Samarium(II) Iodide Mediated Reductions − Influence of Various Additives

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Samarium(II) iodide is a one-electron transfer reagent that has become highly appreciated as a mild and selective reducing agent in recent years. It has been found experimentally that various additives and co-solvents largely control the reactivity of SmI_2. This microreview provides an overview of the current knowledge of the reagent SmI_2 as a reducing agent, in particular with additives that increase its reactivity. The use of various proton sources is covered, as well as the effect of co-solvents. Furthermore, the very powerful reagent mixture SmI_2/H_2O/amine is also described.
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Introduction

Reductions constitute a fundamental class of reactions in synthetic organic chemistry, the most common reducing agents are hydrogen gas in combination with Pd/C or active catalysts, alkali metals and hydrides. However, the chemoselectivity of these reagents is often low, which prevents effective synthesis of new more complex target molecules. It is in this respect that the mild reducing agent SmI_2, introduced by Kagan and co-workers in the late 1970s, is receiving much interest today. Kagan showed that SmI_2 promotes reduction of halides, aldehydes, ketones and carboxylic acids, and reductive eliminations and deoxygenations.[1] Since then, a number of SmI_2-based reductive couplings and sequenced reactions have been developed,[2] and new applications are steadily being discovered. SmI_2 is generally considered a selective single-electron transfer reagent that generates carbon-centred radicals from halides or related species. Therefore, it is particularly useful for ketone-olefin coupling reactions, pinacol coupling reactions and radical addition to alkenes and alkynes. SmI_2 has even begun to appear frequently in natural product and multi-step synthesis.[3] Due to the intense interest in this reagent, SmI_2 is now commercially available as a 0.1 M solution in THF.

Over the years, several reviews have been published on the use of SmI_2 in various reduction and coupling reactions.[4] However, recently there has been considerable progress in the use of SmI_2 as a simple reducing agent. SmI_2 represents an important reagent, but it is often necessary to enhance the reactivity by adding various salts and co-solvents. Due to limited knowledge of the active species in these mixtures, the emphasis in this review is not on the

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MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

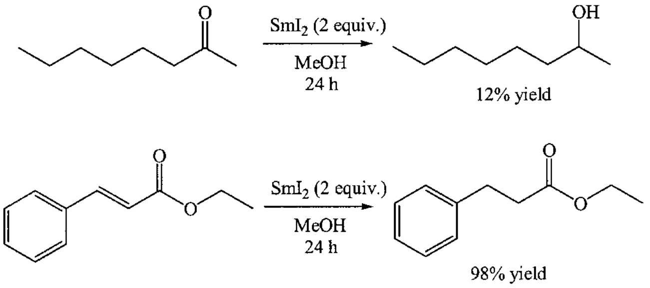
structures, but on the effect of various additives. The possibility to perform coupling reactions catalytically on SmI_2, with the aid of, for example, mischmetal has also been reported. However, this will not be discussed any further since a recent review is available,[5] in addition, the focus here will be on SmI_2-mediated reductions. Our intention is to deliver an updated summary of SmI_2-mediated reductions that may inspire further studies on structures and mechanisms of this highly interesting reducing agent.

Preparation of SmI_2

The compound SmI_2 has been known for more than seventy years,[6] but it did not receive much attention until Kagan and co-workers published their pioneering work.[1] They discovered the mild reducing properties of SmI_2 and a simple method for its preparation. A number of reports of SmI_2 prepared in THF from excess samarium metal and an iodine source, such as diiodoethane, diiodomethane, iodine or iodoform, have been published.[1,7] SmI_2 in THF is often obtained quantitatively as a deep blue solution with a concentration of 0.1 M. If excess iodine is used in the preparation, SmI_3 is formed, and the solution does not reach the intense dark blue, almost black, colour associated with SmI_2. Few reports describe the use of bulk solvents other than THF; however, SmI_2 can be readily produced in tetrahydropyran, acetonitrile, pivalonitrile and DME.[8] Kagan and co-workers concluded that addition of HMPA to SmI_2 in acetonitrile neither enhances the reactivity nor improves the amount of pinacol coupling, and that the maximum concentration of SmI_2 is generally lower in solvents other than THF.[8a] However, a thorough investigation into the reaction rates of various reductions and couplings with SmI_2 in different solvents is unfortunately not yet available.

Addition of Alcohols and Water

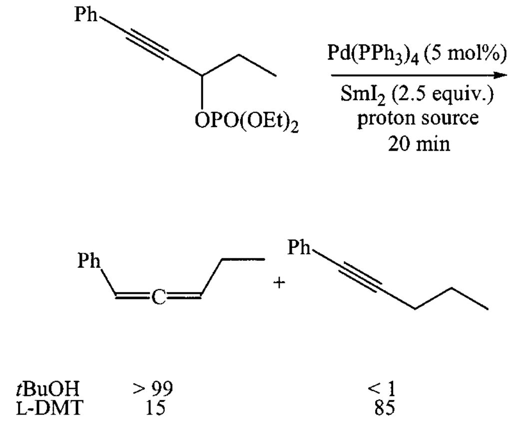
Ever since the introduction of SmI_2 in synthetic applications, it has been realised that various proton sources may be used to alter the product composition. By far the most commonly used alcohols in SmI_2-mediated reductions are methanol and *tert*-butyl alcohol (Scheme 1).[1b,9]



Scheme 1. Reduction of ketones and α,β-unsaturated esters with SmI_2 and methanol

The reductions of α,β-unsaturated esters proceed smoothly with either methanol or *tert*-butyl alcohol, but it appears that both of these alcohols are poor proton donors in the reduction of ketones, thus resulting in low yields.[1b]

The modification of the proton source has been investigated in the reduction of propargylic esters, in which a very high regioselectivity was obtained merely by changing the proton source from *t*BuOH to dimethyl L-tartrate (L-DMT). The allene isomer was obtained with *t*BuOH, while in the case of L-DMT an excess of the acetylene isomer was formed (Scheme 2).[10]



