Reactions of SmI_2 with Alkyl Halides and Ketones: Inner-Sphere vs Outer-Sphere Electron Transfer in Reactions of Sm(II) Reductants

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Abstract: This paper presents the effect of additives on the mechanism and selectivity of the SmI_2-mediated coupling of alkyl halides and ketones. The reaction of 1-iodobutane and 2-octanone was carried out with SmI_2 in the absence of cosolvent and in the presence of HMPA, LiBr, and LiCl. The experiments using cosolvent free SmI_2 and SmI_2−HMPA reductants gave the Barbier product, 5-methyl-5-undecanol predominantly. The same procedure carried out with LiBr as an additive produced the pinacol product, 7,8-dimethyl-7,8-tetradecanediol, exclusively. A careful product analysis of the SmI_2-mediated coupling of 1-iodododecane and 2-octanone in the presence of LiBr, LiCl, and HMPA was also performed. The combination of SmI_2 and LiBr again produced the pinacol coupling product exclusively and left the 1-iodododecane unreduced. In contrast, the SmI_2−HMPA combination gave only the Barbier product. Analysis of the Sm(II) reductants employing cyclic voltammetry and UV−vis spectroscopy coupled with reaction protocol changes and mechanistic studies led to the conclusion that the SmI_2-mediated coupling of alkyl halides and carbonyls in the presence of HMPA gives the Barbier product through an outer-sphere electron-transfer process, while the reaction utilizing SmI_2 with LiBr or LiCl gives the pinacol product through an inner-sphere reductive coupling of ketones. The results presented herein show that it is possible to alter the reactivity and selectivity of Sm(II) reagents through the choice of additives or cosolvents, primarily by changing the steric bulk around the reductant.

Introduction

Samarium diiodide (SmI_2) is presently one of the most diverse reducing reagents utilized by organic chemists.[1] It is employed in numerous important conversions including the reductive cleavage of alkyl halides, the reductive coupling of alkyl halides with π bonds, and the coupling of two π bonds. An important aspect concerning the reactivity of SmI_2 is that the addition of a basic cosolvent (generally HMPA) increases the reducing power of SmI_2.[2] Reactions utilizing SmI_2−cosolvent mixtures generally proceed at accelerated rates compared to reactions without cosolvent.[3]

Although HMPA is the most widely utilized cosolvent, other additives have been employed in reactions of SmI_2. The solvents DMPU[4] and 1,1,3,3-tetramethyl urea[5] have been utilized in SmI_2-mediated bond-forming reactions. Recently Cabri and coworkers examined a number of amine bases as cosolvents and found that they enhanced the rates of cyclizations mediated by SmI_2.[6] Bases such as potassium hydroxide and lithium methoxide have been utilized in concert with SmI_2 to reduce esters, anhydrides, amides, and carbonyls to the corresponding alcohols.[7] In each of the cases cited above, cosolvent or additives were essential for the reductions or bond-forming processes mediated by SmI_2.

Although additives and ligating cosolvents are an important component in the success of many SmI_2-mediated reactions, little mechanistic work has been carried out to determine how they influence the reactivity of the reducing reagent. Molander addressed the utility of HMPA in SmI_2-mediated reactions by examining its role in the cyclization of unactivated olefinic ketones.[8] The results of this study displayed a clear correlation between HMPA concentration and high diastereoselectivities and product distribution in SmI_2-promoted reductive coupling reactions. Crystallographic analysis of SmI_2−HMPA complexes clearly shows that coordination of HMPA to SmI_2 produces a sterically crowded reductant.[9] Work in our laboratory more fully delineated the role of HMPA in THF. We found that HMPA coordinates to monomeric SmI_2 and produces a more powerful reductant. The stoichiometry of the reductant in THF was proposed to be SmI_2HMPA_4.[10]

Since coordination of HMPA produces a sterically crowded reductant, it is likely that different ligands (cosolvents or additives) may provide Sm(II)-based reducing reagents with different selectivities. The mechanistic pathway in reactions of SmI_2 may also be governed by the order of addition of substrates and cosolvents. Hoz found that the sequence of addition of SmI_2,

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substrate, and alcoholic cosolvent had a large impact on the selectivity of reduction of activated olefins[11] because of the ability of SmI$_2$ to coordinate with both the cosolvent and the substrate.

