Samarium enolates and their application in organic synthesis

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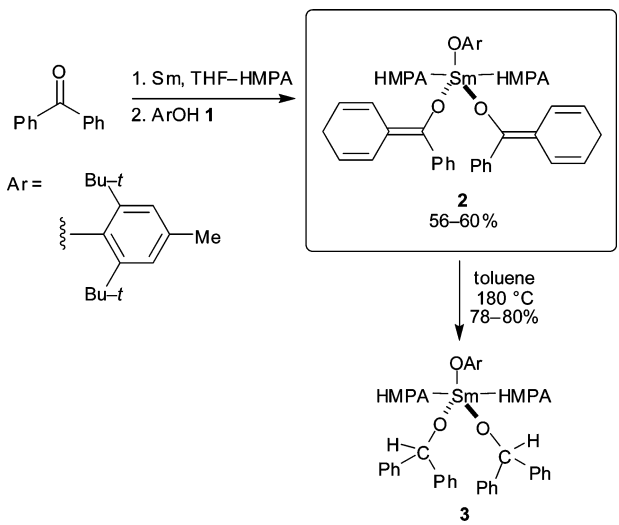
1. Samarium enolates—an introduction

Metal enolates are amongst the most important organometallic species in synthetic chemistry. The generation of lithium enolates, for example, using strong lithium amide bases and reaction with carbon electrophiles represents a cornerstone of synthetic organic chemistry. Whereas the chemistry of many metal enolates is well understood and extensive structural studies have been undertaken, the chemistry of lanthanide enolates is a little studied area. Over the past 25 years, the widespread use of samarium(II) iodide (SmI_2) in organic synthesis[1–3] has brought the chemistry of samarium enolates to the fore as many processes using the popular reducing agent involve the formation and reaction of these organometallic species.

This review will discuss the role that samarium enolates play in organic synthesis drawing on illustrative examples from the recent literature. In the majority of cases, enolates are directly or indirectly formed by the reaction of substrates with SmI_2; a brief introduction to the reagent is therefore given in the following section. The remainder of the review is organised according to the method used to generate the samarium enolate with a section dedicated to the asymmetric protonation of samarium enolates. In recent years, samarium enolates have begun to find application in solution and solid-supported polymer synthesis. This area lies beyond the scope of this article and has recently been reviewed.[4]

One of the few structural studies on a samarium enolate was reported by Hou in 1994.[5] The reaction of a samarium-benzophenone dianion species with bulky phenol **1** led to protonation of the dianion species at the *para*-position of the aromatic ring to give the samarium(III) enolate complex **2** (Scheme 1). An X-ray crystallographic



Scheme 1

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study revealed that this complex possessed a trigonal bipyramid structure with one aryloxy substituent and two benzophenone moieties equatorial and two HMPA ligands at the apical vertices. When heated in toluene overnight, **2** isomerised to samarium complex **3** (Scheme 1).[5]

2. Samarium(II) iodide in organic synthesis

The first applications of the single electron transfer reagent SmI_2 in organic synthesis were reported by Kagan in 1977.[6] In his seminal study, Kagan carried out a thorough investigation of the organic transformations that could be performed using the reagent.[7] The reagent now enjoys a privileged status amongst reducing agents for synthetic organic chemistry.[1–3]

Due to the reagent's inclination to revert to the more stable samarium(III) oxidation state, it operates as a single electron donor. This property enables SmI_2 to mediate both radical and anionic processes or, most commonly, a combination of the two. The reagent has been used for a wide range of synthetic organic transformations such as functional group interconversions, inter- and intramolecular carbon–carbon bond-forming reactions and powerful cascade reactions that can rapidly increase molecular complexity. The popularity of SmI_2 in part arises from its ability to carry out transformations in a highly chemoselective and stereoselective manner. Added to this, the reactivity and selectivity of the reagent can be modified through the use of co-solvents or additives, thus increasing the scope of this already versatile reagent.[8]

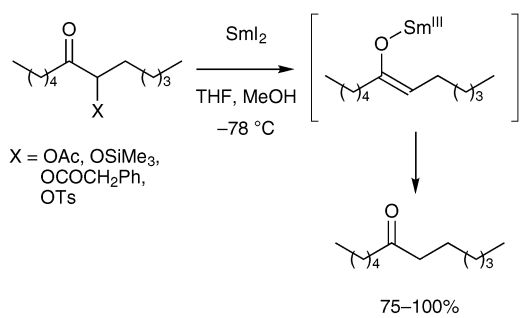
The mechanisms of many SmI_2-mediated organic reactions proceed *via* samarium enolates. Understanding and harnessing the reactivity of these organometallic intermediates is vital to the success of many known transformations and to the future development of powerful, new synthetic procedures.

3. The formation and use of samarium enolates

3.1 Reduction of α-heteroatom substituted carbonyl compounds

The reduction of α-heteroatom substituted carbonyl compounds is an important transformation in organic synthesis. When the reaction is carried out using SmI_2 this transformation provides a simple route to samarium enolates.

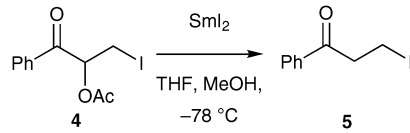
Although the reduction of α-bromoesters was reported by Kagan in 1980,[7] the first detailed study of the reduction of α-heteroatom substituted ketones with SmI_2 was carried out by Molander in 1986.[9] The reduction of a range of α-oxygenated ketones with SmI_2 was found to give the parent ketones in good yield (Scheme 2). Molander proposed the intermediacy of samarium enolates or enols that were protonated by the MeOH co-solvent.[9]



Scheme 2

In order to explore the chemoselectivity of the reaction, α-acetoxy ketone **4** possessing a primary iodide group was treated with the reagent.[9] Chemoselective

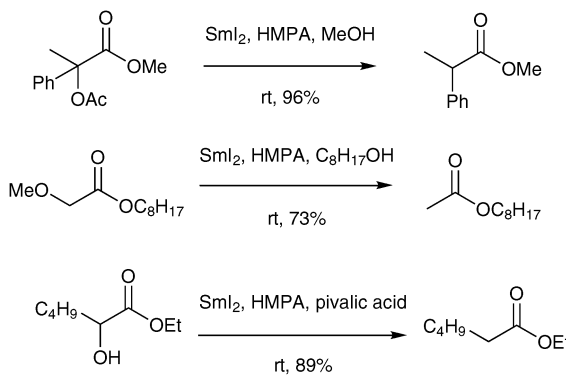
reduction of the α-acetoxy group was observed in the presence of the iodide. Surprisingly, no elimination of iodide from the presumed samarium enolate intermediate was observed and **5** was obtained in good yield. This suggests that either protonation of the enolate intermediate by the MeOH co-solvent is fast, or that an alternative mechanism is in operation for the reduction of aryl ketone **4** (Scheme 3).[9]



Scheme 3

Molander also found that α-halo, α-sulfanyl, α-sulfinyl and α-sulfonyl cyclohexanones underwent smooth reduction with SmI_2 to give cyclohexanone in good yield.[9]

In 1989 Inanaga investigated the reduction of a range of α-oxygenated esters.[10] Deoxygenation of both α-acetoxy and α-methoxy esters proceeded well at room temperature using HMPA to increase the reduction potential of SmI_2. Inanaga found that the use of a more acidic proton source was required for the reduction of α-hydroxyesters (Scheme 4).

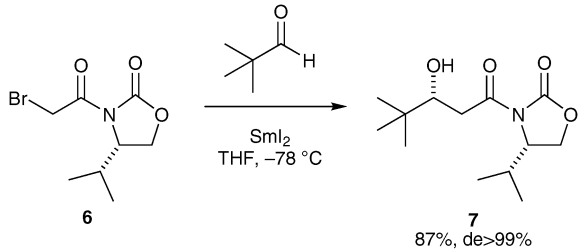


Scheme 4

In contrast, the reduction of α-heteroatom substituted amides with SmI_2 has only recently been studied by Simpkins.[11]

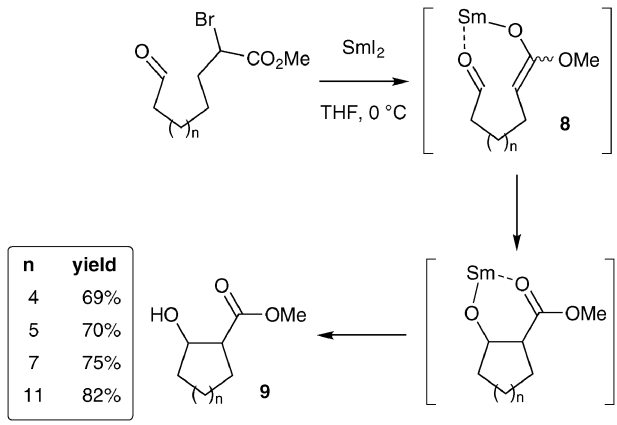
The following sections discuss the use of samarium enolates generated from a range of α-heteroatom substituted substrates.

