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Reduction of Multiple Bonds without Hydrogen or Hydride Complexes: Samarium Diiodide as a Mild Reducing Reagent

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Keywords: Reduction / Samarium

The use of samarium diiodide as a mild and selective reducing agent has become an important tool in organic synthesis. Many reducing agents are reported in the literature. However, due to their low chemoselectivities and various other drawbacks, samarium diiodide has become a useful and readily available reagent. This manuscript provides an update on earlier reviews describing conventional reduction processes of multiple bonds promoted by samarium diiodide. The most recent developments in the use of samarium metal in this field are also discussed.

1 Introduction

Samarium diiodide can be readily prepared in moderate concentrations (0.1 M in THF) by treating samarium metal with diiodomethane, 1,2-diiodoethane, iodine, or iodoform in the presence of sonic waves.[1]

Pioneered by Kagan in 1977,[2] samarium diiodide has rapidly become an important reagent in organic chemistry because of its versatility in one- and two-electron transfer reactions. Since then, SmI_2 has emerged as one of the more useful reducing agents in synthetic organic chemistry. As a consequence of its increasing importance, several reviews have appeared that focus on the utility of samarium diiodide in promoting C–C bond formation reactions.[3]

The reduction potential of the Sm^{+3}/Sm^{+2} system measured in water and in THF are –1.55 and –1.33 V, respectively.[4] The high chemoselectivity exhibited by SmI_2 and its ability to dramatically change its reactivity and selectivity based upon solvent effects further enhance its attractiveness.[5] Also, it is important to point out that the excellent Lewis acid character of samarium ions is to some extent

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Humberto Rodríguez Solla was born in Gijón (Asturias) in 1975 and graduated from the University of Oviedo in 1998. He obtained his Ph.D. at the same University in 2002 supervised by Prof. José M. Concellón. In that year he moved to Oxford (United Kingdom), where he was a post doctoral researcher in the Chemistry Research Laboratory (University of Oxford) under the supervision of Prof. Stephen G. Davies until 2005. During his Ph.D., he developed new methodologies to carry out β-elimination, reduction and cyclopropanation reactions using samarium diiodide or samarium carbenoids. During his post-doc he worked in the area of organometallic compounds and the use of samarium diiodide with oxazolidinone chiral auxiliaries or DKP templates. Currently, he has a Ramón y Cajal contract at University of Oviedo. His research interests are focused in the development of new methodologies using organometallic compounds and asymmetric synthesis. He was awarded with the Ph.D. Prize (Colegio Oficial de Químicos de Asturias y León) in 2003 and with the Ph.D. Extraordinary Prize (University of Oviedo) in 2004.

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

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responsible for the high stereoselectivity exhibited in SmI_2-mediated transformations.

Samarium diiodide-promoted reduction of multiple bonds was widely covered by Molander in a review published more than ten years ago.[6] Nevertheless, because many new transformations have been developed since then, a new review detailing the latest developments is desirable. This review will highlight the most recent methodologies in the area of reduction of multiple bonds promoted by samarium diiodide.

The synthetic applications of samarium metal have been much less developed, and this topic has been covered in a review.[7] The present review also covers the synthetic applications of samarium metal since the previous review.

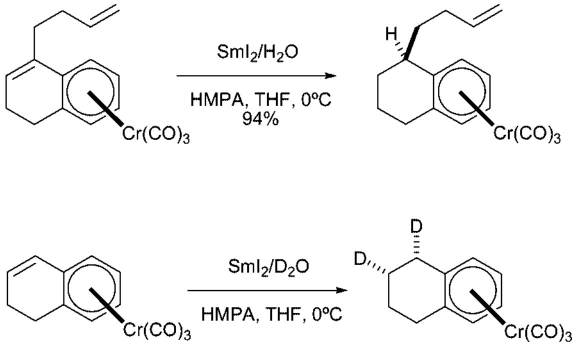
2 Reduction of Conjugated C–C Multiple Bonds

2.1 Reduction of Activated C=C Bonds

There are many published methodologies dealing with the reduction of activated double bonds; however, only a few general methods for the selective reduction of conjugated double bonds are known.[8] Samarium diiodide is a valuable alternative since it promotes the selective reduction of activated C=C bonds under mild conditions that are compatible with other functionality in the molecule.

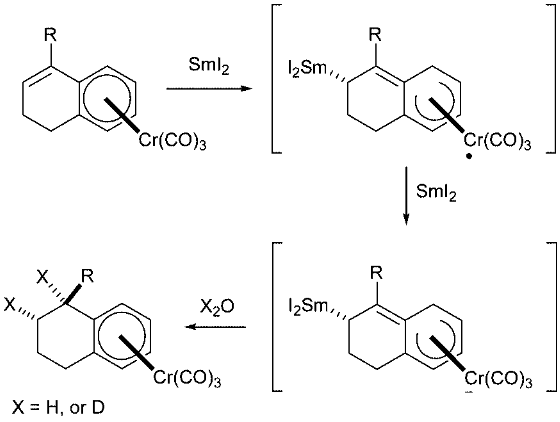
2.1.1 Reduction of Benzylic or 1,3-Dienic C=C Bonds

In 1998 a reduction reaction of a benzylic C=C bond was performed through the use of the $SmI_2/H_2O/HMPA$ system.[9] In that paper, the authors carried out the reduction of the double bond of styrene–$Cr(CO)_3$, and dihydronaphthalene–$Cr(CO)_3$ derivatives (Scheme 1). The reaction seemed to be regio- and diastereoselective. Also, when the same reaction was carried out using D_2O instead of water, the corresponding *cis*-dideuterated complexes were obtained in high yields.



Scheme 1.

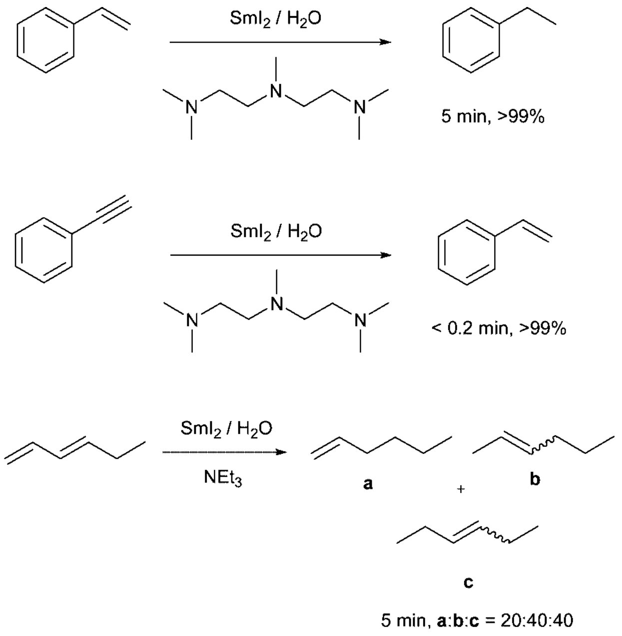
The authors proposed an anionic mechanism based on two successive electron transfers from two equivalents of samarium diiodide. Accordingly, the first equivalent of SmI_2 would transform the starting benzylic double bond to a radical intermediate further reduced by a second SmI_2 equivalent, affording an anion (Scheme 2). Hydrolysis or deuteriolysis of this dianionic intermediate leads to the corresponding saturated or dideuterated products.