During our initial studies on the influence of additives on the reducing power of SmI$_2$ we found that the addition of lithium salts containing a bromide or chloride counterion increased the reducing power of the Sm(II) reductant and promoted the pinacol coupling of ketones.[12] This protocol was also reported to be useful in the reductive cleavage of α-functionalized amides.[13] Herein we report our detailed investigation of the influence of LiBr and LiCl on the reactivity and selectivity of SmI$_2$ coupling of alkyl iodides and ketones. Potential mechanistic pathways for these reactions are discussed based on product distributions, rate studies, and spectroscopic and electrochemical results.

Experimental Section

THF was distilled from sodium benzophenone ketyl, under nitrogen. All solvents employed in this study were degassed by several cycles of evacuating the vessel and refilling with nitrogen. HMPA was dried by vacuum distillation from NaOH pellets or MgSO$_4$. The LiCl and LiBr salts were dried in a vacuum oven at 140 °C. Distilled THF and HMPA were checked by Karl Fischer titration. Dried solvents and salts were stored in an Innovative Technology, Inc. drybox containing a nitrogen atmosphere and a platinum catalyst for drying.

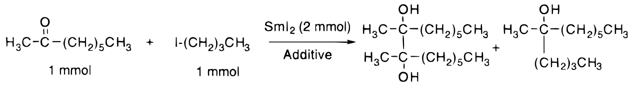
The additive or cosolvent was placed in a flame-dried 100-mL round-bottom flask with a stirring bar. THF (5 mL) was used to dissolve the additive (LiCl required 10 mL of solvent). Next, 20 mL of 0.1 M SmI$_2$ (2 mmol) in THF was added to the flask containing the additive and allowed to stir. In a separate vial, the ketone (1 mmol) and the alkyl iodide (1 mmol) were stirred in 10 mL of THF. The mixture of the alkyl halide and ketone was then added to the SmI$_2$−additive solution. After the reaction was complete (typically a few minutes) the flask was exposed to air to quench the reaction.[4a] Ether extractions were performed with a concentrated Na$_2$S$_2$O$_3$ solution (4×) and a concentrated NaCl solution (3×). In the case of HMPA additive, additional extractions were performed with H$_2$O (5×). The ether layer was dried over MgSO$_4$, filtered, and condensed on the rotary evaporator. The reactions were examined by GC-MS and ^{1}H NMR spectroscopy.

The redox potentials of the SmI$_2$ and SmI$_2$−additive mixtures in THF were independently measured by cyclic voltammetry employing a BAS 100B electrochemical analyzer. The working electrode was a standard glassy carbon electrode. The electrode was polished with 0.05 mm polishing alumina or cleaned in an ultrasonic bath. The electrode was rinsed with acetone or ethanol and dried before each run. The auxiliary electrode was a platinum wire. The reference electrode was an SCE. The electrolyte employed in all experiments was either tetrabutylammonium hexafluorophosphate or lithium iodide. The concentration of SmI$_2$ in each of the electrochemical experiments was 0.5 mM. All solutions were prepared in the drybox and transferred to the electrochemical analyzer for analysis.