3.1.1 Samarium enolates from the reduction of α-halo carbonyl compounds. In 1980 Kagan reported the coupling of ethyl α-bromopropionate with cyclohexanone using SmI_2. This was the first example of a samarium Reformatsky-type reaction.[7] Analogous asymmetric, samarium Reformatsky reactions of chiral 3-bromoacetyl-2-oxazolidinones have been described by Fukuzawa.[12] For example, reduction of **6** with SmI_2 generates a samarium enolate that then reacts with pivalaldehyde to give the α-unbranched β-hydroxy carboximide **7** in 87% yield and in high diastereomeric excess (Scheme 5). The reaction is synthetically noteworthy as highly diastereoselective acetate aldol processes are difficult to achieve. The samarium(III) ion is presumed to play an important role in the transition state of the reaction leading to high diastereoselectivity.[12]



Scheme 5

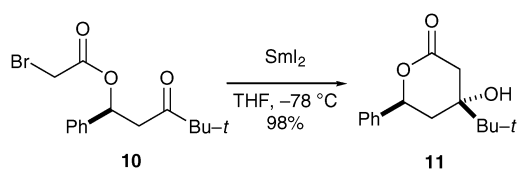
In 1986 Inanaga reported the construction of medium and large ring lactones using SmI_2-mediated *intramolecular* Reformatsky reactions.[13] In 1991 Inanaga then developed a general synthesis of medium and large carbocycles by means of the Reformatsky reaction.[14] The cyclisation of the samarium enolate intermediates **8** to give carbocycles **9** is believed to be aided by the large ionic radius, flexible co-ordination and high oxophilicity of samarium (Scheme 6).



n	yield
4	69%
5	70%
7	75%
11	82%

Scheme 6

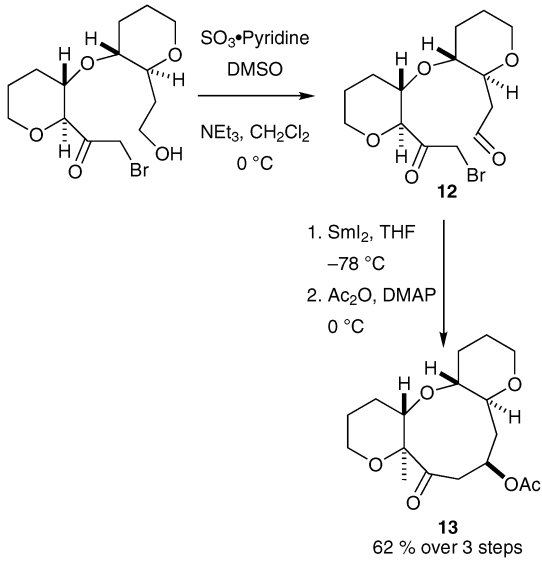
In 1991 Molander investigated the diastereoselectivity of SmI_2-mediated Reformatsky-type cyclisations and found that they often proceed with high levels of selectivity.[15] For example, treatment of α-bromo ester **10** with SmI_2 gave lactone **11** in 98% yield and as a single diastereoisomer (Scheme 7).



Scheme 7

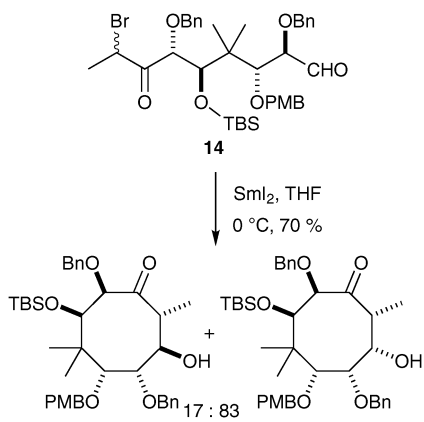
The SmI_2-mediated Reformatsky reaction has since been used as a key ring forming step in the synthesis of a number of natural products and their precursors. In 1997 Tachibana reported the use of SmI_2 in the formation of the fused oxonene

ring F of ciguatoxin.[16] The samarium enolate derived from α-bromoketone **12** underwent efficient cyclisation to give **13** in good yield after acetylation of the Refomatsky product (Scheme 8).



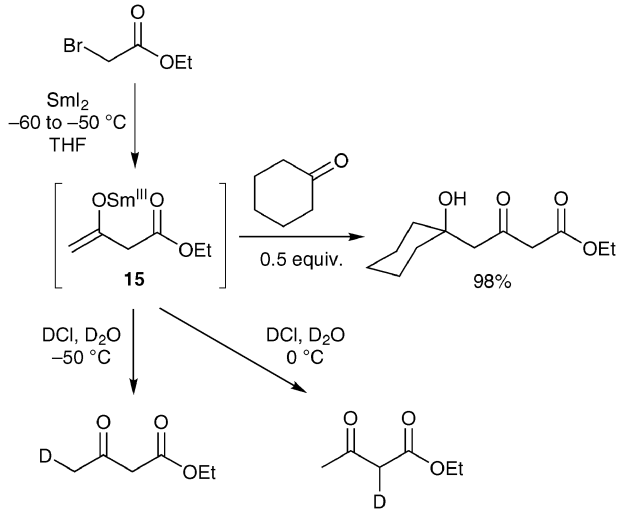
Scheme 8

Mukaiyama reported the use of SmI_2-mediated Reformatsky cyclisations in a programme that culminated in an impressive total synthesis of Taxol.[17,18] α-Bromoketone **14** underwent efficient cyclisation on treatment with SmI_2 to give the eight-membered B ring of the target in high yield and with good stereoselectivity (Scheme 9).



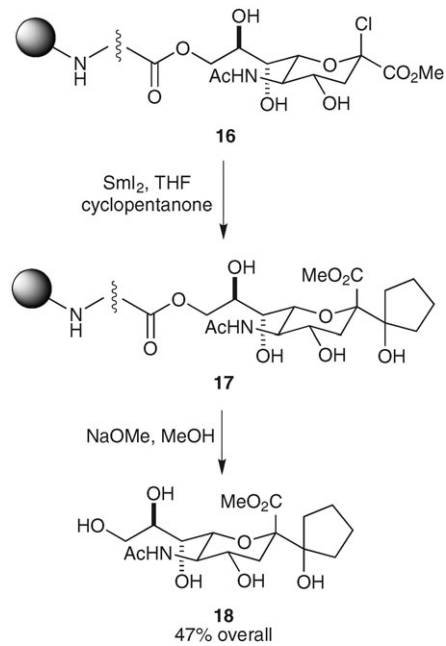
Scheme 9

Utimoto and Matsubara have generated samarium enolates, such as **15**, from α-bromoesters using SmI_2 and have found they undergo efficient aldol reactions.[19] Quenching the samarium enolates with DCl in D_2O shows the enolates are stable at −50 °C but isomerise to the more stable enolate on warming (Scheme 10). The use of two different α-haloesters allows access to more complex samarium enolates before quenching with benzaldehyde.[19]



Scheme 10

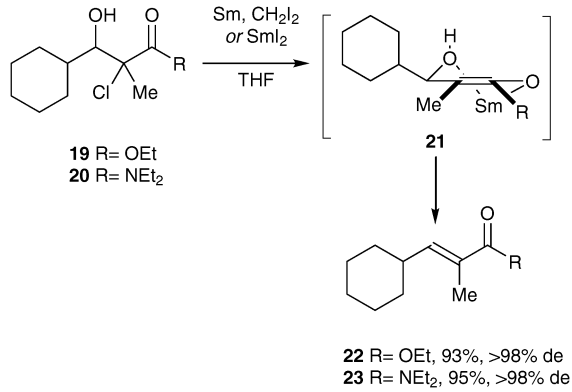
Linhardt has employed samarium enolate-aldol reactions in a solid phase synthesis of *C*-sialosides.[20] Sialyl donor **16**, immobilised on an amino-functionalised, controlled pore glass support, was treated with SmI_2 in the presence of ketone and aldehyde electrophiles, *e.g.* reaction of **16** with cyclopentanone gave adduct **17** (Scheme 11). Cleavage from the support gave *C*-glycoside **18** in good overall yield.[20]



Scheme 11

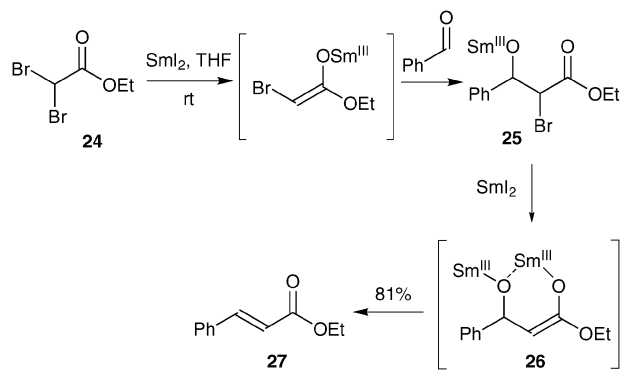
Concellón has reported a highly diastereoselective transformation of α-halo-β-hydroxy esters[21] and amides,[22] such as **19** and **20**, to *E*-α,β-unsaturated esters and amides **22** and **23** using SmI_2. Following two electron transfers, a samarium enolate

