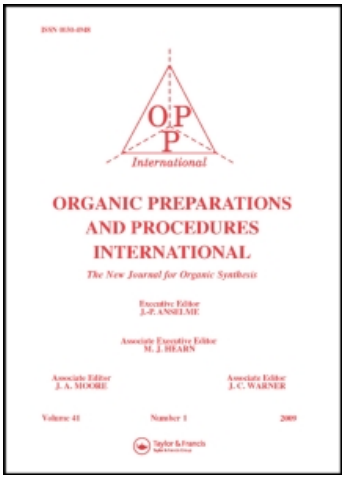

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FRAGMENTATION AND CLEAVAGE REACTIONS MEDIATED BY SAMARIUM IODIDE. PART 2: α- AND β-ELIMINATION REACTIONS OF C-X SUBSTRATES

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PREAMBLE AND INTRODUCTION

Samarium diiodide (SmI_2) has been successfully employed in a number of synthetically useful transformations since its introduction as a viable reagent by Kagan.[1] While most of the work involving SmI_2 has been of a bond-forming nature, many useful fragmentation and cleavage reactions have been forthcoming.

Part 1 of this review[2] focused on cleavage and fragmentation reactions of heteroatom-heteroatom and of carbon-carbon bonds, and provided a brief mechanistic introduction to some of the reactions facilitated by SmI_2. One type of SmI_2-promoted fragmentation reaction that has enjoyed much attention is the elimination of various functional groups situated in a position *alpha* or *beta* to the carbonyl moiety. These include a multitude of examples of the α-elimination of oxygen, sulfur and other functions, each of which shall be dealt with in turn, as well as the various β-elimination (and indeed more remote sequential elimination) type reactions. In Part 2, we shall focus on these types of reactions involving carbon-heteroatom type substrates.

For ease of reference, the work in this part of the review has been categorized primarily according to the carbon atom from which the leaving moiety is eliminated (*i.e.* from the α- or β-carbon relative to the main functional group).

I. DIRECT ELIMINATION REACTIONS

Direct α-elimination reactions may be defined as the simple removal of a group on the alpha carbon with respect to the susceptible moiety, as opposed to the indirect counterparts which will be defined as those involving a tandem elimination-condensation/intramolecular cyclisation/etc. reaction sequence. This division serves a more organizational rather than a chemical descriptional purpose, since the reactions cited possess analogous intermediates in all cases.

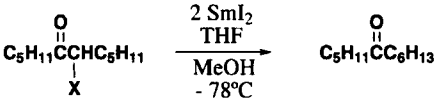
1. α-C-O Elimination Reactions

a. α-Elimination in Aldehydes and Ketones

More classical methods with which to effect α-elimination in ketones normally require relatively harsh reaction conditions and multiple component systems to achieve this type of reduction. For example, $Na_2S_2O_3$ together with a metal halide have been employed to hydrodehalogenate α-haloketones.[3] The introduction of SmI_2 as a potent yet selective one-electron reductant has drastically changed the nature of this type of transformation.[4] A distinct advantage of SmI_2 over various other reductants is the fact that it is soluble in organic solvents, and that it exerts its activity under essentially neutral conditions. These two considerations, together with its remarkable chemoselectivity, have ensured its successful application to a wide array of complex substrates under various conditions.

In most cases, the α-elimination reaction is achieved using the SmI_2 / THF system with methanol as a proton source at low temperatures (-78°C). Reduction of α-hydroxy ketones was noted to give disappointingly low yields. This problem was alleviated to some extent by the simple addition of acetic anhydride to the α-hydroxy ketones in THF.[4] This form of reduction can be divided in two main categories, *i.e.* α-oxygenated ketones and α-heterosubstituted (heteroatoms other than oxygen) ketones.

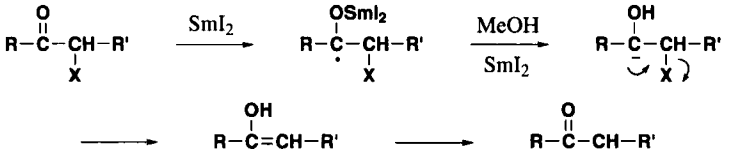
α-Oxygenated ketones undergo reduction under the above mentioned conditions and the reduction appears to occur almost instantaneously (*Scheme 1*).



X = OAc (75%); $OSiMe_3$ (98%); $OCOCH_2Ph$ (100%); OTs (94%); OH (29%)

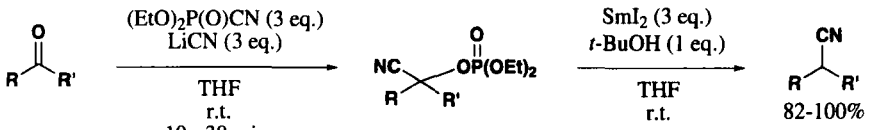
Scheme 1

SmI_2 generates a ketyl radical that is rapidly protonated by methanol and undergoes further reduction by a second equivalent of SmI_2 to produce a carbanion. Elimination and tautomerization of the ensuing enol provides the ketone product (*Scheme 2*).[4-7]



Scheme 2

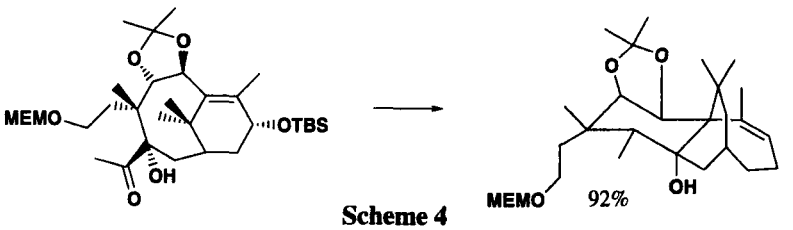
A similar type of reaction has been used in the conversion of saturated or unsaturated carbonyl compounds to the corresponding nitrile *via* the cyanophosphate species (*Scheme 3*).



Scheme 3

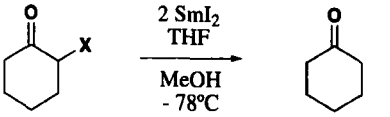
This reduction takes place in the presence of *tert*-butanol,[8,9] and is believed to proceed *via* an initial one-electron reduction of the nitrile, although nitriles are generally relatively unreactive towards SmI_2.

Examples exist where the overall reaction involves a rearrangement as well as the elimination of the α group. Treatment of suitably functionalised α-hydroxy ketones with SmI_2 combines a Lewis acid (Sm^{3+}) mediated ring-expansion with the reductive loss of an hydroxyl substituent and *trans* annular ketyl cyclisation (*Scheme 4*).[10]



Scheme 4

α-Heterosubstituted ketones have been noted to undergo reduction under the same conditions as required for α-oxygenated ketones (*Scheme 5*). The experiments demonstrate that the substrate undergoes reductive elimination of the heteroatom group under the action of two

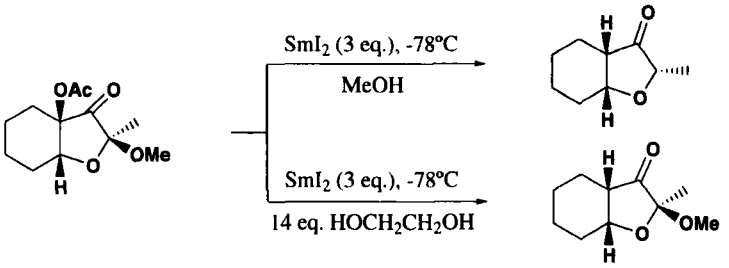


X = Cl; SPh; SOPh; SO_2Ph; HgCl

Scheme 5

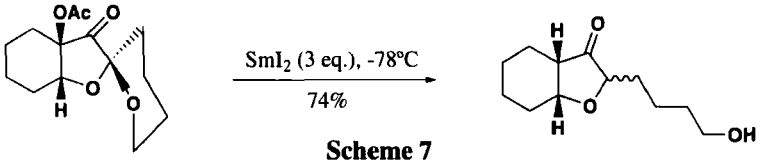
equivalents of samarium diiodide to give the corresponding samarium enolate and finally the reduced ketone product upon protonation and tautomerization.[11] More complex systems have also seen the successful use of samarium diiodide as a reducing agent for ketones in sensitive systems, affording the cleaved products under mild conditions.[12]

It has been discovered that the absence or presence of a proton source can influence the selectivity of SmI_2-mediated deoxygenation. As shown below (*Scheme 6*), double deoxygenation was observed when an α-acetoxy-α'-methoxy ketone substrate was treated with SmI_2 in the presence of a proton source (MeOH).



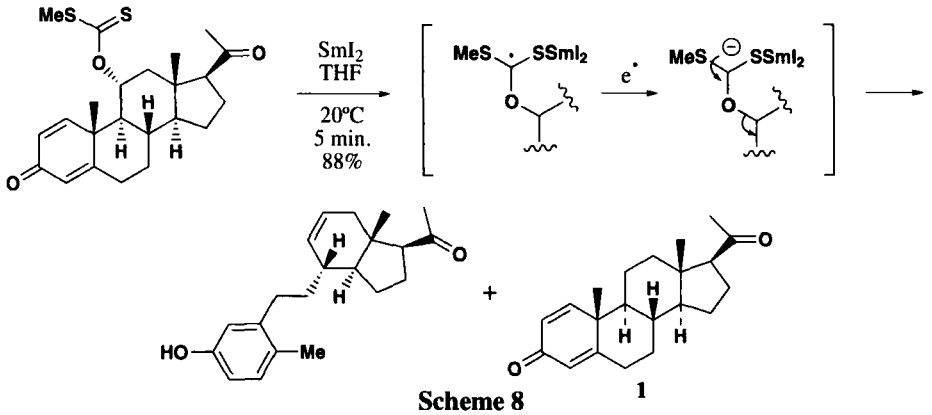
Scheme 6

Conversely, selective elimination of the acetoxy group was effected in the presence of ethylene glycol.[13] The over-reduction observed in the absence of ethylene glycol is possibly related to the Lewis acidity and oxophilic nature of the Sm(III) produced in the reaction. In some cases, this double reductive elimination has been employed to generate specifically functionalized bicyclic ketones (*Scheme 7*; *see Table 1*).[13]



Scheme 7

As a reducing agent, SmI_2 has proved superior to and more selective than numerous other reductants on manifold substrates and in the transformations of a variety of functional groups. As an example of the greater selectivity and efficiency of samarium diiodide over tri-*n*-butyltin hydride in the fragmentation reaction of a C-O bond, the xanthate (*Scheme 8*) underwent

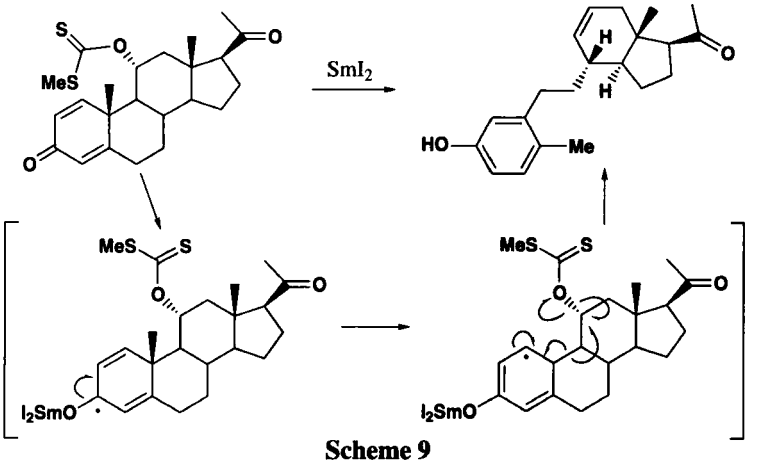


Scheme 8

selective C-O bond and ring-fragmentation to afford the aromatic derivative in a yield of 88%. By comparison, treatment of the same substrate with tri-*n*-butyltin hydride produced the aromatic product along with a product (**1**) of simple deoxygenation (1:1 ratio) in a combined yield of only 50%.[14] This example demonstrates not only the efficient use of SmI_2 to effect fragmentation of a C-O bond but also shows one of the first ever observed and reported C-C bond fragmentations.

This particular C-C fragmentation was also mentioned in Part 1 of this review.[2] An explanation, suggested by those workers, for the fragmentation obtained when using samarium diiodide as opposed to tri-*n*-butyltin hydride (as shown in the proposed mechanism above), may be found in the ability of Sm^{II} to support anion chemistry, as opposed to the exclusive radical domain of the hydride reagent.[14]

A possibility not mentioned by those authors is that the SmI_2-mediated reactions might start with electron transfer to the α,β-unsaturated ketone due to the oxophilic nature of Sm salts (shown as an alternative mechanism below, *Scheme 9*).

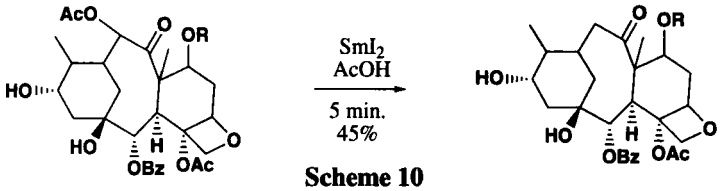


Scheme 9

This step would be followed by C-C bond fragmentation and aromatization while the hydride reductant would certainly exert its influence at the xanthate moiety. In the alternative mechanism, it is also possible that an anionic process precipitates the fragmentation.

Another interesting example makes use of SmI_2 in THF/H_2O to effect a straightforward α-deoxygenation of unprotected tetrono- and pentonolactones, providing a facile access to their 2-deoxy analogs.[15]

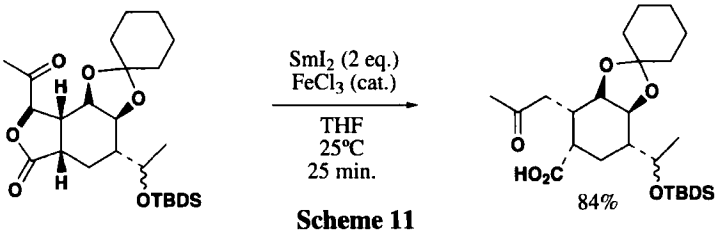
It has been noted that the reaction conditions determine not only the manner of elimination but also the stereoselectivity observed. Treatment of a THF solution of baccatin III with SmI_2, in the presence of *tert*-butyl alcohol for 15 hours (*Scheme 10*), produced the desired 10-deacetoxybaccatin III in 45% yield together with a mixture of by-products (40%) and of starting



Scheme 10

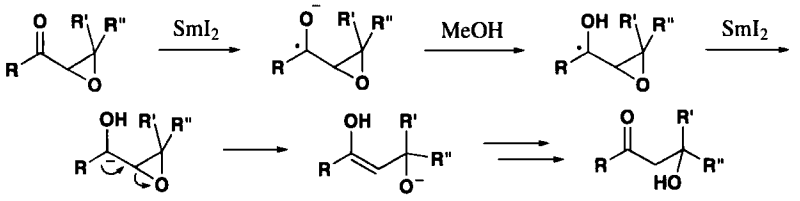
material (10%). However, changing the reaction conditions to SmI_2 and acetic acid delivered the desired product in a yield of 87% in 5 minutes, again demonstrating the influence of the proton source on the outcome of some reactions.[16] This example, together with others of α-deoxygenation in multi-functional compounds, once again demonstrates the selective nature of SmI_2-mediated cleavage.[17,18]

An example of the elimination of an α-acyloxy group involves the ring-opening of a lactone (*Scheme 11*). In this case, the electron transfer would have been initiated at the ketone carbonyl rather than that of the lactone. $FeCl_3$ was added as a catalyst to facilitate the reduction of the substrate to a δ-keto acid, and is usually employed to speed up the reaction in question and allow mild reaction conditions.[19]



Scheme 11

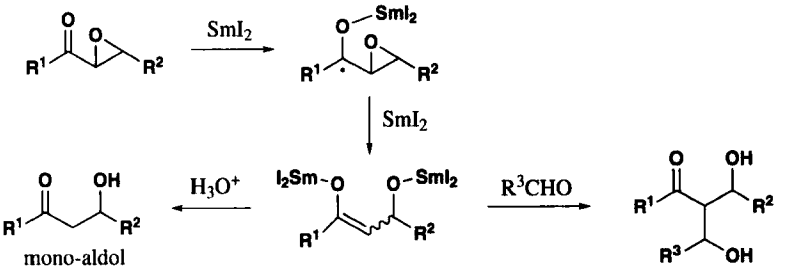
α-Epoxy ketones are also susceptible to SmI_2-mediated elimination reactions (*Scheme 12*). The reaction of SmI_2 with the ketone generates a ketyl radical, which is rapidly protonated by methanol. A second equivalent of SmI_2 causes further reduction to the carbanion, inducing ring-opening of the epoxide. Tautomerisation of the resulting enol provides the ketone, as shown in the scheme below.[20-24]



Scheme 12

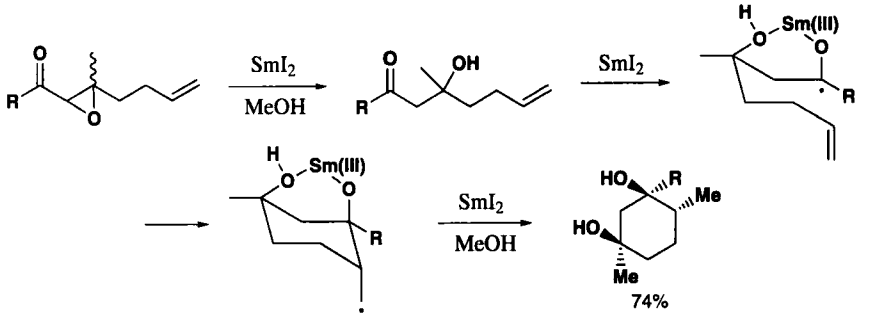
A study of the reaction conditions for epoxide ring-opening using SmI_2 indicated that the addition of HMPA accelerated the electron transfer process, such that the reaction was almost instantaneous. Furthermore, the presence of a proton source increased the chemical yield, and the addition of a chelating agent was crucial to the attainment of a high degree of regioselectivity: the absence of such agents resulted in Lewis acid ring-opening of the epoxide to afford the corresponding α–hydroxy ketone as by product. Chelating agents such as tetramethylethylenediamine (TMEDA) and *N,N*-dimethylethanolamine (DMEA) were used, and the study revealed that the best results were obtained when HMPA (5 equivalents) and DMEA (2 equivalents) were used in combination as additives.[25,26]

This reaction has been developed to allow the quenching of the reaction by making use of aldehydes as electrophiles, instead of a proton source. While the product of ring-opening of the epoxide is an aldol-type product, that of the trapping of the enol/enolate with an aldehyde is one of the *bis*-aldol type (*Scheme 13*).[27]



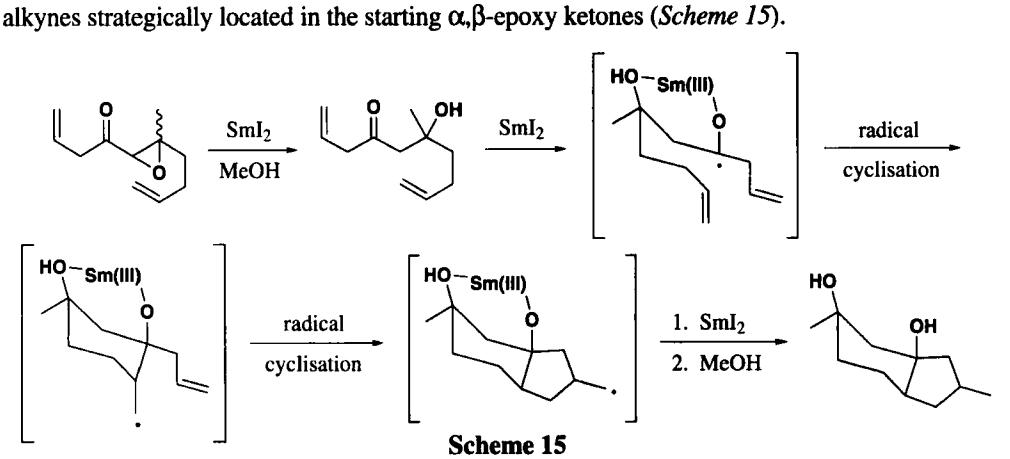
Scheme 13

Sequenced reactions of α-keto epoxides are not limited to those in which aldol-type products are prepared. In the following example (*Scheme 14*), an intramolecular 6-*exo*-trig cyclisation reaction follows the epoxide ring-opening, because of a suitably positioned double bond. The reaction is carried out using 6 equivalents of SmI_2 in THF with HMPA as an additive and MeOH as a proton source at 0°C.[22]



Scheme 14

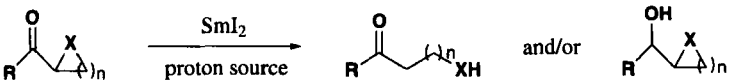
It was later shown that it is possible to trap the methylene radical with alkenes or alkynes strategically located in the starting α,β-epoxy ketones (*Scheme 15*).