Results and Discussion

We examined the influence of lithium halides on the SmI$_2$-mediated reductive coupling of alkyl halides with ketones, initially on the assumption that these additives would be a safe and convenient alternative to HMPA. We chose the SmI$_2$-mediated coupling of 1-iodobutane with 2-octanone as a model for Barbier coupling. The reactions were run by combining 1 mmol each of the alkyl iodide and the ketone. The halide and ketone were then added to 2.2 mmol of SmI$_2$ containing 8 equiv of LiBr in THF. Instead of obtaining the samarium Barbier product (5-methyl-5-undecanol), we obtained the pinacol coupled product (7,8-dimethyl-7,8-tetradecanediol), while the butyl iodide remained unreduced. This startling discovery led us to examine this system more fully to understand the influence of these additives on the outcome of this reaction.

Table 1. Coupling Data for the Reaction of 1-Iodobutane and 2-Octanone with SmI$_2$ and Different Additives[a]



additive	equiv/SmI$_2$	% product formed[b] pinacol	% product formed[b] Barbier	% unreacted starting material
no additive		23	59	18
HMPA	8	<1	91	8
LiCl	8	64	21	15
LiBr	8	98	<1	<1

[a] Conditions: 1 mmol of the ketone and 1 mmol of the alkyl iodide were combined in 10 mL of THF and added to a 20 mL solution of 0.1 M SmI$_2$ in THF containing 4 equiv of additive. [b] Based on GC yields. All products were isolated and examined by ^{1}H NMR and GC-MS.

Table 1 contains the results of the SmI$_2$ coupling of 1-iodobutane and 2-octanone in the presence of no additive, HMPA, LiBr, and LiCl. While the experiment containing no additive provides the Barbier product predominantly, some of the pinacol product is also formed. The reaction in the presence of HMPA provides only reductive coupling of the alkyl halide and ketone. The experiments with LiBr and LiCl provide the pinacol coupling product and very little of the reductive coupling product. We attempted numerous couplings of various alkyl iodides (iodomethane, 1-iodohexane) and ketones (cyclohexanone, 2-butanone, 2-pentanone); all combinations of alkyl halides and ketones yielded predominantly the pinacol product in the presence of LiBr or LiCl. While the addition of lithium bromide and lithium chloride to SmI$_2$ may be a convenient protocol for reductive pinacol couplings in the presence of an easily reduced halide, these findings also raise some interesting mechanistic questions.

Several mechanistic possibilities may explain the experimental results: (1) The lithium cation may coordinate to the carbonyl and make it easier to reduce; (2) the bromide and chloride anions may coordinate to the Sm(II) and alter its reactivity; (3) the lithium salts may enhance or prevent aggregation of SmI$_2$, making it more or less reactive; and (4) Sm^{2+} may ligate to the alkyl iodide and enhance an S$_N$2 reaction with chloride or bromide in solution, thereby producing a less reactive alkyl halide. A combination of some of these effects is also possible. The approaches described below were used to delineate the probable mechanism(s) responsible for the unusual reactivity of SmI$_2$−LiBr or LiCl combinations.

A careful product analysis of the SmI$_2$-mediated coupling of 1-iodododecane and 2-octanone in the presence of HMPA, LiBr, LiCl, and LiI was carried out. This enabled us to easily identify all of the products by GC/MS. The results are contained in Table 2. The noteworthy feature of the reaction products shown in Table 2 is that the combination of SmI$_2$ and LiBr gave exclusively the pinacol coupling product, while the SmI$_2$−HMPA combination gave only the Barbier product. If the reactions were quenched in air 1 min after the introduction of substrates into the SmI$_2$−LiBr reductant, the iodododecane was unreduced. If longer reaction times were employed, dodecane appeared in the mixture with the pinacol product. When 1 mmol of both 2-octanone and iodododecane were added to 1 mmol of the SmI$_2$−LiBr reductant, the pinacol product was formed

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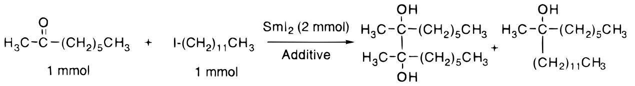
Table 2. Coupling Data for the Reaction of 1-Iodododecane and 2-Octanone with SmI_2 and Different Additives[a]



additive	equiv/SmI_2	% product formed[b] pinacol	% product formed[b] Barbier	% unreacted starting material
no additive		27	63	10
HMPA	8	<1	98	<1
LiCl	8	56	40	4
LiBr	8	99		<1
LiI	8	25	68	7