Scheme 2. Reduction of a propargylic ester with *t*BuOH and L-DMT

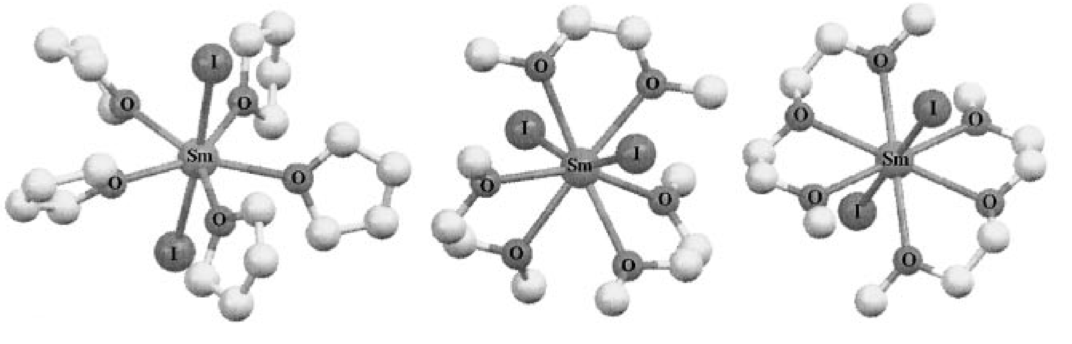
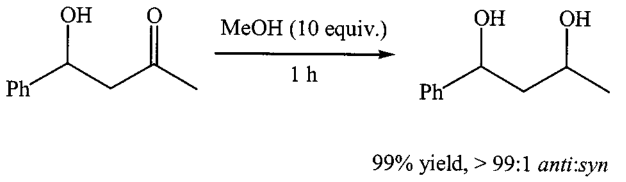


Figure 1. Ball-and-stick representation of the solid-state structures of $SmI_2(THF)_5$, $SmI_2(glyme)_3$ and $SmI_2(diglyme)_2$; hydrogen atoms have been omitted

Keck and co-workers have shown that the presence of nearby chelating groups has a remarkable impact on the rates of reduction.[11] They concluded that methanol is the additive of choice to obtain high yields without loss of diastereoselectivity in the reduction of, for example, β-hydroxy ketones (Scheme 3).



Scheme 3. SmI_2/MeOH-mediated reduction of β-hydroxy ketones

Previous studies on solid-state structures of SmI_2, crystallised from ether solutions, have shown that ethers are excellent coordinating groups to SmI_2 (Figure 1).[8c,12]

As chelating ethers are known to coordinate to SmI_2, we wanted to explore the use of alcohols with coordinating groups as alternatives to other simple alcohols. The initial rate of reduction of a ketone (3-heptanone) with various alcohols was investigated, and chelating ether groups on the alcohol were used since they were expected to coordinate to Sm^{II}, thus placing the proton source close to the source of electrons (Figure 2).[13] This should, therefore, produce a strong reducing agent, resembling hydrogen radicals or hydride reagents.

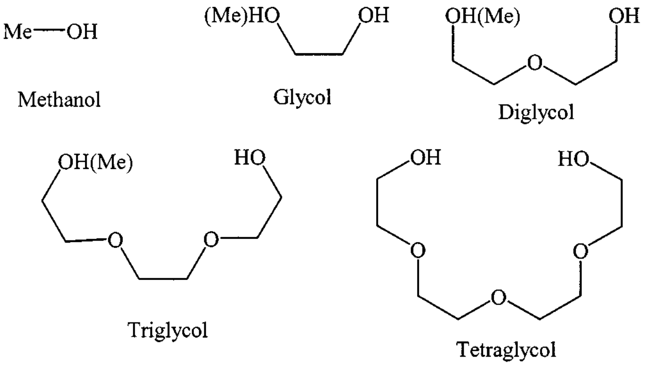


Figure 2. Chelating alcohols/glycols

The introduction of coordinating ether functions to the alcohol revealed a correlation between the rate and the number of coordinating groups. Monomethyl glycols gave higher rates of reduction for each extension of the ethereal group chain. SmI_2/tri(ethylene glycol) monomethyl ether resulted in a rate enhancement of approximately 5 times relative to that of SmI_2/MeOH. Further rate enhancements were noticed when glycols were used; the fastest rate for the glycols appeared to be with di(ethylene glycol) which was more than 70 faster than that with methanol, or 255 times faster than the rate with THF. The significant increase in rate with diglycol suggests that a dimeric transition state is present (Scheme 4). The presence of a primary kinetic isotope effect proved that the rate-limiting step in this reduction is the transfer of at least one proton. It was also shown that full occupancy of the coordination sphere, as with the tetradentate ligand tetra(ethylene glycol), resulted in a decrease in the rate. The coordination plays an important role in SmI_2-mediated reductions.

It has been found that steric hindrance around the substrate also affects the rate of reduction.[14] The less sterically crowded 4-phenyl-2-butanone was reduced approximately 130 times faster than 2-methyl-3-heptanone with the reagent mixture SmI_2/diglycol.

Recently, Flowers and co-workers investigated the role of the acidity constant (pK_a) of the alcohol in the reduction of acetophenone and found a linear correlation for the reaction rate vs. pK_a.[15] The more acidic alcohols resulted in higher reduction rates. However, water did not fit into this correlation, most likely due to unique, unexplained reactivity and complexation properties (Figure 3).[16]