21 is formed which then undergoes elimination. The diastereoselectivity of the elimination has been explained by the intermediate samarium enolate **21** eliminating through a six-membered chelate (Scheme 12).[21,22]



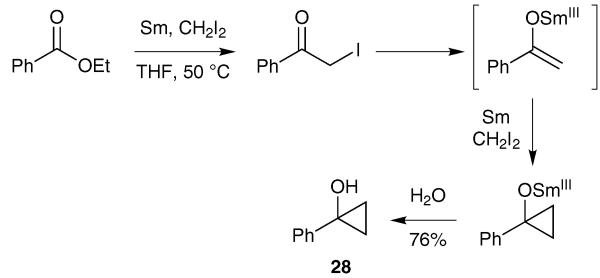
Scheme 12

A similar process involving α-dichlorosubstituted carbonyl compounds has been used to construct (*Z*)-α-chloro-α,β-unsaturated esters.[23] More recently, Concellón has reported a stereoselective method for the formation of (*E*)-α,β-unsaturated esters *via* a sequential samarium enolate-aldol reaction followed by an elimination.[24] For example, ethyl dibromoacetate **24** reacts with benzaldehyde to form samarium alkoxide **25** which is reduced to give samarium enolate **26**. Elimination then affords (*E*)-α,β-unsaturated ester **27** in good yield (Scheme 13).



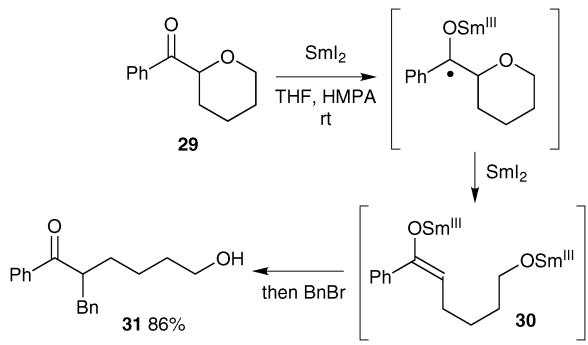
Scheme 13

Imamoto has reported the one-pot synthesis of cyclopropanols from carboxylic acid derivatives using samarium and diiodomethane.[25] The reaction proceeds *via* the preparation of an α-iodoketone, samarium enolate formation and cyclopropanation of the samarium enolate with a second equivalent of diiodomethane and samarium (Scheme 14). In the case of ethyl benzoate, cyclopropanol **28** is obtained in 76% yield. The use of other lanthanide metals led to unsatisfactory results.[25]



Scheme 14

3.1.2 Samarium enolates from the reduction of α-oxygenated carbonyl compounds. In 1995 Enholm reported the reductive cleavage of tetrahydropyrans bearing an α-ketone group.[26] Tetrahydropyran **29** was treated with SmI_2 and HMPA to produce the samarium ketyl-radical anion before a second equivalent of reagent generated the samarium enolate **30**. The enolate was then quenched with benzyl bromide to afford the alkylated product **31** in good yield (Scheme 15).[26]

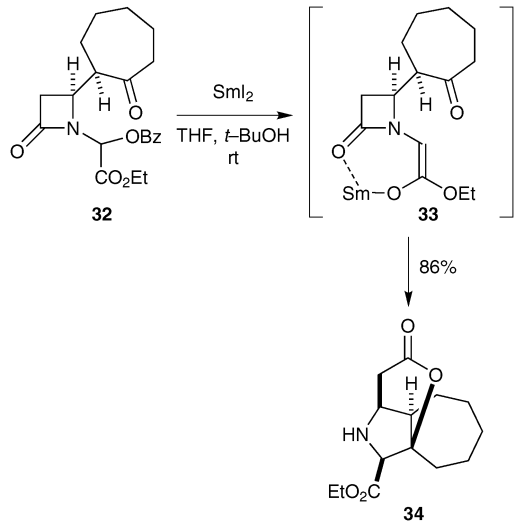


Scheme 15

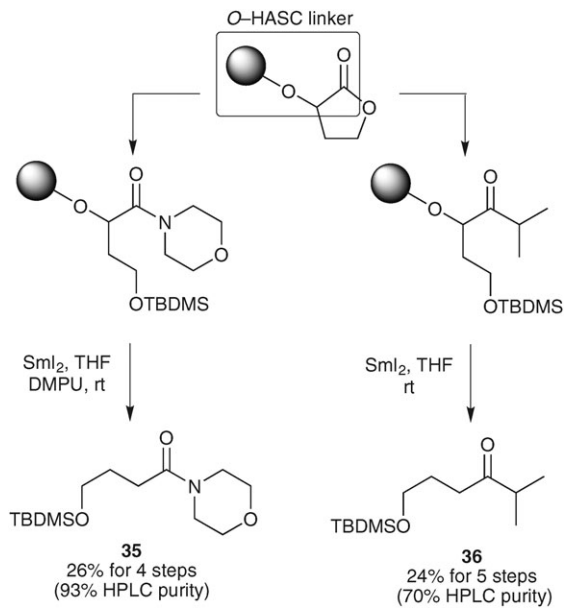
In 2002 Skrydstrup reported the diastereoselective construction of functionalised prolines by a samarium enolate-aldol cyclisation.[27] Treatment of β-lactam-derived α-benzoyloxy esters, such as **32**, with SmI_2 led to the generation of a samarium enolate **33**, aldol cyclisation and addition of the resultant samarium alkoxide to the β-lactam carbonyl. The efficient sequential reaction gave proline derivatives, such as **34**, with high diastereoselectivity and in good yield (Scheme 16).[27]

Procter has developed a linker system for use in phase tag-assisted synthesis based on the reduction of α-heteroatom substituted carbonyl compounds using SmI_2.[28] The linker has been refered to as a HASC linker (α-heteroatom substituted carbonyl linker). In 2002 an ether HASC linker was used to attach substrates to a polymer support and a solid-phase synthesis of ketones and amides, including **35** and **36**, was undertaken to assess the feasibility of the approach. α-Bromo-γ-butyrolactone was immobilised using the linker system and modified to give a range of polymer-supported amides and ketones. At the end of the sequence, traceless cleavage of the HASC linker using SmI_2 released amides and ketones from the solid support in good yields and purity (Scheme 17).[28]

Cleavage of the HASC linker with SmI_2 releases a samarium enolate into solution which is then protonated. As part of their preliminary study, Procter and co-workers carried out model studies evaluating the possibility of trapping the samarium enolate formed on cleavage with carbon electrophiles.[29] Using ketone **37** as a model for an



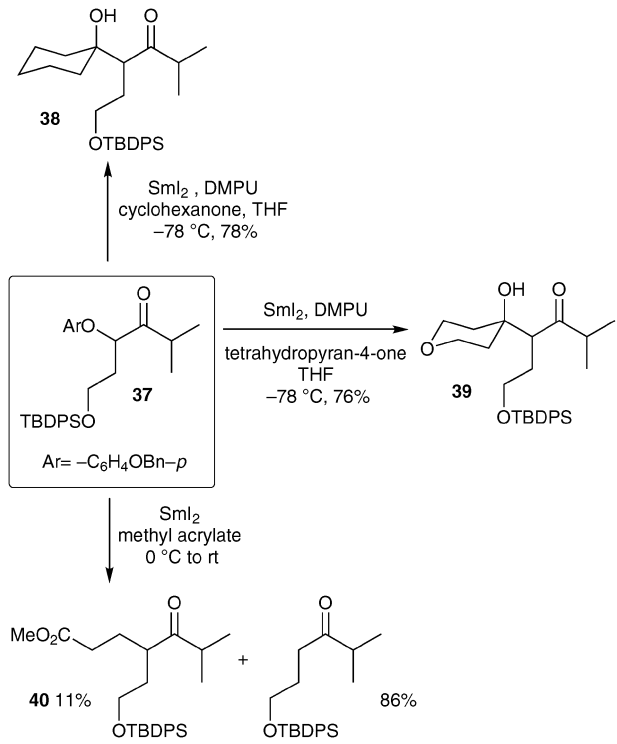
Scheme 16



Scheme 17

immobilised ketone, reduction in the presence of cyclohexanone and tetrahydropyran-4-one resulted in efficient samarium enolate-aldol reactions to give **38** and **39**, resepectively. An attempted samarium enolate-Michael process was less successful and gave the expected adduct **40** in low yield (Scheme 18).[29]

Unfortunately, attempts to trap the samarium enolate formed by the cleavage of a linkage to a polymer support was unsuccessful. It was proposed that residual proton sources contaminating the polymer support led to protonation of the samarium enolate prior to reaction with the carbon electrophile.[29]