Scheme 15

Molander *et al.* neatly demonstrated this cascade epoxide ring-opening and two sequential radical (6- and 5-*exo*-trig, respectively) cyclisations (*Scheme 15*).[28] Once again, 6 equivalents of SmI_2 in THF with HMPA and MeOH were used. The reactions were carried out within a range of temperatures and it was shown that chelation of Sm(III) by the two oxygen atoms allowed substantial diastereocontrol (5.25:1 *cis/trans* at 0°C, 72% yield).

Small ring-fragmentation is not limited to epoxides (*Scheme 16*). It has also been applied to a variety of aziridine derivatives (*Table 1*: yields given are representative for the specific group) and has been observed in α-keto tetrahydropyrans (one such example has already been discussed: *Scheme 7*); the reactions presumably follow the same mechanism as that discussed for the analogous epoxide reactions.[14,21,29,30] Slightly more complex systems have also been successfully ring-opened under similar conditions.[31]

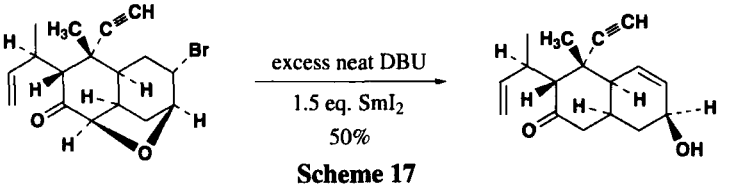


Scheme 16

Table 1. Representative Examples of Ring-fragmentation

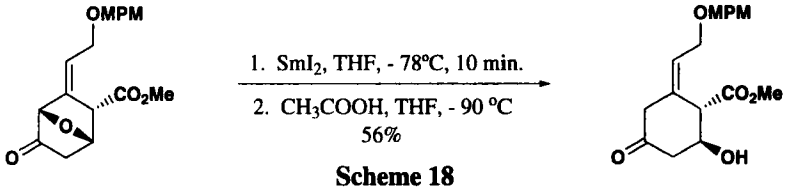
X	R	n	Yield
O	Alkyl, Aryl, *O*-Alkyl	1 or 4	65-86%
TsN	Alkyl, *O*-Alkyl, *N*-Alkyl	1	60-95%
NBoc, NFmoc, NAc, NCO_2Et, NTr, NPh	Alkyl, *O*-Alkyl, Aryl	1	72-98%

A nice application of this type of ring-opening technology can be found in the following example (*Scheme 17*), in which a somewhat ring-strained tetrahydrofuran underwent ring-opening to the corresponding keto alcohol in the presence of SmI_2 and DBU. The latter reagent effected the elimination of HBr from the intermediate product to generate an allylic alcohol.[32]



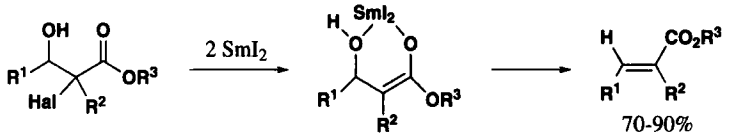
Scheme 17

In another case, a bridged tetrahydrofuran was selectively ring-opened to afford a stereodefined hydroxycyclohexanone (*Scheme 18*). The reductive opening of the oxygen bridge was realized in good yield with SmI_2 in THF/MeOH at -78°C, followed by a careful low temperature quenching with acetic acid in THF at -90°C to avoid double bond migration.[33]



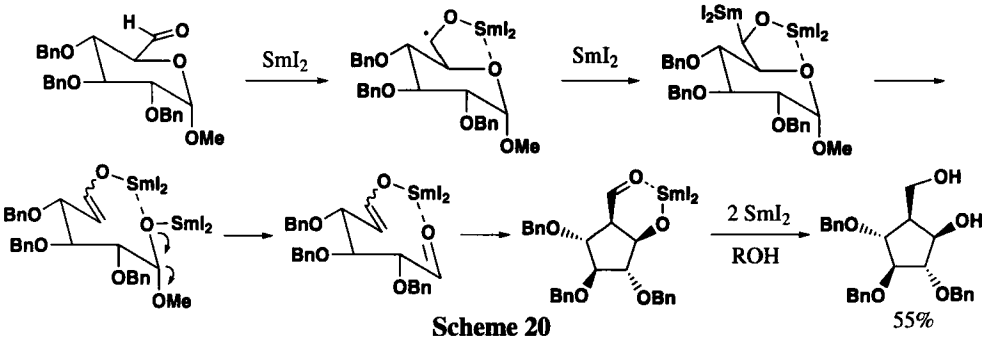
Scheme 18

The α-elimination protocol has also been applied to the synthesis of stereodefined α,β-unsaturated esters (*Scheme 19*). In this case, chelation of Sm(III) by the substrate determines the stereochemistry of the double bond.[34]



Scheme 19

An aldehydic glucose derivative has been used in a SmI_2-mediated ring-contraction reaction (*Scheme 20*).[35]



Scheme 20

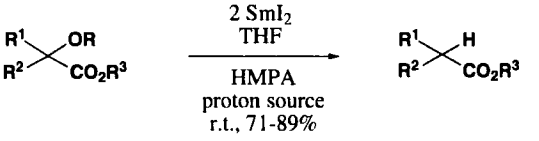
The reaction starts at the aldehyde, where an initial electron transfer from SmI_2 leads to the corresponding ketyl radical. The authors propose that a second equivalent of samarium causes reduction to a dianion, which then undergoes ring-opening and methoxide elimination to a system that is ideal for aldol cyclisation. A final reduction with samarium diiodide afforded the cyclic protected polyol product. Although the mechanism of direct reduction (ketyl radical → dianion) is plausible, the second reduction step is slow, while protonation and further reduction is rapid.[36] The latter scenario would necessarily imply that some intermediates differ from the ones shown.

b. α-Elimination in Esters and Lactones

For many years, esters and lactones were considered inert to the reductive effects of SmI_2. Kagan's early report on SmI_2 indicated that simple esters are unreactive in the presence of that reagent.[1] Inanaga has since shown that the reducing power of the simple SmI_2/THF system can be enhanced by the addition of HMPA and other additives.[37] This enhanced reducing power

has had many beneficial effects, most commonly seen in the form of rate enhancements. It has also been shown that ester functional groups will react with the SmI_2/HMPA system under certain circumstances, and reactions such as coupling and reduction reactions of α,β-unsaturated esters have been observed.[38] In the absence of HMPA, those reactions proceed only slowly, if at all.[38]

A variety of α-oxygenated esters, such as α-acetoxy, α-methoxy, α-OTHP, and α-hydroxy esters, were easily reduced at room temperature to give the corresponding saturated esters in good to excellent yields with the aid of samarium diiodide in THF, HMPA as an additive, and in the presence of a proton source such as MeOH or EtOH (*Scheme 21*).[39]

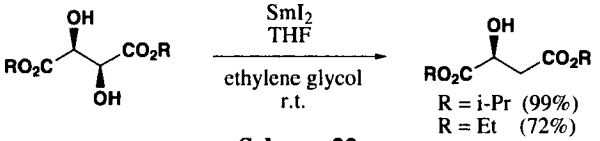


R = H, alkyl, acyl

Scheme 21

As shown in the scheme, both deacetoxylation of α-acetoxy esters and reduction of α-methoxy derivatives proceeded smoothly. However, samarium diiodide showed a differentiating ability when a diastereomeric mixture of an α-OTHP ester was subjected to reduction. This interesting observation points towards the importance of good coordination of the substrates to the samarium ion in order to activate the ester to allow a smooth electron transfer to take place. As a result, it was found that simple esters did not undergo reduction with SmI_2 under similar conditions.[39]

When direct dehydroxylation of simple α-hydroxy esters was attempted, under the same conditions as those used for the reduction of α-acetoxy and α-methoxy esters, the reduction was found to be unsuccessful. It was found that the addition of a more acidic proton source, such as a carboxylic acid, was necessary for a successful reaction. Thus, pivalic acid was used with the devised addition procedure, which involved the dropwise addition of a solution of acid into a mixture of hydroxy esters, HMPA and SmI_2-THF solution over a period of 1-2 hours.[39] A similar method of ester reduction was successfully applied to directly convert (*R,R*)-tartrates to (*R*)-malates; the acidic proton source and addition of HMPA were unnecessary in this case and ethylene glycol was used instead to limit reactivity (*Scheme 22*).[26] In these reactions, it is

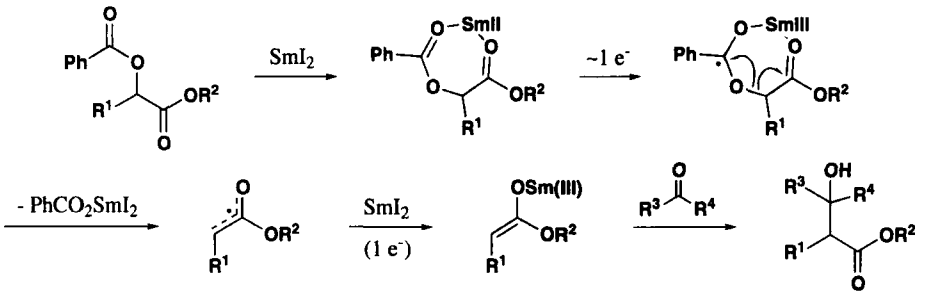


R = i-Pr (99%)
R = Et (72%)

Scheme 22

believed that the reduction sequence is initiated at the ester carbonyl. However, the elimination reaction of α-benzoyloxy esters and, for example, α-acetoxy analogues might well proceed *via* different pathways, as discussed below.

In α-benzoyloxy esters, deoxygenation presumably takes place *via* a benzylic radical. The benzylic pathway involves a sequence of two one-electron transfer steps from SmI_2, the first being through a chelated structure (*Scheme 23*).

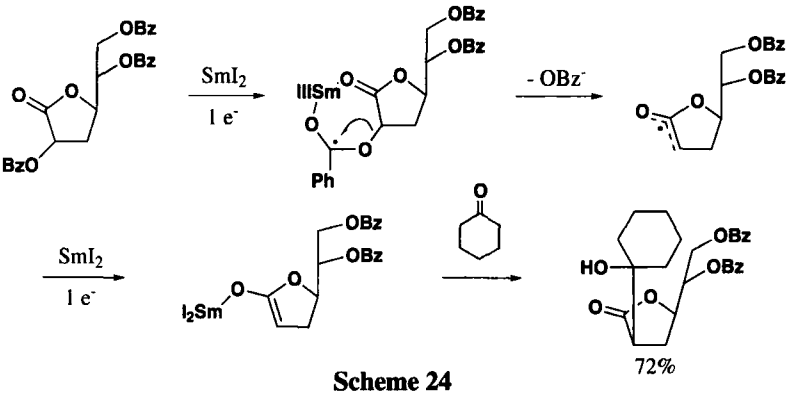


Scheme 23

52-87%

This is supported by the fact that simple esters are not reduced by SmI_2 and HMPA; the presence of oxygenated functions adjacent to the ester, which provide chelation sites for oxophilic samarium species, appears to be essential for the reduction of these substrates. The formation of a benzylic radical anion results in the formation of a chelated radical intermediate. The stability of the benzylic radicals over localized alkyl radicals seems to favor the generation of the former in preference to the latter. C-O bond fragmentation, and concomitant elimination of the Sm(III) benzoate species affords the delocalized radical intermediate. A second one-electron reduction then provides the samarium enolate, which can be followed by a condensation reaction with a ketone to afford the β-hydroxy ester.[40]

A similar mechanism appears to be operative for α-deoxygenation reactions of α-benzoyloxy lactones (*Scheme 24*). Elimination of the benzoate produces a resonance stabilized



Scheme 24

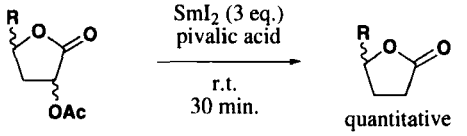
72%

radical species. In this work, most of the elimination reactions were followed by a condensation of the Sm-enolate with a simple ketone, resulting in the formation of β-hydroxy lactones as branched chain carbohydrates. The enolate appeared to be of relatively low reactivity, as it did not react with any of the other benzoate functions in either intra- or intermolecular reactions.[41]

Studies on the effect of the timing of the addition of the ketone in the above-mentioned deoxygenation/carbonyl addition reaction showed that it was necessary for the ketone to be present from the start of the reaction. When it was added *after* the start of the reaction at several delayed time intervals, only elimination of the α-benzoate was observed and no ketone was incorporated into the product. This was rationalized as being the result of rapid decomposition of the Sm(III) enolate (the means of which was not expanded upon) if an electrophile such as a ketone is not present directly after ejection of the benzoate.[39]

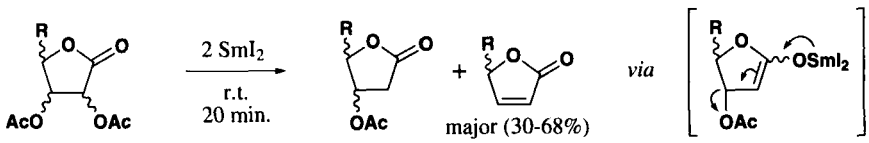
An important point to note is that there is currently no other method available that will both induce a similar deoxygenation and carbonyl addition in a single serial reaction. Moreover, the stereocontrol aspect to this reaction provides an additional attractive element, and is the result of both steric and stereoelectronic control.[42]

When eliminating other oxygen-based leaving groups such as OAc from lactones, we see that their elimination takes place *via* a different mechanism compared to that of the elimination of the benzoate. Here, it is believed that the initial electron transfer is to the lactone carbonyl generating a ketyl radical that is protonated by pivalic acid (or other proton source) and further reduced to the corresponding carbanion, which induces elimination. In this way, 2-*O*-acetyl-3-deoxysugar lactones were cleanly reduced with SmI_2 to give the corresponding 2,3-dideoxysugar lactones in quantitative yields (*Scheme 25*).[43]



Scheme 25

When 2,3-di-*O*-acetylpentose lactones were subjected to the same reduction conditions, the corresponding α,β-unsaturated lactones were obtained as sole or major products with the concomitant formation of 2-deoxy derivatives as by-products in some cases (*Scheme 26*).

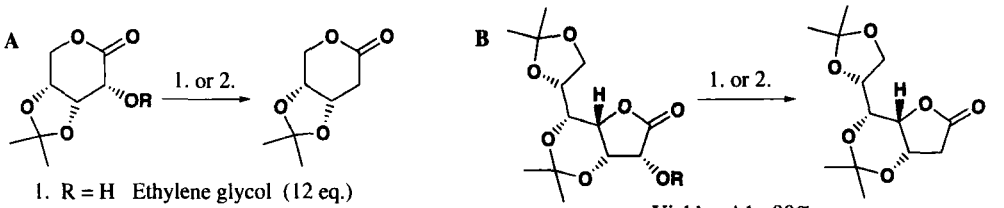


Scheme 26

This reaction seems to proceed *via* the formation of a lactone enolate or enol intermediate followed by elimination of its 3-acetoxy group: it was found that the addition of acetic acid resulted in suppression of the elimination process, presumably *via* a rapid competitive protonation step.[43] Earlier work has shown that the reduction potentials of various samarium-HMPA complexes are such that the formation of the vicinal dianions is not probable.[36] This, therefore, contradicts the elimination mechanism proceeding through a dianion intermediate, as suggested in that article. Similar α-deoxygenation reactions were observed using SmI_2 in THF/HMPA,[44] in

the presence of other proton sources, *e.g.* MeOH,[45,46] *t*-BuOH,[47] etc. The reactions were seen to proceed at temperatures ranging from -78°C to 40°C.

α-Deoxygenation of 2-hydroxylactones or their acetates has been achieved using the SmI_2 in THF/HMPA system, with ethylene glycol as an additive (*Scheme 27*). Two methods

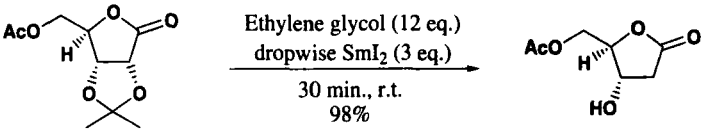


1. R = H Ethylene glycol (12 eq.) dropwise SmI_2 (3 eq.), 30 min., r.t.
2. R = Ac Ethylene glycol (12 eq.) dropwise SmI_2 (3 eq.), HMPA, (5% v/v of SmI_2 solution) 30 min., r.t

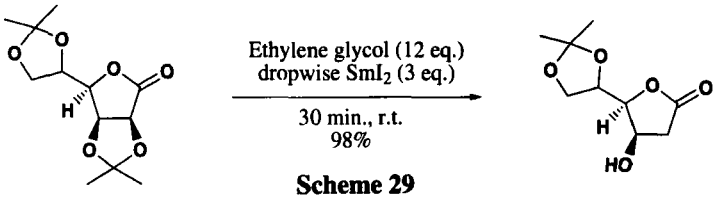
Scheme 27

were attempted with which to effect this reaction, namely adding the SmI_2 dropwise to the reaction mixture, or adding the ethylene glycol in the same manner. It was established that the most favorable reaction conditions were achieved by adding a solution of SmI_2 to the ethylene glycol mixture. The presence of HMPA as cosolvent further improved the yields.