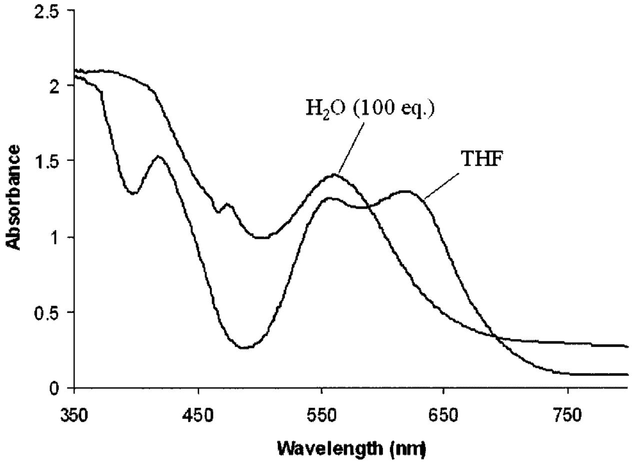
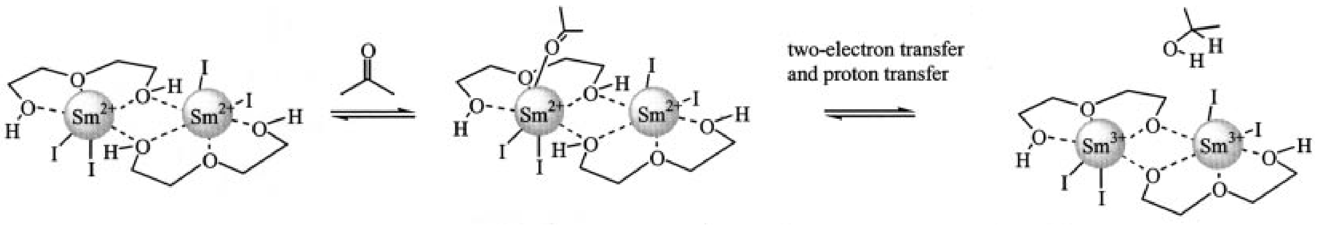


Figure 3. Comparison of SmI_2 in THF and SmI_2 in water

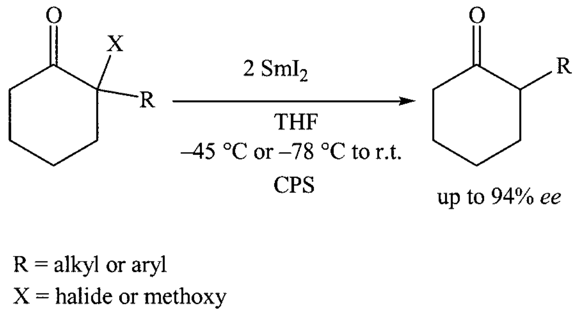
Nakamura and co-workers developed an enantioselective reduction of α-halo- and α-methoxy ketones with C_2-symmetric chiral diols, e.g. (*R*)-2,2′-bis[(*S*)-2-hydroxy-2-phenylethoxy]-1,1′-binaphthyl [(*R*,*S*)-DHPEB].[17] High yields were obtained with up to 94% *ee* within 2 h at −45 °C (Scheme 5). These diols contain four or five coordinating functional groups and, therefore, bind tightly to SmI_2, providing a transition state that facilitates the asymmetric protonation of the enolate.

Alcohols have been the dominating proton sources in SmI_2-mediated reductions, while water, even though it is also a good proton source, has not been employed to the same extent. Some of the previously mentioned studies confirm that the use of water leads to different product compositions and occasionally higher yields.[10,11a] Good to excellent yields were reported in the conversion of aromatic carboxylic acids to alcohols with a SmI_2/H_2O system (Scheme 6).[18]

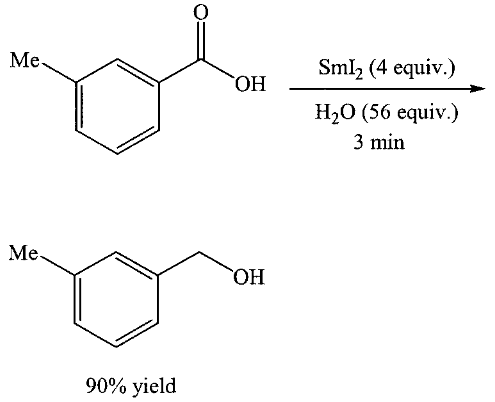
Kamochi and Kudo have extensively studied the use of Brönsted acids and bases as additives in SmI_2-mediated reduction of carboxylic acids, amides, nitriles, pyridines and phenol derivatives. In particular aromatic compounds were reduced in high yields, and the use of acids and bases in



Scheme 4. SmI_2/diglycol-mediated reduction of a ketone



Scheme 5. Enantioselective reduction mediated by a chiral proton source (CPS)

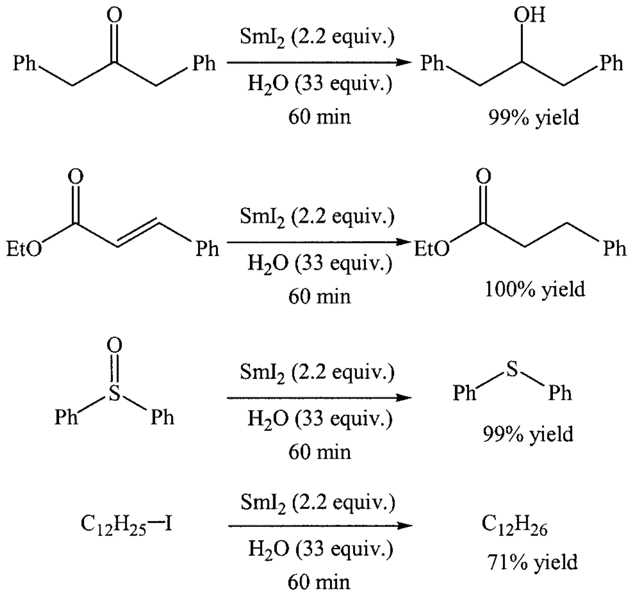


Scheme 6. Reduction of aromatic carboxylic acids with SmI_2/H_2O

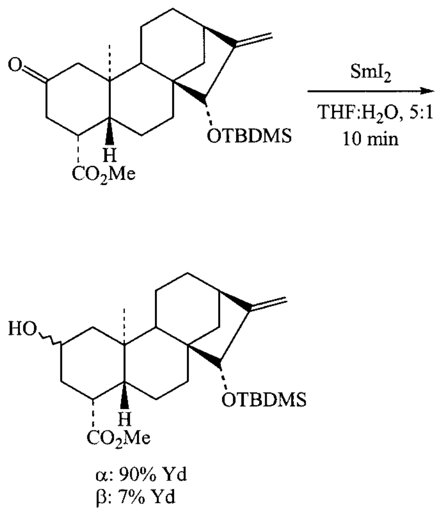
SmI_2-mediated reductions indicates that certain reactions are dependent on pH.[19]

Curran and co-workers reported on the SmI_2-mediated reduction of various functional groups in the presence of water (Scheme 7).[20] The reduction rate of ketones, α,β-unsaturated esters, sulfoxides and alkyl iodides was significantly accelerated by the addition of water. The results indicated that the accelerating role of water may be more intricate than simply acting as a proton donor, i.e. it may both accelerate the reduction by enhancing the reducing power as well as acting as a proton donor.