Scheme 18

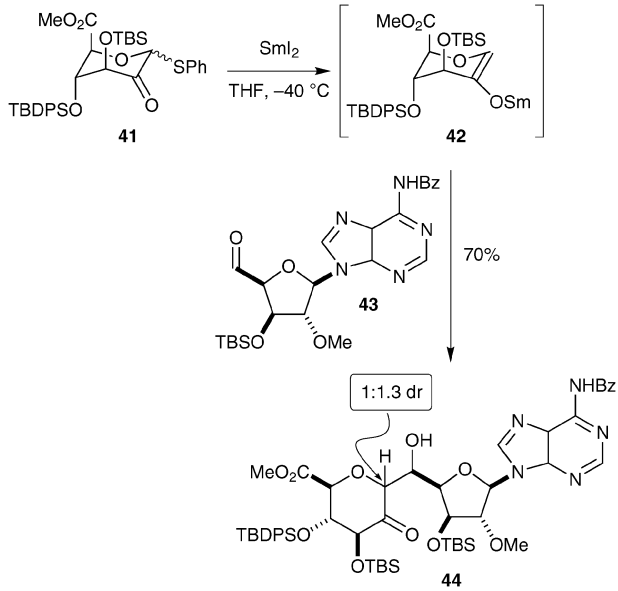
3.1.3 Samarium enolates from the reduction of α-sulfanyl and selenanyl carbonyl compounds. In 1999 Matsuda utilised an intermolecular samarium enolate-aldol reaction in the first synthesis of herbicidin B.[30] The enolate **42** was generated by the reduction of glycosylsulfide **41** with SmI_2. When TLC showed the reduction to be complete, oxygen was passed through the reaction mixture to destroy excess SmI_2 before the addition of aldehyde **43**. Aldol adduct **44** was obtained in high yield and as a mixture of diastereoisomers (Scheme 19).

In 2000 Skrydstrup utilised samarium enolates in a selective method for the introduction of carbinol side chains into glycine residues in peptides and showed the potential of this approach for peptide library synthesis.[31] The chemoselectivity of SmI_2 and the low basicity of the resultant samarium enolate species makes the lanthanide reagent ideal for this application. Treatment of α-pridylsulfide tripeptide **45** with SmI_2 at room temperature gave samarium enolate **46** that underwent aldol reaction with cyclohexanone to give modified peptide **47** in good yield (Scheme 20).

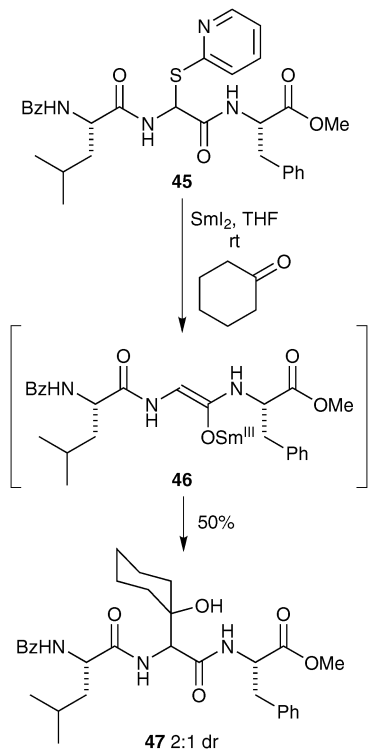
In 2002 Shuto and Matsuda utilised a samarium enolate-aldol reaction to construct 1′α-branched uridine derivatives.[32] Reaction of the samarium enolate formed by the reduction of selenide **48** with benzaldehyde proceeded with high stereoselectivity to give **49** (Scheme 21).

Samarium enolates can also react with electrophiles on oxygen. In Overman's 2001 total synthesis of Shahamin K, a samarium enolate was generated from the reduction of α-phenylsulfonyl ketone **50** and the enolate trapped to give enol acetate **51** by the addition of Ac_2O and DMAP (Scheme 22).[33]

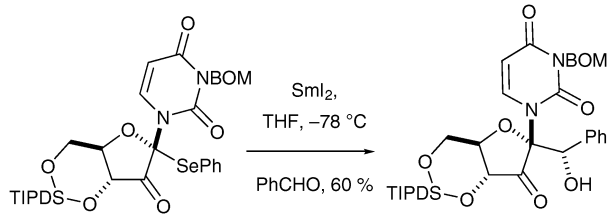
Procter and co-workers have utilised a sulfur version of their HASC linker system for the solid phase synthesis of oxindoles[34] and tetrahydroquinolones[35] using SmI_2 to cleave the linker. The samarium enolates formed by cleavage of the linker have



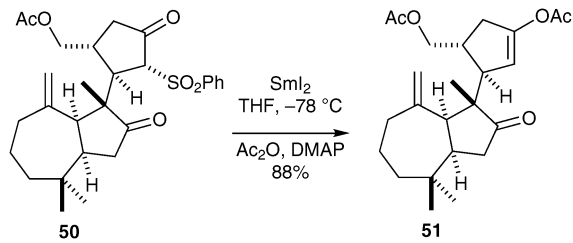
Scheme 19



Scheme 20

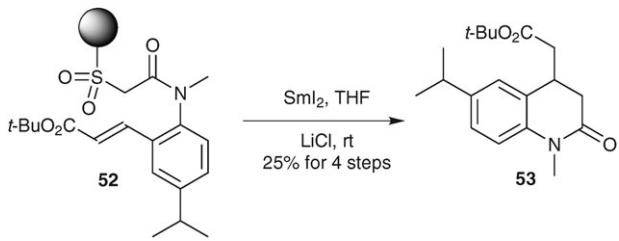


Scheme 21



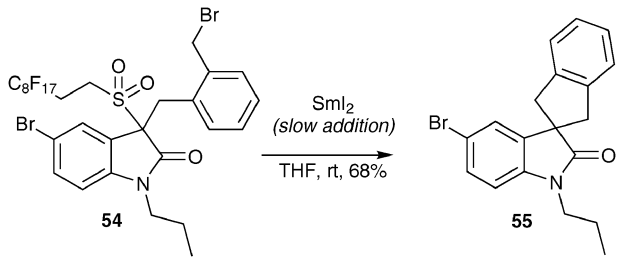
Scheme 22

been utilised, for example, cleavage of the sulfone linkage in **52** results in release of an enolate from the support and cyclisation to give tetrahydroquinolone **53** (Scheme 23).[35,36]



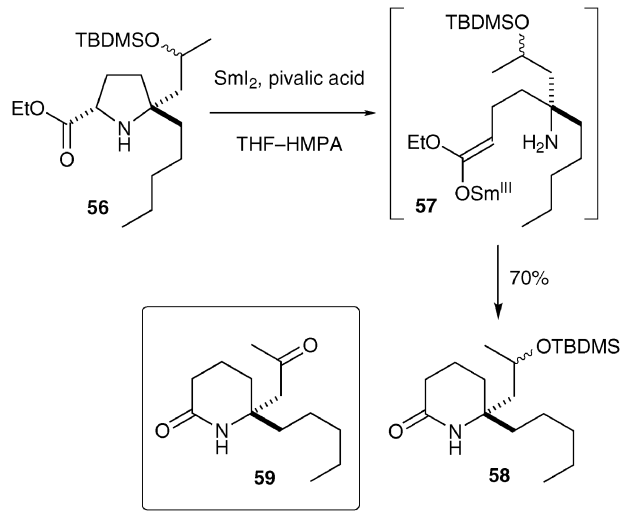
Scheme 23

An analogous sulfur HASC linker system has been utilised by Procter and co-workers for the fluorous synthesis of a range of *N*-heterocycles.[37] Again, the samarium enolate formed on cleavage of the linker can be exploited, for example, removal of the fluorous tag from oxindole **54** generates an enolate that undergoes alkylation in a cleavage-cyclisation sequence to give spirocyclic oxindole **55** (Scheme 24).[38]



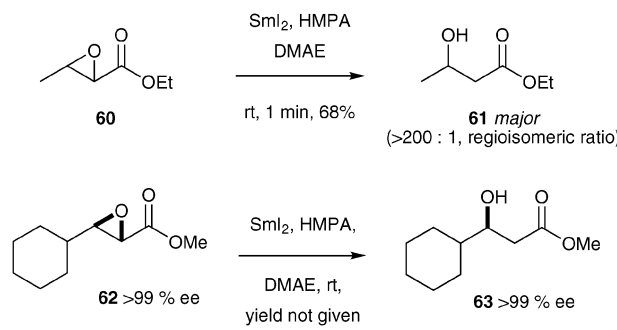
Scheme 24

3.1.4 Samarium enolates from the reduction of α-amino carbonyl compounds. In 1999 Honda reported that α-aminocarbonyl compounds can be reduced using SmI_2 in the presence of HMPA and a proton source.[39] Honda has applied this deamination process to proline derivatives and to the synthesis of a number of naturally occurring alkaloids including a concise enantioselective synthesis of (–)-adalinine **59**, a coccinellied alkaloid.[40] Treatment of **56** with SmI_2 in the presence of pivalic acid leads to generation of samarium enolate intermediate **57** (Scheme 25). Protonation and lactam formation gives **58**, an intermediate *en route* to (–)-adalinine **59**.[40]