It was further found that the deoxygenative removal of a 2,3-isopropylidene protecting group could be effected by adding SmI_2 dropwise to the reaction mixture in the absence of HMPA (*Scheme 28, 29*).[48]

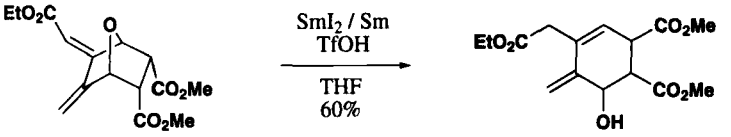


Scheme 28



Scheme 29

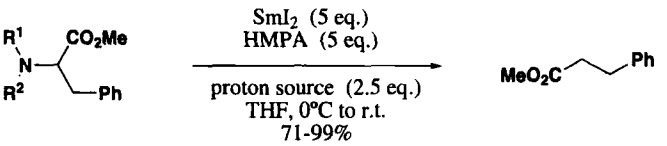
An efficient synthetic route to multisubstituted cyclohexanols and aromatic compounds has been developed by carrying out a samarium (II)-mediated ring-opening reaction of 7-oxabicyclo[2.2.1]heptane derivatives (*Scheme 30*).



Scheme 30

This efficient regiospecific cleavage of C-O bonds of 7-oxabicyclo[2.2.1]heptane derivatives bearing a carbonyl function is the first of its kind.[49] Yoshida *et al.* initially carried out the cleavage reactions on simple substrates to develop a set of partially optimized reaction conditions. A variety of proton sources, additives and Lewis acids were tested with the ultimate choice resting on a SmI_2/Sm system. The SmI_2 / Sm system was believed to be effective because it had a stronger reducing ability than SmI_2 and because of the regeneration of low valent samarium by disproportionation of Sm(III) and Sm(0). Trifluoromethanesulfonic acid (TfOH), a strong acid, was used as an additive to increase yields.

Various α-amino carbonyl compounds, apart from the ring-strained three- and four-membered rings[27-29] already described in this review, have been the subjects of reductive deamination reactions. Yet another case exists where SmI_2 can be used to effect C-N cleavage. These examples are of great interest as the cleaved products can be used in the synthesis of biologically active natural products (*Scheme 31*).[50]



R_1 or R_2 = H; Me; Bn; Ac
Proton source = MeOH or Pivalic acid

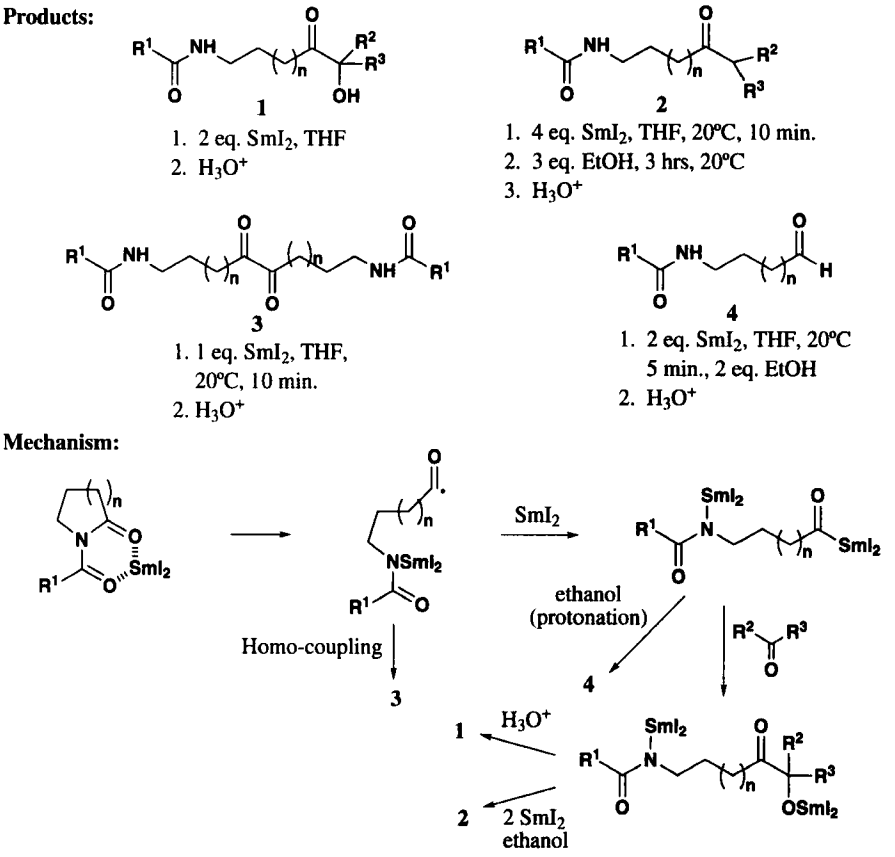
Scheme 31

Reductive deamination of a wide variety of α-amino carbonyl compounds, many of which are derived from α-amino acids, was successfully carried out employing SmI_2 in THF-HMPA in relatively high yields under mild reaction conditions. The range of α-amino carbonyl compounds included phenylalanine derivatives, amino functions including primary, secondary, and tertiary amines, as well as amides. The reaction was normally complete within 30 minutes in the presence of a proton source, such as MeOH or pivalic acid, to give the corresponding methyl dihydrocinnamate in high yields.[51] The reactions of proline derivatives and ethyl pipecolinate derivatives, where the leaving groups were present in cyclic systems, gave corresponding ring-opened products in good yields under the same conditions as those described above.[51] The deamination could be applied not only to α-amino esters but also to α-amino ketones. Thus, deamination of α-acetylpiperidine derivatives was attempted and the desired products were obtained in good yields.

Honda *et al.* further investigated the effects of the proton source and the use of HMPA on these deamination reactions. They found that DMEA was also an effective proton source, as were MeOH and pivalic acid. It was confirmed that the reactions proceeded with or without HMPA but the presence of HMPA made for milder reaction conditions.[51]

The reductive C-N bond cleavage of acyclic *N*-acyl moieties has allowed the *in situ* generation of valuable precursors to coupling reactions with a ketone or aldehyde, respectively.

This reaction sequence has been used to prepare amido α-ketols, amidoketones and diamidodiketones, and is achieved by the formation of an acyl radical that is reduced into a transient acylsamarium species, which is then trapped by an electrophile (ketone, aldehyde or ethanol, *Scheme 32*).

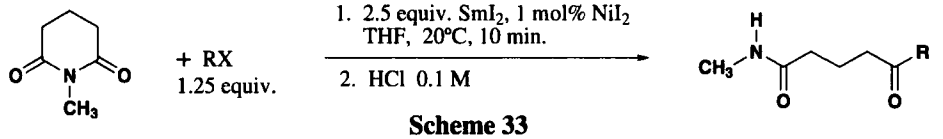


Scheme 32

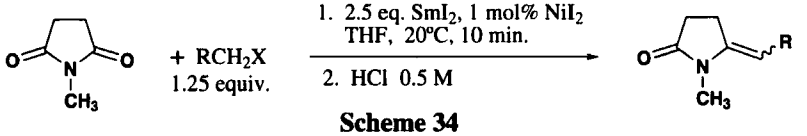
Homo-coupling of the acyl radical accounts for the formation of diamidodiketones in the absence of an electrophile.[52] Formation of amidoketones over amido α-ketols is achieved by using an excess of SmI_2, in the presence of ethanol.

SmI_2 mediates intermolecular coupling of organic halides with cyclic imides in a similar fashion. These intermolecular Barbier-type and Reformatsky-type reactions were carried out with *N*-methylsuccinimide, *N*-methylphthalimide and *N*-methylglutarimide. It was found that the three substrates were reactive in SmI_2-mediated coupling reactions with organic halides in the presence of a catalytic amount of NiI_2. In contrast to acid anhydrides, ring-opening does not occur before hydrolysis. With *N*-methylglutarimide (*Scheme 33*) it readily takes place during hydrolysis furnishing δ-ketoamides. No ring-opening was observed for *N*-methylsuccinimide

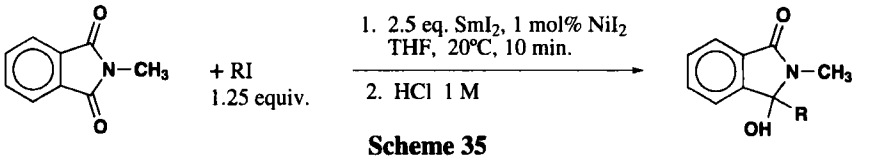
(*Scheme 34*) or *N*-methylphthalimide (*Scheme 35*), affording the corresponding products in yields of 68-92%.[53]



Scheme 33

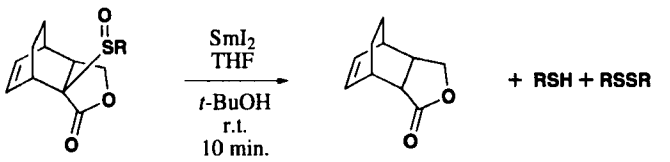


Scheme 34



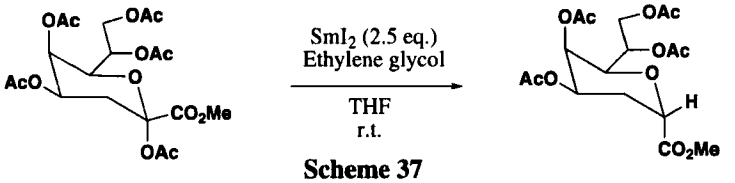
Scheme 35

The following example demonstrates the reductive cleavage of a sulfoxide moiety from a lactone. Treatment of the sulfoxide with SmI_2 in THF in the presence of *t*-BuOH at room temperature gave the reduction product in a yield of 98% (*Scheme 36*).[54]



Scheme 36

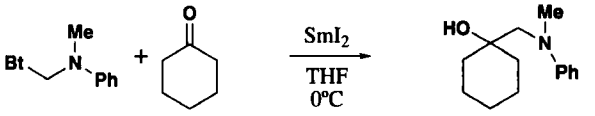
A last form of direct α-elimination to be reported herein involves deacetoxylation using ethylene glycol as an additive (*Scheme 37*). Again we see the almost instantaneous removal of the acetoxy group at room temperature.[55] A large degree of stereocontrol was observed in this reaction, with the exclusive isolation of the α-methoxy-carbonyl product (93%).



Scheme 37

2. Miscellaneous α-Elimination Reactions

Benzotriazole derivatives have also found use in SmI_2-mediated cleavage reactions (*Scheme 38*). In this case, removal of the benzotriazole group was effectively achieved by the

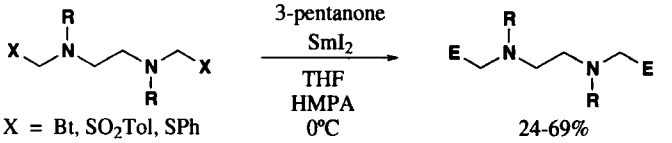


Scheme 38

selective transformation of the *C*-benzotriazole moiety into the corresponding α-aminocarbanion. It was found that the sequence of addition of the reagents in this reaction was of great importance: addition of the benzotriazole compound and cyclohexanone as a THF solution to SmI_2 produced 71% of the desired coupled product together with 29% of *N*-methylaniline. The reverse addition gave only 25% of the adduct along with a pinacol product.[56]

When making use of 3-pentanone instead of cyclohexanone, the reaction afforded a complex mixture of products. Additionally, the authors established that SmI_2 failed to convert *N,N*-(diphenylmethyl)benzotriazole into the corresponding carbanion.[57] They therefore carried out various reactions with a variety of substrates, altering the reaction conditions and conclusively found that, given the correct reaction conditions, SmI_2 could be used to selectively transform the *C*-benzotriazole bond to the corresponding α-aminocarbanions, with good yield of the desired product.

The same authors have found that consecutive generation of various nonstabilized α-amino carbanions is possible by a double C-N bond cleavage reaction (*Scheme 39*). These

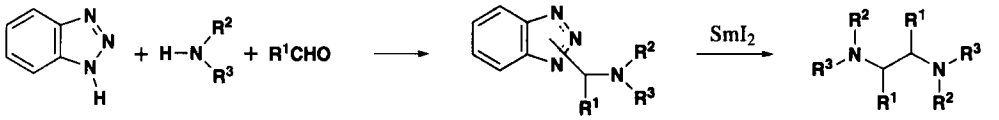


X = Bt, SO_2Tol, SPh
E = Et_2CHOH^-
R = Ph or Me

Scheme 39

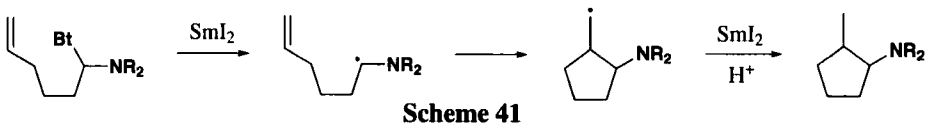
carbanions could then be trapped with a variety of electrophiles including 3-pentanone, which previously failed to selectively afford a coupled product. They extended this methodology further, from Bt-cleavage, to include SO_2Tol and SPh cleavage reactions.[58]

The reductive cleavage of the benzotriazole group offers a convenient route to tertiary vicinal diamines, *via* the reductive coupling of the iminium ions generated from *N*-((*N',N'*-dialkyl)aminoalkyl)benzotriazoles (*Scheme 40*).[59-61]



Scheme 40

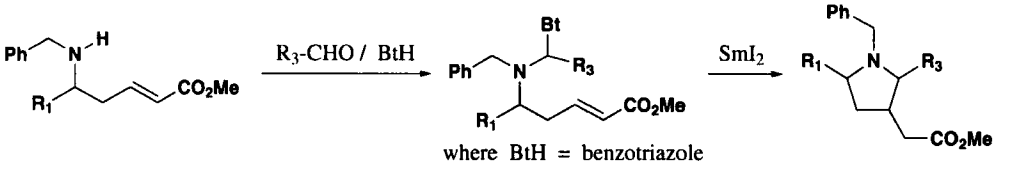
An extension on the work demonstrated above has allowed the reductive removal of the benzotriazole group followed by an intramolecular cyclisation (*Scheme 41*).



Scheme 41

In this particular case, the authors propose that treatment of the starting material with SmI_2 generates an α-amino radical. Due to the presence of a suitably positioned double bond, intramolecular cyclisation takes place to deliver the cyclic product.[60-62] Activation of the C=C bond can be achieved by an electron withdrawing substituent, thereby further enhancing the cyclisation process.[60,61]

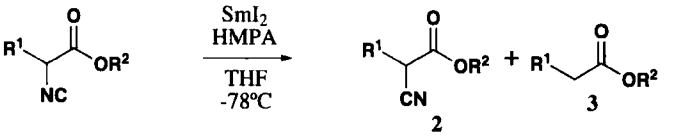
Suitable starting materials may be used to prepare of functionalised pyrrolidines from amines, benzotriazole and aldehydes, using this reductive protocol (*Scheme 42*).



where BtH = benzotriazole

Scheme 42

Isonitrile-nitrile rearrangements have also been mediated by SmI_2 (*Scheme 43*). This form of rearrangement requires an α-alkoxycarbonyl group at the carbon atom bearing the isonitrile group, implying that the reaction is initiated at the carbonyl function.



R^1 = H, -$(CH_3)_2CHCH_2$, $CN(CH_2)_4$, $PMBO_2CCH_2$ R^2 = PMB
R^1 = Bn, Ph R^2 = Me
PMB = p-methoxybenzyl

Scheme 43

Table 2. Yields for Isonitrile-Nitrile Rearrangement

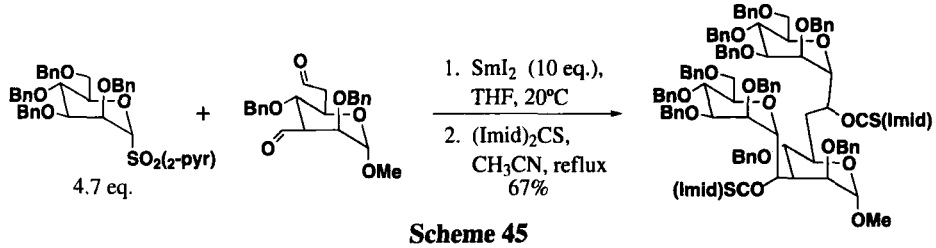
R^1	R^2	Yield (%)
H	H	70
H	^{n}Pr	67
H	^{i}Pr	62
H	Ph	51
Ph	H	67

Reductive isonitrile-nitrile rearrangements generally occur under very mild conditions, in contrast with the thermal rearrangement counterpart, which usually requires high temperatures (up to 300°C). The SmI_2-promoted rearrangement was also found to tolerate various types of functionality as shown below. This tolerance and temperature advantage makes the SmI_2 promoted rearrangement preferable.[63] The reduced, elimination product was observed as a by-product in certain instances. However, by carrying out the reaction out at –78°C the reaction predominantly yielded the rearranged product (**2**, 50-57%). The mechanism of this rearrangement is presently unknown, but is unlikely to be simple.

Another example involves the α-desulfonation of a SO_2Ph group using the simple SmI_2/THF system at room temperature (*Scheme 44*). This α-elimination was achieved within approximately 30 minutes, and stopped at the monosulfonyl product (61%). This result stands in distinct contrast to the outcomes of reactions involving similar monosulfonyl groups at the anomeric position of sugar derivatives (see below).[64]

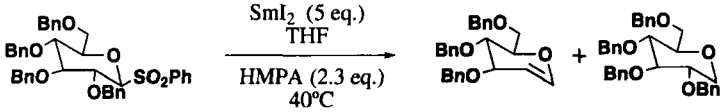
Scheme 44

The reductive cleavage of anomeric sulfur moieties in glycosides has allowed remarkable synthetic transformations towards *C*-glycosides (*Scheme 45*). The cleavage is accompanied by a coupling reaction, the alkoxy intermediate of which is finally quenched with $(Imid)_2CS$ in acetonitrile at reflux. This quenching procedure is interesting as it endows the final product with a different type of sulfur group.[65,66]



Scheme 45

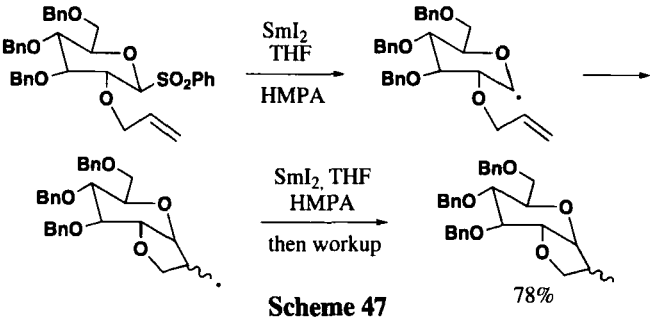
In a similar instance, the main product of the reaction was a glycal (*Scheme 46*),[67] products which have been shown to be key intermediates in the synthesis of many natural and unnatural products.[68] A series of substituted glycosyl phenyl sulfones was readily converted into the



Scheme 46

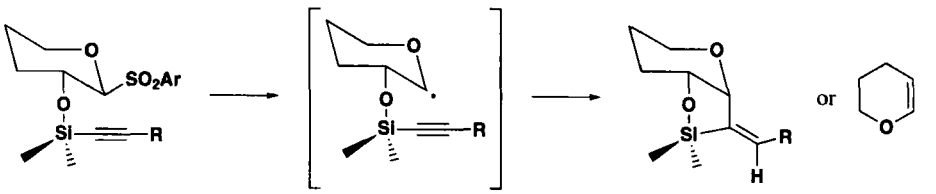
corresponding glycals after initial reduction with SmI_2 in the presence of HMPA, followed by elimination of the substituent at the C-2 position. Quantitative yields were obtained when the leaving group was acetate. However, the outcome of a SmI_2-mediated reaction of the perbenzylated sulfone was somewhat different. In this case, both the anticipated glycal (56%) and the product of simple reduction (33%) were observed. The competition is presumably a function of the leaving group alone (*i.e.* acetate *vs.* benzyloxy).

