Samarium Metal in Organic Synthesis

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Recently organolanthanides have been widely employed as useful reagents in organic synthesis. Since the pioneering studies by Kagan and his co-workers demonstrated the effectiveness of samarium diiodide as a strong one-electron transfer reducing agent, the utility of this reagent in organic synthesis has been dramatically documented. There is increasing attention to performing synthetic transformation by direct reaction of metals. This represents an advantageous approach that avoids the use of sensitive and expensive organometallic compounds. For example, we have demonstrated the direct use of samarium metal in organic synthesis in recent publications. Parallel to our research, several other groups also have demonstrated new chemistry by samarium-induced reactions. This review is focused on the application of samarium-induced organic reactions. The advantages of using samarium metal in terms of reactivity, yield of the products, and selectivity in several organic transformations are discussed. Special attention is paid to the chemistry developed in our laboratory. A suggestion of reactive intermediates is also presented.

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1. Introduction

Organolanthanide chemistry and structural elucidation of reactive molecular species generated from lanthanides are in rapid revolution in organic chemistry.[1] The elements from lanthanum to lutetium constitute a unique family of 15 elements with the only difference being in the number of electrons at the outer 4f orbital. An important characteristic feature of the lanthanides is that they are in general

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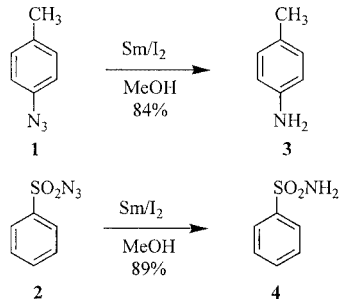
MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

highly oxophilic, and as a result many lanthanides have shown considerable promise for use in the activation of oxygenated organic functions. There is increasing attention to performing a wide variety of synthetic reactions by a direct reaction of metals. There are several advantages of using metal directly in synthetic pathways. The direct approach avoids the use of highly sensitive and expensive organometallic compounds. Synthetic chemists have used most metals of the periodic table for research and in many cases have shown the importance of metal-mediated organic reactions in simple chemical transformations or even complex organic synthesis. For example, synthetic potential of indium-mediated reactions have emerged as a very useful tool in organic synthesis. In contrast, samarium metal, which is cheap, has not received much recognition, although the use of samarium diiodide[2] is extremely popular in organic synthesis. Research in this area has substantiated samarium diiodide's ability to promote reactions that are very difficult to accomplish by many other available reagents. The success of a samarium diiodide reaction, however, depends in many cases on the presence of a suitable base, such as hexamethylphosphoramide. Furthermore, samarium diiodide is very sensitive to oxidation by air, so storage is difficult. On the other hand, samarium metal is stable in air and has a strong reducing power, similar to that of magnesium. As a result of these unique properties, the chemistry of samarium metal has received much attention in recent years. The operational simplicity and effectiveness of samarium metal compared with other metals and commercially available samarium diiodide has been well documented. Although, no one has reviewed the use of samarium metal induced organic transformations, a number of reviews [2] on the applications of samarium diiodide in organic synthesis are documented. Therefore, there is a scope of undertaking a review article that covers important development of samarium metal induced reactions in organic synthesis. This review aims to cover such an objective with special attention of those reactions developed in our laboratory.

2. Reduction of Azido Compounds

Various azides were easily reduced to the amines by samarium-induced reaction in the presence of catalytic amounts of iodine using methanol as the solvent.[3a] For example, aryl and arylsulfonyl azides **1** and **2** were reduced to amines **3** and **4** with excellent yields. It is interesting to note that in all these reactions, the cleavage occurred at the N−N bond, and the C−N or S−N bond remained unaffected (Scheme 1).

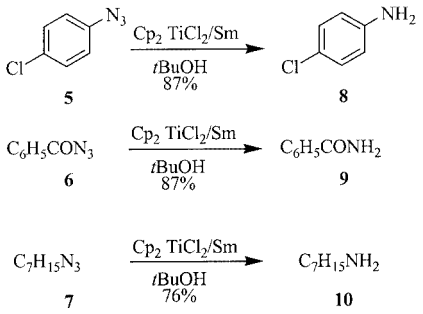


1 3

2 4

Scheme 1

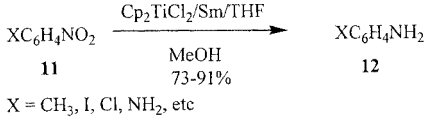
Azides **5**−**7** were reduced to amines **8**−**10** with Cp_2TiCl_2/Sm in excellent yield. A comparative study with respect to samarium diiodide indicated a greater reactivity of the Ti/Sm reagent towards the reduction reaction (Scheme 2).[3b]



Scheme 2

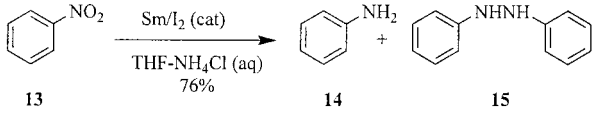
3. Reduction of Nitro Compounds

Reduction of aromatic nitro compounds by catalytic hydrogenation is probably the best method known to produce aromatic amines, although other synthetic methods have also been reported in the literature. For example, reduction of aromatic nitro compounds **11** to the aromatic amines **12** by a combination of samarium metal and Cp_2TiCl_2 was developed.[4] In this reaction, samarium metal reduces Cp_2TiCl_2 in THF to afford a low-valent samarium−titanium complex (Scheme 3).



Scheme 3

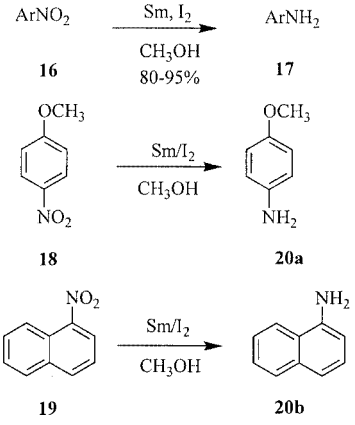
In the presence of a catalytic amount of iodine, aromatic nitro compounds (for example, **13**) were reduced to the corresponding aromatic amines (for example, **14**) and hydrazines (for example, **15**) with samarium and aqueous ammonium chloride in THF as the solvent.[5] (Scheme 4)



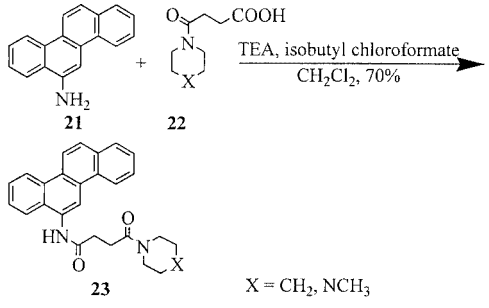
Scheme 4

As part of our experimental goal of synthesizing polycyclic compounds with anticancer properties,[6] we became interested in developing a general method for synthesizing aromatic amines.[7] Aromatic azido compounds, particularly in polycyclic series, are not abundant in Nature, are difficult

to prepare, and in some cases need to be handled with care because of their sensitivity to metallic objects. On the other hand, aromatic nitro compounds are easily accessible by conventional nitration, and many of them are commercially available. We developed a simple method of reduction of aromatic nitro compound **16** to the aromatic amine **17** by samarium metal. A catalytic amount of iodine was necessary, as the reduction did not proceed in the presence of samarium and methanol only. The reduction of monocyclic aromatic compounds proceeded smoothly to give the corresponding amines in high yields. 4-Nitroanisole (**18**) and 1-nitronaphthalene (**19**) were reduced under identical condition to 4-anisidine (**20a**) and 1-aminonaphthalene (**20b**) (Scheme 5). Subsequently, several polycyclic nitro compounds under identical conditions were reduced and the products were isolated in good yield. Some of the resultant polyaromatic amines (for example **21**) were used in a structure-activity relationship study for the development of anticancer agents. The amine **21** was coupled with the acid **22** to afford the diamide **23**. Several of these diamides have anticancer activities (Scheme 6).