Scheme 25

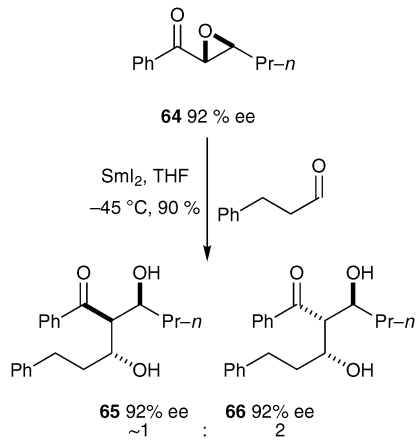
3.1.5 Samarium enolates from the reduction of epoxides and aziridines. In 1987 Inanaga investigated the opening of α,β-epoxy esters.[41] The reduction of ethyl 2,3-epoxybutyrate **60** to ethyl 3-hydroxybutyrate **61** using SmI_2 was found to be accelerated by the addition of HMPA and the yield increased greatly when a proton source was added. The presence of a strong chelating agent such as *N*,*N*-dimethylaminoethanol (DMAE) was crucial in attaining a high level of regioselectivity (Scheme 26). Inanaga surmises that the additive DMAE not only acts as a proton source, but also sequesters the Lewis acidic samarium(III) species thus preventing non-regioselective opening of the epoxide.[41] Using the optimised conditions, Inanaga converted enantiomerically pure α,β-epoxy ester **62** to β-hydroxy ester **63** with complete retention of configuration at the β-carbon (Scheme 26).



Scheme 26

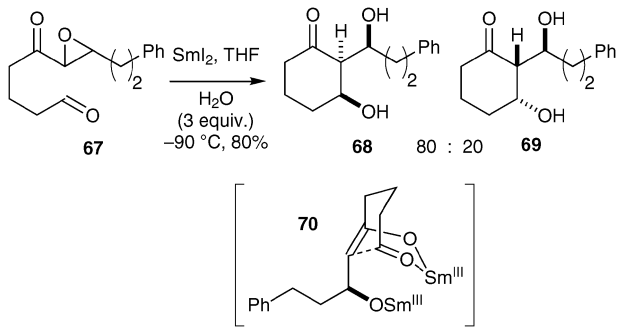
Concellón described a similar reduction of α,β-epoxy esters[42] and amides[43] that led to the formation of (*E*)-α,β-unsaturated esters and amides with high diastereoselectivity. The reaction proceeds by samarium enolate formation and elimination.[42,43]

Mukaiyama has investigated the use of samarium enolates generated from oxiranyl carbonyl compounds in aldol reactions. In 2000 the group developed a method for the synthesis of unsymmetrical *bis*-aldols using a SmI_2-mediated reaction between aldehydes and aryl or alkyl oxiranyl ketones (Scheme 27).[44] Only the *syn*,*syn* **65** and *anti*,*anti* **66** *bis*-aldols were obtained from the reaction of epoxide **64**.



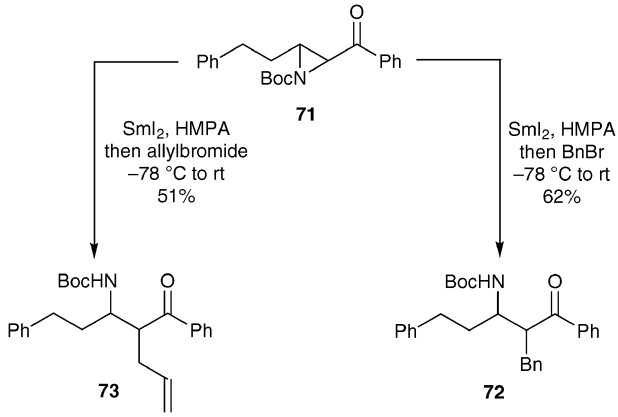
Scheme 27

Mukaiyama has also reported an intramolecular variant of this aldol process.[45] Treatment of epoxide **67** with SmI_2 leads to samarium enolate generation and aldol cyclisation to give diastereoisomeric products **68** and **69** (Scheme 28). The major product diastereoisomer is thought to be formed *via* transition structure **70**.[45]



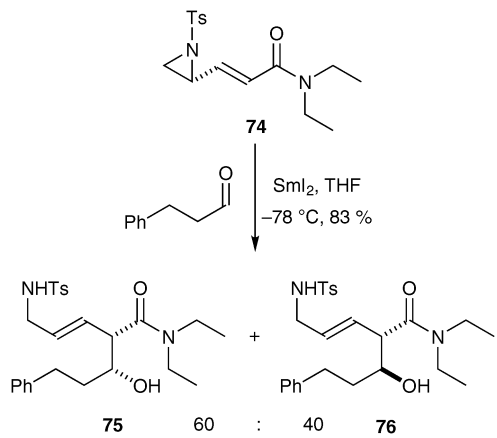
Scheme 28

In 1997 Molander described the preparation of β-amino carbonyl compounds by the reduction of 2-acylaziridines and alkylation of intermediate samarium enolates.[46] Phenyl ketone **71** was reduced using SmI_2 to give an enolate that could be alkylated using benzyl or allyl bromide affording the substituted β-amino ketones **72** and **73**, respectively, in moderate yield and as a mixture of diastereoisomers (Scheme 29).[46]



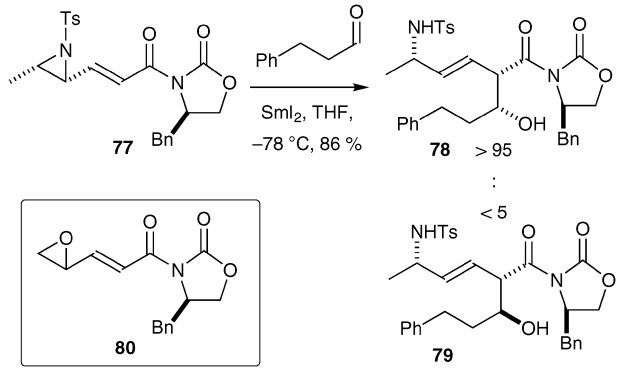
Scheme 29

In 2004 Mukaiyama investigated the synthesis of β-amino-β′-hydroxy ketones using samarium-enolate aldol reactions between aldehydes and enolates derived from aziridinyl ketones.[47] Mukaiyama also examined the construction of δ-amino-β′-hydroxy-β,γ-unsaturated carbonyl compounds, such as **75** and **76**, using the samarium enolate-aldol reaction of aldehydes and γ,δ-aziridinyl-α,β-unsaturated carbonyl compounds **74** (Scheme 30).[48] He found that the reaction was successful for both esters and amides giving good yields and high selectivity.



Scheme 30

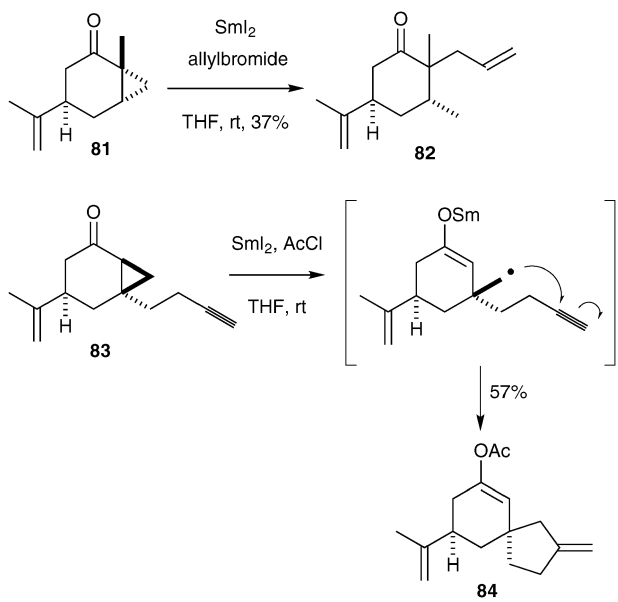
Most noteworthy was the development of an asymmetric samarium enolate-aldol process using an unsaturated aziridine bearing an Evans oxazolidinone auxiliary. For example, on treatment with SmI_2, aziridine **77** underwent smooth ring-opening, enolate formation and a highly *syn* diastereoselective aldol process to give diastereoisomers **78** and **79** in good yield (Scheme 31). Mukaiyama used epoxide **80** in an analogous asymmetric samarium enolate-aldol process to construct the C11–C17 fragment of mycinolide IV.[49]