When the C-2 position was *O*-allylated no glycal formation was observed (*Scheme 47*). Instead, a reductive 5-*exo*-trig radical cyclisation took place *via* the anomeric radical initially formed by one-electron reduction of the sulfone. The resulting exocyclic primary radical is then reduced to an organosamarium species, which is subsequently protonated.



Scheme 47

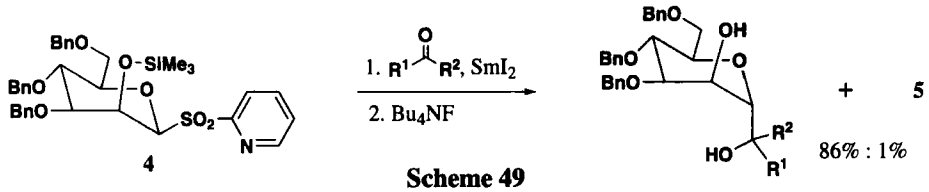
In contrast to the case mentioned above, some elimination of a silyloxy group at C-2 of a pyran derivative was observed in a reaction in which the alkyne was anticipated to act as an efficient trap for the anomeric radical (*Scheme 48*).[69]



Scheme 48

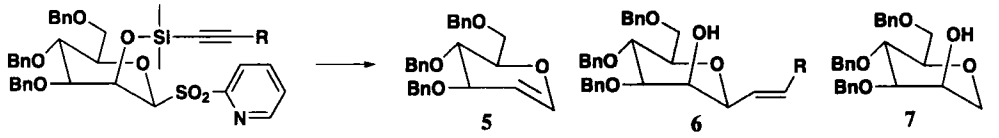
This observation may be the result of the reversibility of the 5-*exo*-dig cyclisation step, which allowed the anomeric radical to be further reduced by a second equivalent of SmI_2. In a separate case, the reaction was carried out in the absence of HMPA and yielded the cyclised products and glycal in yields of 76% and 5%, respectively.

Mazéas prepared 1,2-*trans*-*C*-glycosides by the SmI_2-mediated reduction of mannosyl and glucosyl 2-pyridyl sulfones and the coupling of the correspondingly formed glycosyl samarium(III) reagent under Barbier conditions with carbonyl compounds (*Scheme 49*).



Scheme 49

However, the attempted SmI_2-induced free radical cyclisation of an alkyne derivative yielded (*Scheme 50*), instead of the anticipated glucal (**5**) and β-*C*-mannoside (**6**) as major products, the 1,5-anhydro derivative (**7**).[70] This result implied that the organosamarium(III) species is exceptionally stable towards β-elimination in this particular substrate (compare the observed elimination in an analogous pyran derivative), and suggested the possibility of condensation of the organosamarium(III) intermediate with a carbonyl compound. The authors showed this to be true of a 2-pyridyl sulfone derivative **4** protected at *O*-2 of the ring (*Scheme 50*).[70]



Scheme 50

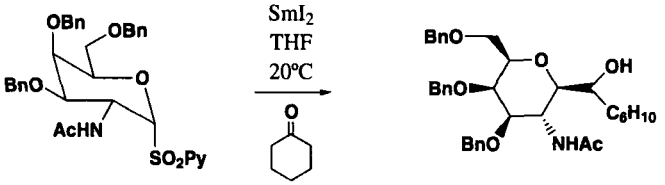
The stability of the anomeric organosamarium intermediate discussed above, which deviates from results obtained with corresponding lithium derivatives, can be explained in part by the requirement of a *syn*-orientation of the C1-Sm and C2-$OSiMe_3$ bonds for effective elimination. Further studies were carried out to determine what affected the yield of β-elimination product relative to the amount of condensation product being formed. Jarreton *et al.* carried out these reactions under the same conditions as discussed above, independently varying the carbonyl electrophile and the protecting groups.[71] In cases where MEM and THP protecting groups were used, an approximately 50:50 ratio was obtained between the condensation product and elimination product. Conversely, carbonate and carbamate derivatives afforded virtually no condensation product (presumably due to rapid elimination of the good leaving groups) and the bulkier $SiMe_2$-*t*-Bu protecting group decreased the formation of the elimination product to almost zero. Changes in the carbonyl compound varied only the amount of condensation product formed and had no real affect on the ratio between the two products under discussion.

The few examples cited above serve to highlight the sensitivity of the outcomes of the reactions to the group at C-2. Good leaving groups (esters) afford products of elimination only (no simple reduction is observed), intermediate leaving groups allow both elimination and intramolecular C-C bond formation to take place, while poorer leaving groups slant the selectivity towards 5-*exo*-trig/dig C-C bond formation only.

Overall, we see that SmI_2 reduction of glycosyl pyridyl sulfones in the presence of ketones or aldehydes under Barbier conditions leads to the rapid and stereospecific formation of

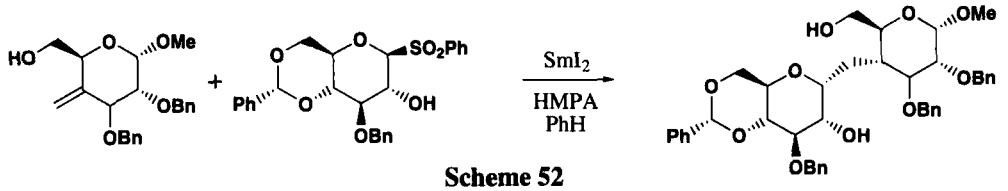
1,2-*trans*-*C*-glycosides in moderate to good yields. Mannosyl pyridyl sulfones produce α-*C*-glycosides, with minimal β-elimination. In contrast, glucosyl pyridyl sulfones lead to the corresponding β-*C*-glycosides and show an increase in β-elimination, thereby demonstrating the influence of the *C*-2 stereochemistry on the outcome of the reaction. Similarly, galactosyl pyridyl sulfones afforded their corresponding β-C-galactosides.[72] A point to note is that, unlike the corresponding glycosyl phenyl sulfones, the pyridyl derivatives react almost instantaneously with SmI_2 and do not require a cosolvent such as HMPA. Under these conditions radical cyclisation precedes the second reduction step.[73]

It has also been shown that direct coupling of the pyridylsulfone derivative of *N*-acetylgalactosamine with aldehydes or ketones is promoted by SmI_2 giving the corresponding *C*-glycoside (75%) as a single epimer (*Scheme 51*).[74,75]



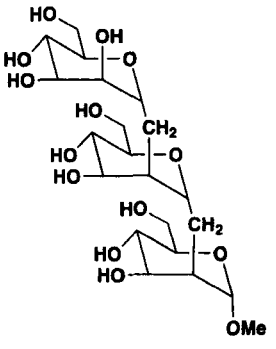
Scheme 51

The results discussed above suggest the possibility of synthesizing *C*-disaccharides by this protocol. The use of samarium diiodide in HMPA-benzene affords a mild convenient route to the synthesis of *C*-disaccharides from readily available sulfones (*Scheme 52*). In the example below, a glucosyl phenyl sulfone was coupled to an *exo*methylene sugar (41%).[76]

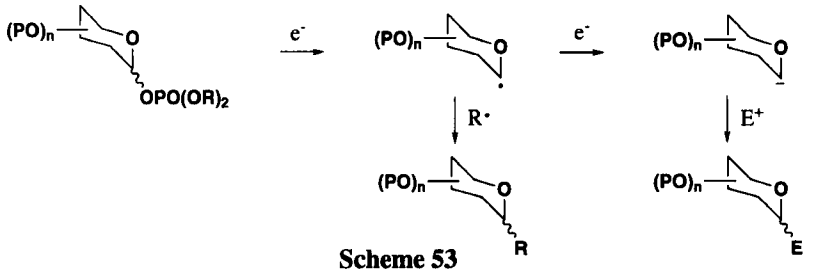


Scheme 52

This methodology can be applied to the retrosynthetic analysis of another *C*-disaccharide Man(α1→2)Man and *C*-trisaccharide Man(α1→2)Man(α1→2)Man, the former of which



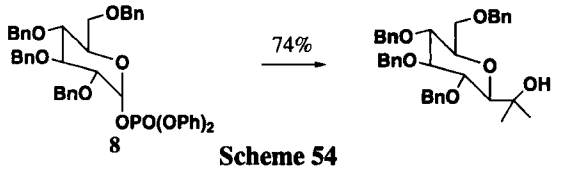
was prepared using this strategy.[77] Another type of substrate that may be used to effect the synthesis of *C*-glycosides is represented by anomeric phosphated glycosides (*Scheme 53*).



Scheme 53

With regard to the mechanism of the *C*-glycosylation, the reduction of glycosyl phosphates with SmI_2 is believed to proceed through two consecutive one-electron processes, similar to the mechanism proposed for the reaction of glycosyl sulfones.[67,72] After the generation of the glycosyl anion, addition to a carbonyl compound and *syn* elimination compete, as was found with sulfonyl derivatives. As suggested by Beau[72] *et al.*, unproductive *syn* elimination might occur when the C1-Sm and C2-O bonds are *syn*-coplanar.[78]

In the reaction of glycosyl diphenylphosphate **8** (*Scheme 54*), high diastereoselectivity was observed and no elimination was detected, perhaps due to the lack of coordination between

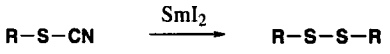


8

Scheme 54

samarium(III) and the oxygen atom at C2,[78] or to a stereochemical bias leading exclusively to an α- or β-organosamarium(III) intermediate (possibly opposite to that obtained in the reaction depicted in *Scheme 46*).

Focusing again on C-S cleavage, we now take a look at reductive dimerisation of thiocyanates mediated by SmI_2. This dimerisation of thiocyanates is a new approach that has been developed to synthesize disulfides (70-85%) and thiolesters (67-83%) (*Scheme 55, 56*).



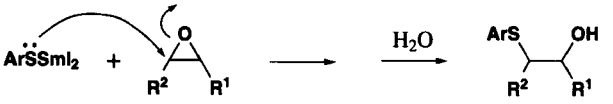
Scheme 55

Scheme 56

It was speculated that single electron transfer from the SmI_2 to the thiocyanate forms the corresponding radical anion, which cleaves into RS• and CN^-.[79] Homo-coupling of two RS• radicals gives the disulfide. In the presence of excess SmI_2, the radical RS• may be converted

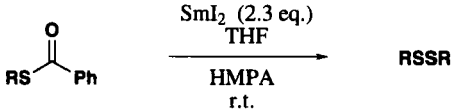
into the thiolate anion RS^-, which smoothly reacts with acyl chloride to give thiolesters. Still *et al.* investigated thiocyanate utility as a versatile synthetic unit. Amongst others, they reported on the successful conversion of ArSCN to aryl alkyl sulfides and aryl thioesters.[80]

A further application of the cleavage of thiocyanates is seen in their reaction with epoxides. Reduction of aryl thiocyanate with SmI_2, followed by a reaction with epoxides provides an interesting route to β-hydroxy sulfides (*Scheme 57*), affording products in yield of 60-92%.[81,82]



Scheme 57

Successful C-S cleavage of the thiocyanates by SmI_2, led Yoo *et al.* to continue to experiment with C-S cleavage reactions. They found that thiolesters could be cleaved into acyl anions ($PhCO^-$) and thiyl radicals (RS•) promoted by SmI_2 in the THF-HMPA system.[83] Reductive cleavage of aromatic thiobenzoates proceeded smoothly to give the corresponding disulfides in good yields (*Scheme 58*), along with a small amount of benzil $(PhCO)_2$ as a by-product. The



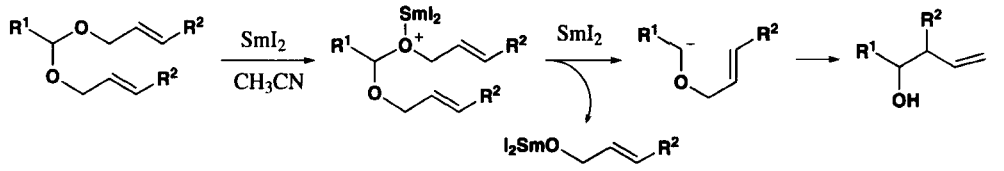
R = aromatic = Ph, 4-CH_3Ph, 4-ClPh, 2-BrPh, 2-Naphthyl
R = aliphatic = $PhCH_2CH_2$, 4-$ClPhCH_2$, $CH_3(CH_2)_7$, $CH_3(CH_2)_{11}$, $CH_3(CH_2)_{15}$, Cyclohexyl

Scheme 58

reaction was complete within an hour at room temperature in the presence of a slight excess (2.3 equivalents) of SmI_2. However, the aliphatic thiobenzoates were relatively low yielding and required longer reaction times (1-4 hrs). This result may be attributed to the difference in stability of the radical intermediates. A thiophenyl radical intermediate (ArS•) from an aromatic thiobenzoate is stabilized by the neighboring aromatic ring and therefore has enough time to react with another radical to form the disulfide product. To improve the yields obtained with the aliphatic thiobenzoates an additional equivalent of SmI_2 was added. An interesting point to note was that the halogen atom (Cl or Br) on the aromatic ring remained intact under the present conditions (Cl is normally relatively inert to SmI_2, while Br will react, but substantially slower than iodides). It was also observed that the addition of HMPA not only accelerated the reaction but also increased the product yield (70-86%).[83]

The 2,3-Wittig rearrangement is a useful tool for transforming allyl ethers into homoallyl alcohols. Deprotonation by an alkyllithium or a lithium amide is the most general method for generating the α-allyloxy carbanion undergoing rearrangement. This method, however, sometimes suffers from the formation of an undesired regioisomeric carbanion because

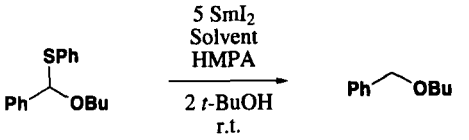
deprotonation also occurs at the relatively acidic proton α to the ether oxygen. In the present example, the generation of α-allyloxy carbanions by 1,5-hydrogen transfer of vinyl radicals is mediated by SmI_2 (*Scheme 59*).



Scheme 59

In this case, SmI_2 provided a direct route for regioselective generation of α-allyloxy carbanions by reduction of diallyl acetals with SmI_2 in acetonitrile (66-81% yield).[84]

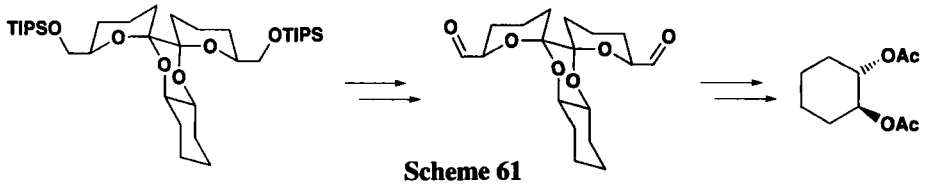
The above mentioned reaction is not only a new method for effecting the [2,3]-Wittig rearrangement but also indicates that the reduction of acetals can be achieved by SmI_2. *Scheme 60* shows the partial reduction of *O,S*-acetal to its corresponding ether by reductive elimination of a sulfenyl group using SmI_2.[85] Note the selectivity in terms of which group (RS^-) is eliminated (80%).



Solvent: THF or Benzene

Scheme 60

Dispiroketals have proved to be useful intermediates in synthesis, especially in the selective protonation of vicinal diols.[86] Deprotection was achieved by removing the TIPS group of the dispiroketal using tetrabutylammonium fluoride in THF to give an intermediate alcohol, which was oxidized to the corresponding dialdehyde (*Scheme 61*). Subsequent reductive cleavage was then achieved by treatment with SmI_2. The resulting diol was isolated as its diacetate in 87% yield.[87]



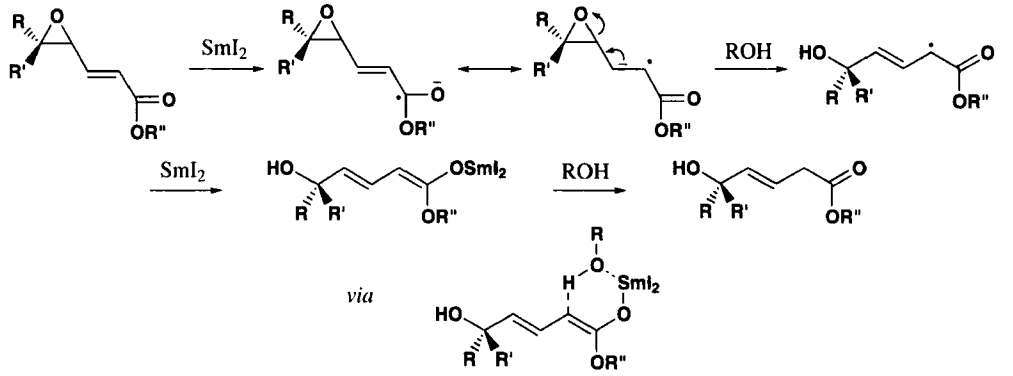
Scheme 61

II. INDIRECT AND SEQUENTIAL A-ELIMINATION REACTIONS

Apart from the direct elimination reactions discussed above, manifold examples exist in which elimination steps are observed as part of a two or more step sequence. For this part of the discussion, and to distinguish these from other multistep sequences, the characteristic feature is

that the elimination step occurs after an initial step or resonance, as will become clear from the examples described below.

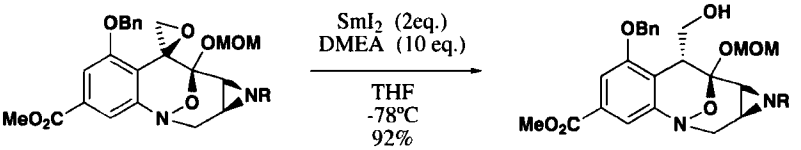
Functionalized vinyloxiranes undergo facile reductive epoxide ring-opening with samarium diiodide in THF in the presence of a proton source to provide (*E*)-allylic alcohols. Ketones, esters, nitriles and other similar functional groups not only survive these mild conditions intact, but are essential for the success of these reactions. Furthermore, reactions take place under essentially neutral conditions and lead to the exclusive generation of a single regio- and stereoisomeric (*E*)-allylic alcohol in nearly all cases (73-90%). Unsaturated esters are known to be suitable substrates for SmI_2 reduction and this therefore allowed for effective reduction of unsaturated epoxides by the mechanism shown below (*Scheme 62*).[25,88] Of practical interest is



Scheme 62

the selectivity for the β,γ-unsaturated product, as opposed to the thermodynamically favored α,β-unsaturated analogue. The exact timing of the protonation or reductive steps in this sequence have not been established, and it is possible that co-ordinated Sm(III) directs the proton donor ROH to the α-position to afford the observed product. Such a process would involve a favorable six-membered transition state, as shown.