Scheme 5

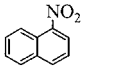
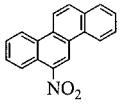
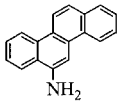
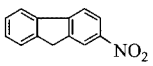
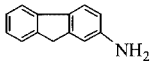
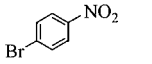
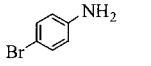
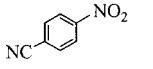
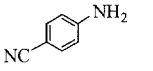
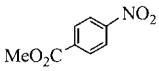
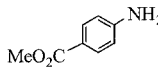
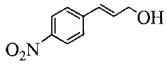
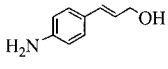
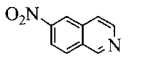
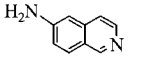


Scheme 6

To compare the effectiveness of this samarium-induced reduction process with that of the samarium diiodide mediated reduction process, we reduced 2-nitrofluorene, 6-nitrochrysene, and 1-nitropyrene. We isolated 15−20% unchanged starting materials from the crude reaction mixtures by column chromatography. The isolated yield of the products from the same reaction under samarium metal/iodine induced condition was 92−95%. Use of some salts and Lewis acids in some cases produced hydroxylamine derivatives under samarium diiodide induced reduction conditions. Prolonged reaction time or drastic conditions did not alter the product distribution. However, no hydroxylamine derivatives were observed in the present reduction method by samarium/iodine. The intermediates, if any, may be transformed to the final amines very rapidly without building sufficient concentration.

Recent reports have described many novel reducing agents for the reduction of aromatic nitro compounds to aromatic amines, such as decaborane in methanol, electrochemically generated Raney nickel, indium/ammonium chloride in ethanol, *N*,*N*-dimethylhydrazine/ferric chloride, hydrazine hydrate/ferric oxide/magnesium oxide, diethyl chlorophosphite, and sodium borohydride/sodium methoxide in methanol.[8] In general, of such reducing agents the main drawbacks are long reaction times, non-chemoselectivity and the requirement of reflux temperature. We developed a highly effective reducing agent by combining samarium with ammonium chloride under sonication[9] (Table 1).

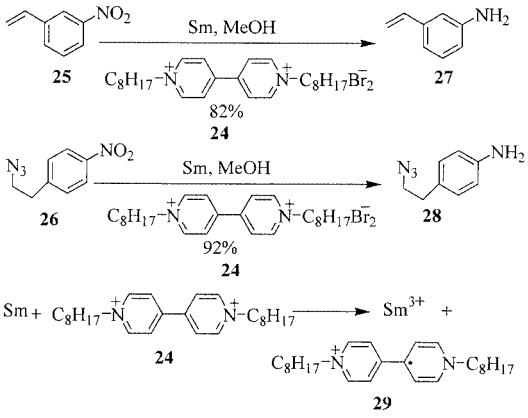
Table 1. Ultrasound-promoted reduction of various aromatic nitro compounds by Sm/NH_4Cl/EtOH

Entry	Starting material	Product	Time (min)	Yield (%)
1			10	88
2			10	86
3			10	92
4			10	88
5			10	87
6			10	74
7			10	90
8			25	56

A wide variety of aromatic nitro compounds were treated with samarium metal and ammonium chloride in methanol by using ultrasound at room temperature. For example, 6-nitrochrysene (Entry 2) was reduced to the 6-aminochrysene in only 10 min by this method with an excellent yield (86%). No reaction was observed in the absence of sonication.

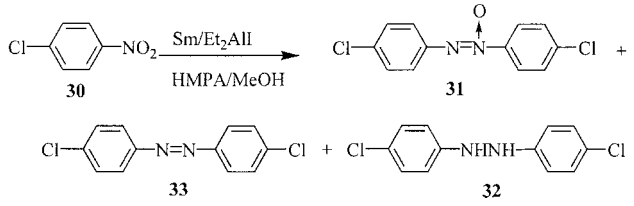
Samarium metal and 1,1′-dioctyl-4,4′-bipyridinium dibromide (**24**) were found to constitute an excellent novel electron-transfer system for the chemoselective aromatic nitro group (**25** and **26** to **27** and **28**) (Scheme 7).[10] Elec-

tron transfer from samarium metal to the pyridine rings of 1,1′-dioctyl-4,4′-bipyridinium dibromide (**24**) led to the formation of a hyperconjugated radical cation **29** that is the actual reactive species.



Scheme 7

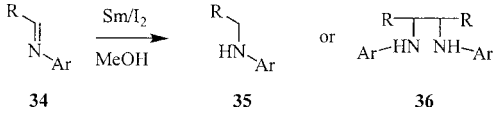
The reduction of aromatic nitro groups by samarium in the presence of HMPA produced azoxy compounds.[11] For example, 4-chloronitrobenzene (**30**) afforded a mixture of 4-chloroazoxybenzene (**31**), hydrazine **32** and azo compounds **33** (Scheme 8). Interestingly, chloro and bromo groups remained unaffected during the reaction. Similar reactions with other metals, such as Mg and Ti gave a complex mixture or low yield of the products.



Scheme 8

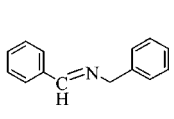
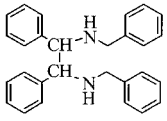
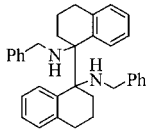
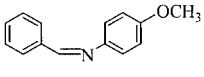
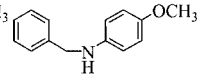
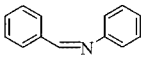
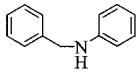
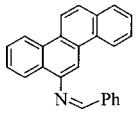
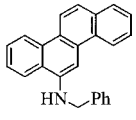
4. Reduction of Aldimines

Having a practical method of reduction in hand, our attention was turned to the preparation of secondary amines. Several groups have described the synthesis of secondary amines using various reagents.[12] However, the catalytic hydrogenation of imines is still the reaction of choice to produce secondary amines in reasonably good yield. The use of the samarium-mediated reduction method on various imines produced secondary amines. Reaction of various imines **34** with samarium metal and iodine using methanol as the solvent was accomplished and useful selectivities were observed (Scheme 9).[13] The nature of the final product (monoamine **35** or diamine **36**) was found to depend on the structures of the starting imines and from a series of experiments, a generalization could be made. Thus, imines from polyaromatic amine (Table 2, Entry 5) and aniline derivatives (Table 2, Entries 3 and 4) gave rise to monomeric secondary amines **35**, whereas Schiff bases from alkyl(aryl)-amines (Table 2, Entries 1 and 2) yielded dimeric products **36**. In contrast, SmI_2-mediated reaction of the imines produced a mixture of dimeric products (*dl* and *meso*)[14] The formation of the dimeric structures by SmI_2-mediated reaction was explained by postulating a one-electron transfer mechanism across the C=N bond and subsequent coupling of the two-carbon radical as was observed during pinacol-type reactions.