Only a few examples of high diastereoselectivity have been reported for SmI_2/H_2O-mediated reductions of ketones. One example of such a reduction is a step in the total synthesis of Atractyligenin (Scheme 8), which gave selectivity for the α-isomer.[21]

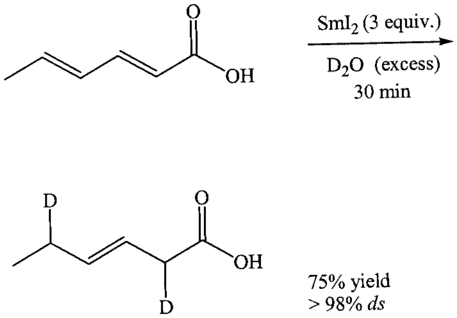


Scheme 7. Various SmI_2/H_2O-mediated reductions



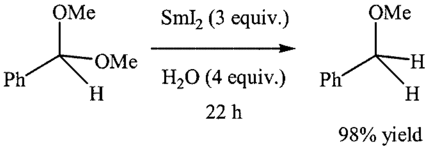
Scheme 8. Diastereoselective reduction of Atractyligenin with SmI_2/H_2O

Selective isotopic labelling with deuterium is an important feature, since it can be used to establish mechanistic pathways. This can be readily accomplished using deuterium oxide instead of water in SmI_2-mediated reductions. Deuterium oxide is one of the most inexpensive available sources of deuterium; in addition, it is a nonhazardous compound. Dideuterated carboxylic acids have been successfully synthesised from unsaturated acids in high yields and diastereoselectivities (Scheme 9).[22]



Scheme 9. SmI_2/D_2O reduction of unsaturated carboxylic acid

Studer and Curran have reported on the reductive demethoxylation of aromatic dimethylacetals in the presence of SmI_2/H_2O with excellent yields. Comparison was also made with TFA and $BF_3{\cdot}Et_2O$ in this study, which gave pinacol as the major product, while addition of water gave mostly reduction (Scheme 10).[23]

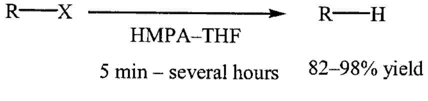


Scheme 10. Reductive demethoxylation with SmI_2/H_2O

SmI_2-HMPA-Mediated Reductions

The Effect of HMPA on Various Simple Reductions

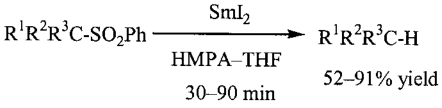
In 1987, Inanaga and co-workers reported that the addition of hexamethylphosphoramide (HMPA) to THF solutions of SmI_2 resulted in a substantial enhancement of the rate of reduction and reductive coupling.[24] Carbon−halogen bonds were effectively and quantitatively reduced to C−H bonds by a mixture of SmI_2-HMPA in THF (Scheme 11). Alkyl, vinyl and aryl halides were rapidly reduced, with approximately 5% HMPA as co-solvent in THF. Upon the addition of HMPA to the SmI_2 solution in THF, the colour changed from blue to purple.



Scheme 11. General SmI_2-HMPA-mediated reduction of alkyl halides

The mixture of SmI_2-HMPA was reported to promote reductive dimerisations of, for example, unsaturated carbonyl compounds.[25] Cabrera and Alper reported that SmI_2-HMPA was also efficient for selective reduction of α,β-unsaturated carbonyl compounds (the compounds investigated were esters, acids, amides and anhydrides).[26]

The reactive SmI_2-HMPA mixture was later proven to be useful for desulfonylation of various phenyl sulfones, as reported by Künzer and co-workers (Scheme 12).[27]



Scheme 12. SmI_2-HMPA-mediated reduction of phenyl sulfones

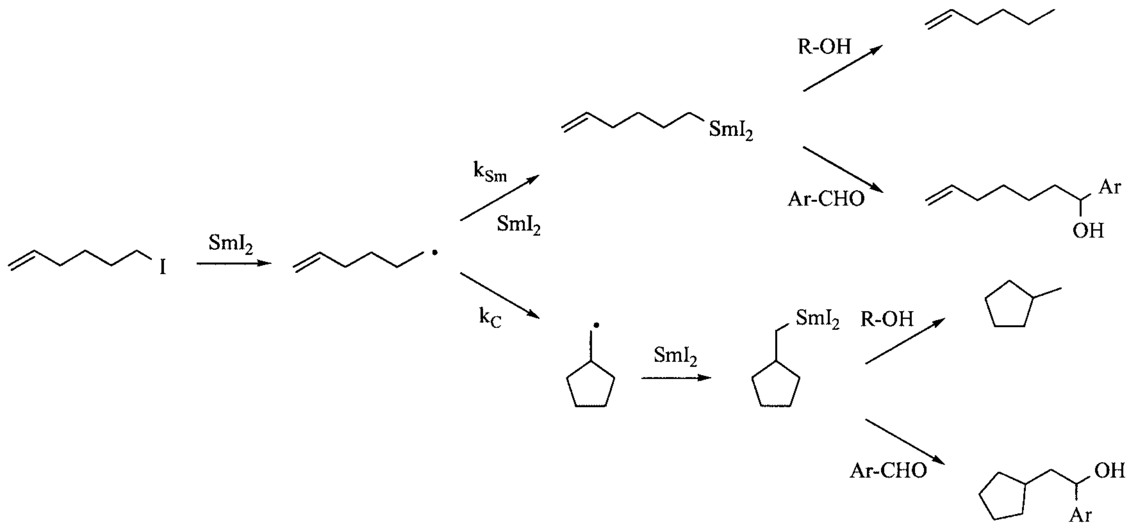
Fuh and co-workers have studied the kinetics of the SmI_2-mediated reduction of an aliphatic ketone to an alcohol. In the absence of HMPA, the reduction of 2-heptanone to 2-heptanol is very slow, only 28% of the ketone is reduced after 16 days. However, with only one equivalent of HMPA added, the reactions are reported to be complete in less than one hour.[28]