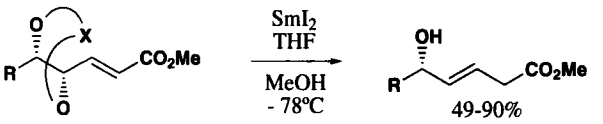
DMEA has also been used as an additive for epoxide ring-opening with SmI_2. This cosolvent was an essential component in the reaction in that it prevented formation of the elimination product (alkene, by dehydration). It was postulated that this reagent not only acts as a proton source but also sequesters the Lewis acid, *i.e.* samarium(III), formed thus favoring retention of the hydroxymethyl group (*Scheme 63*).[89] This reaction is presumably initiated at the ester moiety and proceeds *via* the conjugated aromatic ring.



DMEA = N,N-dimethylethanolamine

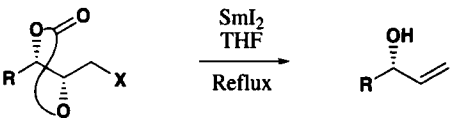
Scheme 63

This type of reaction is not limited to the strained epoxide-type substrates, but has also been applied to less strained substrates. For example, the reductive elimination of acetonides, cyclic carbonates or cyclic sulfites of γ,δ-dihydroxy (*E*)-α,β-unsaturated esters yield similar products to those of the above case (*Scheme 64*).[90]



Scheme 64

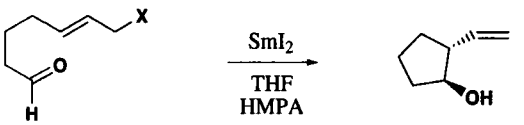
In a similar vein, SmI_2 has been used to effect the ring opening of a five-membered ring (*Scheme 65*), ultimately providing chiral allylic alcohols, which are versatile chiral building blocks for the synthesis of natural products.[91]



R = $BnOCH_2$, X = Br (62%)
R = n-C_5H_{11}, X = Br (59%)

Scheme 65

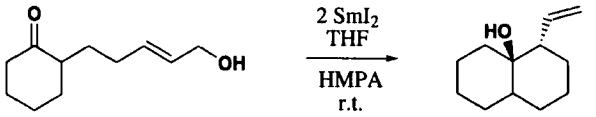
A sequential reductive elimination has been observed to take place in a manner similar to that discussed for direct elimination of suitable α-functionalized carbonyl groups from carbonyl compounds. In the sequential case, substrates bearing allylic leaving groups are typically used, allowing the elimination step to follow on a cyclization step in which a C-C bond is formed. Kan's report neatly shows the relative stereochemistry expected of such radical cyclizations.[92] In contradistinction to oxygen leaving groups, which almost certainly leave as anions, it is possible that these sulfur-based moieties can eliminate as radicals *or* as anions, depending on the relative rates of further reduction *versus* elimination (*Scheme 66*).[93]



X = SPh (-10°C, 55%)
X = SO_2Ph (-78°C, 85%)

Scheme 66

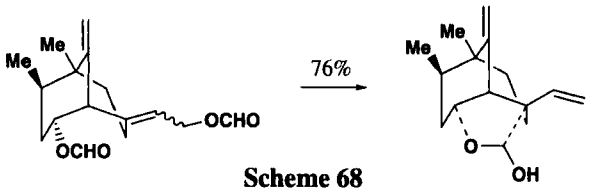
The previous example showed that the formation of a ketyl radical at the aldehyde, followed by intramolecular cyclization, ultimately led to the elimination of the sulfur group. Similar cyclization-elimination sequences have been observed from cyclic ketones in which the intramolecular cyclization is followed by the elimination of a sulfur[92] or of an hydroxyl group (*Scheme 67*).[94] Examples exist where the leaving group is attached to the ring system and the



Scheme 67

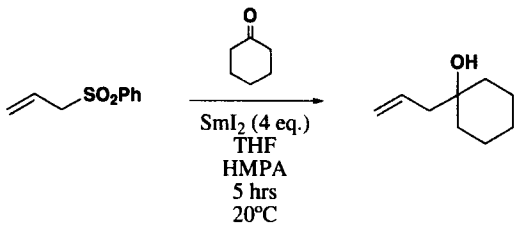
carbonyl is on the side chain. The reaction takes place in a similar fashion in both instances, *i.e.* initiation at the carbonyl functionality.[95]

In a rare example of an ester-derived ketyl radical reaction, a formyl ester was employed in the synthesis of a somewhat strained, multicyclic system (*Scheme 68*). Here, treatment of the ester-functionalized bicyclononane derivative with SmI_2 allowed the generation of a lactol after a radical cyclization onto a suitably disposed alkene, and final elimination of the leaving group.[96]



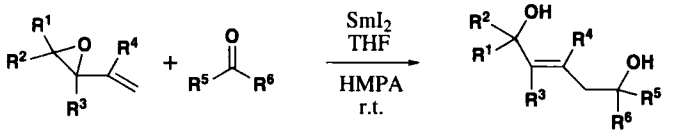
Scheme 68

Homoallylic alcohols have also been generated from the samarium diiodide-mediated intermolecular coupling of allylic sulfones with carbonyl compounds (*Scheme 69*). Successful conversion (87%) was obtained within 5 hours using SmI_2 in THF with HMPA as an additive.[97]



Scheme 69

α,β-Unsaturated epoxides have also been the subjects of keto-olefin coupling / elimination sequences (*Scheme 70*).



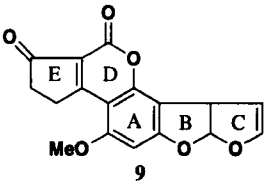
Scheme 70

This reaction begins with the generation of a ketyl-radical, which undergoes C-C bond formation with the olefin present in the reaction mixture. The secondary radical is presumably further reduced to the carbanion leading to the anionic β-elimination process. (The β-elimination

step is also possible at the radical stage.) In contrast to the previously mentioned sulfur-based leaving groups, the functionality remains appended to the product in the epoxide ring-opening process. The coupling of ketones with vinyl epoxides (5-*exo*-trig), therefore, provides access to functionalized carbocycles (17-83%) having an allyl alcohol side chain, when the reaction is designed to proceed in an intramolecular fashion (*Scheme 71*).[94]

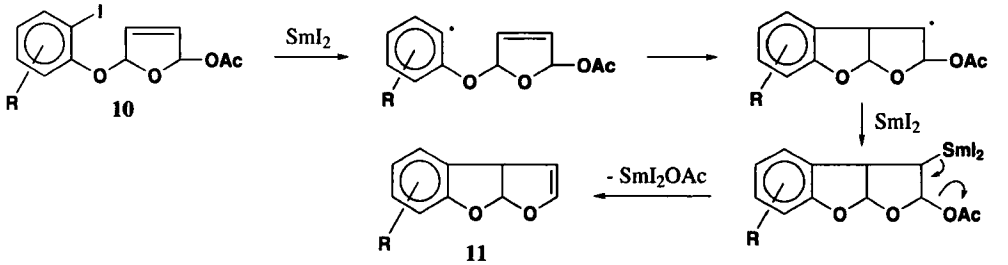
Scheme 71

Several analogues of the ABC enol ether moiety of aflatoxin B_1 (**9**) have been synthesized, in yields ranging from 60-78%, making use of a SmI_2-mediated cascade.[98] Treatment of **10** with freshly prepared SmI_2 afforded the desired tricyclic enol ethers **11** resulting from a 5-*exo*-trig radical cyclisation (*Scheme 72*). The product presumably arises *via* a reduction-elimination sequence subsequent to the cyclisation step, as shown below.



9

This methodology was used to prepare a variety of analogues (R = CH_3, $CH(CH_3)_2$, Cl, OBn), and in one instance a product that contained a pyridine ring as part of the ABC system



Scheme 72

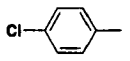
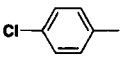
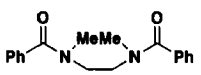
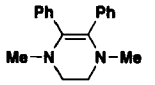
could be readily prepared. In addition to **11**, small amounts of *o*-iodophenol were detected, possibly arising by Lewis-acid (Sm^{3+}) catalysed decomposition of **10**. The proportion of *o*-iodophenol increased when SmI_2 that was not freshly prepared (*i.e.* a commercial solution) was used.

In an interesting deoxygenative coupling of amides to form enediamine systems, use was made of an unprecedented Sm/SmI_2 system (*Scheme 73*).[99] A variety of substrates were successfully employed in this reaction (*Table 3*).

Reaction conditions:
Amide (1 mmol)
Sm (0.65-0.70 mmol), SmI_2 (0.1 M in THF, 0.55 mmol)
67°C, 2-4 hrs

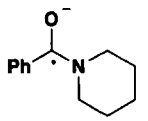
Scheme 73

Table 3. Amide Homocoupling[a]

Amide		Product		Yield (%)
Ar	R_2N	Ar	R_2N	
Ph	Et_2N	Ph	Et_2N	72
				50
				62

a) See reference 97 for a variety of other substrates.

The use of SmI_2 alone was unsuccessful in effecting the desired coupling reaction. Varying molar ratios of Sm/SmI_2 showed that the yield of the coupling product was dependent on the amount of samarium metal used. The coupling reaction was found to proceed in the presence of only catalytic amounts of SmI_2. From these results, and the fact that both Sm and SmI_2 are essential for this coupling reaction, it was proposed that the SmI_2 activates the surface of Sm metal. The reason why this should be so is unclear. A more probable scenario is that Sm^{3+} is the agent that activates the metal surface in a disproportionation reaction which regenerates Sm^{2+}. Two mechanistic pathways leading to the product have been proposed. The first postulates a dimerisation of ketyl radical **12** in a pinacol-type reaction, followed by reductive deoxygenation to provide the desired *vic*-diaminoalkene (*Scheme 74*). The second hypothesis suggests that the



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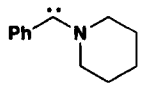

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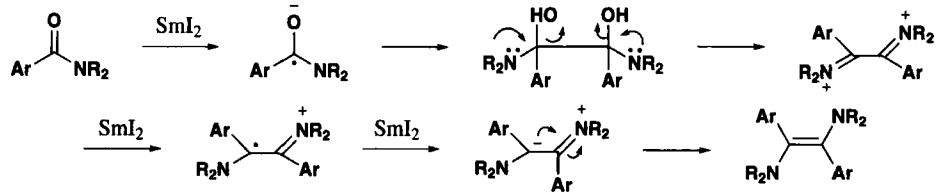
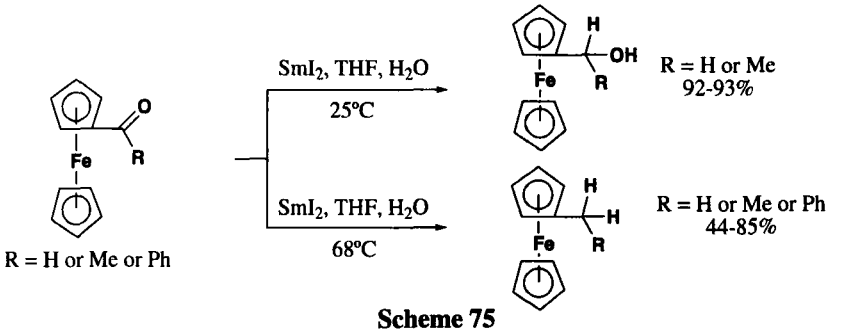


Scheme 74

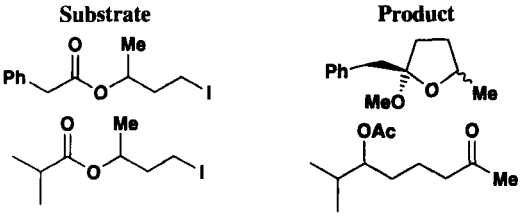
initially formed anion radical **12** undergoes further reduction to give an α-aminocarbene intermediate **13**, which dimerises to afford the product. Two issues count against the latter scenario. Firstly, it is possible that SmI_2 is not a sufficiently strong reductant to effect this transformation, and, secondly, dimerisation of carbenes is usually uncompetitive with other reactions such as C-H insertion.

The following interesting example demonstrates the importance of temperature on the outcome of some SmI_2-mediated reactions (*Scheme 75*). This particular reaction shows the ability of SmI_2 to reduce aromatic aldehydes and ketones in the presence of water. When the reaction was carried out at ambient temperature a simple reduction of ketone to the anticipated alcohol was observed. However, when raising the temperature to 68°C, cleavage of the C-O bond resulted. Such a deoxygenation could result from the subsequent reduction of the intermediate ferrocenyl alcohol with an excess of SmI_2, and these processes might be facilitated by the *in situ* generated Lewis acidic Sm(III) ion.[100]



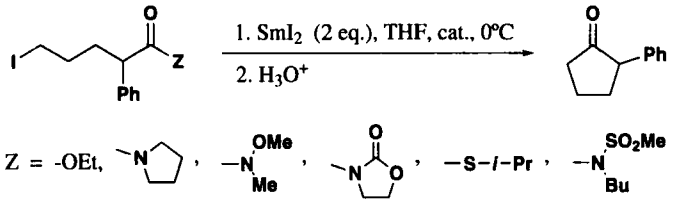
Scheme 75

The samarium-Barbier reaction has been the subject of much research, and has been used to in the preparation of a number of functionalized ketones with stereogenic centres distal to the carbonyl functionality, providing a sequential process and a convenient entry into chiral, nonracemic δ-hydroxyketones.[101] SmI_2 has proven superior to other reducing agents typically used in Barbier-type processes. The mechanism of the intramolecular SmI_2 promoted Barbier reaction, not unlike its more traditional lithium and magnesium counterparts,[102] is somewhat of an enigma. It is likely that a carbanionic mechanism is operative in many instances, although evidence exists that more than one mechanism may be applicable depending on the particular substrate under consideration.[103,104]



While initial experiments focussed on the use of esters, subsequent work looked to include other acyl type functional groups. It was successfully shown that this was possible not only with esters but also with amides, sulfonamides, etc. (*Scheme 76*). The reaction was carried

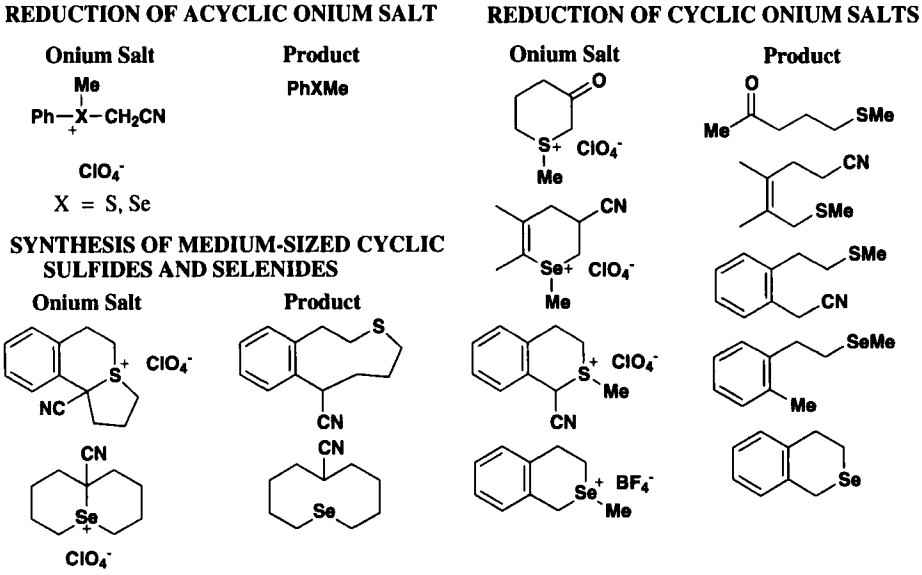
out by adding the substrate to a 0.15 M solution of SmI_2 in THF at 0°C containing a catalytic amount (1 mol%) of an iron(III) complex (iron(III) acetylacetonate, $[Fe(acac)_3]$, and iron(III)



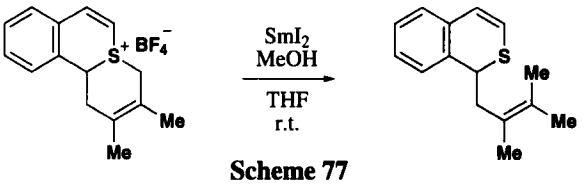
Scheme 76

tris(dibenzoylmethane), $[Fe(DBM)_3]$ yield the same results). The reaction was complete within 30 minutes and afforded the products in yields of 68-81%. In some instances, it was found that the iron(III) complex was not effective and therefore the reaction was run in the presence of 4 equivalents of tripiperidinophosphine oxide (a strong donor ligand).[104] In addition to the carboxylic acid derivatives (iodoalkyl acyl derivatives), the reaction was successfully carried out with nitriles and halo esters. Nitriles delivered similar products to the carboxylic acid derivatives, shown above, while the cyclisation of the halo esters delivered a number of products ranging from those of simple ring closure to the formation of dimers and ring expanded products.[104]

Treatment of sulfonium and selenonium salts, in which a suitably disposed nitrile or carbonyl group was present, with 2 equivalents of a THF solution of samarium diiodide caused the reductive cleavage of the C-S or C-Se bonds in high yields.[105] The bond cleavage took place regioselectively between the positive sulfur or selenium atom and the carbon atom with an electron withdrawing group or vinyl group. Some medium sized cyclic sulfides or selenides were synthesised by this method, which was found to be applicable on acyclic, bicyclic and tricyclic systems (yields typically 80-90%).

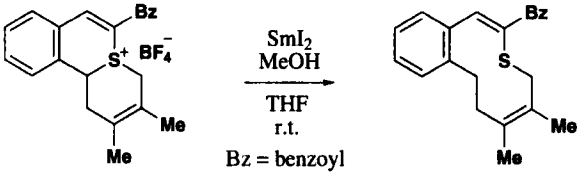


In another example, the cleavage of one of the C-S bonds in benzothiopyrylium salts was readily effected (*Scheme 77*). The reaction was carried out in THF in the presence of methanol at room temperature.



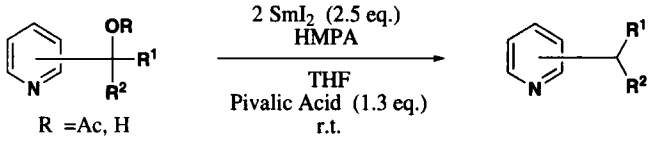
Scheme 77

Two different cleavages were noted, depending on whether or not an interfering substituent (benzoyl; Bz) was present.[106] In the instances (which are the majority of the examples cited here, directly above and below) where a CN or carbonyl moiety is present, the mechanism of the reaction is easy to rationalise as one that is initiated at that group. However, the two instances mentioned in which such a functional group is not present are not so readily explained. Suffice it to say that the probability of an entirely different mechanism is high, as is witnessed by the different outcome of these last two reactions (*Scheme 77, 78*).