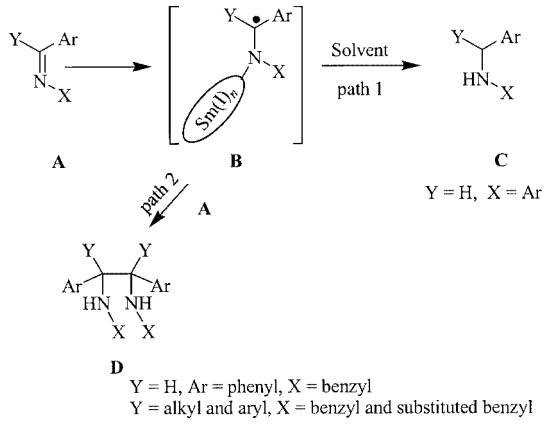
Scheme 9

Table 2. Reduction of the Schiff base **34** with Sm/I_2/MeOH

Entry	Starting Schiff bases	Product amines	Yield	Time and conditions
1			52%	r.t., 30min
2			66%	r.t., 30min
3			55%	r.t., 30min
4			58%	r.t., 30min
5			70%	overnight reflux

Although the reactive species formed by the reaction between samarium metal and iodine (SmI_2 or SmI_3 or any other iodosamarium complex) cannot be identified at this time, the final distribution of products can be tentatively explained by postulating two competing pathways resulting in the generation of the reduction product (Scheme 10, path 1) or the dimeric product (Scheme 10, path 2). Mechanistically, the formation of the monoamine **C** can be explained by the second electron transfer to the initially formed radical **B**, to generate the dianion and then protonation of the dianion by the solvent. This process could be due to the presence of the electron-releasing substituent at the nitrogen atom, which can change the reduction potential of the radical anion **B** so that a second electron transfer becomes the only path. Alternatively, the radical **B** in the polyaromatic system may prevent self-coupling due to steric considerations. Increased congestion around the carbon radical inhibits the C−C bond formation. The basis for the formation of monoamines with simpler aromatic amines (path 1) and diamines (path 2, **D**, radical−radical

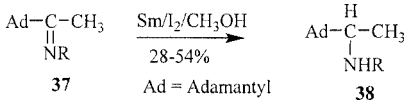
coupling) with alkyl(aryl)amines is not clearly understood at this time. These results indicate that the nature of the products by samarium-induced iodine-catalyzed reduction of the imines depends entirely on the substituent present at the N atom of the imines.



Scheme 10

To gain a more complete mechanistic insight into this novel reduction method and to apply this method to prepare biologically active compounds, we became interested in the reduction study of adamantylmethanimine **37**. The reductive amination of aldehydes and ketones is widely studied reaction used for the synthesis of amines. Various hydride donors, such as sodium borohydride, sodium cyanoborohydride and zinc borohydride have been used for this purpose.[15] To overcome the problems associated with the use of these reagents, Bhattacharyya [16] demonstrated similar transformations with titanium isopropoxide and sodium borohydride. In an elegant study, he showed that biologically active (1-adamantylethyl)amines could be prepared by a direct reductive amination reaction using titanium isopropoxide and borohydride reagents. Indirect synthesis of such (1-adamantylethyl)amines was known.

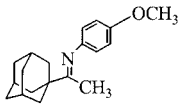
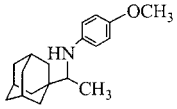
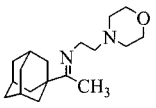
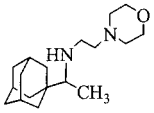
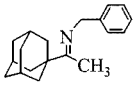
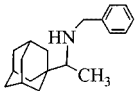
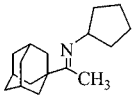
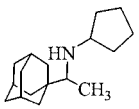
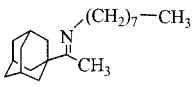
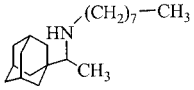
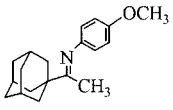
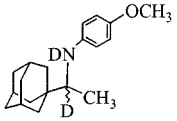
The synthesis of imine **37** with adamantyl methyl ketone was performed with a wide variety of amines.[17] Reduction of **37** by samarium in the presence of iodine produced monoamine **38** (Scheme 11, Table 3).



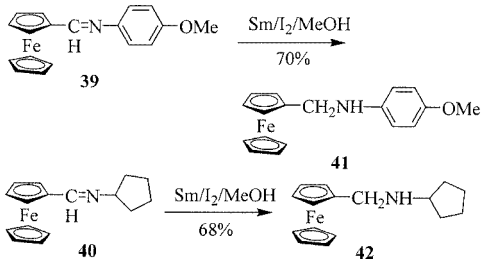
Scheme 11

Experiments with CD_3OD produced the D-labeled compound, indicating the trapping of the dianion by the solvent (Table 3, Entry 6). The dianion is probably formed by a single-electron transfer to the C−N bond to generate the ion-radical **B** and then by a further electron transfer to the ion radical **B**. Radical−radical coupling product (dimeric product **D**) could not be formed because of the considerable steric crowding at the radical center due to the bulkier adamantane system (Scheme 10).

Table 3. Sm/I_2-induced reduction of adamantylmethanimine **37** in methanol

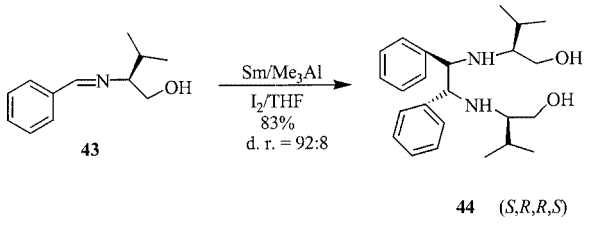
Entry	Starting material	Product	Yield (%)
1			50
2			28
3			51
4			47
5			54
6			45

By applying the above methodology, we prepared several (ferrocenylmethyl)amines (**41** and **42**) from imines **39** and **40**. We consider this samarium-induced reduction reaction to be the best alternative to the reductive amination reaction for the synthesis of (ferrocenylmethyl)amines (Scheme 12).[18] In a recent elaborate study on the electronic conjugation pathways in ferrocenylmethanimines the electron density around the C=N bond is not affected too much by the presence of an aromatic or aliphatic group.[19] Thus, our study demonstrates a unique role of the ferrocene moiety in controlling the product distribution. These results indicate that the nature of the products by samarium-induced iodine-catalyzed reduction of the ferrocenylmethanimines depends on the substituent present at the N atom and also at the C atom of the imines.