Scheme 31

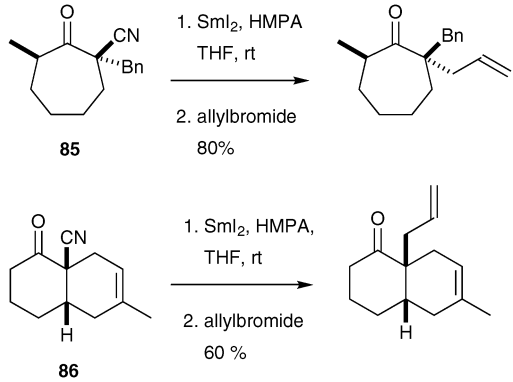
3.2 Samarium enolates from the cleavage of C–C bonds

Samarium enolates can also be formed by the SmI_2-mediated cleavage of carbon–carbon bonds. In 1991 Motherwell used the reagent to generate samarium enolates from cyclopropyl ketones.[50] The samarium enolates formed in this way could be trapped with allyl bromide—for example, the formation of **82** from **81**—acetyl chloride, and silylhalides. Of particular interest is the reaction of cyclopropyl ketone **83** with SmI_2 which triggers a radical cyclisation, concomitant enolate formation, and trapping to give enol acetate **84** (Scheme 32).[51]



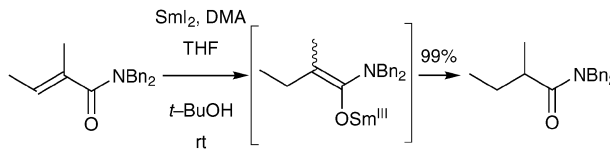
Scheme 32

The SmI_2 reduction of α-cyano carbonyl compounds, such as **85** and **86**, has been carried out by Liu and the resultant samarium enolates trapped with allylbromide (Scheme 33).[52] In most cases, the products were obtained as single diastereoisomers in good yield. It is likely HMPA serves a dual role in these reactions, increasing the reduction potential of SmI_2 in the enolate-generating step, and increasing the reactivity of the samarium enolate in the reaction with the carbon electrophile.



Scheme 33

3.2.1 Samarium enolates from the reduction of α,β-unsaturated carbonyl compounds. In 1991 Inanaga reported the conjugate reduction of α,β-unsaturated esters and amides using SmI_2.[53] Inanaga's reagent system, SmI_2-DMA-proton source, provided a mild method for the transformation (Scheme 34). Reduction using d_4-methanol as the proton source showed deuterium incorporation on both α and β-carbons indicating the intermediacy of samarium enolates.



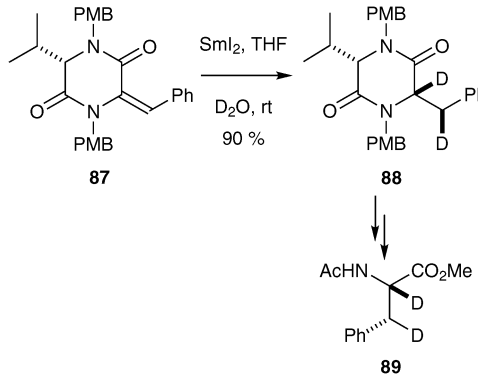
Scheme 34

In 1992 Alper extended the reduction to include α,β-unsaturated acids and anhydrides using HMPA as a promoter for the reaction.[54] Fukuzumi and Otera developed the process further still in 1997 by performing the reduction on a number of unsaturated carbonyl compounds including α,β-unsaturated cyclic ketones and lactones.[55] Interestingly, ring size plays an important role in this reaction as cyclohexenone and 5,6-dihydro-2*H*-pyran-2-one failed to undergo reduction, while larger, macrocyclic ketones and lactones underwent reduction in good yield.

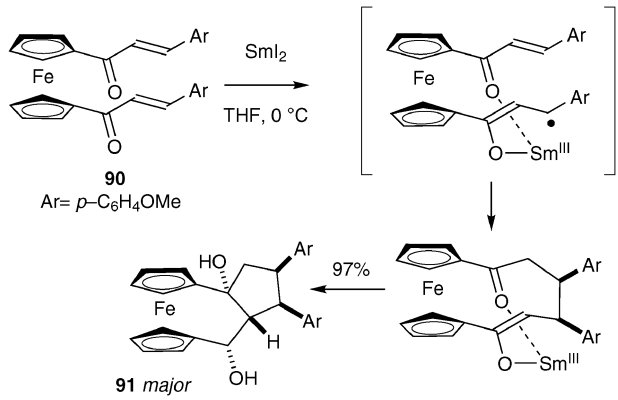
More recently, Davies has performed a diastereoselective conjugate reduction with SmI_2 and D_2O to gain access to isotopically labelled α-amino acids.[56,57] Reduction of enantiomerically pure diketopiperazine **87** generated a samarium enolate intermediate that was diastereoselectively deuterated to give **88**. Further synthetic steps yielded labelled α-amino acid **89** (Scheme 35).

While the conjugate reduction of α,β-unsaturated carbonyl compounds is a potentially useful way of accessing samarium enolates, there are few examples of the use of samarium enolates generated in this way. Fang has reported the SmI_2-mediated reductive cyclisations of 1,1′-dicinnamoylferrocenes such as **90** to give the corresponding [3]-ferrocenophane diols **91**.[58] The reactions proceed *via* a radical coupling, the aldol cyclisation of a samarium enolate intermediate and ketone reduction in a highly diastereoselective, one-pot operation (Scheme 36).

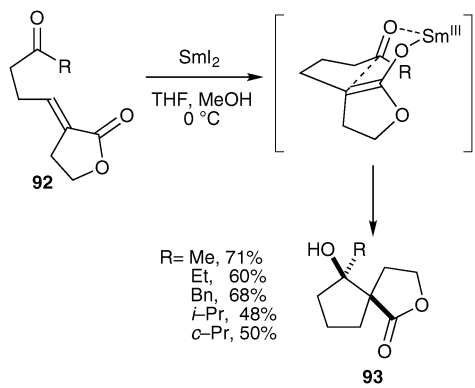
Procter has reported the diastereoselective spirocyclisation of unsaturated ketones **92** using SmI_2.[59] The cyclisation proceeds by conjugate reduction, samarium enolate generation, and a chelation-controlled aldol cyclisation to give *syn*-spirocycles **93** in good yield (Scheme 37).



Scheme 35



Scheme 36

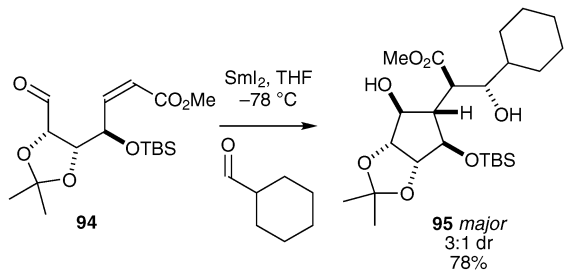


Scheme 37

3.3 Samarium enolates from the addition of radicals to α,β-unsaturated carbonyl compounds

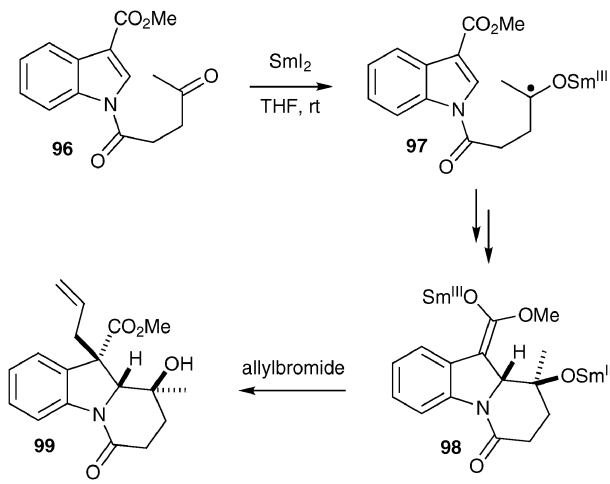
In 1994 Enholm described a SmI_2-mediated ketyl-olefin cyclisation/intermolecular aldol sequence.[60] A samarium ketyl-radical anion is generated by reduction of the aldehyde in carbohydrate-derived substrate **94**. Radical cyclisation and a second

reduction step then generates a samarium enolate that undergoes aldol reaction with aldehydes or ketones. Products, such as **95**, are formed in high yield and as a remarkably simple diastereoisomeric mixture considering four contiguous new stereocentres are formed in the process (Scheme 38).[60]



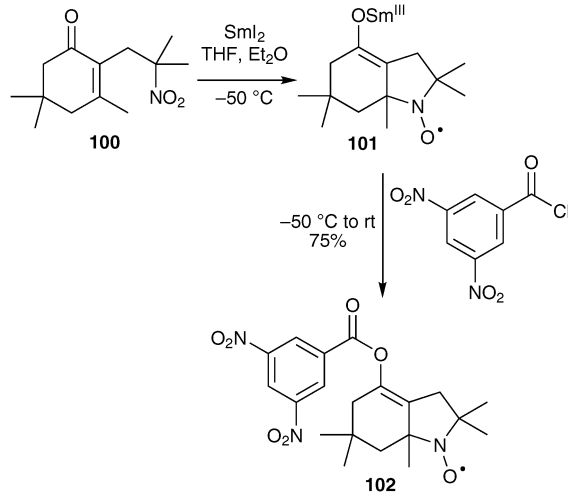
Scheme 38

In 2003 Reissig described a stereoselective synthesis of highly functionalised benzannulated pyrrolizidines and indolizidines through the SmI_2-induced cyclisations of indole derivatives.[61] After the cyclisation of samarium ketyl radical **97**, a second electron transfer gives a samarium enolate **98** that can be quenched with carbon electrophiles such as allylbromide to give products such as **99**. These cascade reactions selectively generate three contiguous stereogenic centres including a challenging quaternary centre at the 3-position of the indole moiety—a structural motif found in many indole alkaloids (Scheme 39).