[a] Conditions: 1 mmol of the ketone and 1 mmol of the alkyl iodide were combined in 10 mL of THF and added to a 20 mL solution of 0.1 M SmI_2 in THF containing 8 equiv of additive. [b] Based on GC yields. All products were isolated and examined by ^1H NMR and GC-MS.

exclusively, with quantitative recovery of the 1-iodododecane. The addition of LiCl to SmI_2 produces a minor amount of the Barbier coupling product and a majority of the pinacol product. The addition of LiI to SmI_2 led to the production of the Barbier product and a smaller amount of the pinacol product.

It is possible that coordination of Li^+ to the carbonyl could decrease the reduction potential of the carbonyl[14] and enhance the rate of reduction, thus providing a pathway to pinacol formation. Curran and co-workers recently described a method for the reductive coupling of aromatic dimethylacetals utilizing SmI_2 in conjunction with Lewis acids.[15] To test this supposition, tetra-*n*-hexylammonium bromide (THAB) (4 equiv) was used in place of lithium bromide to replace the hard Lewis acid, Li^+. The reaction of cyclohexanone and 1-iodobutane employing SmI_2−(THAB) again produced the pinacol coupling product exclusively. The addition of 2 equiv of THAB to SmI_2 in THF gave a UV−visible spectrum that was identical to the one obtained by the combination of SmI_2 and LiBr. The addition of lithium iodide produced similar results as those obtained for SmI_2 with no additive. Although the lithium cation may play a small role in the pinacol coupling reactions, the reducing species created by the combination of SmI_2 and the halide counterions evidently provides the impetus for this reaction.

The addition of LiBr or LiCl to SmI_2 resulted in a color change from blue to purple. Examination of SmI_2 in combination with each of the additives employing UV−vis spectroscopy showed it is likely that the halide counterions are coordinating to the Sm(II) as shown in Figure 1. The charge-transfer bands of SmI_2 at 552 and 616 nm were shifted to lower wavelengths with the addition of LiBr or LiCl. These results suggest that the reducing power of SmI_2 should increase upon the addition of the lithium halide salts assuming that its HOMO is raised in energy.

Table 3 contains electrochemical data for the oxidation potentials of SmI_2, SmI_2−LiBr, SmI_2−LiCl, and SmI_2−HMPA. Although SmI_2 containing the additives all display more negative oxidation potentials than SmI_2 alone, they are all within a few hundred millivolts of each other. The reducing power of the complexes is therefore probably not the only factor affecting the selectivity of the reductants produced from the SmI_2 and additives. When λ_{max} is plotted against the redox potential, a linear correlation with a correlation coefficient of 0.997 is obtained. Although the use of three data points is statistically precarious, a correlation is suggested. Ryan[16] and Nugent[17] have found similar correlations between the reduction potential and the electron-transfer bands of halocoordinated M^{4+} and M^{3+} ions in acetonitrile. We found that the addition of excess lithium halide had no effect on λ_{max} or the redox potential of the complex. These results lead us to postulate that the bromide and chloride counterions displaced the iodide ligands on SmI_2 thereby producing $SmBr_2$ and $SmCl_2$.