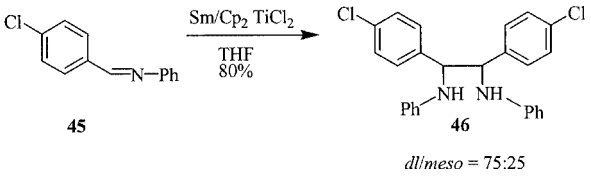
Scheme 12

Intermolecular dimerization of optically active imine **43** with samarium and catalytic amounts of iodine was achieved.[20] The stereochemistry of product **44** was explained by assuming a chelate-controlled reaction of a trivalent samarium species generated in the medium. Application of this method to compounds with free β-hydroxy groups afforded the corresponding amino alcohols. Trimethylaluminum had a great effect on the diastereoselectivity (diastereomeric ratio, 90:10) of the dimerization reaction.[21] (Scheme 13).



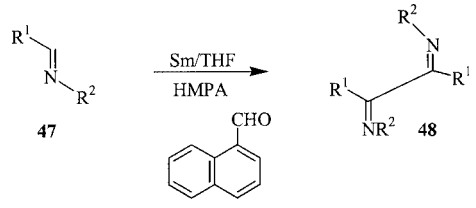
Scheme 13

Pinacol couplings of imines (for example, **45**) were also investigated by Sm/Cp_2TiCl_2 and the results were encouraging. Various imines were dimerized to a mixture of vicinal diamines (for example, **46**) (Scheme 14).[22]



Scheme 14

Dehydrogenative coupling of various aldimines **47** mediated by samarium metal was investigated by Fujiwara and his group.[23] Several vicinal diimines **48** were prepared from the reaction of arylaldimines **47** with samarium metal followed by treatment with an appropriate oxidant (Scheme 15).



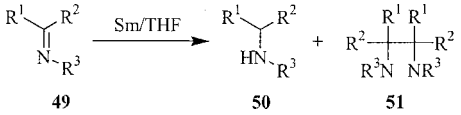
Scheme 15

5. Reductive Dimerization of Ketimines

Since the biological activities of vicinal diamines are well known, we investigated our reduction method in detail. Reductive dimerization of aldimines has been widely used for this purpose. For example, samarium diiodide, indium, titanium, lead/aluminum, zinc/copper couple, electrochemical reduction and niobium have been used directly for the reduction experiments with various degrees of success.[24] Dicarbonyl compounds, amino acid esters, and olefins were also used as starting materials for the synthesis of vicinal diamines in indirect approaches.[25] Surprisingly, analogous reactions of ketimines to the vicinal diamines proved unsuccessful. Zinc powder[26] and low-valent titanium[27] were used to achieve reductive dimerization of ketimines in an attempt to achieve a synthesis of this type of compounds. However, both attempts failed completely.

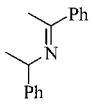
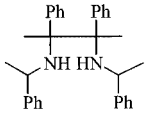
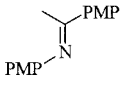
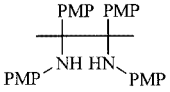
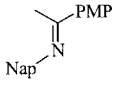
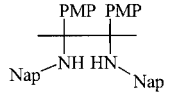
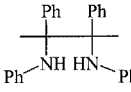
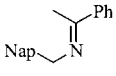
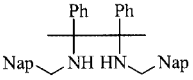
During the course of this study, a rapid and convenient method for the iminopinacol-type of coupling of ketimine **49** to the vicinal diamine **51** by samarium metal in the presence of catalytic amounts of iodine was developed (Scheme 16).[28] The yield of the monoamine **50** was significantly low. To the best of our knowledge, this is the first successful report on the reductive dimerization of ketimines with an excellent yield (Table 4). This dimerization of ketimines is interesting from a mechanistic point of view. Single-electron transfer across the carbon−nitrogen unsaturated bond by samarium produces the ion radical in the first step. This electron-transfer process is presumably not dependent on THF or methanol. The presence of an activator (in this case iodine) seems essential in catalyzing the process. The generated ion radical can follow two different pathways leading to two different products. The first path is the hydrogen abstraction and subsequent protonation during workup leading to the monoamine **50**. The second path is a coupling process of the ion radical and subsequent protonation by the solvent during workup. Our results clearly indicate that the second process is exclusively operating in THF, indicating that the stability of the ion radical in THF is high enough to permit a radical−radical coupling and consequent formation of diamine **51** (for example, Scheme 10). Thus, it is interesting to observe the formation of diamines in THF with sterically congested ketimines. Mechanistically, this is in sharp contrast with the observation reported by Talukdar and Banerji[27] in their low-valent titanium induced process. These authors proposed a similar reaction pathway that involves single-electron transfer from titanium to explain the distribution of the products in their low-valent titanium induced iminopinacol-type reaction of imines. According to them, the reactions of ketimines with titanium trichloride/lithium/THF did not yield the dimer but produced amines exclusively. The steric bulk of the ketimines was believed to favor the unimolecular quenching of the intermediate by THF in preference to dimerization. Although, the pathways involved in the titanium-induced process and our samarium-induced process are similar in principle, they differ entirely in the production of the final products. This observation can be explained only by assuming a tremendous role taken by the metal species (Ti and Sm) that dictates the formation of the product. Apparently, samarium as a cation stabilizes the ion radical in the transition state so that a coupling can occur. However, further work is essential to delineate the differences between the

titanium- and samarium-induced reduction processes of ketimines.



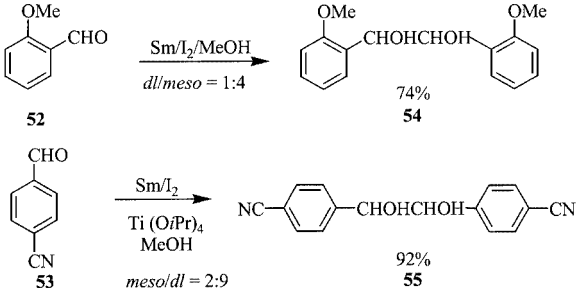
Scheme 16

Table 4. Dimerisation of ketimines **49** in THF (Ph = phenyl, PMP = *p*-methoxyphenyl, Nap = 1-naphthyl)

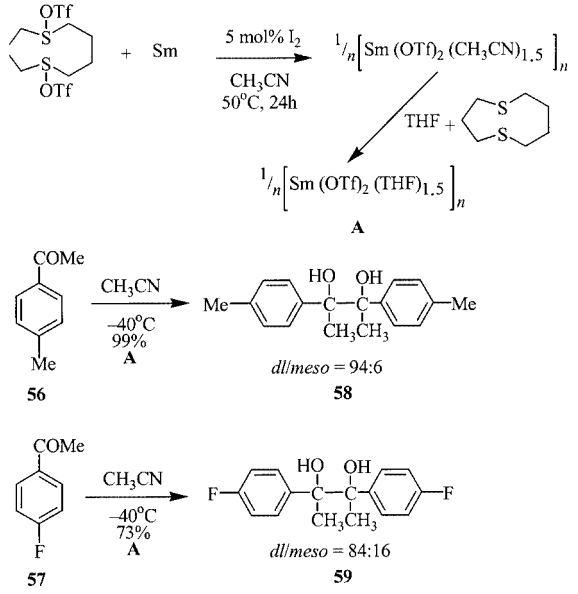
Entry	Reactant	Product	*dl*/*meso*	Yield (%)	Time (min)
1			3:1	90	30
2			1:1	92	30
3			2:3:1	85	30
4			3:2:1	91	30
5			2:1	89	30