Scheme 39

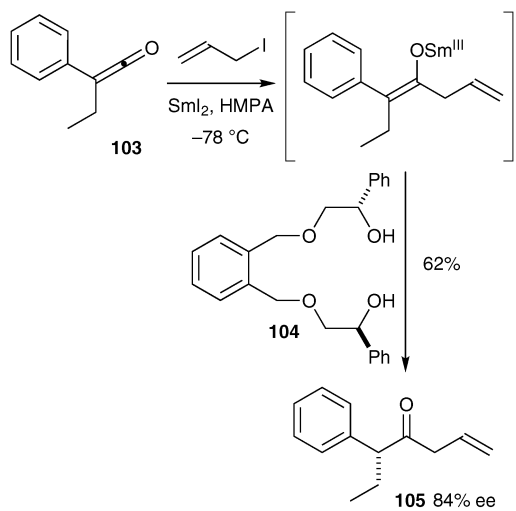
Tamura has reported the preparation of samarium enolates by the addition of nitrogen-centred radicals to α,β-unsaturated carbonyl compounds. Treatment of nitroenone **100** with SmI_2 generated the samarium enolate-radical **101** which was found to be relatively stable.[62] *O*-Acylation of the samarium enolate could be carried out using 3,5-dinitrobenzoyl chloride to give nitroxide radical **102** (Scheme 40).



Scheme 40

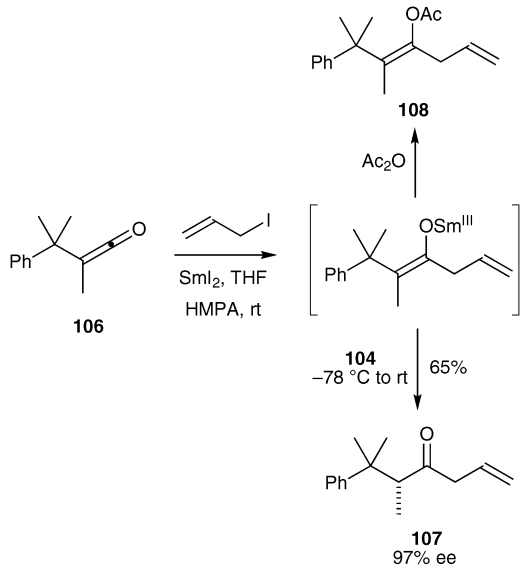
3.4 Enantioselective protonation of samarium enolates

Samarium enolates have found extensive use in asymmetric protonation studies. Takeuchi has generated samarium enolates for asymmetric protonation studies by adding an allylsamarium to ketenes, such as **103**.[63] After screening a number of chiral protonating agents in the reaction, *o*-xylene-derived diol **104** was found to give the enantiomerically enriched ketone **105** in 84% ee (Scheme 41).



Scheme 41

Takeuchi investigated the use of alkylsamariums with a range of unsymmetrical ketenes with the best result being observed for the reaction of ketene **106** giving ketone **107** in 97% ee (Scheme 42).[64] The enantioselectivities were not high in every case and Takeuchi speculated that this was due to the possibility of forming samarium enolate isomers. In order to investigate further, the samarium enolates formed from a range of ketenes were trapped as the corresponding enol acetates, such as **108** and the double bond geometry determined by NMR spectroscopy. It was



Scheme 42

apparent that the ratio of samarium enolate isomers varied with the steric difference between the groups on the ketene. In cases where single enolate isomers were produced, as in Scheme 42, high enantiomeric excesses were obtained.[64]

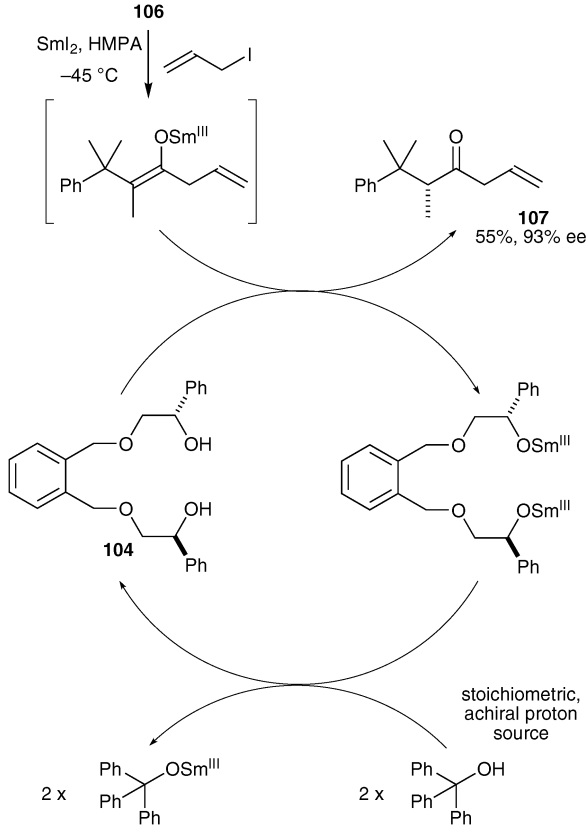
Takeuchi also studied the *catalytic* enantioselective protonation of samarium enolates,[65] where an achiral proton source is used to regenerate the chiral proton source **104**. Generation of a samarium enolate intermediate from ketene **106** was followed by protonation using a catalytic amount of **104** (15 mol%) in conjunction with trityl alcohol (Scheme 43). The trityl alcohol efficiently protonated the conjugate base of the chiral proton source but crucially did not carry out the achiral protonation of the samarium enolate.[65] This led to a highly selective *catalytic* process giving products in up to 93% ee (only slightly lower than the selectivities obtained in the analogous stoichiometric reaction).[64]

Takeuchi and Curran have also reported the use of fluorous, chiral and achiral proton sources in a biphasic, catalytic enantioselective protonation of the samarium enolate derived by allylsamarium addition to ketene **106**.[66]

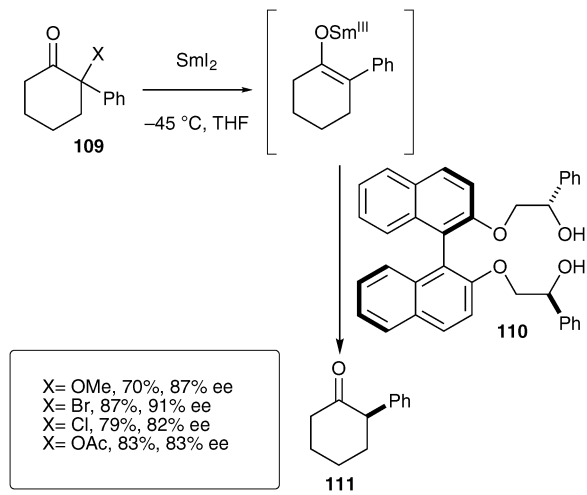
In 1997 Takeuchi turned to the SmI_2 reduction of α-heteroatom substituted carbonyl compounds as a means for forming the requisite samarium enolates needed for his asymmetric protonation studies.[67] Takeuchi examined the reduction of α-heterosubstituted cyclohexanone **109** bearing a phenyl substituent in the α-position. A number of ketone substrates were employed using the BINOL derived chiral proton source **110**. In all cases, ketone **111** was obtained in good yield and high enantiomeric excess (82% to 91% ee) (Scheme 44).

Subsequent work resulted in a library of tetradentate chiral alcohols that were effective for the protonation of samarium enolates formed from a range of cyclic, α-heterosubstituted ketones and lactones.[67,68] Scheme 45 shows the SmI_2 reduction-asymmetric protonation of bromo-lactone **112** using tetradentate chiral alcohol **113** (Scheme 45).

