Coupling of Organic Halides with Carbonyl Compounds Promoted by SmI_2, the Kagan Reagent

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1. Introduction and General Principles

Samarium diiodide (SmI_2) was introduced in organic synthesis by Kagan.[1] This reagent "proved, among the plethora of contemporary reagents at the disposal of organic chemists, perhaps the most remarkable. This unique, polyvalent reducing agent has been applied to a multitude of important synthetic transformations, which generally proceed with high chemoselectivity and high levels of stereochemical control".[2] Samarium diiodide reduces chemoselectively a large variety of functional groups such as organic halides, carbonyl compounds, α-heterosubstituted carbonyl compounds, cyclopropyl ketones, epoxides, amine oxides, sulfoxides, phosphine oxides, sulfones, sulfonates, nitro and nitroso compounds, azo compounds, allyl acetates, and isoxazoles.[2−17]

SmI_2 **[**32248-43-4**]** is easily prepared in tetrahydrofuran (THF) from the metal itself finely ground as a powder, and diiodomethane, diiodoethane, or iodine.[3,6,14] The reaction has also been carried out

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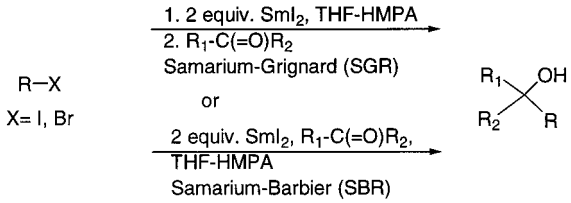
with diiodoethane in tetrahydropyran (THP)[18] or alkylnitriles,[19,20] especially pivalonitrile.[20] The reactions must be carried out under an inert atmosphere with freshly purified and degassed reagents and solvents or better with dry THF containing an antioxidant. THF (0.1 M) blue solutions, *prepared in situ* or commercially available (Acros, Aldrich), have been routinely used especially for the Barbier–Grignard reaction.

SmI_2 reacts with an alkyl halide and a carbonyl compound to provide an alcohol. The organic halide is reduced by SmI_2 to the corresponding organosamarium intermediate in the samarium Grignard reaction (SGR), and either the organic halide[14,16,21] or the carbonyl compound[14] can be first reduced in the samarium Barbier reaction (SBR). Several reviews describe the reducing ability of SmI_2 toward different functional groups including alkyl halides but, except early reports from Kagan[7] and Curran,[9] none of them specifically describe its role in Barbier–Grignard reactions. This paper exclusively deals with these specific reactions. We will show how useful the SmI_2 promoted versions of the old Barbier and Grignard reactions can be and will compare, whenever it is possible, the results to those reported with magnesium or lithium reagents instead.[22]

2. Generalities

Since its discovery by Kagan,[1,7,23–25] SmI_2 promoted alkylation of carbonyl compounds with organic halides has found wide application in organic synthesis (Scheme 1).[9] In comparison with existing methods,

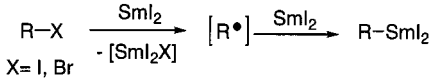
Scheme 1



using main group metals such as magnesium,[1,26–28] lithium,[27–34] or zinc,[26,35,36] SmI_2 promoted reactions offer the advantage of homogeneity of the reaction medium and high chemoselectivity which proved particularly useful for intramolecular reactions.

The reaction is achieved with 2 molar equiv of SmI_2 and occurs by stepwise one-electron transfer to the organic halide (Scheme 2).[25] Although conflicting

Scheme 2



mechanisms have been proposed,[7,37] the consensus[37] is that the intermolecular reaction usually proceeds via organosamarium species (with half-lives on the order of minutes to hours at room temperature) which then react with the carbonyl compounds[9,37–39] to produce the corresponding alcohols.

Reduction of alkyl halides (mainly the iodides) to the corresponding radicals by the first equivalent of SmI_2 and their further reduction to alkyldiiodosamariums by the second equivalent of SmI_2 occur with different rates which depend on the nature of the alkyl chains and of the solvent used.[9,40] (Comparative results with those performed with tributyltin hydride have been from time to time described.[29,33,41,42])

The Barbier–Grignard reaction has been carried out successfully on a large variety of organic halides such as

- primary and secondary alkyl halides,
- allylic and benzylic halides,

- 1-iodoalkynes,
- α-heterosubstituted alkyl halides,
- alkyl halides bearing a carbonyl group in the ω-position,
- α-halogeno carbonyl compounds (the samarium Reformatsky reaction).