Scheme 2.

Dahlén and Hilmersson have recently published the use of a SmI_2/H_2O/amine system to promote the selective reduction of conjugated double and triple C–C bonds to afford the corresponding alkane or alkene moiety.[10] The reactions took place quantitatively in less than five minutes, and it is important to point out that the mixture of SmI_2/H_2O/amine is considered non-hazardous.

The main disadvantage of this reaction is the formation of mixtures of products when unsymmetrical substrates are utilised (Scheme 3), and the authors mentioned that this particular SmI_2/H_2O/amine mixture may prove too powerful for selective reactions involving multifunctional substrates.

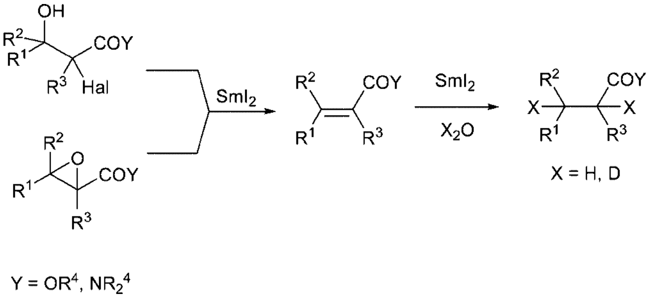


Scheme 3.

2.1.2 Reduction of α,β-Unsaturated Carboxylic Acid Derivatives

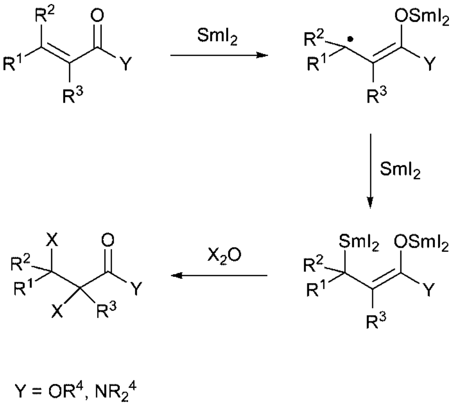
At first, additives such as *N*,*N*-dimethylacetamide, or HMPA were typically employed to facilitate the samarium-promoted reduction of carboxylic acid derivatives.[6] More recent studies have shown that these conjugate reductions can be carried out by just using SmI_2 and either H_2O or D_2O without any other additive in the reaction pool. The first general reduction of activated double bonds using SmI_2 and either H_2O or D_2O in the absence of another cosolvent has been recently reported. This process was performed through a sequential elimination-reduction reaction carried out on α-halo-β-hydroxy esters or amides,[11] α,β-epoxy esters,[12] α,β-epoxy amides,[13] and α,β-unsaturated acids.[14]

In the former three cases, the first common transformation was the generation of the corresponding α,β-unsaturated carboxylic acid derivative through a conventional SmI_2-promoted 1,2-elimination or deoxygenation process[3f] (Scheme 4).



Scheme 4.

Once the α,β-unsaturated derivative was generated in the reaction media, the SmI_2-promoted 1,4-reduction was triggered with the donation of an electron from SmI_2 to generate an enolate radical, which was further reduced by a second electron transfer from another equivalent of samarium diiodide. Hydrolysis with X_2O (X = H, or D) afforded the corresponding saturated or 2,3-dideuterated ester or amide (Scheme 5). In order to prove this mechanism, the authors applied these reduction conditions to α,β-unsaturated esters or amides.



Scheme 5.

Similar results were obtained with α-halo-β-hydroxy carboxylic acid derivatives when this process was performed by using SmI_2 generated in situ from a mixture of Sm/CH_2I_2 and subsequent addition of D_2O.[15]

Di-, tri-, or tetrasubstituted double bonds can be reduced. When α-halo-β-hydroxy compounds were used, the formal reduction products arising from the intermediate di-, and trisubstituted α,β-unsaturated esters or amides generated in the first transformation of the sequence were obtained. When the reduction process took place with α,β-epoxy esters or amides as starting materials, the formal reduction products from di-, tri-, and tetrasubstituted α,β-unsaturated compounds were isolated. It is necessary to mention that in the case of trisubstituted aliphatic α,β-epoxy amides, the addition of HMPA was necessary, and the reaction only took place when samarium diiodide was added in two steps.

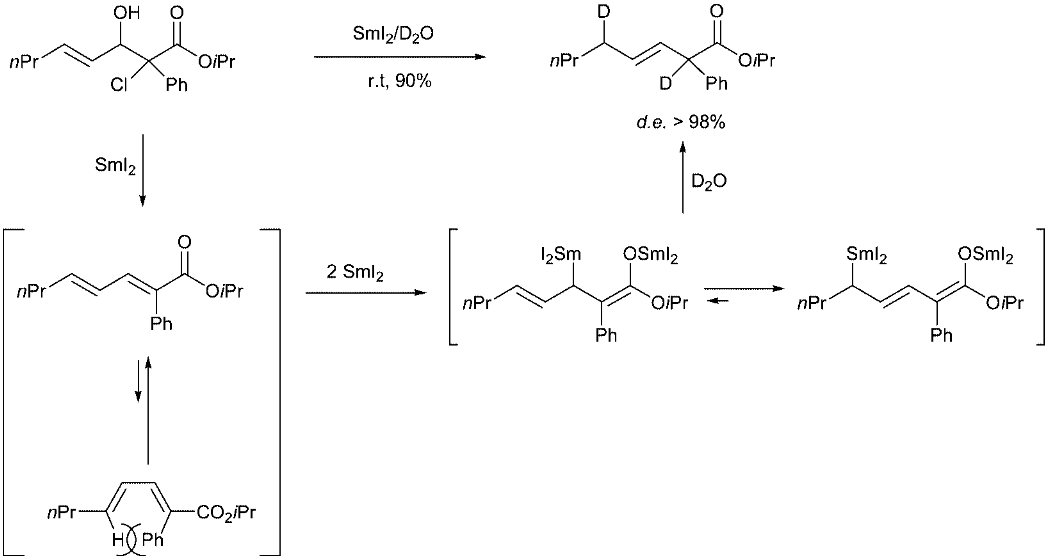
When the aforementioned sequential method (β-elimination-reduction reaction) was performed on α-halo-β-hydroxy-γ,δ-unsaturated esters, the corresponding (*E*)-β,γ-unsaturated and (*E*)-α,δ-dideuterio-β,γ-unsaturated esters were obtained with total or high diastereoselectivity, when H_2O or D_2O was employed, respectively.[16] After formation of the corresponding (2*E*,4*E*)-alka-2,4-dienoate (through a β-elimination reaction on the α-halo-β-hydroxy-γ,δ-unsaturated esters),[3f] the SmI_2-promoted 1,4-reduction of the two conjugated C–C double bonds, which is initiated by oxidative addition of SmI_2, produced an enolate radical. A second electron transfer from SmI_2 afforded an allylic dianion and its hydrolysis or deuteriolysis produced the corresponding (*E*)-β,γ-unsaturated or (*E*)-α,δ-dideuterio-β,γ-unsaturated esters (Scheme 6).