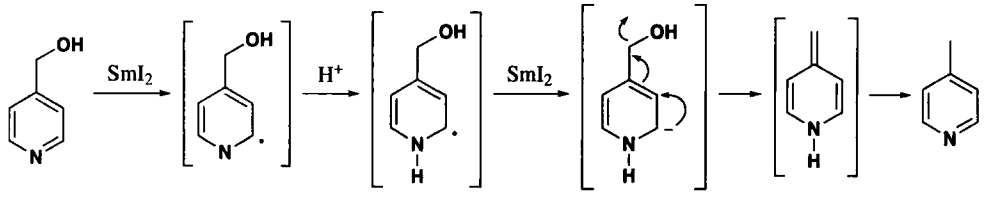
Scheme 78

An interesting sequential elimination has been reported by Kato *et al.* where the elimination is initiated by electron transfer to a pyridine ring (*Scheme 79*).[107]



Scheme 79

The mechanism is believed to proceed *via* electron transfer to the pyridine ring to generate a radical anion, followed by protonation and further reduction to produce an anion which eliminates a remote oxygen function (*Scheme 80*). This protocol allows for the efficient synthesis of alkylpyridine derivatives (49-82%) from SmI_2-mediated deoxygenation of pyridinemethanol derivatives.



Scheme 80

III. β-ELIMINATION REACTIONS

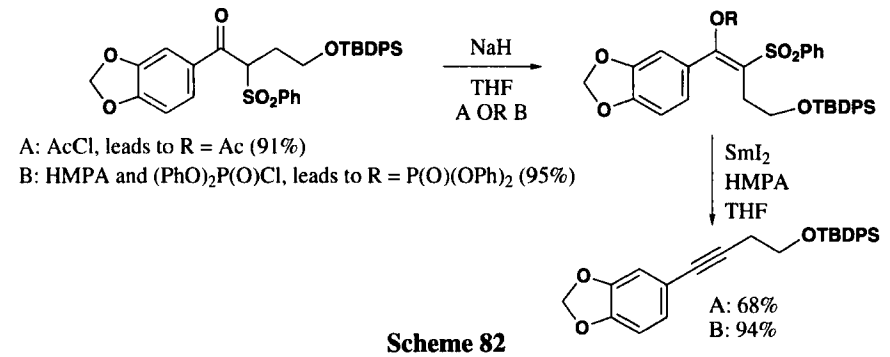
1. Direct β-Elimination Reactions

Alkenes are important structural moieties in a wide variety of compounds, ranging from petrochemical commodities to the lowest volume higher value fine chemicals and pharmaceuticals. Thus, alkenes represent an important group of desirable compounds both as starting materials, as intermediates and as end products.

The coupling of two units to form an olefin is a common procedure in organic synthesis using, for example, the McMurry,[108] the Wittig[109] and metathesis[110] type coupling reactions. Olefination may also be achieved *via* elimination-type reactions, of which the Julia-Lythgoe reaction is a good example.[111] This method allows for regiospecificity and in some cases provides excellent stereoselectivity. The Julia-Lythgoe procedure utilises the readily available α-sulfonyl carbanions to produce predominantly *E* olefins, depending on conditions and the substitution pattern of the starting material. In the first SmI_2-mediated reactions of this nature, the procedure involved the use of SmI_2 in THF in the presence of HMPA at room temperature,[112] and allowed the preparation of olefins from both sulfonyl alcohols and sulfonyl acetates (*Scheme 81*).

Scheme 81

This form of β-elimination is not only successful in preparing olefins but can also be used to prepare acetylenes. These acetylenes are prepared from their corresponding enol acetates or enol phosphates by reductive elimination, which themselves are prepared from the corresponding β-keto sulfones, as shown in *Scheme 82*. The β-keto sulfones are easily obtained from the substrates used to prepare the olefins mentioned above by a simple oxidation with PCC / 4 Å MS / CH_2Cl_2.[113]

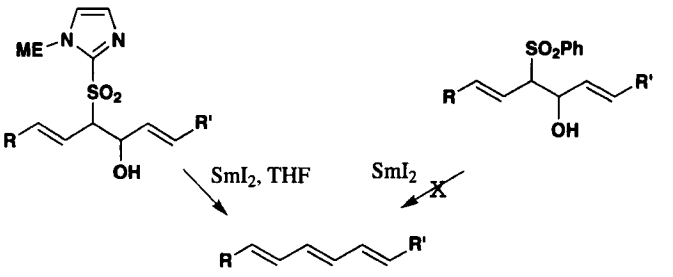


Scheme 82

Kende showed that β-hydroxy imidazolyl sulfones could easily be reduced in one step to the corresponding olefins using SmI_2 in THF at room temperature.[114] Conversely, the reduc-

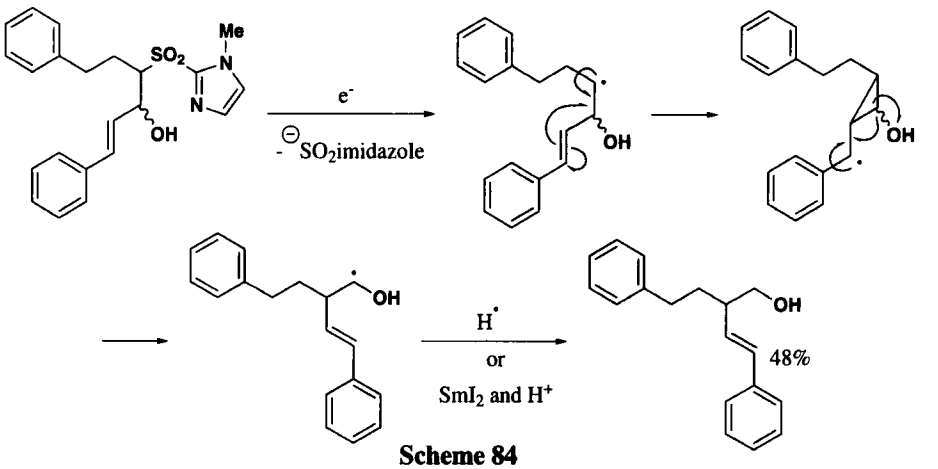
tive elimination of β-hydroxy phenyl sulfones without adding HMPA gave poor results, with only trace amounts of the desired product being detected (*Scheme 83*).

Keck *et al.*[115] carried out a series of studies into the use of samarium diiodide in the reductive elimination of 1,2-acetoxy sulfones and the reductive cleavage of vinyl sulfones. They found that additives like *t*-BuOH, H_2O and MeOH did not enhance the rate of the reaction compared to 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) or HMPA. DMPU



Scheme 83

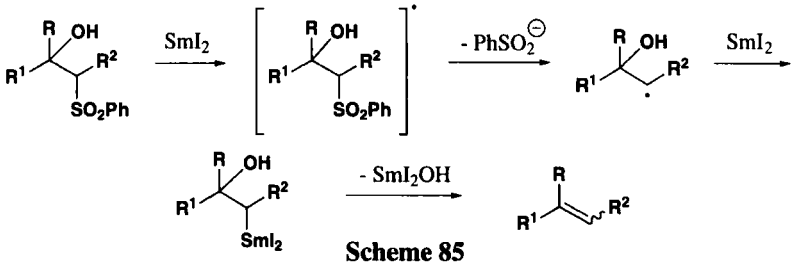
proved to be a better additive than HMPA, but either additive used alone (*i.e.* no proton source) gave low stereoselectivities in the products. When DMPU was used in conjunction with MeOH, high yields (60-80%) and good stereoselectivities were observed.[115] One particular β-hydroxy imidazolyl sulfone was subjected to the conditions described in *Scheme 83* and a rearranged homoallylic alcohol was obtained instead of the expected diene (*Scheme 84*).



Scheme 84

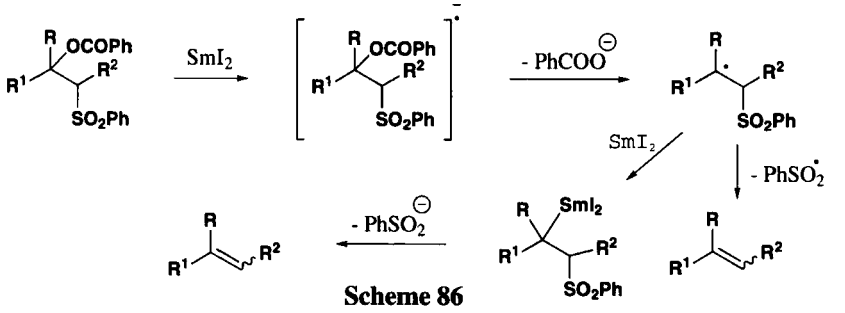
The formation of the product was rationalised on the basis of a one-electron transfer process. The reaction of SmI_2 with the sulfone generates a radical anion, which, upon loss of the imidazolesulfinate anion, forms a carbon radical. This then adds to the double bond (3-*exo*-trig) forming a cyclopropane ring, yielding a benzylic radical. This radical reopens the ring in a different orientation to generate the alkyl radical which may be quenched by H• transfer from the solvent to afford the homoallylic alcohol, or further reduced by SmI_2 and protonated.

Examples of the reductive elimination of β-sulfoxybenzoates display intriguing features. For example, the benzoate derivative affords the required olefin at temperatures as low as -84°C within a few minutes, while the hydroxy sulfone is recovered unchanged under similar conditions. These observations strongly suggest that the SmI_2 mediated reductive elimination of these two substrates takes place by different mechanisms (*Scheme 85, 86*).[116] Markó *et al.* discussed the two mechanisms in some detail.[117] With β-hydroxy sulfones, a single electron transfer from SmI_2 to the *aromatic sulfone* takes place, generating a radical anion. This step, which appears to be unfavourable, is followed by the ejection of phenylsulfinate ion, producing the new radical species. A second electron transfer from SmI_2 to this radical then affords the intermediate organosamarium derivative, which undergoes β-elimination, leading to the observed alkene product (*Scheme 85*).



Scheme 85

Conversely, it is plausible that, in the case of the benzoate (*cf.* section I.1.b. discussion on α-benzoyloxy lactones), the initial electron transfer takes place at the *benzoate* rather than at the sulfonyl group (*Scheme 86*).

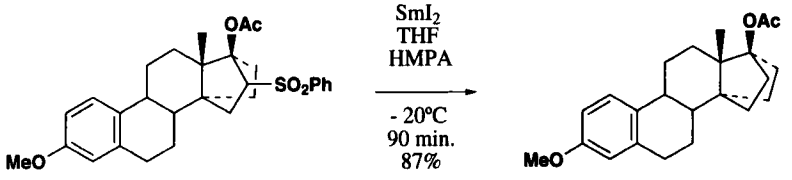


Scheme 86

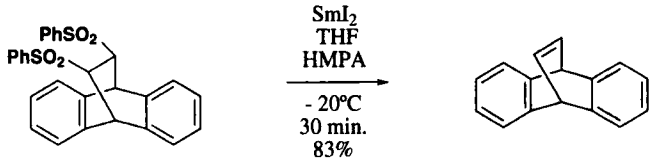
This electron transfer process appears to be an easier process, taking place rapidly even at –84°C and leads to the radical anion. Subsequent collapse of this intermediate liberates the benzoate ion and produces a radical. Further transformation of this radical into the organosamarium intermediate and elimination of the phenylsulfinyl group eventually affords the olefin.[117] This process has been used in a variety of reactions to afford a selection of di- and trisubstituted alkenes (66-84%).[117]

Elimination reactions of β-acetoxy sulfones in steroidal derivatives such as the one in *Scheme 87* are not observed, in accordance with Bredt's Rule.[118] Instead, products of simple reduction are isolated.[119]

However, SmI_2 readily reduced the Diels-Alder adduct disulfone shown in *Scheme 88* to the corresponding alkene.[120]

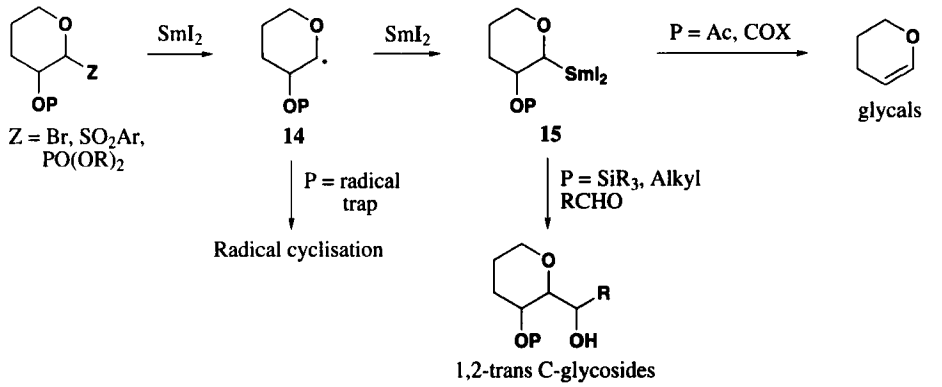


Scheme 87



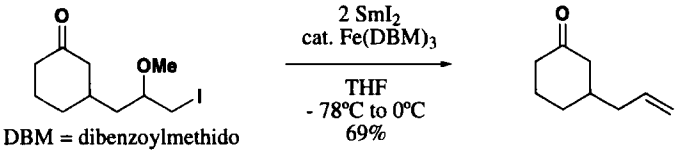
Scheme 88

In carbohydrates, reactive intermediates generated at the anomeric position using SmI_2 tend to follow certain trends. Electron transfer to appropriate anomeric substituents (halogens, aryl sulfones, phosphates) leads to an anomeric radical **14** which is either trapped by a suitably located radical trap (*e.g.* C-C unsaturation) or is further reduced to an anomeric Sm(III) species **15**. With an oxygen at position 2, as found in neutral hexoses, the anomeric organosamarium can either suffer monomolecular elimination (preferably in the presence of 2-OAc, 2-OCOR, -$OCNR_2$, *i.e.* glycal synthesis) or undergo C-C bond formation with carbonyl compounds (preferably in the presence of 2-O-alkyl or silyl ether, *i.e. C*-glycoside synthesis) under Barbier procedures (*Scheme 89*). We have already dealt with many of these examples in the discussion involving α-elimination, and the remaining examples will be discussed below.[121]



Scheme 89

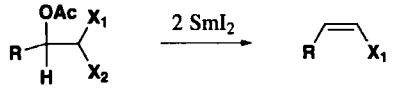
Another predominant form of β-elimination involves the reduction of β-halo ethers, where elimination is believed to proceed *via* a carbanion upon treatment with SmI_2. This anion then precipitates the elimination of the β-group, affording the corresponding alkene (*Scheme 90*).[103,122]



DBM = dibenzoylmethido

Scheme 90

An example involving the reductive elimination of a halo group is seen in the stereoselective 1,2-elimination in *O*-acetylated 1,1-dihaloalkan-2-ols with samarium diiodide (*Scheme 91*).

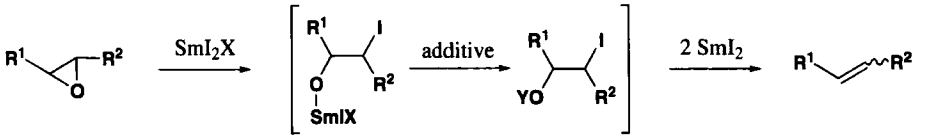


X = Cl, Br, I

Scheme 91

When 1,1-diiodononan-2-ol was added to a solution of SmI_2 in THF, the desired vinyl iodide was obtained in high yield but with very poor stereoselectivity. A similar result was obtained when the *O*-silyl ether of 1,1-diiodononan-2-ol was used. However, when attempted with *O*-acetylated 1,1-diiodononana-2-ol, the desired vinyl iodide was obtained in good yield with high stereoselectivity.[123] These reaction conditions were also found to be suitable for β-elimination reactions of *O*-acetylated 1,1-dibromo- and 1,1-dichloroalkan-2-ol substrates. In the latter case, heating to reflux and longer reaction times were necessary to effect a successful reaction.[123]

A similar example of this form of β-elimination involves the deoxygenation of epoxides to olefins (*Scheme 92*).[124]

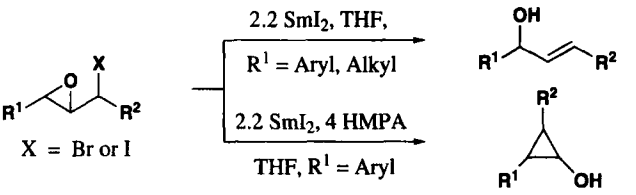


additive = DMEA, glutaric anhydride
Y = H, Acyl
Z/E: 91/9-90/10
54-95%

Scheme 92

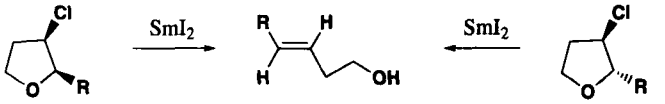
This transformation is normally effected by the efficient SmI_2-THF-HMPA electron transfer system in the presence of either *N,N*-dimethylethanolamine (DMEA) or glutaric anhydride. The initial epoxide ring opening is believed to be Sm^{3+}-catalysed, and generates an iodohalide as an intermediate. This is then susceptible to the normal Sm^{2+}-mediated reaction that leads to the olefin. SmI_2-induced iodomethylation,[125] which is a rapid and mild one-pot carbonyl methylenation method is also believed to proceed *via* a similar intermediate to that shown in the scheme below.

β-Elimination reactions often involve the reductive removal of an halide followed by ring opening. An interesting instance of this phenomenon is seen in the following example, where SmI_2 promoted ring opening, to afford the corresponding alkenes, occurs in the absence of HMPA. However, in the presence of HMPA, the reaction results in the formation of a cyclopropanol derivative (69-75%). The reactions are product-selective in the presence/absence of HMPA (*Scheme 93*).[126]



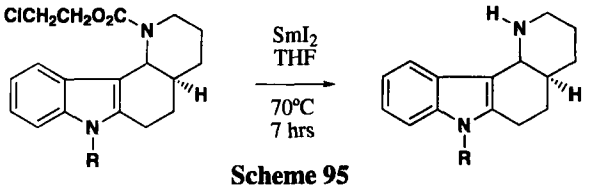
Scheme 93

The use of samarium diiodide in place of the sodium metal for the ring opening of cyclic β-halogeno-ethers alters the stereochemistry of the resulting olefinic alcohols. Making use of this samarium diiodide method results in the highly stereoselective syntheses of enols (>95% yield), compared to sodium metal affording a mixture of (*E*)- and (*Z*)-alk-3-enols (*Scheme 94*).[127,128]



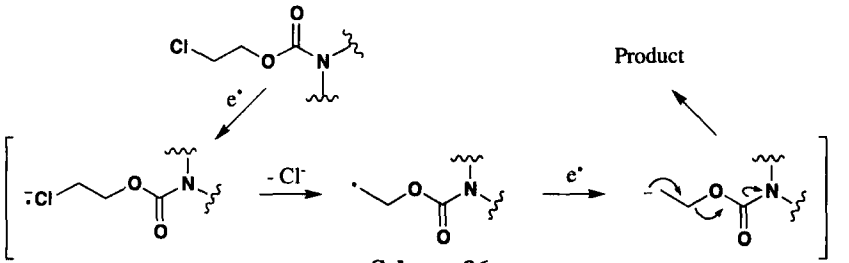
Scheme 94

β-Elimination can also be used as a form of deprotection. Magnus reported a C-N cleavage that left the nitrogen deprotected (*Scheme 95*).[129]



Scheme 95

This reaction is believed to proceed *via* the sequence primary radical formation, reduction by SmI_2 to form the primary anion, elimination of ethylene, and decarboxylation to afford a samarium amide (*Scheme 96*).