6. Reductive Dimerization of Carbonyl Compounds

Reductive coupling of carbonyl compounds (**52** and **53**) to pinacols (**54** and **55**) by using samarium/iodine in methanol (a *dl*/*meso* mixture) and samarium/iodine/titanium isopropoxide (*meso* preferred) was achieved (Scheme 17).[29] In many instances, particularly with aliphatic aldehydes, a substantial amount of simple reduction product was obtained. Reaction of samarium metal with the hypervalent compound 1,5- dithioniabicyclo[3.3.0]octane produced a bivalent salt-free samarium bis(trifluoromethanesulfonate) complex. This complex was used for intermolecular pinacol coupling reactions of aromatic ketones **56** and **57** to diols **58** and **59** with high diastereoselectivity (*dl* isomer was predominantly formed) (Scheme 18).[30]

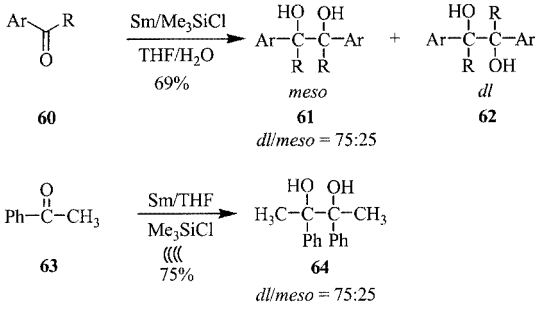


Scheme 17



Scheme 18

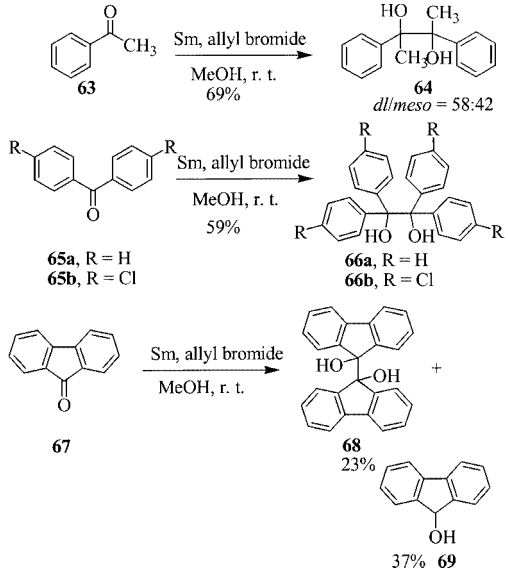
Diastereoselective pinacol coupling of alkyl aryl ketones with samarium in the presence of trimethylsilyl chloride was also accomplished. The yield of products (**61** and **62**) was very low when the reaction was performed without trimethylsilyl chloride. However, the use of trimethylsilyl chloride and ultrasonic irradiation resulted in a relatively better yield (**63** to **64**) (Scheme 19).[31]



Scheme 19

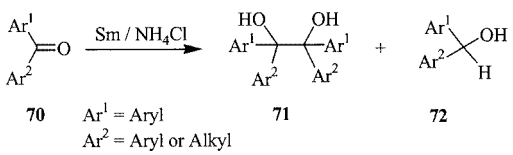
During our ongoing research into the application of samarium metal in organic synthesis, we decided to investigate the Grignard-type addition of an allyl group to ketones in the presence of samarium metal. Treatment of acetophenone (**63**) with allyl bromide in the presence of samarium metal unexpectedly produced the alcohol derivative **64**.[32] No traces of the allyl group were detected in the crude reaction mixtures. Experiments showed that with 2.5 equiv. of samarium metal and 0.6 equiv. of allyl bromide, acetophenone was completely converted into the diol **64** in 3 h in 75% yield (*dl*/*meso* = 58:42, Scheme 20). From the results, it is evident that as the bulk of the aromatic part

of the ketone increased, the tendency to form the simple reduction product increased. When benzophenone (**65a**) was used as the substrate, the reductive coupling product **66a** was formed exclusively in 59% yield. On the other hand, tricyclic fluorene **67** resulted in a mixture of fluorenol (**69**, 37%) along with the dimerized product (**68**, 23%). Other halides, particularly dibromoethane and bromobutane, gave the products in satisfactory yield. Although the mechanism of the reaction remains unclear, it seems that alkyl halides have an important role in the reduction reaction, since the reaction did not proceed without it.



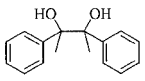
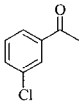
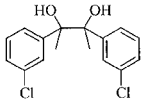
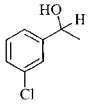
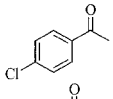
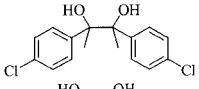
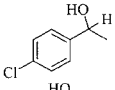
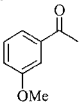
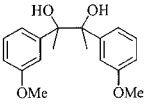
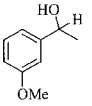
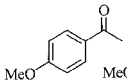
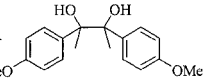
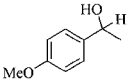
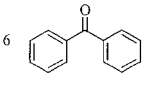
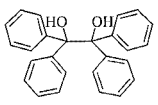
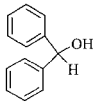
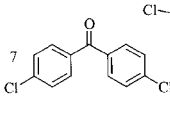
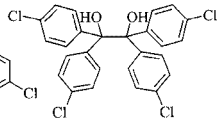
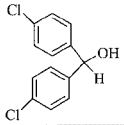
Scheme 20

These results prompted us to examine the reducing ability of samarium metal in the presence of other reagents, and towards this goal we demonstrated a facile pinacol-type coupling of aromatic ketones in the presence of alkyl halides. We envisioned that such a dimerization of ketones could be improved in the presence of other activating agents that could improve the reducing ability of the metal. A literature search revealed that indium metal in the presence of ammonium chloride greatly enhances the reaction rates in some cases. A facile reduction of several aromatic ketones (**70** to diol **71**) by samarium in the presence of ammonium chloride under sonication at room temperature was developed by us (Scheme 21).[33] Reaction of acetophenone derivatives (Table 5, Entries 1−5) was studied in detail. Ultrasonic exposure of a solution of acetophenones in the presence of samarium/ammonium chloride at room temperature produced the diol **71** in excellent yield (66−98%). In some cases, alcohol **72** (11−51%) was also isolated.