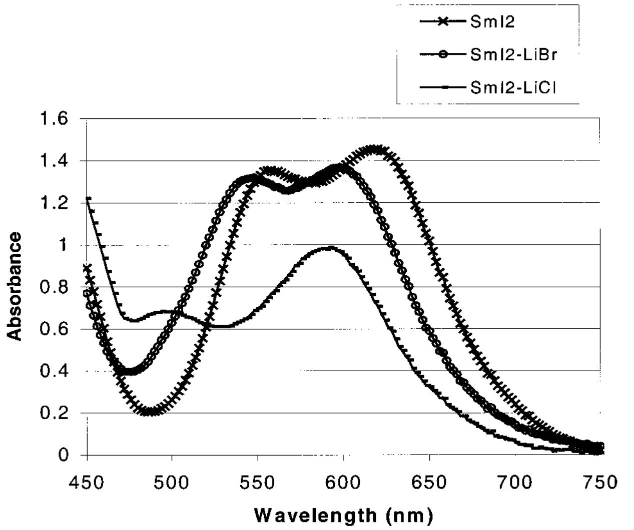


Figure 1. UV−vis spectra of SmI_2 (×), SmI_2−LiBr (○), and SmI_2−LiCl (−) in THF.

Table 3. Electrochemical Data for SmI_2 and SmI_2−Additive Complexes[a]

SmI_2−additive	$E_{1/2}$ (V)
SmI_2	−0.98 ± 0.04
SmI_2−HMPA	−1.75 ± 0.06
SmI_2−LiBr	−1.55 ± 0.07
SmI_2−LiCl	−1.78 ± 0.10

[a] Conditions: All redox data were determined with cyclic voltammetry using a sweep rate of 100 mV/s vs a SCE reference, and 0.5 M LiI (for SmI_2 and SmI_2−HMPA) electrolyte in THF. Tetra-*n*-hexylammonium bromide (0.5 M) or tetra-*n*-hexylammonium chloride (0.5 M) was used for SmI_2−LiBr and LiCl measurements. The concentration of SmI_2 in all experiments was 5 mM.

Samarium(II) bromide and samarium(II) chloride have been previously synthesized, but they are insoluble in THF.[18,19] We prepared $SmBr_2$ by the reduction of the $Sm^{III}Br$ salt with lithium metal. Treatment of a heterogeneous mixture of $SmBr_2$ in THF via sonication produced a purple solution. Examination of the solution by UV−vis spectroscopy showed that the spectrum was identical to the one obtained for the SmI_2−LiBr combination. We were unable to dissolve the $SmCl_2$, even after extended sonication. The reductant produced from the combination of SmI_2 and LiCl begins to precipitate out of solution after a few hours. If the preparation of both $SmBr_2$ and $SmCl_2$ from Sm(III) precursors produces reductants that are insoluble in THF, why would the same reductants be soluble (initially) when produced from SmI_2? The standard preparation of $SmBr_2$ and $SmCl_2$ involves reduction of $SmBr_3$ and $SmCl_3$, both of which are insoluble in THF. Many lanthanide salts are known to be highly aggregated, so reduction of the poorly solvated starting material can lead to an insoluble Sm(II) species. Work in our

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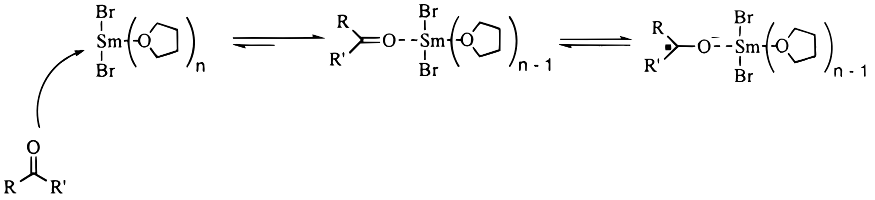
Scheme 1



laboratory has clearly shown that SmI_2 is a solvated monomer in THF under standard conditions.[10] Displacement of I^- from solvated SmI_2 is more likely to produce a soluble, solvated $SmBr_2$ or $SmCl_2$ reductant.