Scheme 96

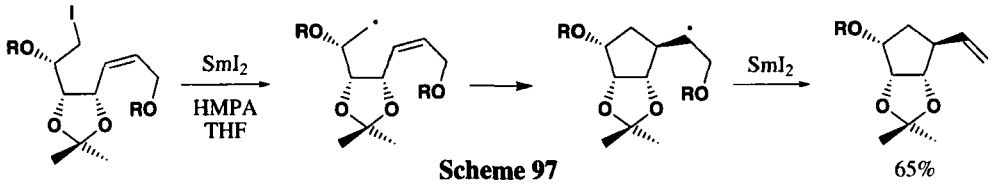
Workup affords the free-base alkaloid. Various other reagents failed to effect the selective removal of the chlorocarbamate protecting group to give the free amine. These reagents had no effect when using Zn-AcOH or $CrCl_2$-HCl and resulted in an undesired product in the presence of tri-*n*-butyltin hydride azobisisobutyronitrile or resulted in decomposition of the starting material due, amongst others, to extended reaction times when using Zn-H_2O-THF-aquo-vitamin B_{12}. (2,2,2-Trichloroethoxy)-methoxy ether groups are also susceptible to similar deprotection reactions, affording thee free alcohol.[130]

Samarium diiodide has also been used in an efficient and neutral deprotection strategy of esters. In these cases, 2-bromoethyl and 2-iodoethyl esters could be readily deprotected to afford the anticipated carboxylic acids (*via* β-elimination) in good yield.[131]

2. Indirect/sequential β-Elimination Reactions

Many examples of elimination reactions that take place subsequent to an initial step are found in the literature. In most instances, the first step is one of bond formation, although simple "resonance isomerisation" is sometimes seen to precede a fragmentation / elimination step. As in the case of the SmI_2-mediated reduction of carbonyl compounds, the reduction of halides by that reagent proceeds *via* a one-electron transfer. Decomposition of the halo radical-anion leads to a SmI_2-halide species and the corresponding carbon radical. Reactivity in the system may already be seen at the radical stage or after further reduction to a carbanion by a second equivalent of SmI_2. Some examples of the use of halides as well as carbonyl precursors in this context are described below.

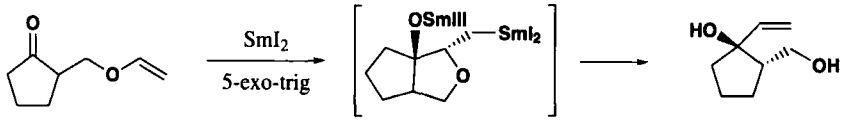
In the first example, an iodo-allyl ether (derived from D-ribose) was treated with SmI_2 in the presence of HMPA to generate a primary radical which underwent 5-*exo*-trig cyclisation (*Scheme 97*).



Scheme 97

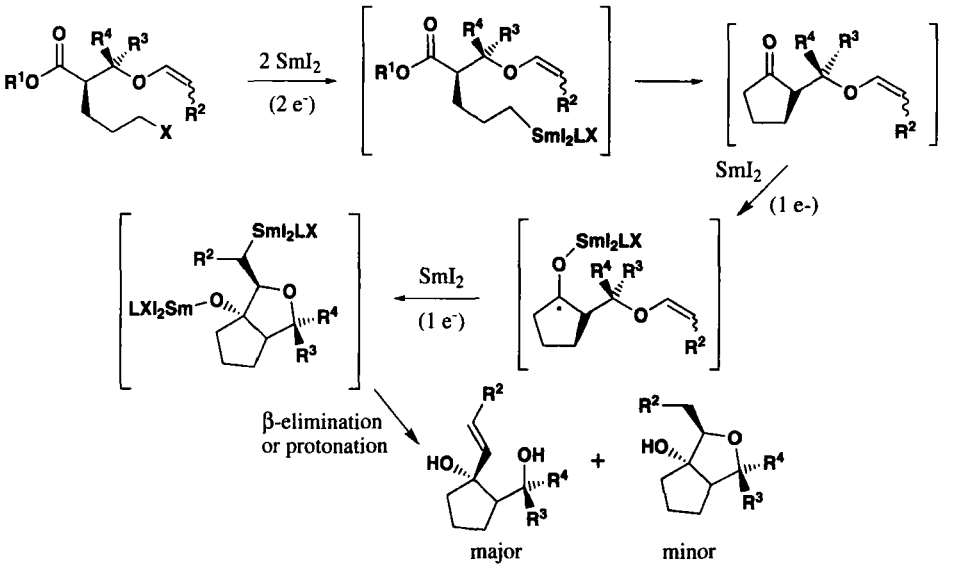
The secondary radical underwent reduction to the analogous anion, which resulted in elimination of the alkoxy group to generate the α-olefin product. In this reaction, the stereochemistry of the cyclisation is controlled such that the pendant vinyl moiety in the product is *trans* with respect to the isopropylidene protecting group.[132]

Sequential ketyl-olefin coupling / β-elimination reactions follow the same principal mentioned above (*Scheme 98*). Again we see the formation of a ring (50%) after treatment with samarium diiodide resulting from the addition of the ketyl radical to the alkene moiety, followed by β-elimination at the carbanion stage. The overall course of events in this example resulted in the net addition of an alkenyl species to a ketone carbonyl.[133]



Scheme 98

A nucleophilic acyl substitution / alkenyl transfer process has been developed as a complementary method to the previous example. This novel three-step, one-pot protocol provides a new method for the introduction of an alkenyl moiety to a carbonyl species in good yield (60-77%), while maintaining an high degree of stereocontrol over three to five stereocentres (*Scheme 99*). The proposed three-step reaction sequence proceeds *via* an

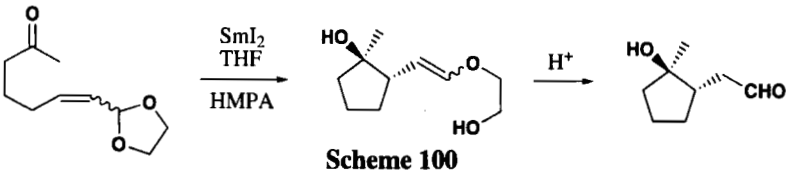


Scheme 99

anionic/radical/anionic process. Initial generation of an organosamarium species that is poised to effect an intramolecular nucleophilic acyl substitution on the ester, results in the liberation of a cycloalkanone. The ketone moiety subsequently enters a radical ketyl-olefin coupling reaction, generating an exocyclic organosamarium species that undergoes a rapid β-elimination (or competitive protonation).[134]

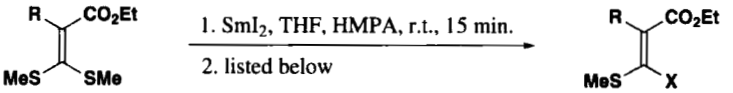
Acetals are also susceptible to opening by adjacent carbanions. Here, radical cyclisation, reduction of the secondary radical to the anion, and elimination generate a vinyl ether, which is subsequently unmasked to afford the analogous aldehyde in a yield of 61% (*Scheme 100*).[135] As expected of cyclisations of this type, the ketyl radical forms a new C-C bond onto the alkene such that the alcohol and pendant chain possess a *trans* relative stereochemistry(E/Z: 7/3).

Alkoxycarbonyl ketene dithioacetals can be cleanly cleaved by SmI_2, providing a new and efficient route to the stereoselective generation of the corresponding highly functionalised



Scheme 100

vinyl samarium species (*Scheme 101*). These can be allowed to react, respectively, with a proton source, allyl bromide and aldehydes to give the corresponding reduction products, allylation products and β-thiobutenolides (*Table 4*).[136]

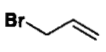
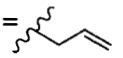


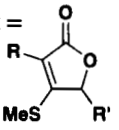
Scheme 101

Table 4. Electrophile-product Relationship for Scheme 101

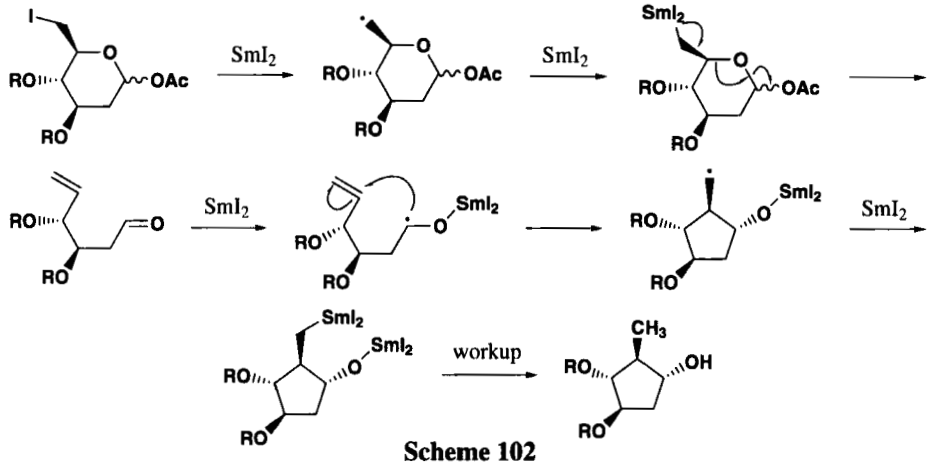
A. Sat. Aq. NH_4Cl X = H

B. D_2O X = D

C.  X = 

D. R'CHO Product = 

In some cases, the specific reaction in question does not end after the fragmentation step, but may be followed by other sequential reactions. [137-141] An example from our previous work demonstrates a sequential transformation of carbohydrates into carbocycles (*Scheme 102*).[139] In

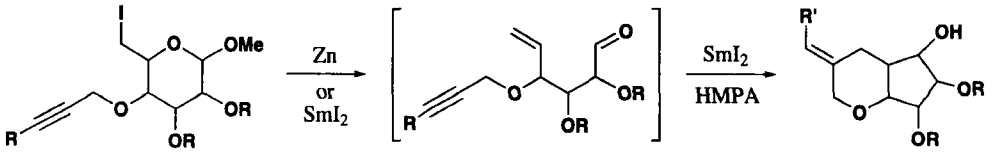


Scheme 102

these examples, both anionic and radical reactions (both SmI_2-mediated) were observed, once again highlighting the utility and selectivity of SmI_2, even in sequential, multistep processes. In

order to effect the overall ring contraction, two complete reaction sequences are necessary. These include a reductive dealkoxyhalogenation to give the ring-opened hex-5-enal followed by an intramolecular ketyl-olefin reductive coupling, to afford the ring-contracted organosamarium intermediate. Intermolecular trapping of this organosamarium with an appropriate electrophile produces the branched cyclopentanol derivative.[139]

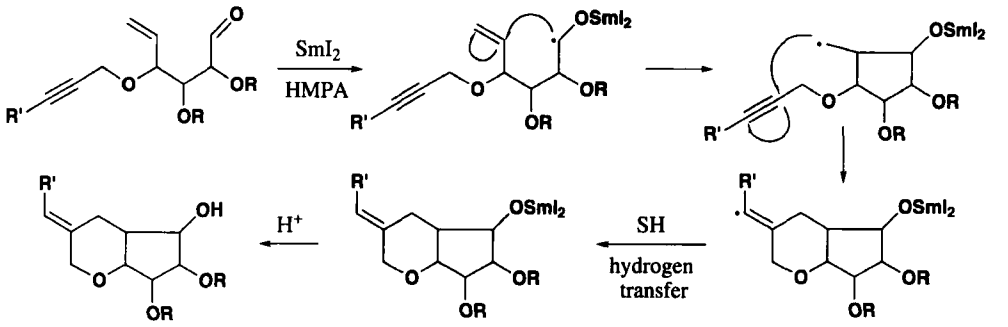
The intermolecular electrophile trapping protocol may be complemented by the presence of intramolecular radical traps. This approach allows the rapid assembly of bicyclic ring systems with stereodefined double bonds, *via* an appropriate intramolecular cyclisation, from readily available carbohydrate derivatives (*Scheme 103*).[140,141]



Scheme 103

This result neatly demonstrates that alkyne-type radical traps may be efficiently employed in situations where competitive elimination reactions are not taking place (*vide supra*, *Scheme 48*).

It was demonstrated that either Zn or SmI_2 can be used to effect the dealkoxy-halogenation. The mechanism of the SmI_2 mediated cyclisation is shown in *Scheme 104*. The cyclisation process is probably initiated by a single electron reduction of the aldehyde to form a ketyl

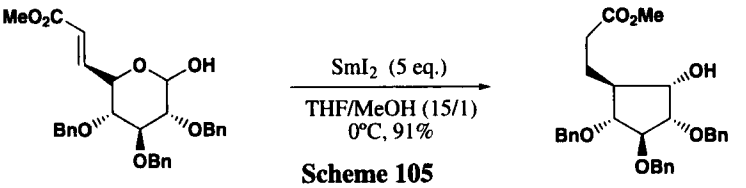


SH = Solvent

Scheme 104

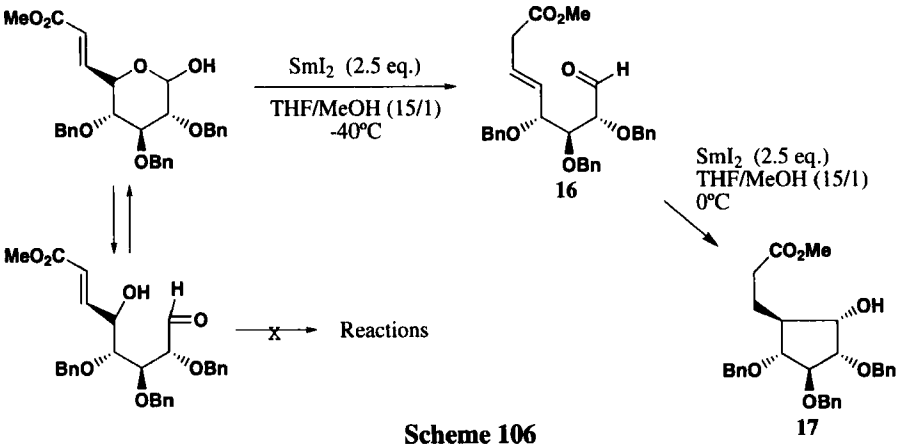
radical, followed by an *exo* cyclisation onto the double bond. A primary radical results, which undergoes cyclisation onto the tethered alkyne. The highly reactive vinyl radical that results is quenched by abstraction of an hydrogen atom from the solvent.[142]

Using an approach that is conceptually similar to those described above, an α,β-unsaturated ester derivative of glucose has also been subjected to a SmI_2-mediated ring contraction (*Scheme 105*). Reaction of the substrate with excess SmI_2 in a THF/MeOH solution allowed the isolation of a chiral cyclopentanol derivative.[143]



Scheme 105

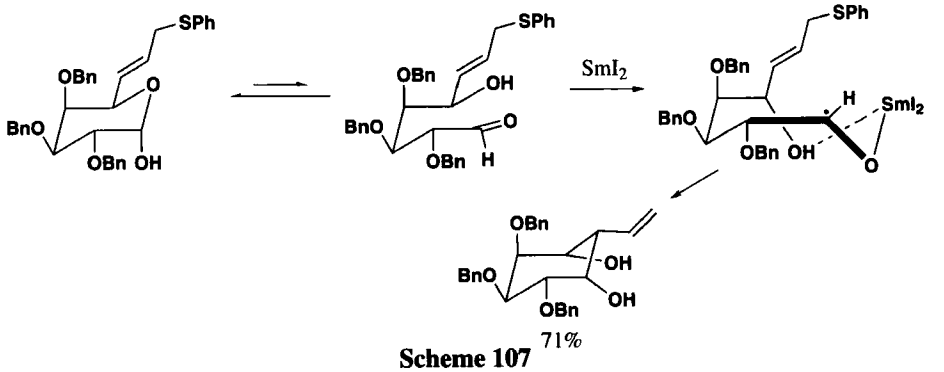
On examining the effect of temperature and the number of added equivalents of samarium diiodide on the outcome of the reaction, more insight was obtained on the mechanism and intermediates of this reaction. After adding 2.5 equivalents SmI_2 at -40°C in THF/MeOH (15/1), the β,γ-unsaturated methyl ester **16** was obtained as a major product (*Scheme 106*).[143]



Scheme 106

Further addition of 2.5 equivalents SmI_2 at 0°C in THF/MeOH (15/1) afforded the cyclic product **17**. These results indicate that the reaction is initiated at the α,β-unsaturated ester moiety, and that the ring oxygen is eliminated to generate the observed enal. While it is possible that the ring oxygen is eliminated from the open-chain form (see *Scheme 106*), it is unlikely that the observed selectivity would be preserved since aldehydes are more reactive towards SmI_2 than are esters.

The following example highlights the use of anomeric position unprotected carbohydrate derivatives as direct precursors in SmI_2-promoted reactions (*Scheme 107*). Here, the ketyl



71%

Scheme 107

radical cyclises (6-*exo*-trig) onto the alkene moiety, the radical intermediate of which would readily eliminate PhS•, or PhS^- if the radical is first reduced to the corresponding anion by a second equivalent of SmI_2. The cyclisation reaction proceeds with a large degree of stereocontrol as a result of the Sm(III) chelate structure.[143]

IV. CONCLUSION

The discussion contained in this review describes the use of SmI_2 as an highly selective reductant in a great variety of fragmentation reactions. As the many examples illustrate, this reagent is tolerant of a large number of functional groups, which is the main reason for its observed selectivity in the many reactions it mediates. Not only is this compound selective in a broad spectrum of reactions and tolerant of multifunctional substrates, it often greatly surpasses many of the more traditional reducing agents. These attributes should see the continued employment of SmI_2 in the field of synthetic organic chemistry, and should continue to give rise to new applications and to improvements on older chemistry, including fragmentation and cleavage reactions.