Scheme 21

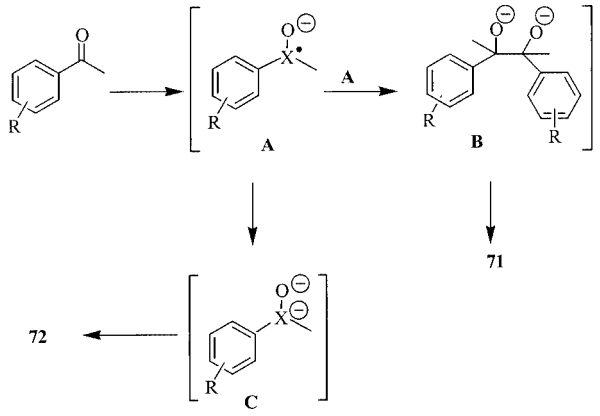
Table 5. Ultrasound-promoted pinacol coupling of aromatic ketone **70** by $Sm/NH_4Cl/EtOH$

Entry	Ketone **70**	**71**	**72**	**71**/**72**	Yield of alcohol (%)	Yield of diol (%)
1				82:18	11	54
2				76:24	22	69
3				76:24	22	72
4				70:30	27	66
5				53:47	51	46
6				51:49	48	46
7				40:60	37	55

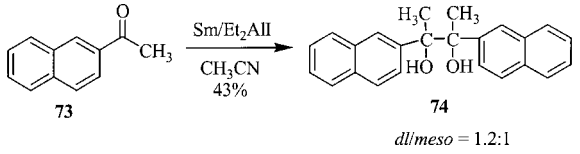
The mechanism of the samarium/ammonium chloride mediated reduction had not been investigated. Given the nature of the products, the most probable mechanism would be a reaction very similar to our samarium/iodine-induced reduction reaction of imines (Scheme 22). Single-electron transfer to the unsaturated carbon−oxygen bond can generate the ion radical **A** and because of the stability of the benzylic radical, a self-coupling process (**A** to **B**) is feasible. As a result, pinacol-type compound **71** is formed. In concentrated solution, further electron transfer to the ion radical **A** can be a competitive path to the dianion **C**, which can be easily protonated by methanol to generate the alcohol **72**. The formation of substantial amounts of alcohol **72** in the benzophenone reduction (Entries 6−7) indicates a severe steric hindrance at the ion-radical center **A**, and we assume that this prevents the self-coupling process.

The distinct advantages of the reduction of aromatic ketones for the synthesis of diols reported herein over other methods included a very short reaction time, environmentally benign reagents, less by-products, and an overall high yield.

Sm/Et_2AlI was used for the reductive coupling of carbonyl compounds. For example, methyl 2-naphthyl ketone (**73**) was dimerized to a mixture of alcohols **74** (Scheme 23). The stereoselctivity of the products was rationalized by considering the chelation of the samarium or aluminum atom by oxygen atoms.[34]

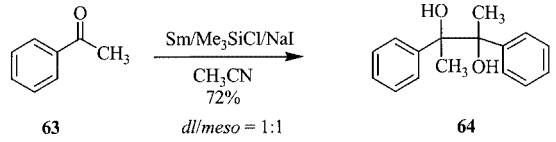


Scheme 22



Scheme 23

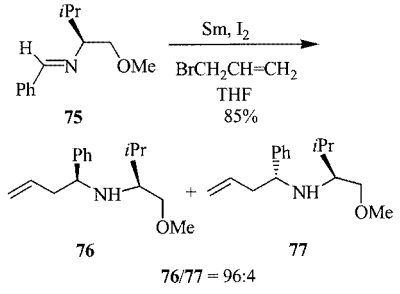
A dimerization of carbonyl compounds was developed by the use of Sm/TMSCl/NaI. However, the yield of the product (**63** to **64**) was temperature-dependent (Scheme 24).[35]



Scheme 24

7. Barbier Reactions

Barbier-type allylation of optically active imine **75** to amines **76** and **77** was investigated with metallic samarium, catalytic amounts of iodine and allyl bromide (Scheme 25). The notable feature includes the use of different types of functionalities, for example, ether, ester, alcohol at the nitrogen atom of the imines.[36] Among the imines, the use of methyl ether resulted in the best yield and an excellent diastereoselectivity. The absolute configurations at the chiral centers were determined by a direct comparison with authentic samples.

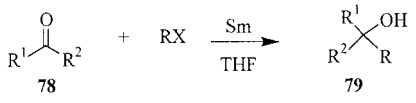


Scheme 25

The substituent effects at the aldehyde side of the imine affect the diastereoselectivity. Imines that have a 4-cyanophenyl group gave a complex mixture, while imines that have a electron-donating group (for example, 4-methoxyphenyl) gave a product with outstanding diastreoselectivity. The formation of an allylsamarium complex and involvement of trivalent samarium were proposed to explain the product distribution.

The development of Barbier-type carbon−carbon bond formations offers tremendous opportunities in synthetic organic chemistry [37] and major advances of this type of reaction have been developed. The metals in use include primarily Sn, Zn, Mg, Bi, and Cd. There are drawbacks, however; these metals take long reaction times, and only reactive halides have been found to be effective. Indium in aqueous solution has shown a considerable promise in the addition of unsaturated halides to the carbonyl groups.[38] Kagan et al. have demonstrated and favorably compared samarium diiodide mediated Barbier reaction of aldehydes and ketones with other available methods.[39]

Recognizing the importance of Barbier reactions in organic synthesis, we continued to examine this reaction in detail (**78** to **79**, Scheme 26).[40] Reaction of acetophenone with allyl bromide in the presence of samarium and catalytic amounts of iodine in tetrahydrofuran as the solvent produced the unsaturated alcohol as the major product (Table 6, Entry 1). Analyses of the crude reaction mixtures revealed the presence of small amounts of pinacol-type compounds (10%). Allyl bromide, benzyl bromide, and napthyl bromide produced products in good yield (Table 6, Entries 1−6). 2-Phenylethyl iodide resulted in a product in relatively low yield (Entry 8).

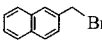
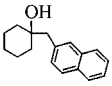
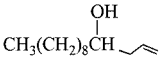
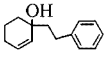


Scheme 26

Samarium metal was used previously for the Barbier reaction in the presence of trimethylsilyl bromide and trimethylsilyl chloride/sodium iodide with a single substrate. The reactive species was claimed to be a bivalent samarium cation, although no justification was provided, and the structure of the bivalent samarium equivalent was not confirmed. In addition, this method required freshly distilled silyl chloride and reflux temperature. In contrast, our method has a much wider application, requires only samarium and catalytic amounts of iodine, and can be performed at room temperature.

Recently, a trivalent samarium cation was proposed to be a reactive species when imines were allylated or alkylated by samarium metal and catalytic amounts of iodine. The yield of the desired product from the reaction of imines and benzyl bromide was low, and bibenzyl was found to be the major product from the reaction. However, when benzyl

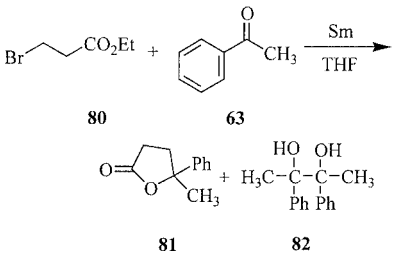
Table 6. Barbier reaction of **78** in the presence of samarium metal and catalytic amounts of iodine in THF

Entry	Carbonyl compounds	Halides	Products	Time (min)	Yield (%)
1				20	80
2				20	70
3				20	70
4				20	90
5				30	52
6				30	56
7	$CH_3(CH_2)_8CHO$			20	81
8				20	31

bromide was added to the ketones by using our method, benzyl alcohol was formed in excellent yield, a small portion of which was dimerized. Thus, the involvement of trivalent samarium species in this type of addition reaction remains a question. Our study indicates that a pre-generated bivalent or trivalent samarium species is not required for the Barbier addition of halides to carbonyl compounds. We favor the formation of an activated samarium−R reagent that attacks the carbonyl group in THF solution. Further studies are needed to define the critical role of solvents in the samarium-induced addition and dimerization of carbonyl compounds in the presence of halides.