The results and observations described above are consistent with the following: (1) The lithium cation plays at best a small role in the pinacol coupling observed with SmI_2−LiBr or LiCl combinations; (2) bromide or chloride counterions do not displace the iodide from 1-iodododecane; (3) bromide and chloride counterions coordinate to SmI_2, probably displacing the iodide ligands; (4) the addition of bromide and chloride salts to SmI_2 produces a more powerful reductant; and (5) deaggregation of SmI_2 does not occur, it exists as a solvated monomer. Clearly it is the coordination of bromide and chloride counterions to SmI_2 that provides the change in selectivity and reactivity of the Sm(II) reductant.

The question as to why the SmI_2−LiBr or −LiCl combinations (which are presumably $SmBr_2$ and $SmCl_2$) preferentially reduce a ketone in the presence of a more easily reduced alkyl iodide remains to be answered.[20] Lanthanides are known to be highly oxophilic, so it is reasonable to suppose that a carbonyl group would have a higher affinity for Sm(II) than a halide. If coordination between a ketone and a Sm(II) reductant is energetically favored, this will lead to an increased probability of inner-sphere ET. Even though alkyl halides are thermodynamically easier to reduce than ketones (based on redox potentials), an inner-sphere ET will lead to a dramatic rate enhancement as compared to an outer-sphere process. The pioneering work of Kochi provides examples that show that inner-sphere electron transfer can occur at a rate 10^5 times faster than expected for an outer-sphere process.[21] In the organometallic compounds employed by Kochi and co-workers, steric substituents played a large role in determining whether electron transfer occurred via an inner- or outer-sphere process.

The recent work of Skrydstrup and co-workers supports the hypothesis described above. They found that electron transfer (ET) from SmI_2 in THF to benzophenone was an inner-sphere process, while ET to benzyl bromide was much closer to an outer-sphere process.[22] These results indicate that SmI_2 has a higher affinity for THF than for a benzyl halide, while carbonyls are capable of displacing THF ligands bound to SmI_2. We propose that during the reductive coupling of an alkyl halide and a ketone, SmI_2 reductively cleaves the alkyl halide to a radical and a halide anion, and another equivalent of SmI_2 reduces the radical to an organosamarium reagent. Simultaneously, ketones can coordinate to SmI_2 and be reduced to ketyls. The competing pathways lead to a mixture of products. It is our supposition that the reagent formed from SmI_2 and LiBr or LiCl reduces ketones through an inner-sphere mechanism (Scheme 1). The electrochemical results in Table 3 show that SmI_2−LiBr and −LiCl combinations are more powerful reductants than SmI_2, so it is reasonable to expect that they would reduce a ketone much faster than SmI_2 alone. The soluble SmI_2−LiBr combination reduces ketones selectively in the presence of an alkyl halide. The SmI_2−LiCl combination produces a less soluble but more powerful reductant capable of easily reducing alkyl halides or ketones, which leads to a mixture of products.

Attempts to determine the bimolecular rate constant for the reduction of ketones by SmI_2−LiBr or −LiCl utilizing standard techniques were unsuccessful, because the reactions occurred too rapidly. Estimation of the bimolecular rate constants for outer-sphere reductions were carried out using the redox potentials of the samarium reductants and ketones in combination with Marcus theory. We used a lower limit of −2.5 V for the $E_{1/2}$ (vs SCE) of an alkyl ketone.[23] The bimolecular rate constant for the reduction of an alkyl ketone by $SmBr_2$ was estimated to be in the range of 3.4×10^{-6} M^{-1} s^{-1} while the rate constant for $SmCl_2$ was found to be 4.9×10^{-3} M^{-1} s^{-1}. These estimated rate constants are inconsistent with the observed reaction rate and suggest that the reduction of ketones by $SmBr_2$ and $SmCl_2$ occurs through an inner-sphere ET.