The Structure and Mechanism of the SmI_2-HMPA Reagent

The reduction of a simple functional group with a single electron transfer reagent must involve the formation of a radical intermediate. If there are several functional groups in the compound, there is a chance that this radical rearranges or undergoes an intramolecular reaction. Curran has utilised the radical clock technique to investigate the kinetics of reductions in the presence of HMPA.[29] The amount of directly reduced product was observed to increase upon addition of HMPA. They also predicted the presence of an alkylsamarium intermediate, which could either be coupled with an aldehyde or reduced in the presence of an alcohol, directly or through rearrangement, depending on the ratio of the rate constants k_{Sm}/k_C (Scheme 13).

It was not until Hou and Wakatsuki reported on the solid-state structure of $SmI_2(HMPA)_4$ that mechanistic details for the increased reactivity of the SmI_2-HMPA mixture could be rationalised (Figure 4).[30] The square-planar arrangement with four HMPA molecules coordinating to Sm^{II} could be the key for the selectivity of these reactions. The substrates can either approach the metal centre from above or below.

Interestingly, when 10 equivalents of HMPA were added to the SmI_2 solution, purple crystals of $Sm(HMPA)_6I_2$ were formed.[31] It was suggested that the six bulky HMPA molecules, coordinated to the samarium centre, block the approaching substrate, thereby giving rise to a lowering of selectivity through an outer-sphere mechanism. Flowers and co-workers reported, based on linear sweep voltammetric studies,[32] that the oxidation potential of SmI_2 in THF increases from −1.33 V to −2.05 V (vs. $Ag/AgNO_3$ in THF) when four equivalents of HMPA was added. Further addition of HMPA did not affect the oxidation potential. They also determined the standard potentials $E°(SmI_2^+/SmI_2)$ and $E°(SmI_2^+\text{-HMPA}/SmI_2\text{-HMPA})$ in THF to be −0.98 ± 0.04 and −1.75 ± 0.06 V vs. SCE, respectively.[33] Accordingly, the change in reducing power for SmI_2 upon



Scheme 13. Suggested pathways of the alkylsamarium intermediate

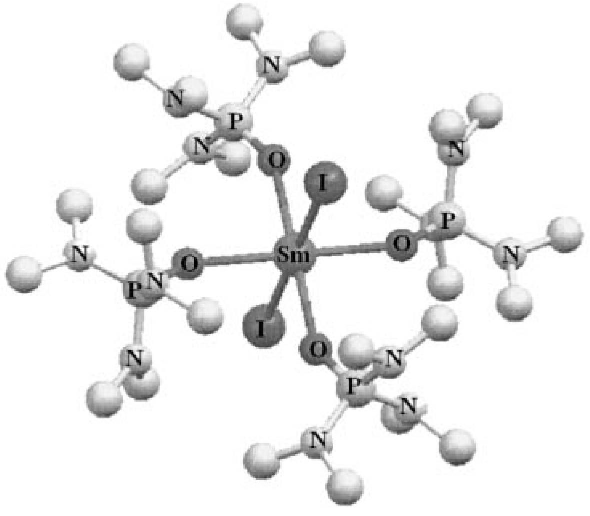
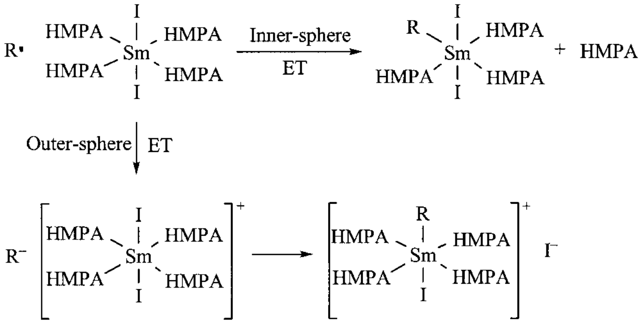


Figure 4. Ball-and-stick representation of the solid-state structure of $SmI_2(HMPA)_4$; hydrogen atoms have been omitted

addition of HMPA was 0.8 V (corresponding to a decrease in free energy of 18 kcal mol^{-1}). Skrydstrup and co-workers also determined the standard potential $E°$ of SmI_2^+/SmI_2 by cyclic voltammetry, which was -1.41 ± 0.08 V vs. Fe^+/Fe.[34]

Further work on the SmI_2-HMPA reagent proved, by vapour pressure osmometry (VPO), that SmI_2 is a monomer in HMPA-THF.[35] Based on UV/Vis studies it was also concluded that there are four HMPA molecules coordinated to SmI_2 in solution. Moreover, the strength of the bonds between Sm and O in SmI_2-HMPA was investigated by detailed VPO analysis. It was concluded that the fourth HMPA molecule is not very tightly bonded, indicating that some reduction may occur through an inner-sphere electron transfer after dissociation of one HMPA molecule (Scheme 14).