The authors observed lower diastereoselectivity of the C=C bond formation when non-α-alkylated dienoates were utilised. This was explained assuming that in the case of α-alkylated dienoates, the *s-cis* conformation of the dienoates (necessary to obtain *Z*-selectivity) is disfavoured due to the steric hindrance produced by the substitution at the α-carbon atom. When non-α-alkylated dienoates were used, 1,4-reduction of the conjugated C=C bond took place through both the *s-cis* and *s-trans* conformations. The complete incorporation of deuterium at position C-5 rather than at C-3 in the diorganosamarium intermediate has also been explained assuming that in this resonance-stabilised dianion, the 1,4-dianionic structure is more stable than the 1,2-dianionic one due to the charge repulsions.

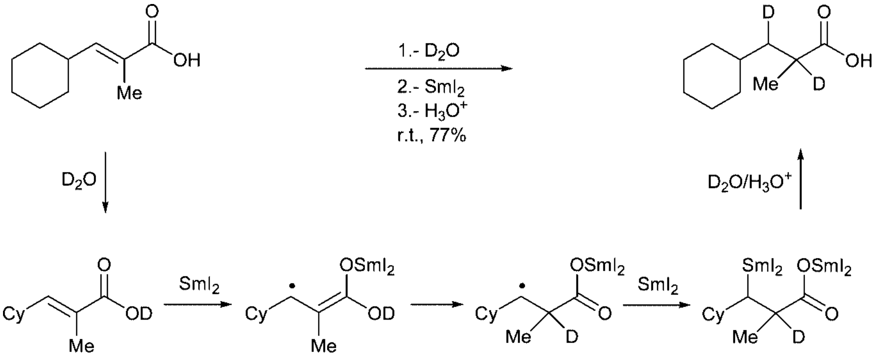
In the case of α,β-unsaturated carboxylic acids, a similar methodology was established. In this case, a pretreatment with D_2O was desirable to avoid competition between H and D incorporation in the final product.[14]

When the unsaturated acids were not previously treated with D_2O, and the reaction was carried out directly with SmI_2 and D_2O, a mixture of mono-, di-, and nondeuterated acids were obtained. The 2,3-dideuterio acids were isolated as a mixture of diastereomers, with ratios ranging between 2:1 to 1:1.

Despite the general character of this methodology, when aliphatic non α-alkylated acids were used as starting materials, no reduction took place. The authors explained the different behaviours of these substrates by considering that the initial oxidative addition of SmI_2 is favoured in the case of the aromatic or α-substituted-α,β-unsaturated acids but not



Scheme 6.



Scheme 7.

in the case of non-α-substituted acids. In the aromatic acids, the enolate radical (shown in Scheme 7) is stabilised by resonance. Also, the enolate radical derived from diacids or aliphatic α-substituted-α,β-unsaturated acids is more stable than that derived from non-α-alkylated α,β-unsaturated acids due to resonance in the first case, and to the higher substitution of the C=C bond in the second.

When alka-2,4-dienoic acids were used as starting materials, no α,β-dideuterio-γ,δ-unsaturated acids were obtained. Similar to alka-2,4-dienoates, (*E*)-α,δ-dideuterio-β,γ-unsaturated acids were isolated, and the new C=C bond was generated with total *E*-selectivity (Scheme 8).

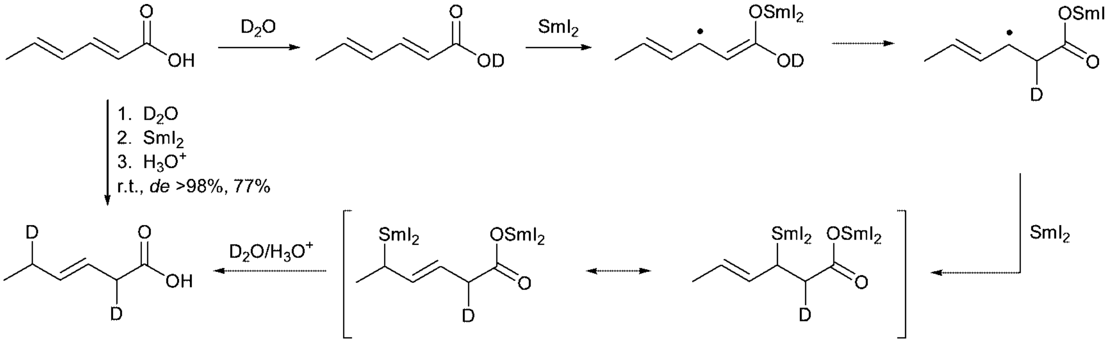
The proposed mechanism assumed that this reduction took place through first an oxidative addition of SmI_2, thus generating the corresponding enolate radical, which was deuterated in the acidic medium. The resulting radical underwent a second electron transfer from another equivalent of SmI_2, affording an allylic anion. Deuteriolysis of this anion generated the final product, which was deuterated at position C5 rather than at C3. The explanation given when discussing Scheme 6 is also applicable to this situation.

Building on the reduction processes promoted by samarium diiodide and X_2O (X = H, or D) in the absence of cosolvents, Davies et al. developed a highly diastereoselective conjugated reduction of homochiral (*E*)- and (*Z*)-benzylidene[17] and isobutylidene diketopiperazine (DKP) chiral templates.[18] This methodology allowed the asymmetric synthesis of interesting substrates, such as methyl (2*S*,3*R*)-dideuteriophenylalanine and (2*S*,3*R*)- or (2*S*,3*S*)-dideuterioleucine-(*S*)-phenylalanine dipeptides.

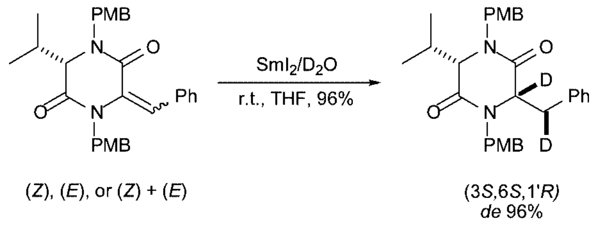
When this reduction protocol was performed on either (*E*)-, (*Z*)- or a mixture of (*E*) + (*Z*)-benzylidene diketopiperazines, the same diastereomer of the corresponding dideuterio compound was obtained. This indicated the high stereoselectivity but complete lack of stereospecificity of the process (Scheme 9).[17]

Deprotection of the reduced DKP backbone, subsequent hydrolysis, esterification and *N*-acetylation yielded methyl (2*S*,3*R*)-*N*-acetyl-2-amino-2,3-dideuterio-3-phenylpropionate in a 71% overall yield and >98% *ee* (Scheme 10).

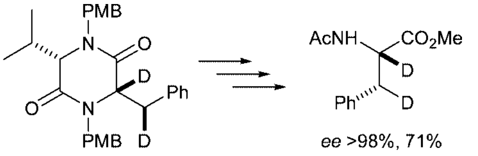
When identical reduction conditions were applied to isobutylidene-DKP templates, the reaction outcome was different. In this case, reduction of (*E*)- and (*Z*)-isobutylidene-DKP afforded (3*S*,6*S*,1′*R*)- and (3*S*,6*S*,1′*S*)-dideuterio compounds, respectively, as major diastereomers (Scheme 11).[18]



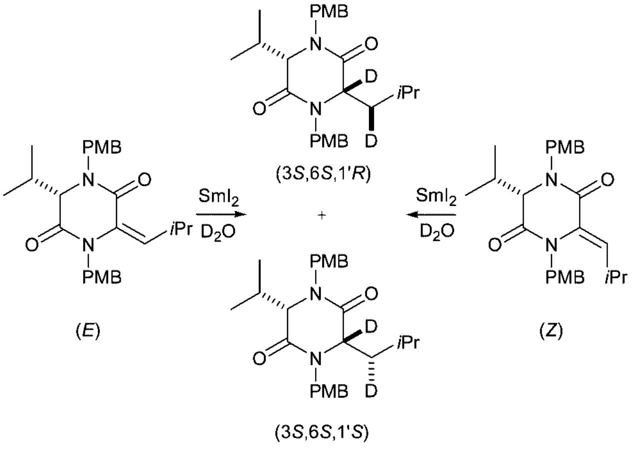
Scheme 8.