If the reagent produced from the combination of a bromide or chloride with SmI_2 produces a reductant that coordinates to ketones and reduces them selectively over alkyl iodides, then why does HMPA promote reductive coupling of halides and ketones so efficiently? Examination of the crystal structure of $[SmI_2(HMPA)_4]$ shows that the reductant is very hindered. Bulky ligands such as HMPA produce sterically congested complexes that make it difficult for reducible species such as carbonyls and halides to enter the inner sphere of the Sm(II) complex. Calorimetric experiments verify that HMPA has a high affinity for SmI_2, so it is unlikely that typical ketones, aldehydes, and alkyl halides will displace it.[10] Therefore, we hypothesize that basic cosolvents such as HMPA will produce Sm(II) reagents that carry out reductive transformations via outer-sphere electron transfer (Scheme 2).

Recent mechanistic studies in our lab support the hypothesis described above. Standard redox potentials in conjunction with Marcus theory were utilized to estimate the bimolecular rate constant for outer-sphere ET from $SmI_2(HMPA)_4$ to a primary radical.[24] Comparison of the estimated rate constant with one determined utilizing a "radical clock" only differed by a factor of 2, suggesting that the $SmI_2(HMPA)_4$ reductant reduces primary radicals through predominantly an outer-sphere process. This finding indicates that there is very little interaction between the Sm−HMPA reductant and radical in the transition state leading to carbanion formation.[25] Since alkyl halides are reduced via an outer-sphere mechanism by SmI_2, it is reasonable to

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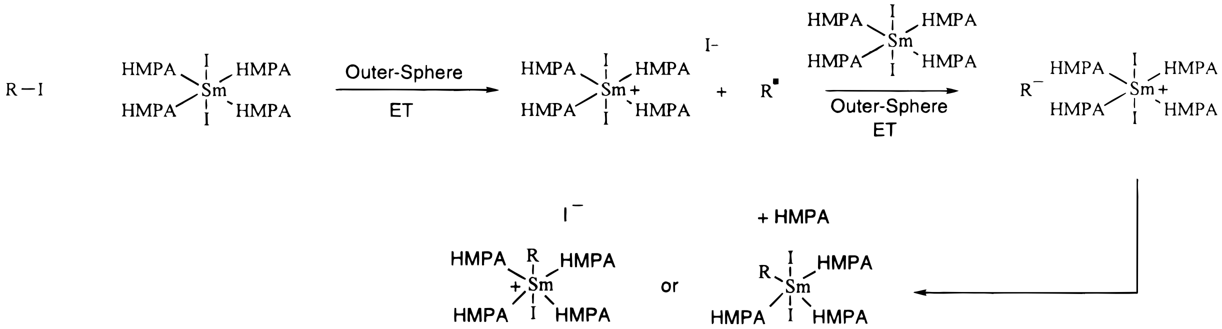
Scheme 2



assume that they will be reduced through the same mechanism by the sterically crowded Sm(II)−HMPA reductant.

During the SmI_2-mediated reductive coupling of halides and carbonyls in the presence of HMPA, the sterically congested $[SmI_2(HMPA)_4]$ reductant can reduce either a carbonyl or a carbon−halogen bond. The alkyl iodide bond will be reduced at a much faster rate (via an outer-sphere mechanism) because it has a lower (less negative) reduction potential than the carbonyl. Reduction by the outer-sphere pathway leads to the formation of an organosamarium reagent (Scheme 2) which can attack a ketone and produce a carbinol after workup, but the same procedure utilizing LiBr in place of the HMPA produces $SmBr_2$, a reagent that is capable of coordinating with a ketone, reducing it preferentially through an inner-sphere electron transfer (Scheme 1) leading to pinacol formation.

Conclusions

The experiments described in this paper show that it is possible to alter the mechanism of Sm(II)-mediated reactions by changing the steric bulk around the reductant. Furthermore, our findings clearly reveal the ability to “fine tune” both the selectivity and reactivity of Sm(II) reagents. We are currently exploring the use of the protocols described above to carry out selective inter- and intramolecular reductive couplings of multifunctional substrates. These findings will be presented in a forthcoming series of papers.

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Supporting Information Available: Cyclic voltammograms, digital simulation data, and UV−vis spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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