Scheme 14. Inner- and outer-sphere mechanistic pathways

Addition of HMPA to SmI_2 in THF was reported by Daasbjerg and co-workers to result in a strong increase in conductivity, which strongly indicates that HMPA induces ionic cluster formation.[36] In addition, cyclic voltammetry, conductivity measurements, UV spectroscopy and kinetic measurements were performed. The equilibria shown in Equation (1) and Equation (2) are suggested.

$$\mathrm{Sm(THF)_5I_2} + 4\ \mathrm{HMPA} \rightleftharpoons [\mathrm{Sm(HMPA)_4(THF)_2}]^{2+}\,2\mathrm{I}^- + 3\ \mathrm{THF} \qquad (1)$$

$$[\mathrm{Sm(HMPA)_4(THF)_2}]^{2+}\,2\mathrm{I}^- + 2\ \mathrm{HMPA} \rightleftharpoons [\mathrm{Sm(HMPA)_6}]^{2+}\,2\mathrm{I}^- + 2\ \mathrm{THF} \qquad (2)$$

With four equivalents of HMPA, almost all Sm^{2+} exists in the complex $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$, while approximately 10 equivalents of HMPA are necessary to drive the equilibrium towards $[Sm(HMPA)_6]^{2+}2I^-$. The redox couple

$[Sm(HMPA)_4(THF)_2]^{3+}2I^-/[Sm(HMPA)_4(THF)_2]^{2+}2I^-$ was determined to be -1.79 ± 0.08 V vs. SCE (or 0.9 V larger than that of Sm^{3+}/Sm^{2+} in THF). The degree of outer-sphere character of the reduction of alkyl halides is smallest for chlorides and increases with increasing atomic number ($Cl < Br < I$). Altogether, the rate of reduction was observed to increase by a factor of up to 15 000 with four equivalents of HMPA per SmI_2 in THF.

The knowledge of Sm^{II}-HMPA complexes was expanded with additional kinetic and mechanistic studies by Flowers and co-workers.[37] The reduction of a series of halides and ketones were investigated again, and it was suggested that the halides are reduced by $[Sm(HMPA)_4(THF)_2]I_2$ through an outer-sphere electron transfer, while the ketones are reduced by $[Sm(HMPA)_4(THF)_2]I_2$ through an inner-sphere electron transfer. The activation parameters for ketone reductions were almost identical using either $[Sm(HMPA)_4(THF)_2]I_2$ or $[Sm(HMPA)_6]I_2$, indicating that the reduction proceeds via the same or a similar transition state regardless of the amount of HMPA.

Other Co-Solvents

The addition of HMPA to SmI_2 has been found to give a very reactive, yet selective, reducing agent. However, its toxicity has encouraged several research groups to search for viable nontoxic co-solvents or additives as replacements for HMPA. Hasegawa and Curran reported that DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) could be used as an alternative to HMPA (Figure 5).[20] However, in order to obtain similar results they had to use acetonitrile as solvent instead of THF, as the effect of DMPU was too small. Later, Flowers and co-workers studied the reducing power of SmI_2 in THF in the presence of various additives, for example, trimethyl phosphate (TMP), pentamethylphosphoramidate (PMP) and DMPU.[38] It was necessary to use a large excess (30 equiv.) of DMPU to attain the maximum increase of 0.9 V in the oxidation potential. It was also found that the reduction potential for SmI_2-DMPU in acetonitrile was between that of SmI_2 in THF and that of SmI_2-HMPA in THF.[39] Cabri and co-workers reported promising results using nitrogen additives [Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,1,3,3-tetramethylguanidine (TMG)] in a SmI_2-mediated cyclisation reaction.[40]

Addition of Metal Salts and Other Counterions

Beside the extensive use of co-solvents and various proton donors, a few reports also describe the addition of metal salts and the use of different counterions. However, these methods often provide coupling in the absence of a proton source.

Flowers and co-workers reported on the addition of LiBr and LiCl to SmI_2. A large rate enhancement was observed in the pinacol coupling of cyclohexanone when adding LiBr or LiCl. Undried salts resulted in reduction of the ketone to the corresponding alcohol.[41] An extended study of the SmI_2/LiBr mixture showed that the redox potential had increased to -2.07 V vs. $Ag/AgNO_3$ (relative to SmI_2 with a redox potential of -1.58 V).[42] This suggests that $SmBr_2$ and LiI are formed, since $SmBr_2$ is known to be a stronger reductant than SmI_2. Addition of HMPA to the mixture of SmI_2 and LiBr made led to a more powerful mixture with a redox potential of -2.63 V vs. $Ag/AgNO_3$ and, as expected, a significant rate enhancement was observed in the reduction of various functional groups. Samarium(II) bromide is also readily prepared from Sm metal and tetrabromoethane, as recently reported by Namy and co-workers.[43] They used the black suspension of $SmBr_2$ in THF in combination with mischmetal in various pinacol couplings of ketones.

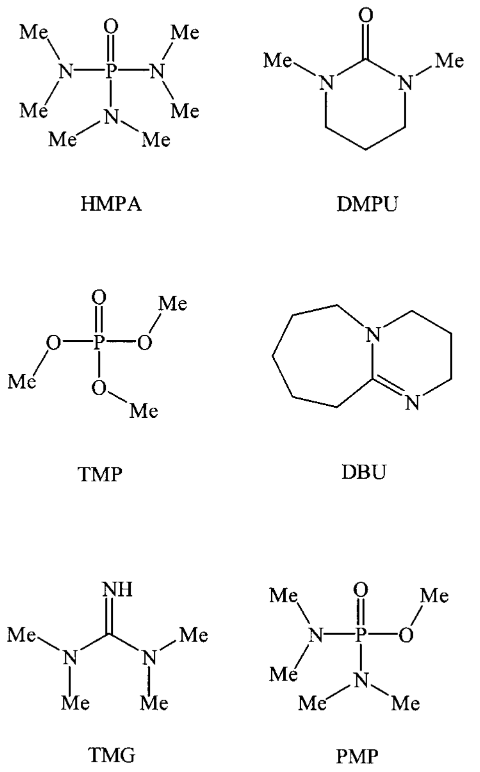
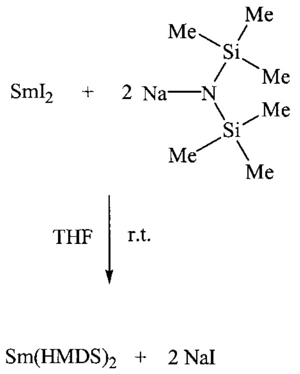