Scheme 9.



Scheme 10.

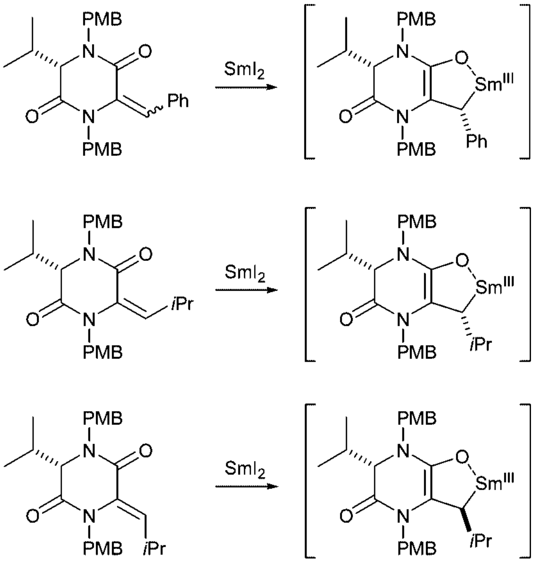


	(3*S*,6*S*,1'*R*):(3*S*,6*S*,1'*S*)	others	Yield (%)
(*E*)	79:16	5%	94
(*Z*)	13:85	2%	98

Scheme 11.

Mechanistically, the reduction of these derivatives might be rationalised by assuming a mechanism that proceeds through two stepwise single-electron transfers from SmI_2 to the α,β-unsaturated system, similar to that shown in Scheme 5. The stereoselective deuterium incorporation at the α-carbon of the unsaturated system could be explained by considering previous results from the same group[17] where analogous lithium enolates were protonated from the *re* face leading to products with the same spatial configuration. Nevertheless, in the case of the benzylidene template, both the (*E*)- and (*Z*)-olefins gave the same reduction product. This might be explained by presuming an interconversion of the (*Z*)-unsaturated compound to the more stable *E*-benzylidene prior to reduction. For the isobutylidene substrates, the configuration of the β-carbon in the unsaturated system after reduction is consistent with a formal *anti* addition of samarium with respect to the isopropyl group from the DKP and retention of configuration of organosamarium intermediates after deuteriolysis.

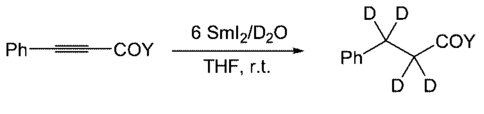
In the following Scheme, the dianionic intermediates generated after the two electron transfers from SmI_2 to the DKP templates are shown (Scheme 12).



Scheme 12.

2.2 Reduction of Activated C≡C Bonds

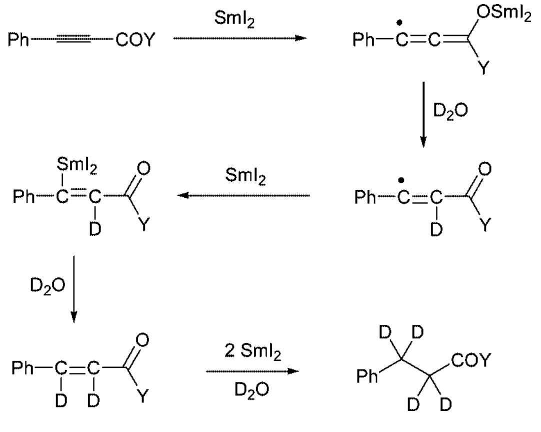
Only one process has been described concerning the tetradeuteration of α,β-acetylenic carboxylic acid derivatives by using a deuterium source such as [D]methanol and magnesium.[19] In particular, for the synthesis of tetradeuterated carboxylic acids, two steps were necessary: deuteration of the corresponding α,β-acetylenic esters, and further hydrolysis. It is also noteworthy that in the reduction of acetylenic esters, a mixture of transesterification products was obtained. In this sense, samarium diiodide has played a crucial role in the reduction–deuteration protocols of α,β-acetylenic esters, amides or carboxylic acids. Some examples of the preparation of saturated or 2,2,3,3-tetradeuterio esters, amides or acids employing this methodology are reported, and unimportant differences were observed in the yields of the reduction of α,β-acetylenic esters and amides. Comparatively, tetradeuterio carboxylic acids were obtained in lower yields (Scheme 13).[20]



Y	Yield (%)
OEt	84
NEt_2	81
OH	71

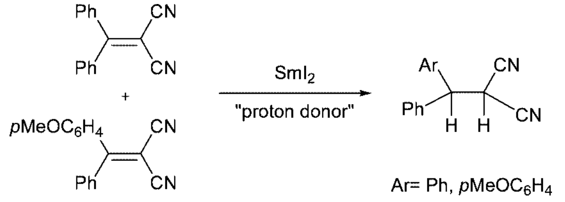
Scheme 13.

The reduction reaction takes place through a single electron transfer from SmI_2 to generate the anion radical, which is then hydrolyzed by the D_2O present in the reaction medium. This affords the alkene radical, which is further transformed into an anion by a second electron transfer. Hydrolysis of this anion generates the corresponding α,β-unsaturated carboxylic compound, which, after a process similar to that shown in Scheme 5 yielded the corresponding 2,2,3,3-tetradeuterio carboxylic compounds (Scheme 14).



Scheme 14.

Yacovan and Hoz published a paper where they studied the mechanism and the complexation effect on chemoselectivity.[21] The reaction studied is represented in Scheme 15.



Scheme 15.

The authors used mainly MeOH as proton donor, and they stated that the product ratio was found to depend on the concentration of the proton donor. At low proton donor concentration, the selectivity was relatively high, and when the proton donor concentration increased, the selectivity decreased. They also showed that SmI_2 forms complexes with the proton donors being bound to Sm (especially trivalent samarium), and their labile proton becomes more labile than one would expect. This feature of Sm can be used to affect the chemoselectivity during the reduction process.