REFERENCES

1. H. B. Kagan, J. L. Namy and P. Girard, *Tetrahedron*, **37**, 175 (1982).

2. D. B. G. Williams, K. Blann and J. Caddy, *Org. Prep. Proced. Int.*, **33**, 565 (2001).

3. S. S. Pizey, "*Synthetic Reagents*", Vol. 1, p. 101, John Wiley and Sons Inc., 1974.

4. G. A. Molander, and G. Hahn, *J. Org. Chem.*, **51**, 1135 (1986).

5. J. Castro, H. Sörensen, A. Riera, C. Morin, A. Moyano, M. A. Pericàs, and A. E. Greene, *J. Am. Chem. Soc.*, **112**, 9388 (1990).

6. A. B. Smith (III), N. K. Dunlap, and G. A. Sulikowski, *Tetrahedron Lett.*, **29**, 439 (1988).

7. Y. Nakamura, S. Takeuchi, Y. Ohgo, M. Yamaoka, A. Yoshida and K. Mikami, *Tetrahedron Lett.*, **38**, 2709 (1997).

8. R. Yoneda, S. Harusawa, and T. Kurihara, *J. Org. Chem.*, **56**, 1827 (1991).

9. R. Yoneda, S. Harusawa, and T. Kurihara, *Tetrahedron Lett.*, **30**, 3681 (1989).

10. R. A. Holton, and A. D. Williams, *J. Org. Chem.*, **53**, 5981 (1988).

11. Y. Nakamura, S. Takeuchi, Y. Ohgo, M. Yamaoka, A. Yoshida, and K. Mikami, *Tetrahedron*, **55**, 4595 (1999).

12. K. M. Specht, C. R. Harris, G. A. Molander, and D. Kahne, *Tetrahedron Lett.*, **40**, 1855 (1999).

13. R. J. Linderman, K. P. Cusack and W. R. Kwochka, *Tetrahedron Lett.*, **35**, 1477 (1994).

14. T. P. Ananthananarayan, T. Gallagher and P. Magnus, *J. Chem. Soc., Chem. Commun.*, 709 (**1982**).

15. S. Hanessian, and C. Girard, *Synlett.*, 861 (**1994**).

16. G. L. Georg, and Z. S. Cheruvallath, *J. Org. Chem.*, **59**, 4015 (1994).

17. G. I. Georg, G. C. B. Harriman, A. Datta, S. Ali, Z. Cheruvallath, D. Duut and D. G. Vander Velde, *J. Org. Chem.*, **63**, 8926 (1998).

18. L. A. Paquette, H.-L. Wang, Z. Su and M. Zhao, *J. Am. Chem. Soc.*, **120**, 5213 (1998).

19. J. D. White, E. G. Nolen Jr. and C.H. Miller, *J. Org. Chem.*, **51**, 1151 (1986).

20. G. A. Molander, and G. Hahn, *J. Org. Chem.*, **51**, 2596 (1986).

21. E. J. Enholm and J. A. Schreier, *J. Org. Chem.*, **60**, 1110 (1995).

22. G. A. Molander and C. del Pozo Losada, *J. Org. Chem.*, **62**, 2935 (1997).

23. A. Bartelts, P. G. Jones and J. Liebscher, *Tetrahedron: Asymmetry*, **6**, 1539 (1995).

24. T. K. Chakraborty and S. Dutta, *Tetrahedron Lett.*, **39**, 101 (1998).

25. K. Otsubo, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **28**, 4437 (1987).

26. J. Inanaga, *Rev. Heteroat. Chem.*, **3**, 75 (1990).

27. T. Mukaiyama, H. Arai and I. Shiina, *Chemistry Lett.*, 580 (**2000**).

28. G. A. Molander and C. del Pozo Losada, *Tetrahedron*, **54**, 5819 (1998).

29. G. A. Molander and J. Stengel, *J. Org. Chem.*, **60**, 6660 (1995).

30. G. A. Molander and P. J. Stengel, *Tetrahedron*, **53**, 8887 (1997).

31. N. H. Kawahata and M. Goodman, *Tetrahedron Lett.*, **40**, 2271 (1999).

32. D. V. Pratt, and P. B. Hopkins, *Tetrahedron Lett.*,**28**, 3065 (1987).

33. J. De Schrijver and P. J. De Clercq, *Tetrahedron Lett.*, **34**,4369 (1993).

34. J. M. Concellón, J. A. Pérez-Andrés and H. Rodriguez-Solla, *Angew. Chem. Int. Ed. Engl.*, **39**, 2773 (2000).

35. A. Chénedé, P. Pothier, M. Sollogoub, A.J. Fairbanks, and P. Sinaÿ, *J. Chem. Soc., Chem. Commun.*, 1373 (**1995**).

36. J. W. Huffman, W.-P. Liao and R. H. Wallace, *Tetrahedron Lett.*, **28**, 3315 (1987).

37. J. Inanaga, Y. Yokayama, Y. Handa and M. Yamaguchi, *Tetrahedron Lett.* 6371 (1991).

38. E. J. Enholm, S. Jiang, and K. Abboud, *J. Org. Chem.*, **58**, 4061 (1993) and references therein.

39. K. Kusuda, J. Inanaga and M. Yamaguchi, *Tetrahedron Lett.*, **30**, 2945 (1989).

40. E. J. Enholm, and S. Jiang, *Tetrahedron Lett.*, **33**, 313 (1992).

41. E. J. Enholm, and S. Jiang, *Heterocycles*, **34**, 2247 (1992).

42. E. J. Enholm, and S. Jiang, *Tetrahedron Lett.*, **33**, 6069 (1992).

43. J. Inanaga, J. Katsuki and M. Yamaguchi, *Chem. Lett.*, 1025 (**1991**).

44. B. V. Yang, and A. Massa, *J. Org. Chem.*, **61**, 5148 (1996).

45. A. B. Charette, and B. Côté, *J. Org. Chem.*, **58**, 933 (1993).

46. B. Brown, and L. S. Hegedus, *J. Org. Chem.*, **63**, 8012 (1998).

47. J. D. White and T.C. Somers, *J. Am. Chem. Soc.*, **109**, 4424 (1987).

48. S. Hanessian, C. Girard and J. L. Chiara, *Tetrahedron Lett.*, **33**, 573 (1992).

49. A. Yoshida and H. Takayama, *Tetrahedron Lett.*, **42**, 3603 (2001).

50. T. Honda, S. Yamane, K. Naito and Y. Suzuki, *Heterocycles*, **37**, 515 (1994).

51. T. Honda and F. Ishikawa, *J. Chem. Soc., Chem. Commun.*, 1065 (**1999**).

52. S. Farcas and J.-L. Namy, *Tetrahedron Lett.*, **41**, 7299 (2000).

53. S. Farcas and J.-L. Namy, *Tetrahedron Lett.*, **42**, 879 (2001).

54. Y. Arai, M. Matsui and T. Koizumi, *J. Chem. Soc., Perkin Trans. I*, 1233 (**1990**).

55. S. Hanessian, and C. Girard, *Synlett.*, 863 (**1994**).

56. A. R. Katritzky, M. Qi, D. Feng and D. A. Nichols, *J. Org. Chem.*, **62**, 4121 (1997).

57. A. R. Katritzky and M. Qi, *J. Org. Chem.*, **62**, 4116 (1997).

58. A. R. Katritzky, M. Qi and D. Feng, *J. Org. Chem.*, **63**, 6712 (1998).

59. J. M. Aurreoechea and A.Fernández-Acebes, *Tetrahedron Lett.*, **33**, 4763 (1992).

60. J. M. Aurrecoechea, A. Fernández-Acebes, J. M. Gorgojo and C. Saornil, *Tetrahedron*, **55**, 7345 (1999).

61. J. M. Aurrecoechea, B. Lopez, A. Fernández, A. Arrieta and F. P. Cossío, *J. Org. Chem.*, **62**, 1125 (1997).

62. J. M. Aurrecoechea and A. Fernández-Acebes, *Synth. Lett.*, 39 (**1996**).

63. H.-Y. Kang, A. N. Pae, Y.S. Cho, H. Y. Koh and B. Y. Chung, *J. Chem. Soc., Chem. Comm.*, 821 (**1997**).

64. B. M. Trost, J. B. Neilsen, and K. Hoogsteen, *J. Am. Chem. Soc.*, **114**, 5432 (1992).

65. L. M. Mikkelsen, S. L. Krintel, J. Jimenez-Barbero and T. Skrydstrup, *J. Chem. Soc., Chem. Commun.*, 2319 (**2000**).

66. O. Jarreton, T. Skrydstrup and J.-M. Beau, *J. Chem. Soc., Chem. Commun.*, 1661 (**1996**).

67. P. de Pouilly, A. Chénedé, J.-M. Mallet and P. Sinaÿ, *Tetrahedron Lett.*, **33**, 8065 (1992).

68. S. Hanessian, "*Total Synthesis of Natural Products: The 'Chiron' Approac*h", Vol. 3, Pergamon Press, Oxford, 1983.

69. D. Mazéas, T. Skrydstrup, O. Doumeix and J.-M. Beau, *Angew. Chem. Int. Ed. Engl.*, **33**, 1383 (1994).

70. D. Mazéas, T. Skrydstrup and J.-M. Beau, *Angew. Chem. Int. Ed. Engl.*, **34**, 909 (1995).

71. O. Jarreton, T. Skrydstrup and J.-M. Beau, *Tetrahedron Lett.*, **38**, 1767 (1997).

72. T. Skrydstrup, O. Jarreton, D. Mazéas, D. Urban and J.-M. Beau, *Chem. Eur. J.*, **4**, 655 (1998).

73. T. Skrydstrup, D. Mazéas, M. Elmouchir, G. Doisneau, C. Riche, A. Chiaroni and J.-M. Beau, *Chem. Eur. J.*, **3**, 1342 (1997).

74. D. Urban, T. Skrydstrup, C. Riche, A. Chiaroni and J.-M. Beau, *J. Chem. Soc., Chem. Commun.*, 1883 (**1996**).

75. I. R. Vlahov, P. I. Vlahova and R. I. Linhardt, *J. Am. Chem. Soc.*, **119**, 1480 (1997).

76. A. Chénedé, E. Perrin, E. D. Rekaï and P. Sinaÿ, *Synlett.*, 420 (**1994**).

77. O. Jarreton, T. Skrydstrup, J.-F. Espinosa, J. Jiménez-Barbero and J.-M. Beau, *Chem. Eur. J.*, **5**, 430 (1999).

78. S.-C. Hung and C.-H. Wong, *Angew. Chem. Int. Engl. Ed.*, **35**, 2671 (1996).

79. X. Jia, Y. Zhang, and X. Zhou, *Tetrahedron Lett.*, **35**, 8833 (1994).

80. F. D. Toste, F. LaRonde and I. W. J. Still, *Tetrahedron Lett.*, **36**, 2949 (1995).

81. I. W. J. Still and L. J. P. Martyn, *Synth. Commun.*, **28**, 913 (1998).

82. I. W. J. Still and F. D. Toste, *J. Org. Chem.*, **61**, 7677 (1996).

83. B. W. Yoo, H. S. Baek, S. R. Keum, C. M. Yoon, G. S. Nam, S.H. Kim and J. H. Kim, *Synth. Commun.*, **30**, 4317 (2000).

84. K. Hioki, K. Kono, S. Tani and M. Kunishima, *Tetrahedron Lett.*, **39**, 5229 (1998).

85. D. Nakata, C. Kusaka, S. Tani and M. Kunishima, *Tetrahedron Lett.*, **42**, 415 (2001).

86. S. V. Ley, R. Downham, P.J. Edwards, J.E. Innes and M. Woods, *Contemp. Org. Synth.*, **2**, 365 (1995).

87. D. Lainé, M. Fujita and S.V. Ley, *J. Chem. Soc., Perkin Trans. I*, 1639 (**1999**).

88. G. A. Molander, B. E. La Belle and G. Hahn, *J. Org. Chem.*, **51**, 5253 (1986).

89. J. M. Schkeryantz and S. J. Danishefsky, *J. Am. Chem. Soc.*, **117**, 4722 (1995).

90. S.-K. Cang, S.-G. Kim, D.-C. Park, J.-S. Lee, W.-J. Yoo, and C. S. Pak, *J. Chem. Soc., Perkin Trans. I*, 9, (**1993**).

91. S.-K. Kang, S.-G. Kim, D.-G. Cho and J.-H. Jeon, *Synth. Commun.*, **23**, 681 (1993).

92. T. Kan, S. Hosokawa, S. Nara, M. Oikawa, S. Ito, F. Matsuda and H. Shirahama, *J. Org. Chem.*, **59**, 5532 (1994).

93. Kan, T., Nara, S., Ito, S., Matsuda, F. and Shirahama, H., *J. Org. Chem.*, **59**, 5111 (1994).

94. G. A. Molander, and S. R. Shakya, *J. Org. Chem.*, **61**, 5885 (1996).

95. T. Tanaka, R. Wakayama, S.-I. Maedea, H. Mikamiyama. N. Maezaki and H. Ohno, *J. Chem. Soc., Chem. Commun.*, 1287 (**2000**).

96. a. H. Nagaoka, K. Shibuya and Y. Yamada, *Tetrahedron Lett.*, **34**, 1501 (1993). b. H. Nagaoka, K. Shibuya and Y. Yamada, *Tetrahedron*, **50**, 661 (1994).

97. J. Clayden, and M. Julia, *J. Chem. Soc., Chem. Commun.*, 2261 (1994).

98. C. W. Holzapfel and D. B. G. Williams, *Tetrahedron*, **51**, 8555 (1995).

99. A. Ogawa, N. Takami, M. Sekiguchi, I. Ryu, N. Kambe and N. Sonoda, *J. Am. Chem. Soc.*, **114**, 8729 (1992).

100. S-J. Jong, J-M. Fang and C-H. Lin, *J. Organomet. Chem.*, **590**, 42 (1999).

101. G. A. Molander and J. A. McKie,. *J. Am. Chem. Soc.*, **115**, 5821 (1993).

102. G. Molle, and P. Bauer, *J. Am. Chem. Soc.*, **104**, 3481 (1982).

103. G. A. Molander and J. A. McKie, *J. Org. Chem.*, **56**, 4112 (1991).

104. G. A. Molander and J. A. McKie, *J. Org. Chem.*, **58**, 7216 (1993).

105. T. Kataoka, T. Iwama, H. Shimizu and M. Hori, *Phosphorus, Sulfur and Silicon*, **67**, 169 (1992).

106. H. Shimizu, S. Miyazaki, T. Kataoka and M. Hori, *J. Chem. Soc., Perkin Trans. I*, 1583 (**1995**).

107. Y. Kato and T. Mase, *Tetrahedron Lett.*, **40**, 8823 (1999).

108. J. E. McMurry, *Chem. Rev.*, **89**, 1513 (1989).

109. B. E. Maryanoff and A.B. Reitz, *Chem. Rev.*, **89**, 863 (1989).

110. R. R. Schrock, *J. Organomet. Chem.*, **300**, 249 (1986).

111. M. Julia and J.-M. Paris, *Tetrahedron Lett.*, **14**, 4833 (1973).

112. M. Ihara, S. Suzuki, T. Taniguchi, Y. Tokunaga, and K. Fukumoto, *Synlett.*, 859 (**1994**).

113. M. Ihara, S. Suzuki, T. Taniguchi, Y. Tokunaga, and K. Fukumoto, *Tetrahedron*, **51**, 9873 (1995).

114. A. S. Kende and J. S. Mendoza, *Tetrahedron Lett.*, **31**,7105 (1990).

115. G. E. Keck, K. A. Savin and M.A. Weglarz, *J. Org. Chem.*, **60**, 3194 (1995).

116. I. E. Markó, F. Murphy and S. Dolan, *Tetrahedron Lett.*, **37**, 2089 (1996).

117. I. E. Markó, F. Murphy, L. Kumps, A. Ates, R. Touillaux, D. Craig, S. Carballares and S. Dolan, *Tetrahedron*, **57**, 2609 (2001).

118. K. J. Shea, *Tetrahedron*, **36**, 1683 (1980).

119. P. de Pouilly, A. Chénedé, J.-M. Mallet and P. Sinaÿ, *Bull. Soc. Chim. Fr.*, **130**, 256 (1993).

120. H. Kunzer, M. Stahnke, G. Sauer and R. Wiechert, *Tetrahedron Lett.*, **32**, 1949 (1991).

121. G. Doisneau and J.-M. Beau, *Tetrahedron Lett.*, **39**, 3477 (1998).

122. S. M. Bennett, R. K. Biboutou, Z. Zhou and R. Pion, *Tetrahedron*, **54**, 4761 (1998).

123. J. M. Concellón, P. L. Bernad and J. A. Pérez-Andrés, *Angew. Chem. Int. Ed. Engl.*, **38**, 2384 (1999).

124. M. Matsukawa, T. Tabuchi, J. Inanaga and M. Yamaguchi, *Chem. Lett.*, 2101 (**1987**).

125. T. Imamoto, T. Takeyama and H. Koto, *Tetrahedron Lett.*, **27**, 3243 (1986).

126. H. S. Park, S. H. Chong and Y. H. Kim, *Synlett.*, 1073 (**1998**).

127. L. Crombie and L.J. Rainbow, *Tetrahedron Lett.*, **29**, 6517 (1988).

128. L. Crombie and L. J. Rainbow, *J. Chem. Soc., Perkin Trans. I*, 673 (**1994**).

129. C. Exon, T. Gallagher and P. Magnus, *J. Am. Chem. Soc.*, **105**, 4739 (1983).

130. D. A. Evans, S.W. Kaldor, T. K. Jones, J. Clardy and T. J. Stout, *J. Am. Chem. Soc.*, **112**, 7001 (1990).

131. A. J. Pearson and K. Lee, *J. Org. Chem.*, **59**, 2257 (1994).

132. Z. Zhou, and S. M. Bennett, *Tetrahedron Lett.*, **38**, 1153 (1997).

133. G. A. Molander and C. R. Harris, *J. Org. Chem.*, **63**, 812 (1998).

134. G. A. Molander and C. R. Harris, *J. Org. Chem.*, **63**, 4374 (1998).

135. G. A. Molander, J. C. McWilliams, and B. C. Noll, *J. Am. Chem. Soc.*, **119**, 1265 (1997).

136. M. Hojo, H. Harada, J. Yoshizawa, and A. Hosomi, *J. Org. Chem.*, **58**, 6541 (1993).

137. J. L. Chiara, S. Martínez, and M. Bernabé, *J. Org. Chem.*, **61**, 6488 (1996).

138. D. J. Jenkins, A. M. Riley and B. V. L. Potter, *J. Org. Chem.*, **61**, 7719 (1996).

139. J. J. C. Grové, C. W. Holzapfel and D. B. G. Williams, *Tetrahedron Lett.*, **37**, 5817 (1996).

140. J. J. C. Grové, and C. W. Holzapfel, *Carbohydrate Lett.*, **2**, 329 (1997).

141. J. J. C. Grové, C. W. Holzapfel and D. B. G. Williams, *Tetrahedron Lett.*, **37**, 1305 (1996).

142. T. L Fevig, R. L. Elliott and D. P. Curran, *J. Am. Chem. Soc.* **110**, 5064 (1988).

143. T. Kan, S. Nara, T. Ozawa, H. Shirahama and F. Matsuda, *Angew. Chem. Int. Ed.*, **39**, 355 (2000).

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