Figure 5. Various co-solvents

Another fascinating counterion for Sm^{II} is the silylamide. Samarium(II) disilylamide [$Sm(HMDS)_2$] has been prepared from sodium hexamethyldisilazane (Na-HMDS) and SmI_2 (Scheme 15).[44]

The samarium disilylamide has a redox potential of -2.1 V vs. $Ag/AgNO_3$, and is thus a stronger alternative to SmI_2. In addition, the $Sm(HMDS)_2$ provides a somewhat higher rate of reaction than $[Sm(HMPA)_6]I_2$, is less carcinogenic and has better solubility properties than SmI_2, especially in solvents other than THF.[45] However, this reagent has so far not seen any widespread use. The solid-state structure of $Sm(HMDS)_2$ has the shape of a distorted tetrahedron (Figure 6).[44]

Addition of catalytic amounts (1%) of, for example, $ZrCl_4$, VCl_3 and NiI_2 to SmI_2 have been reported to improve the reaction rates to the extent that HMPA can be



Scheme 15. Preparation of $Sm(HMDS)_2$ from SmI_2 and Na-HMDS in THF

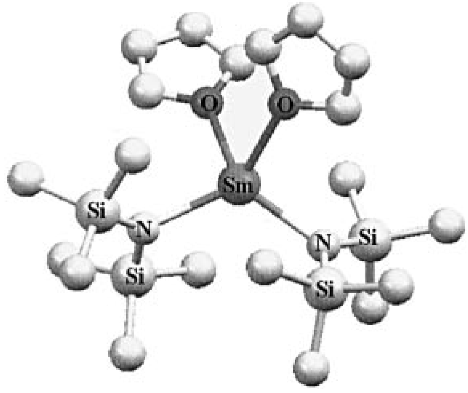


Figure 6. Ball-and-stick representation of the solid-state structure of $Sm(HMDS)_2$; hydrogen atoms have been omitted

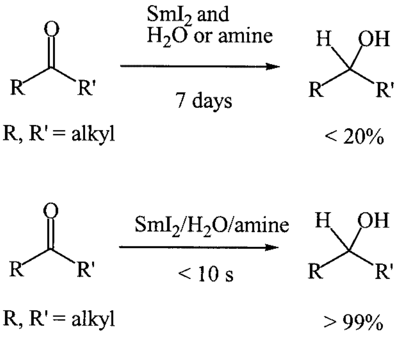
avoided in several reactions.[46] Especially, reduction of epoxides to alkenes is considerably accelerated with NiI_2 (the reaction time is 20 minutes, while the uncatalysed reaction requires 12 h). Furthermore, reduction of dodecyl phenyl sulfone to dodecane occurs in good yield after 2 h at reflux. Several couplings and reductions are completed in less than 30 minutes. In addition, hetero couplings between ketones and imines are obtained in high yields by the SmI_2/NiI_2 mixture within five minutes.[47] However, the details regarding the high reactivity of this catalytic system is not yet available preventing full utilisation of this interesting additive.

SmI_2/H_2O/Amine-Mediated Reductions

With the aim of finding a nontoxic replacement for HMPA in SmI_2-mediated reductions, a number of ligands were screened in a simple reduction of a ketone, in combination with methanol or water as proton source. The rate of reduction was not affected by mono or polyethers. However, addition of triethylamine and water had a dramatic effect on the reduction rate.[48] Other amines (e.g. TMEDA and PMDTA) were employed in the reduction and showed similar results. With one or two equivalents of amine, there is a very fast initial reduction, but the reaction stops with a low chemical yield. This reaction requires water as a proton source, while methanol can be used, it is considerably less powerful. Incremental addition of amine and water proved that the reduction of ketones requires two equivalents of SmI_2, four equivalents of amine and six equivalents of water in order to obtain a quantitative yield of the alcohol. The product in the reaction is often very simple to purify since all water, amine, samarium and iodide precipitates as $Sm(OH)_3$ and $R_3N{\cdot}HI$. The by-products can be removed by filtration, which leaves the THF solution of the reduced alcohol. The balanced reduction reaction is given in Equation (3).

$$R_2C{=}O + 2\,SmI_2 + 6\,H_2O + 4\,R_3N \rightleftharpoons R_2CHOH + 2\,Sm(OH)_3 + 4\,R_3N{\cdot}HI \qquad (3)$$

The combination of SmI_2, amine and water gives significantly increased rates of reduction relative to the commonly used SmI_2-HMPA mixtures. The rates of reduction of ketones using the combination of water and amine is more than 100 000 times higher than those without proton sources (Scheme 16).[48] Recently, we showed that this instantaneous and quantitative reduction of ketones also constitutes a simple and accurate quantitative determination of $[SmI_2]$, $[SmBr_2]$ and $[YbI_2]$.[7f]

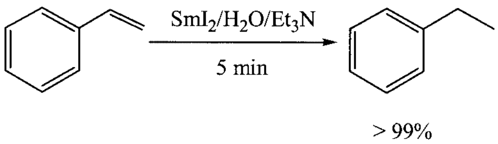


Scheme 16. The rate of reduction of ketones mediated by SmI_2/H_2O/amine is more than 100 000 times faster than with SmI_2 and H_2O or amine

During our continuing study on the reactivity of the SmI_2/H_2O/amine mixtures, we observed that not only ketones but also imines and α,β-unsaturated esters were reduced instantaneously, i.e. reactions were complete in less than 10 seconds.[14] The SmI_2/H_2O/amine mixture is particularly useful for the reductive imino-pinacol coupling of hindered imines and iminium perchlorates, since these are difficult to couple by other methods.[49]