3 Reduction of C–Heteroatom Multiple Bonds

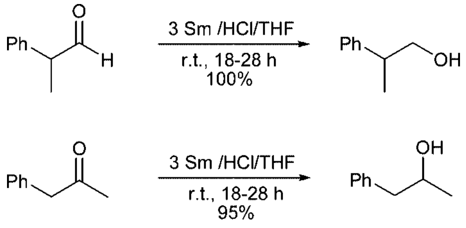
3.1 Transformation of Carbonyl Compounds Into Alcohols

3.1.1 Reduction of Isolated Carbonyl Compounds

Several papers have appeared concerning the SmI_2 reduction of carbonyl compounds (ketones or aldehydes). For example, Flowers' group published a complete mechanistic study using acetophenone as a model substrate. They studied the role of proton donors in the SmI_2-mediated acetophenone reduction, and the relevance of substituents on the aromatic group in the same process.[22]

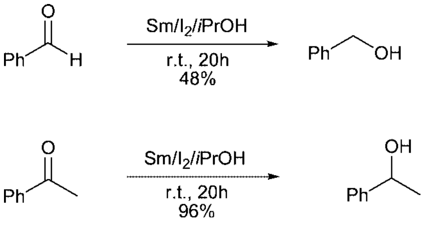
Many examples appeared some years ago of the reduction of carbonyl compounds by using a mixture of samarium diiodide and HMPA as cosolvent. In this sense continuous efforts have been made to replace this well-known carcinogenic additive with others with less toxicity and analogous properties. Dahlén and Hilmersson studied and developed alternative strategies to the use of SmI_2/HMPA in the reduction of carbonyl groups. In an early publication, they reported how chelating alcohols are able to accelerate the samarium diiodide-mediated reduction of 2-heptanone.[5c] Also, they published the first report where a combination of SmI_2/H_2O/amine increases the reduction rates of dialkyl ketones in a remarkable way. It was stated that the increasing rate in the reduction reaction is far beyond that expected, i.e. the sum of the rates of water and amine, respectively.[23] The effects of several additives has been widely covered in a review previously published by the same authors.[5d]

Carbonyl reduction reactions can also be performed by using samarium metal in aqueous media.[24] Several conditions were tried in order to reduce carbonyl compounds and minimise the pinacol coupling of these substrates. Attempts on aliphatic, acyclic and cyclic aldehydes and ketones were successful, but aromatic carbonyl groups proceeded through a pinacol coupling. The best conditions found were those in which the system Sm/2 M HCl/THF was used (Scheme 16).



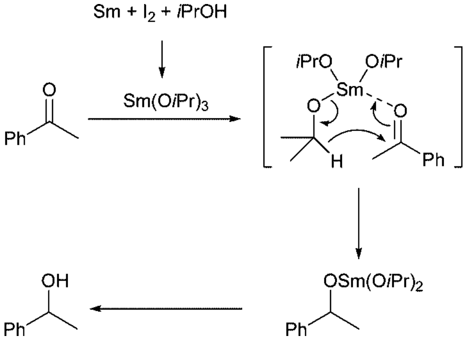
Scheme 16.

Other methodologies for the reduction of aldehydes or ketones using samarium metal as reducing agent appeared later.[25] The reaction conditions employed seemed to be more general, hence they could be applied to the reduction of aromatic ketones and aldehydes. It was necessary to conduct the reactions in *i*PrOH as the solvent, and with traces of iodine. When solvents other than *i*PrOH were used (THF, MeOH, or EtOH), significant amounts of pinacol coupling products were observed. Also, although the use of other lanthanides was attempted, the best results were obtained when Sm was employed (Scheme 17).



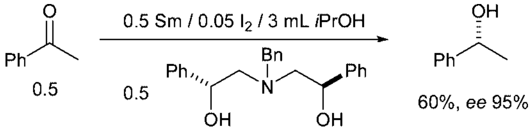
Scheme 17.

Mechanistically, this reaction does not seem to proceed through a single electron transfer. When the reduction was carried out using 10 equivalents of acetophenone with respect to the amount of Sm under the same conditions discussed before, an 80% yield of 1-phenylethanol was obtained. This suggested the possibility of a samarium isopropoxide intermediate as responsible for this process. In this sense, a Meerwein–Ponndorf–Verley mechanism of hydride transfer from an isopropoxy group to the carbonyl compound was proposed (Scheme 18).



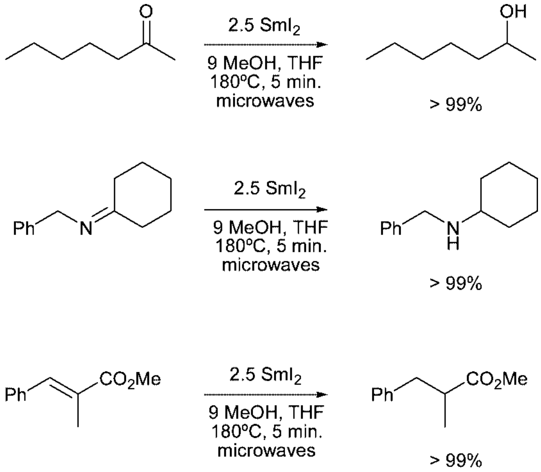
Scheme 18.

The same authors[25] also studied the enantioselective version of this reaction by reducing acetophenone in the presence of some chiral ligands. The most efficient ligand was the Evan's amino alcohol, which required a stoichiometric amount of the ligand and samarium relative to acetophenone. When the catalytic version of this reaction was carried out, lower yields and *ee* values were obtained (Scheme 19).



Scheme 19.

Recently, Hilmersson et al. developed a microwave-induced reduction reaction promoted by SmI_2, $SmBr_2$ or YbI_2.[26] In this case, reduction of carbonyl compounds such as ketones, aldimines or ketimines was carried out in the presence of microwaves at 180 °C in MeOH/THF. All these transformations took place quantitatively and with very short reaction times. This methodology is remarkable, because normally the reduction of ketones with SmI_2 is very slow, and these reaction conditions accelerate the process (Scheme 20).



Scheme 20.

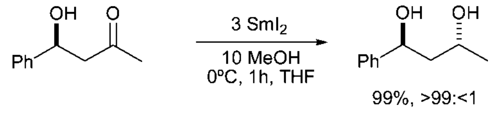
Also, the use of this microwave-assisted reduction is described for the case of α,β-unsaturated esters in the same paper. Again, this process took place quantitatively and needed only short reaction times under the same conditions.

Hoz et al. studied the role of proton donors in these carbonyl-type reduction processes[27] by using benzophenone as a model substrate. Although reduction of benzophenone by SmI_2 yields benzopinacol, addition of proton donors increases the amount of alcohol obtained. They observed that the ratio of alcohol to pinacol products reaches a maximum, decreases, and then levels off as the proton donor concentration is further increased. Thus, the concentration of SmI_2 and the characteristic of the proton donor can be tailored, in principle, for most substrates to channel the reaction to the desired products. Several mechanistic aspects have also been investigated, and it is necessary to mention that Daasbjerg and Skrydstrup wished to determine whether samarium diiodide is an inner- or outer-sphere electron-donating agent for this kind of processes.[28] So, from the measured value of $E°$ (SmI_2^+-SmI_2) in THF, and using free energy plots, the electron transfer between samarium diiodide and acetophenone (as the model substrate) was demonstrated to be of an inner-sphere nature.

3.1.2 Diastereoselective Reduction of β-Functionalised Carbonyl Compounds

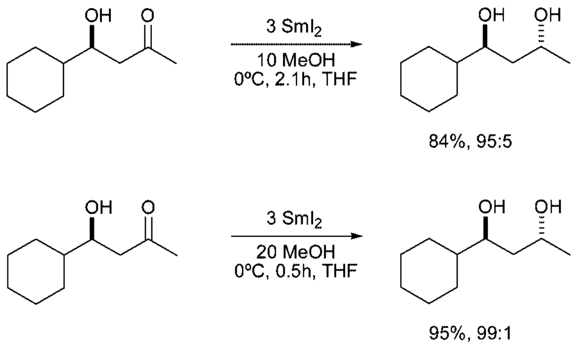
1,3-diols and related structures have increasingly become of interest to both chemists and biologists because these subunits are frequently found in biologically active natural products. Due to the availability of different synthetic methods for the preparation of β-hydroxy carbonyl compounds in an enantio- or diastereoselective way, they have appeared to be very useful starting materials for preparing 1,3-diols through reductions mediated by hydride complexes.

