
MeOH	99	56
Pinacol	33	0
1,3-diphenylurea	97	4

a: SmI_2: 0.05 mmole, Subs: 0.5 mmole, Ligand: 0.8 mmole, H-bond donor: 2 mmole, TMSCl: 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 SmI_2 and is a key step in the synthesis of several natural products.[4] 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.[16,24] 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.

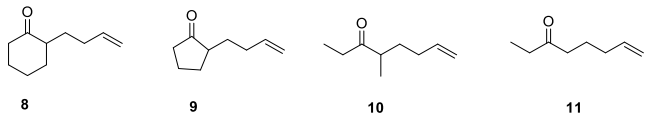


Chart 2: Substrates for cyclization study.

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

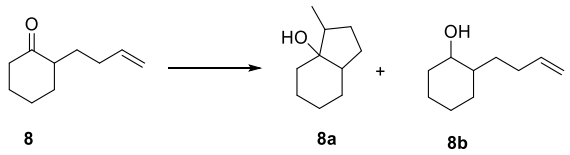


Table 5: Reduction vs cyclization for 8 with tetraglyme and HMPA

Ligand	Proton donors	8a (%)	8b (%)	Conversion (%)[a]
Tetraglyme	TFE	33	66	99
HMPA	TFE	54	45	99

a: SmI_2: 0.05 mmole; Subs: 0.5 mmole; Ligand: 0.8 mmole; HMPA: 0.8 mmole; TFE: 2 mmole; TMSCl: 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 SmI_3 compared to SmI_2.[62] 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.[68] Unlike HMPA, tetraglyme shows higher affinity towards SmI_2 rather than SmI_3 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.

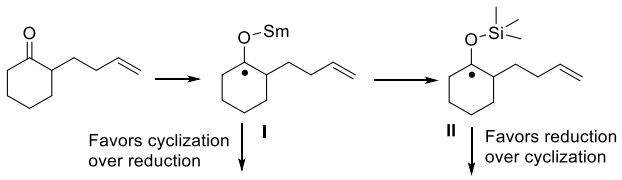
Table 6: Results of cyclization vs reduction for substrate 8-11.

Substrate	10 mole percent reaction		5 mole percent reaction	
	Cyclization	Total conversion	Cyclization	Total conversion
8	54 (1:1)	99	56 (1:1)	99
9	60 (2:1)	99	63 (2:1)	99
10	95 (12:1)	99	95 (12:1)	99
11	66 (2:1)	99	67 (2:1)	99

a: SmI_2: 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.[16] 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.[16] 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 TMSCl was required to initiate the reaction reduction of **9** and **11**. Results of these reactions and distribution of TMSCl are summarized in Table 7.

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

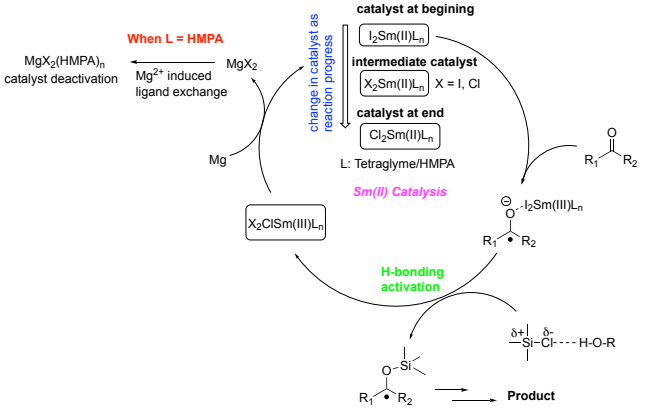
Substrate	TMSCl (mmole) in reaction mixture	TMSCl (mmole) added slowly	Cyclization/Conversion (%)[a]
8	0	2.8	80 (2:1)/99
9	1.4	1.4	75 (2:1)/99
11	1	1.8	82 (2:1)/99

a: SmI_2: 0.05 mmole; Subs: 0.5 mmole; HMPA: 0.8 mmole; TFE: 2 mmole; total TMSCl: 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 TMSCl 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.[43,46] Mechanistic studies provided compelling evidence that during the course of Sm(II) catalysis, SmI_2 transforms into the more reactive $SmCl_2$. The conversion of SmI_2 into $SmCl_2$ 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 Mg^{+2} 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 TMSCl 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 $MgCl_2$ provides a deactivating pathway for reactions 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 isothermal titration calorimetry data. This material is available free of charge via the Internet at http://pubs.acs.org.

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