UV/Vis studies have revealed that water is a very good ligand for samarium(II), i.e. it readily replaces THF. The amine Et_3N, however, does not compete with the bulk THF for coordination to samarium. Unfortunately, the reduction of ketones with SmI_2/H_2O/amine is too fast for kinetic investigations. Phosphor ligands, on the other hand, also form hydrohalide salts. We found that the reductions of ketones indeed are accelerated using a phosphorus ligand, i.e. $Me_2PCH_2CH_2PMe_2$. Since the rate of reduction using this ligand was much lower, we could determine that there is a kinetic isotope effect, $k^{H2O}/k^{D2O} = 4.5$, indicating a rate determining hydrogen-transfer in the reduction of ketones. The driving force for the reaction has been suggested to be the precipitation of the by-products.[14]

When conjugated double and triple bonds were found to be rapidly reduced to simple alkenes or alkanes, it was concluded that the SmI_2/H_2O/amine mixture is a very powerful reductant (Scheme 17).[50]



Scheme 17. Reduction of conjugated olefins

The reagent mixture SmI_2/H_2O/amine is also superior for the reduction of halides relative to various other additives (Scheme 18). The reduction of bromides, which takes hours with SmI_2-HMPA, proceeds in minutes with SmI_2/H_2O/amine. Alkyl and aryl iodides are reduced in less than one minute with SmI_2/H_2O/amine.[51]

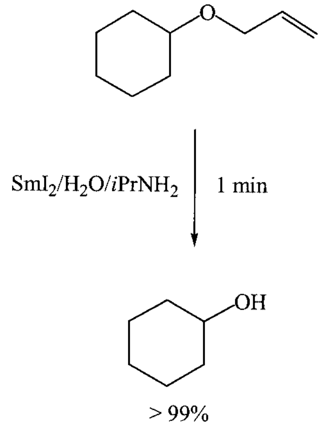
$$R{-}X \xrightarrow[\text{1 min – several hours}]{SmI_2/H_2O/\text{amine}} R{-}H \qquad I > Br > Cl$$

Scheme 18. Reduction of alkyl and aryl halides mediated by SmI_2/H_2O/amine

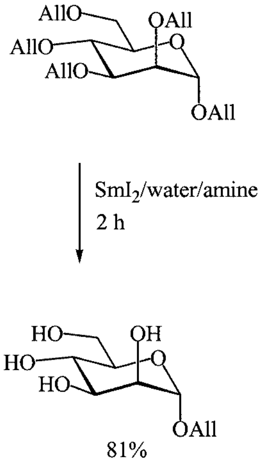
Kinetic studies have proven that there is a first-order dependence on amine, indicating that the amine is part of the rate-limiting step of the reduction. There is no observed kinetic isotope effect on addition of water. Electrochemical investigations were also carried out on the SmI_2/H_2O/amine mixture. The addition of only amine had no effect on the oxidation potential. Addition of both water and amine to a THF solution of SmI_2 resulted in an irreversible oxidation, and the redox potential could not be determined. The oxidized Sm^{3+} precipitates rapidly from the solution, preventing the measurement of the redox potential of the Sm^{2+}/Sm^{3+} couple.[51]

Recently, we discovered that SmI_2/H_2O/amine mixtures also mediate deallylation reactions (Scheme 19).[52]

This novel deprotection reaction was employed in the cleavage of various allyl ether-protected carbohydrates. The high yields observed with this method makes it particularly useful for the simultaneous deprotection of several allyl groups. There is an unusual chemoselectivity for deprotection. The allyl group on the anomeric carbon does not undergo any deprotection when SmI_2/H_2O/amine is used (Scheme 20), while the other allyl groups are rapidly deprotected.



Scheme 19. Allyl ether cleavage



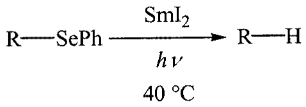
Scheme 20. Selective deallylation of allylmannoside with SmI_2/water/amine

The use of SmI_2/H_2O/amine is particularly advantageous for reductions, since it does not react violently with moisture or oxygen, in strong contrast to most other strong reducing agents, for example alkali metals, hydrogen gas or different hydrides.

Photoinduced Reduction System

The very reactive $SmI_2/h\nu$ system developed by Ogawa and co-workers deserves to be mentioned in this review even though it is not strictly an additive. Ogawa and co-workers discovered in 1997 that alkyl halides, and in particular chlorides that are generally difficult to reduce with SmI_2 (even with SmI_2-HMPA), are efficiently reduced by SmI_2 in THF upon irradiation with visible light ($700 > h\nu > 300$ nm).[53] Irradiation with light of higher or lower wavelengths has no effect on the reactions. Interestingly, the optimum wavelength is similar to the absorption maxima for SmI_2 in THF at 565 and 617 nm, respectively, indicating that SmI_2 is activated by light irradiation.

Additionally, it was found that $SmI_2/h\nu$ also gives excellent results for the cleavage of C−Se, C−Te and C−OTs bonds (Scheme 21).[54] Organic selenides cannot be reduced by SmI_2-HMPA.



$$R{-}SePh \xrightarrow[h\nu\ \ 40\ ^{\circ}C]{SmI_2} R{-}H$$

Scheme 21. Photoinduced reduction of selenides by SmI_2 in the presence of visible light

Conclusion

Herein we have summarised that the reactivity of SmI_2 can be significantly adjusted using various additives and or co-solvents. The addition of various additives to SmI_2 clearly gives the working chemist tools to modify and control the reducing properties, which is important for selective reduction of one particular group of several similar groups within the same substrate. SmI_2 is beginning to be appreciated as a mild and selective reducing agent in synthetic organic chemistry, but the reaction mechanisms through which the addition of various additives and co-solvents act are far from understood. The current mechanistic knowledge is mainly based on the initial suggestion made by Kagan some 25 years ago, and since then only small achievements have been reported. New applications for SmI_2 and for other lanthanide(II) reagents will most likely emerge from detailed structural and mechanistic studies of SmI_2 and other lanthanide(II) reagents. SmI_2 is attractive as a general reducing agent, since it is considered nontoxic and its handling procedures are nonhazardous, in contrast to most other reducing agents.

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