Samarium diiodide has also been used for the transformation of β-hydroxy carbonyl compounds and related structures to the corresponding reduced products. Keck et al. developed a stereoselective reduction of β-hydroxy ketones to the corresponding *anti*-1,3-diols.[29] The use of both H_2O and MeOH as proton sources was studied. The best results were obtained when an excess of methanol was used (Scheme 21). The use of water as a proton source yielded the desired product in lower yields and diastereomeric ratio.



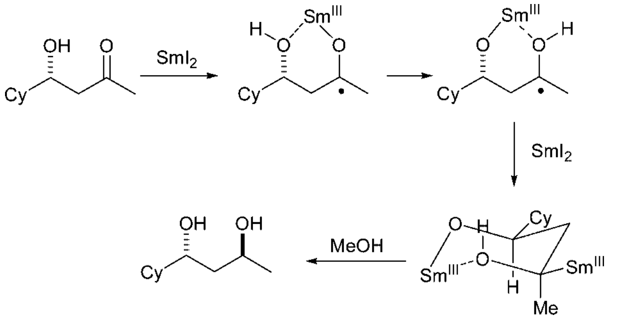
Scheme 21.

When they tried to reduce the corresponding cyclohexyl derivative under the same optimal conditions, larger amounts of methanol were necessary to achieve high yields and high diastereoselectivities. Again, the amount of methanol was crucial to achieving high diastereoselectivity and yield (Scheme 22).



Scheme 22.

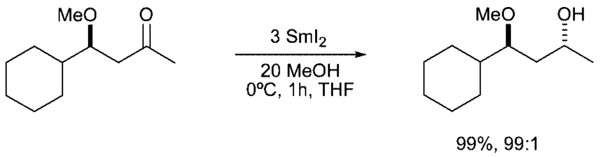
The proposed mechanism (Scheme 23) envisages a chelation control model. First, an electron transfer to the keto group takes place. After protonation of the samarium ketyl, another electron from a second equivalent of samarium diiodide is transferred, and a samarium carbanion is generated. This produces a six-membered ring due to the chelation of the oxophilic samarium(III) centre by the two oxygen atoms of the molecule. Alcoholysis of this anionic intermediate generates the corresponding 1,3-diol.



Scheme 23.

When this reduction was carried out on *O*-protected (OBn or OTBS) substrates, no reaction took place. The authors stated that "a β-OH moiety is responsible not only for the stereoselectivity observed but also for a very dramatic rate enhancement". Yet the same authors later found that under the conditions previously reported, *O*-protected β-alkoxy ketones were indeed reduced when the hydroxyl was protected with groups other than benzyl or TBS.[30]

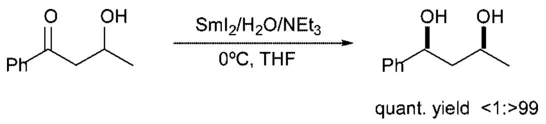
The reaction was carried out with different hydroxy ketones, where the alcohols were protected as ethers such as methoxymethyl, methoxythiomethyl, methoxyethoxymethyl and benzyloxymethyl. The yield and the *anti*/*syn* ratio depended on the nature of the protecting group used. The best results were obtained when a methyl ether was used (Scheme 24).



Scheme 24.

A complete study of the diastereoselectivities observed in these reductions of β-hydroxy carbonyl compounds related to the solvation of SmI_2 has also been published by Flowers et al.[31] This study revealed that the solvation of this metallic species plays an important role in the outcome of the reaction, and that this process is sensitive to the substitution, the nature of the proton source and the temperature.

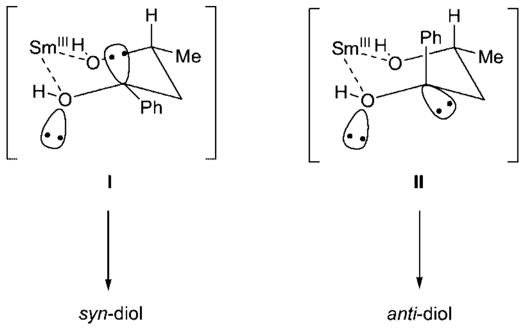
The same group has recently reported a similar process where different cosolvents were used in the reduction of β-hydroxy ketones. The system $SmI_2/H_2O/NEt_3$ was demonstrated as a suitable method for performing this transformation.[32] So, when the reaction was carried out on similar systems according to the conditions shown by Keck et al. (SmI_2/MeOH),[29] the *anti* diol was predominantly isolated. With Flowers' system ($SmI_2/H_2O/NEt_3$), however, *syn* diols are obtained. The usefulness of this methodology is unquestionable: different diastereomers of the same substrate can be obtained by just changing the solvent, proton source or additive employed in the reaction (Scheme 21 and Scheme 25).



Scheme 25.

In both cases, the products are obtained quantitatively without need for further purification apart from a standard workup.

A mechanism based on two successive single electron transfers from two equivalents of SmI_2 (similar to that shown in Scheme 23) was proposed. It would generate two possible intermediates, **I** and **II**, depicted in Scheme 26.

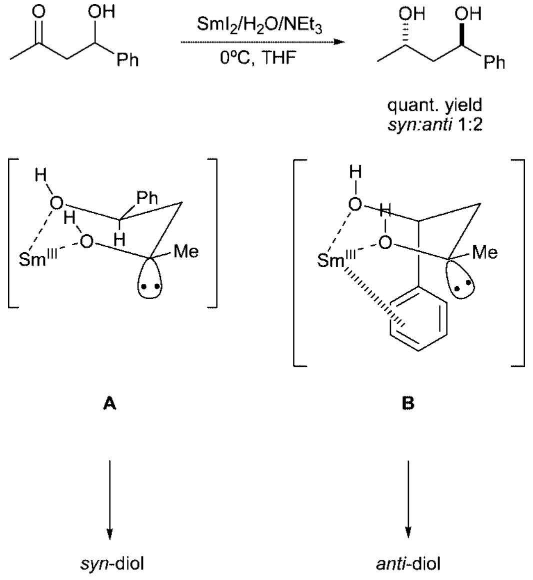


Scheme 26.

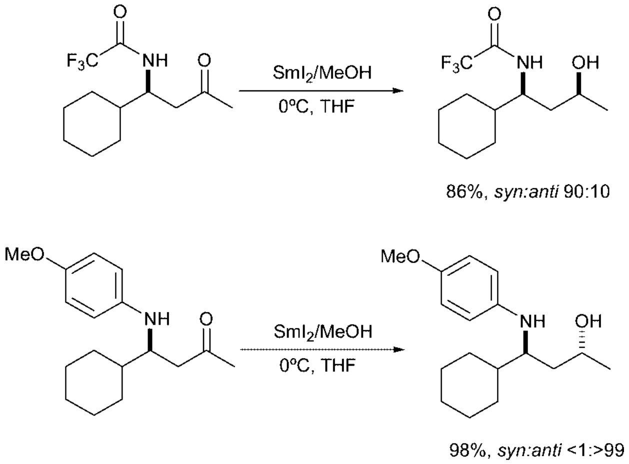
In the chair-like model **I**, the antiperiplanar disposition of both lone pairs would make this transition state of lower energy. Similarly, the unfavourable electrostatic interactions created by the spatial proximity of the lone pairs would make **II** less favoured. Transition states **I** and **II** would afford the *syn* and *anti* diols, respectively. In this sense, the *syn* diastereoselectivity would be explained through this mechanistic proposal.