8. Homo Reformatsky Reaction

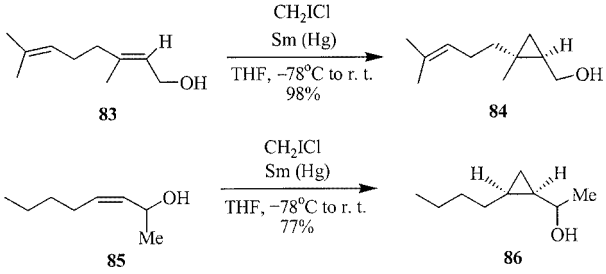
The chemistry of metal homoenolates has been well known for many years. Direct reaction of 3-halo carbonyl compounds and a metal is one of the best choices for the generation of homoenolates. The reaction of a lithium homoenolate and zinc ester homoenolates has been investigated. Preparation of lanthanoid ester homoenolates from 3-halo esters and lanthanum metals and their reaction with carbonyl compounds to give lactones in good yields under mild conditions was reported.[41] Reaction of 2-bromopropionate **80** with acetophenone (**63**) in the presence of samarium metal produced γ-lactone **81** and a diol **82** (mixtures of *dl* and *meso* forms) in 71% and 22% yield, respectively (Scheme 27). With 2-iodopropionate, however, formation of the γ-lactone **81** was suppressed completely and the yield of the diol **82** could be increased to 63%. The characteristics of the samarium-mediated reaction of 3-bromo esters with ketones include a successful reaction without the need of additives or catalysts; reaction conditions are mild. The intermediate is believed to be a samarium ester homoenolate from the study of the IR spectra in THF solution. The IR spectrum shows bands at 1737 and 1621 cm^{-1}, due to the two strong carbonyl absorptions; the lower absorption is due to the chelated carbonyl group, and the higher absorption is believed to be due to the nonchelated one.



Scheme 27

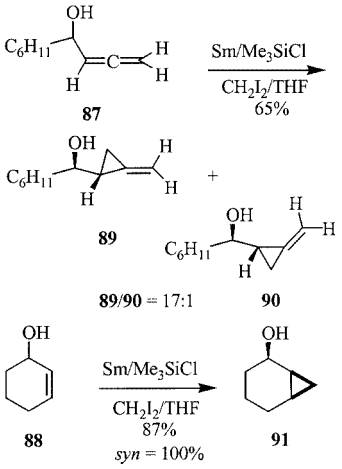
9. Simmons−Smith Cyclopropanation Reactions

The samarium-promoted cyclopropanation reaction was discovered by Molander and his group[42] and worked very well compared with the traditional zinc-mediated method. An efficient cyclopropanation of geraniol (**83**) to **84** was accomplished with samarium amalgam in the presence of choloroiodomethane. The samarium-promoted reactions had a higher diastereoelectivity than did the Simmons−Smith reaction, presumably because of mild reaction conditions (**85** to **86**) (Scheme 28).



Scheme 28

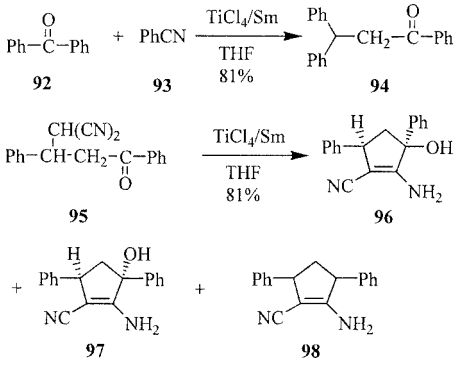
In order to improve several problems, Lautens and Ren[43] demonstrated an effective Simmons−Smith cyclopropanation reaction using samarium metal and chlorotrimethylsilane as the activating reagent (Scheme 29). The role of chlorotrimethylsilane in cleaning the surface of zinc and in activating titanium is well known. Replacement of mercuric chloride by trimethylsilyl chloride improved the diastereoselectivity and decreased the toxicity. Under this condition, allenic alcohol **87** and allylic alcohol **88** were cyclopropanated (**89** to **91**) by using samarium/dichloromethane/trimethylsilyl chloride. The reaction was found to favor the formation of the major diastereoisomer, as predicted by the Houk model. These examples clearly demonstrated the requirement of a hydroxy group in chemoselective and stereoselective cyclopropanation reactions.



Scheme 29

10. Miscellaneous Reactions

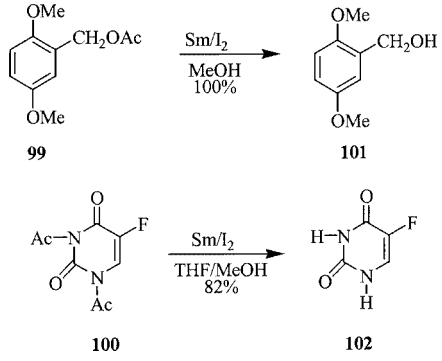
A reductive cross-coupling reaction of nitriles with carbonyl compounds promoted by titanium tetrachloride/samarium in anhydrous THF is reported (Scheme 30). Treatment of carbonyl compounds with nitriles in the presence of samarium/$TiCl_4$ gave substituted ketones or olefins depending upon the structures of the starting materials and the reaction conditions. Benzophenone (**92**) and nitrile **93** at THF reflux temperature with the reagent system gave the ketone **94** as the only isolated product.[44] With aromatic aldehydes at room temperature, the product was the olefin, not the ketone. On the other hand, with samarium diiodide the product was the hydroxy ketone.



Scheme 30

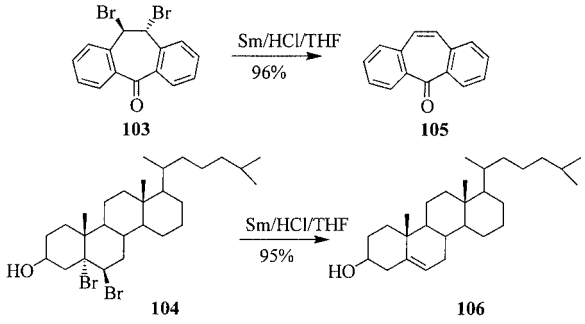
Intramolecular ketone/nitrile reductive coupling reaction can also be achieved by this reagent combination. For example, reaction of the substrate **95** under nitrogen produced three products: the amino-cyanocyclopentanol **96**, its diastereomer **97**, and the unsaturated cyanocyclopentenamine **98**. This reaction has been shown to be temperature-dependent. Thus, at −20 °C, only cyclopentenes **96** and **97** were formed. However, at 65 °C, only **98** was formed along with small amounts of **96** and **97**. The formation of these products in the $TiCl_4$/Sm-induced reductive coupling is clearly different from the other existing methods available in the literature, particularly the samarium diiodide, the electroreductive, the Zn/TMSCl, the Cp_2TiPh methods which produce α-hydroxy ketones.[38]