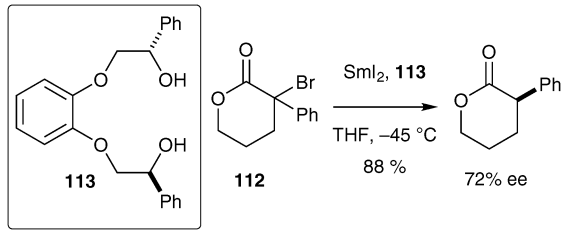
Takeuchi has proposed a transition state model to explain the enantioselectivity observed in the reaction (Fig. 1). In transition state T_1—**114**, the aryl substituent on the enolate has no unfavourable interactions with the phenyl ring of the proton source. As a result, protonation by the chiral alcohol takes place from the *si* face giving the product with (*R*)-configuration. Conversely in transition model T_2—**115**, steric interactions between the aryl substituent on the enolate and the phenyl ring of



Scheme 43



Scheme 44



Scheme 45

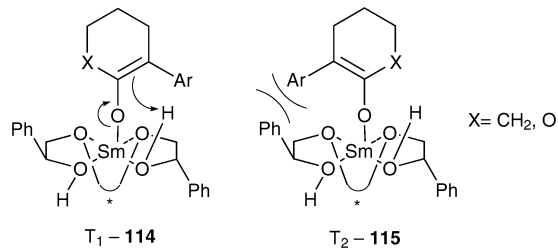
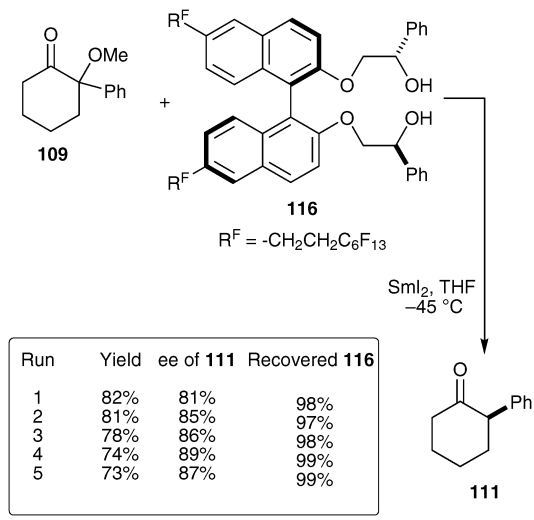


Fig. 1

the proton source gives rise to a higher energy conformation disfavouring protonation by this path.[67,68]

In 2000 Takeuchi reported the synthesis of the fluorous BINOL derivative **116** and used it in the stoichiometric asymmetric protonation of the samarium enolate derived from **109** (X = OMe) (Scheme 46).[69] The chiral proton source **116** could be easily recovered from the product mixture using fluorous solid phase extraction (FSPE). Recycling **116** gave little loss in the yield and enantioselectivity of the process.

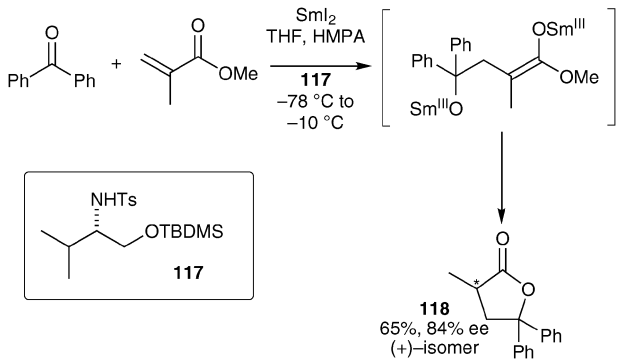


Run	Yield	ee of **111**	Recovered **116**
1	82%	81%	98%
2	81%	85%	97%
3	78%	86%	98%
4	74%	89%	99%
5	73%	87%	99%

Scheme 46

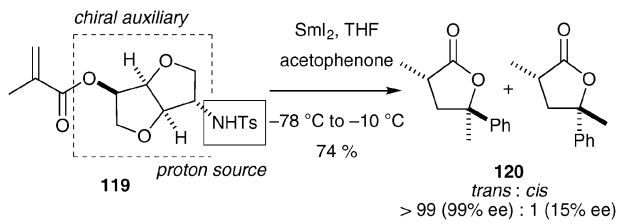
Aside from the work of Takeuchi there are few examples of the enantioselective protonation of samarium enolates. One notable exception is the recent work of Lin on the reductive coupling of ketones with methyl methacrylate. Lin's process also

involves the interception of a samarium enolate with a chiral proton source (Scheme 47).[70] Prior to Lin's studies, Fukuzawa examined the role of the proton donor in this reaction and used deuterium labelling to show that a samarium enolate is protonated during the course of the reaction.[71,72] Lin looked at a range of chiral alcohols, amides, and amino alcohols for the enantioselective protonation of the presumed, acyclic samarium enolate intermediate. Chiral sulfonamides were the most promising chiral proton sources. For example, in the coupling of benzophenone with methyl methacrylate, the product γ-butyrolactone **118** was obtained in good yield and enantiomeric excess using the sulfonamide chiral proton source **117** (Scheme 47).[70]



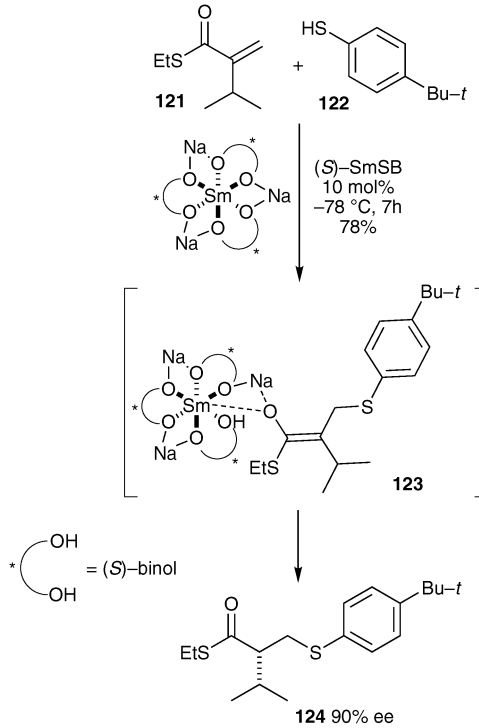
Scheme 47

Lin followed up these studies by examining the reactions of enoate substrates bearing carbohydrate-derived auxiliaries that also functioned as chiral proton sources.[73] Lin found that the diastereoselectivity of the coupling of substrate **119** with acetophenone varied greatly (50:50 to 99:1 in favour of the *trans* isomer) as did the enantiomeric excess of each diastereoisomer of the product **120** (Scheme 48).[73]



Scheme 48

Finally, Shibasaki has reported the use of a samarium-sodium-binol, heterobimetallic complex ([Na_3(Sm(binol)$_3$], SmSB) in the asymmetric conjugate addition of thiols to α,β-unsaturated carbonyl compounds.[74] For example, treatment of thioester Michael acceptor **121** with thiophenol **122** generates a samarium/sodium enolate intermediate **123** that undergoes catalytic asymmetric protonation from the samarium complex to generate product **124** in high enantiomeric excess (Scheme 49).[74]



Scheme 49

4. Conclusions

This review has examined the many methods reported for the generation of samarium enolates. The resultant samarium enolates have been shown to react with a range of electrophiles although it is clear that they have a very different reactivity profile compared to more conventional metal enolates. There are several examples of sophisticated, intermolecular samarium enolate-aldol reactions, including asymmetric variants employing substrates bearing chiral auxiliaries. Samarium enolate-aldol processes are presumably facile due to the Lewis acidic properties of the samarium(III) ion resulting in activation of the aldehyde and ketone electrophiles. The reaction of samarium enolates with alkylhalides is more limited and appears to require reactive electrophiles such as allyl- and benzylbromide. Samarium enolates have also played a major role in the development of asymmetric protonation as a synthetic methodology.

Although relatively little is still known about the structure and reactivity of samarium enolates, they are clearly versatile intermediates for synthesis. The literature reports discussed in this review show that it is often necessary to generate the samarium enolate in the presence of the carbon electrophile in order to obtain good yields of adducts. This suggests that samarium enolates are less stable than other common metal enolates. Despite this limitation, processes involving samarium enolates are beginning to find application in a number of areas including target synthesis and the development of high-throughput methods using solid-phase and fluorous technologies. Further study, including detailed kinetic investigations and a fundamental understanding of the coordination chemistry of these intriguing organometallic species, is needed to fully assess their synthetic potential.

Abbreviations

BINOL	1,1′-Binaphthalene-2,2′-diol
Boc	*tert*-butoxy carbonyl
BOM	Benzyloxymethyl
Bz	Benzoyl
DMA	*N*,*N*-dimethylacetamide
DMAE	*N*,*N*-dimethylaminoethanol
DMAP	4-Dimethylaminopyridine
DMPU	1,3-Dimethyl-3,4,5-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
equiv.	Equivalents
FSPE	Fluorous solid phase extraction
h	Hour
HASC	Heteroatom substituted carbonyl
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
Mol	Moles
NMR	Nuclear magnetic resonance
PMB	*para*-methoxybenzyl
rt	Room temperature
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	see TBDMS
THF	Tetrahydrofuran
TIPDS	Tetraisopropyldisiloxane-1,3-diyl
TLC	Thin layer chromatography
Ts	*para*-toluenesulfonyl

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