When the reaction was performed on other regioisomers (4-phenylalkan-2-ones), lower diastereoselectivities were observed (Scheme 27). This behaviour could be explained by taking into account an interaction between the π-system of the phenyl group and the electron-deficient samarium centre. This interaction would partially stabilise a transition state like **B** in Scheme 27 (similar to transition state **II** in Scheme 26), thus decreasing the *syn*/*anti* ratio.

The samarium diiodide-mediated reductions discussed herein have been also carried out on β-amino ketones.[33] Different *syn*/*anti* ratios were obtained for the same substrate under the same conditions by simply changing the *N*-protecting group. So, when *N*-acyl or *N*-aryl-β-amino ketones were utilised, *syn*- or *anti*-amino alcohols were obtained, respectively (Scheme 28).



Scheme 27.

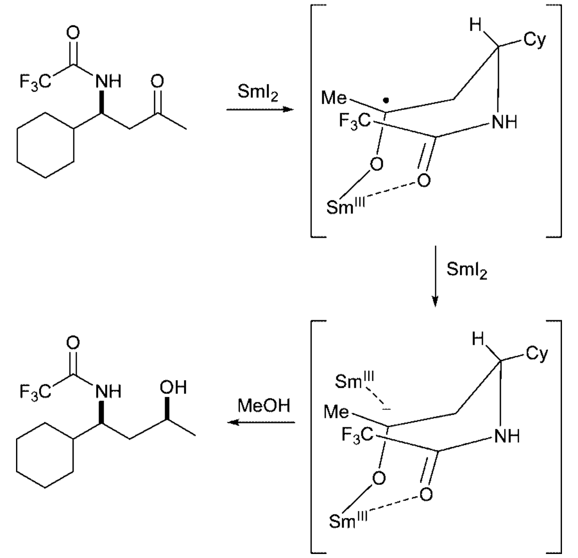


Scheme 28.

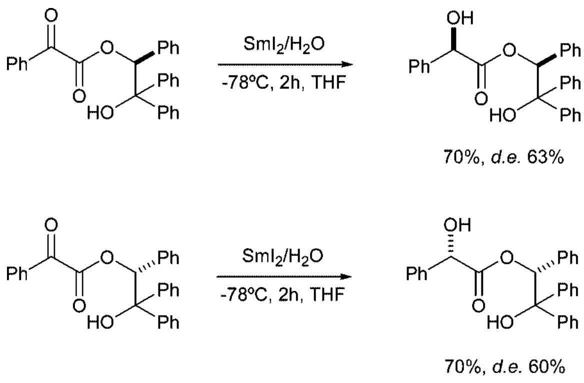
A different mechanism has been proposed for each reaction. In the case of *N*-aryl-β-amino ketones treated with SmI_2/MeOH/THF, a model similar to that illustrated in Scheme 23 would explain the *syn*/*anti* ratios observed. Nevertheless, the authors expect a more complex mechanism in comparison with the oxygen series. For the *N*-acyl-β-amino ketones, the acyl group plays a special role. Chelation between the oxygen from the amide and the samarium (III) atom would generate, after the first electron transfer, the eight-membered ring shown in Scheme 29.

A second electron transfer from another equivalent of SmI_2 would reduce the radical to the corresponding carbanion, which would be protonated by the methanolic medium, affording the *syn* amino alcohols.

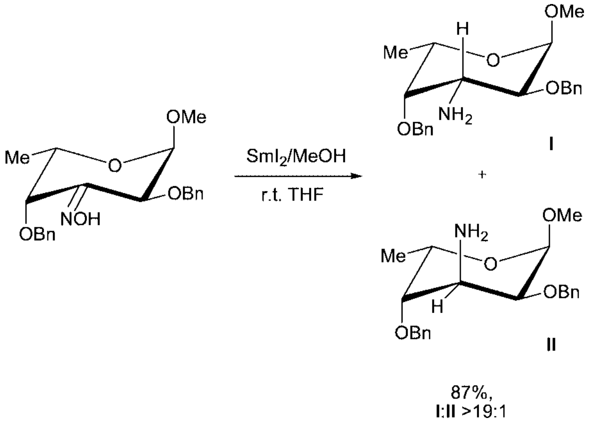
Finally, samarium diiodide has also been used to perform reductions of α-keto esters and α-ketoamides to the corresponding α-hydroxy acid derivatives.[34] Although the stereoselectivities observed are moderate, the stereocontrol is induced by inexpensive chiral auxiliaries. In the Scheme shown below, the best results obtained with this method are shown. The effect exerted in this process by different protic media (methanol, *tert*-butyl alcohol, tetrahydrofurylmethyl alcohol) has been studied within this process. The use of water as a proton source gave the best results in terms of yield and selectivity (Scheme 30).



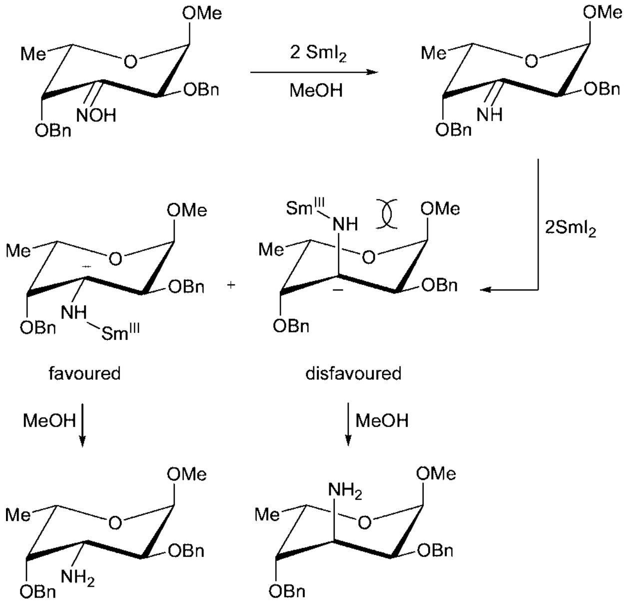
Scheme 29.



Scheme 30.



Scheme 31.



Scheme 32.

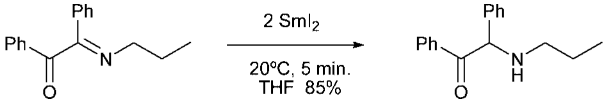
3.2 Reduction of CN Multiple Bonds

The possibility of reduction of C=N bonds in alcoholic medium has made SmI_2 a valuable reagent for the synthesis of natural products like, for example, some ravidosamine derivatives.[35] This reagent was successfully employed in the reduction of the oxime to the primary amine **I** shown in Scheme 31.