Deacylation and dealkoxycarbonylation of protected alcohol **99** and lactam **100** were achieved by samarium and iodine in alcohol (Scheme 31). The products were alcohol **101** and *N*-deacylated **102**. Trivalent samarium species may have been involved.[45]



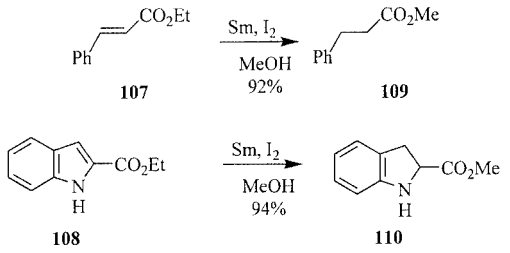
Scheme 31

Debromination of vicinal dibromides **103** and **104** to alkenes **105** and **106** was successfully achieved by samarium metal in the presence of catalytic amounts of acid (Scheme 32).[46]



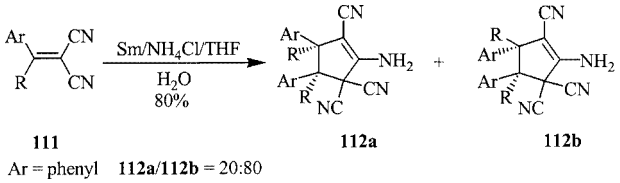
Scheme 32

Selective 1,4-reduction of α,β-unsaturated carboxylic acid derivatives **107** and **108** to saturated derivatives **109** and **110** was performed by samarium and iodine in alcohol (Scheme 33).[47] These reactions supported a mechanism similar to the Birch-type reduction involving a radical-anion formation, followed by additional electron capture and subsequent protonation.



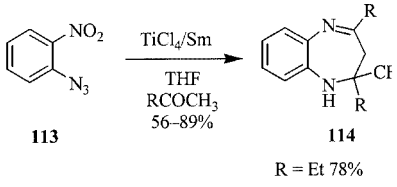
Scheme 33

Reductive dimerization cyclization of 1,1-dicyanoalkenes **111** to functionalized cyclopentene **112** was achieved in a one-pot reaction by samarium in the presence of trimethylsilyl chloride and a trace amount of water (Scheme 34).[48]



Scheme 34

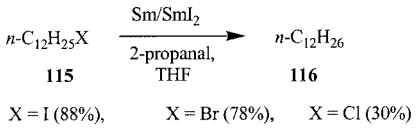
Simultaneous reduction of the aromatic nitro and azido groups were investigated by $Sm/TiCl_4$ towards the synthesis of benzodiazepines (**113** to **114**, 56−89%) (Scheme 35).[49]



Scheme 35

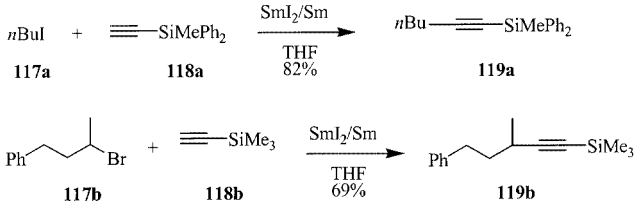
11. Samarium Metal in the Combination with Samarium Diiodide

The reducing ability of samarium metal can be dramatically improved by a combination with samarium diiodide, as has been shown in the reduction of alkyl halides (Scheme 36).[50] The reduction of these halides **115** and **116** with samarium diiodide alone requires long heating in THF. The same reduction can be accomplished very efficiently at room temperature in the presence of a mixture of samarium metal and samarium diiodide. However, the yields of the reduction of chloroalkanes, even with this mixed reagent system are very low. The differences in reactivities between bromides and chlorides towards Sm/SmI_2 enable a selective reduction of a compound that has chloro and bromo substituents in the same molecule, for example, 1-bromo-6-chlorohexane to *n*-hexyl chloride.



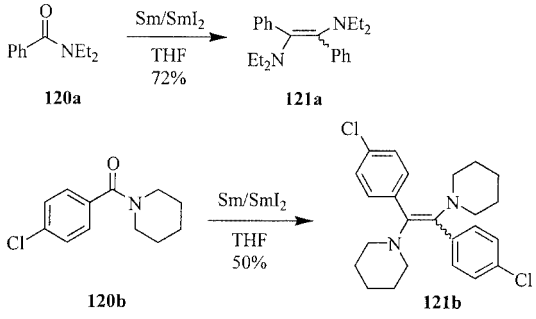
Scheme 36

The combination of Sm/SmI_2 was found to be effective for the synthesis of alkynylsilanes **119** through alkylation of ethynylsilanes **118** with haloalkanes **117** (Scheme 37).[51] In general, alkylation at an sp-carbon atom is necessary by a metallation/nucleophilic substitution reaction to produce alkynylsilanes. However, many side reactions, including elimination reactions with secondary, tertiary, and β-branched primary haloalkanes, were shown to be common in this type of process. On the other hand, primary haloalkanes and secondary haloalkanes can be used in the Sm/SmI_2-mediated process with equal success. Differentiation of reaction sites with unsymmetrical dihalides is also possible using this method. The reaction of an iodoalkane and ethynylsilane in THF solution reduced the iodo compound; no coupling reaction could be detected.



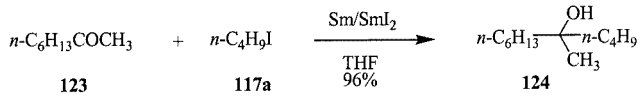
Scheme 37

A very interesting paper has described the first deoxygenative coupling of amide **120** to vicinal diaminoalkene **121** by a combination of samarium metal and samarium diiodide (Scheme 38).[52] A low-valent titanium reagent and samarium diiodide alone did not work. The coupling reaction proceeded in the presence of even catalytic amounts of samarium diiodide.



Scheme 38

The combination of samarium metal with samarium diiodide has been shown to be very effective in the Barbier reaction of alkyl halide **122** to the 2-octanone **123**. The yield of product **124** is excellent (Scheme 39).[50]



Scheme 39

12. Conclusion

The reactions described in this review demonstrate that samarium metal in the presence of additives can be a versatile reagent with wide applications in various synthetic procedures. Notably, most of the reactions resulted in excellent product yields. It is believed that electron transfer from samarium to the organic molecules is the mechanistic route involved in these processes. Synthetic transformations mediated by samarium diiodide end up with formation of trivalent samarium species. These processes have drawbacks since only one third of the reducing ability of the original samarium metal is exploited. However, the nature of the reactive species formed in the samarium metal induced reactions in the presence of different types of additives is not firmly established. Whether these additives form bivalent, trivalent or low-valent samarium species remain a subject of discussion. Whether these additives activate the surface of samarium metal is not clear at this time. Although the scope of samarium-induced reactions has not been fully established, these methods will continue to be useful for the preparation of simple organic compounds of interest. It can be anticipated that samarium-induced reactions will play a major role in the synthesis of biologically active compounds in the near future.

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