Several hydride reducing agents ($LiAlH_4$, Red-Al, $LiAlH_4$-$AlCl_3$) and an electron transfer system (Zn/AcOH) have been assayed for the same transformation. However, when hydride reagents were used, poor to moderate stereoselectivities and average yields were found. In the case of Zn/AcOH only starting material was recovered.

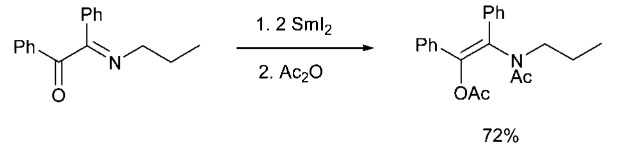
The authors proposed a mechanism based on the partial reduction of the oxime to the corresponding imine mediated by samarium diiodide. Subsequently, two consecutive single-electron transfers took place, giving the anionic intermediates, as presented in Scheme 32. Alcoholysis of these anionic species afforded the corresponding isomeric amines in a >19:1 ratio.

SmI_2-promoted reductions were also investigated on other imino substrates. When an α-imino ketone reacted with samarium diiodide, the corresponding amino ketones were obtained in good yields after hydrolysis.[36] This process can be also carried out in the presence of ethanol as an in situ proton source; however, in this case some byproducts were recovered (Scheme 33).



Scheme 33.

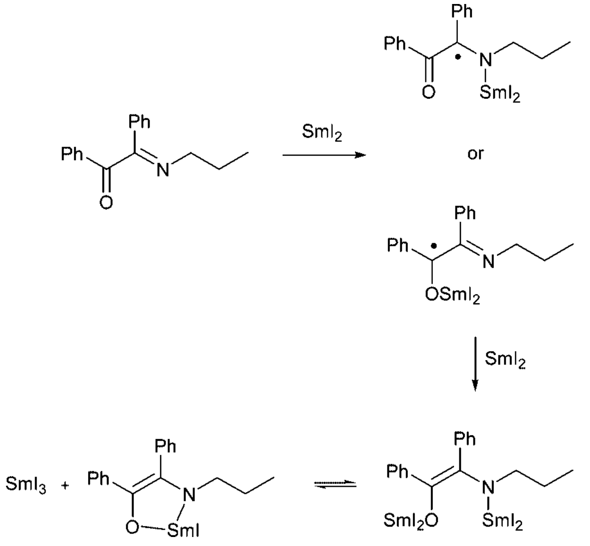
The authors tried to identify the samarium species generated in the reaction. Hence the reaction was quenched with an excess of acetic anhydride. The diacetylated species shown in Scheme 34 was recovered in high yield after workup.



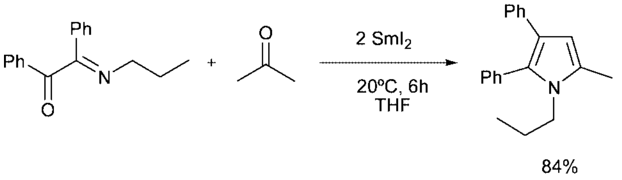
Scheme 34.

Based on this outcome, the authors presumed that the reduction reaction proceeded through two single-electron transfers to the α-imino ketone, generating a dianionic intermediate.

This reaction also proved to be a good method for synthesizing pyrrole derivatives. When the dianionic intermediate shown in Scheme 35 was quenched with a carbonyl compound, the corresponding pyrrole was obtained through a Knorr-type pyrrole synthesis (Scheme 36).



Scheme 35.



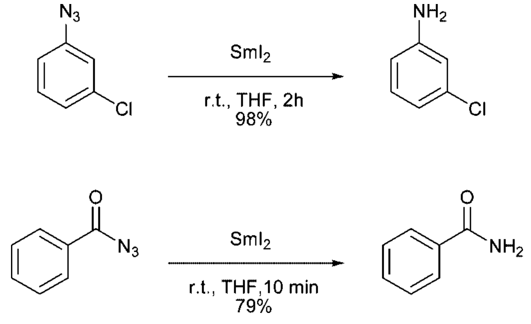
Scheme 36.

4 Reduction of Heteroatom-Heteroatom Multiple Bonds

4.1 Reduction of Azides

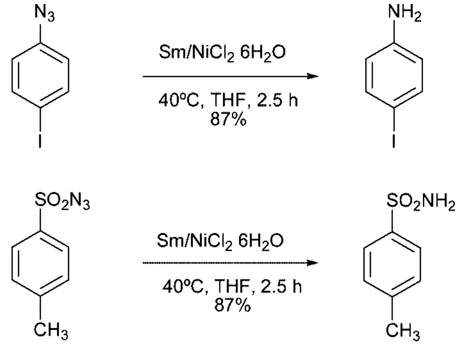
One of the first papers reporting the reduction of azides to primary amines promoted by samarium diiodide appeared 10 years ago.[37] Around the same time, a similar process was published.[38] In both contributions, the reduction was carried out employing similar conditions and slightly different amounts of samarium diiodide (3 and 2.5 equiv., respectively). In addition, the process has also been evaluated for the conversion of aroyl azides to amides.[38]

Generally, the process took place with good yields, although major details about the mechanism are not provided. The authors assumed a one-electron transfer to the azido group, which afforded a nitrene radical anion or an aminyl radical by the loss of N_2 (Scheme 37).



Scheme 37.

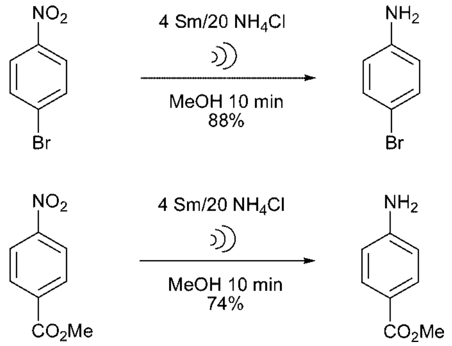
More recently, a samarium-based reduction of azides to amines has been reported using a $Sm/NiCl_2{\cdot}6H_2O$ system.[39] In this paper, several examples of amine and amide syntheses were reported, but a mechanistic proposal was not given. The conditions for this reaction are compatible with other functionalities such as halogens, carbonyl groups, sulfonyl groups or double bonds (Scheme 38).



Scheme 38.

4.2 Reduction of Nitro Groups

Banik et al. reported the reduction of aromatic nitro compounds to the corresponding aromatic amines utilizing a samarium metal/ammonium chloride system in the presence of sonic waves.[40] It is noteworthy that when the reaction was performed in the absence of sonication, the starting material was recovered and sensitive groups such as halogens, nitriles, esters, unsaturated bonds or heterocyclic groups remained unaltered (Scheme 39).



Scheme 39.

A mechanistic study of this nitro group reduction process promoted by samarium (II) species has recently been published by Brady et al.[41] Different intermediate species were isolated depending on the number of equivalents of samarium employed.

5 Conclusions

In summary, samarium diiodide has become an important and useful reagent for the reduction of multiple bonds. Samarium is now a valuable alternative to cases were hydrogen or hydride complexes were typically required. Generally, samarium-mediated reductions are carried out under mild conditions that are compatible with other functionalities existing in the molecule. Also, in most cases, these reactions proceed with high chemo- and stereoselectivity. This fact makes samarium diiodide or samarium metal an important reagent to be considered when dealing with reduction processes.

In conclusion, although samarium diiodide is still in its relative infancy, many processes have been already explored, and future work will undoubtedly reveal some new applications.

Acknowledgments

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