It, however, does not usually occur with

- aryl, vinyl (section 3.2.3), or tertiary alkyl halides (section 3.1), which are reduced to the radical stage but are not usually reduced further to the organosamarium reagents,
- β-heterosubstituted alkyl halides such as 1,2-diiodoethane, tetrahydrofurfuryl bromide, epichloridrin, or β-methoxyalkyl halides which instead produce olefinic compounds from competing β-elimination reaction,[7,9,14,31,43]
- dibromodifluoromethane (Br_2F_2C).[43]

The reactions have been performed (Scheme 1) stepwise as in the Grignard reaction[44,45] (samarium Grignard reaction) by first reacting the organic halide with SmI_2 and then adding the carbonyl compound[9,10,15,46] or in one single pot, as in the Barbier reaction[22,47,48] (samarium Barbier reaction), by mixing SmI_2 together with the organic halide and the carbonyl compound.[1,3−5,7−13,15,24,38] The samarium-Barbier conditions offer several advantages over the classical Barbier conditions involving Mg or Li instead and have been used especially in intramolecular reactions (intramolecular samarium Barbier reaction: ISBR).[2,8−13,15,17,29]

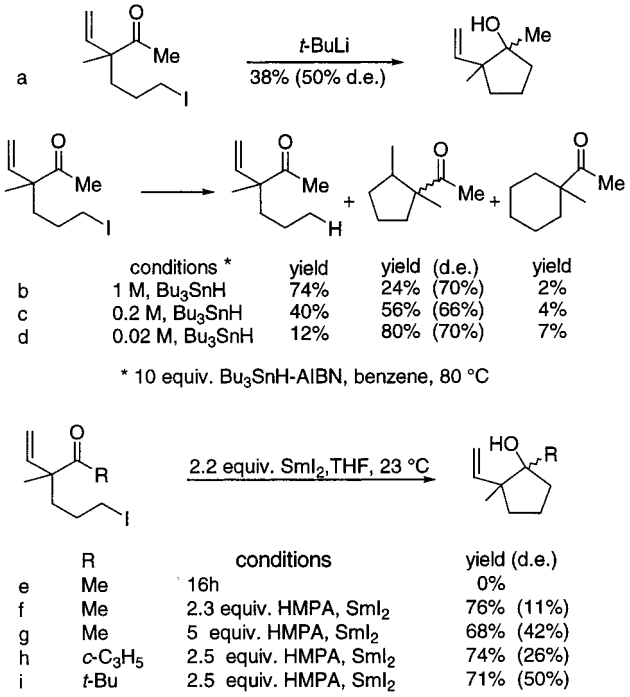
The samarium diiodide promoted reaction proceeds consistently well under both SBR and SGR conditions for organic halides and dialkyl ketones but

- the SBR conditions[23] have to be used with those organic halides which (i) are prone to *dimerize* (such as allyl or benzyl halides), (ii) tend to decompose via an α-*elimination reaction* (such as α-heterosubstituted alkyl halides), or (iii) are capable to *react with themselves* inter- or intramolecularly (such as halogeno carbonyl compounds).
- the SGR conditions are significantly better with those carbonyl compounds which (i) exhibit a tendency to be reduced faster by SmI_2 than the organic halide,[9,23] (ii) are subject, as is the case for aliphatic aldehydes, to Meerwein-Ponndorf reactions,[23,25,49] or (iii) are particularly prone to pinacol coupling as are aromatic carbonyl compounds.[3,12,25,37]
- the ISBR proved to be particularly efficient, especially when applied to esters, for the synthesis of ketones.[17] These ketones can in turn react with SmI_2 if another chain bearing a suitably positioned halogen or C,C double or triple bond is present.[17,50] These sequenced reactions employing samarium diiodide allow the spectacularly short construction of very complex molecules.[17,50]

Furthermore the SGR, SBR, and ISBR occur in all cases faster on aldehydes and ketones than on esters or amides, thus allowing chemoselective reactions if these functional groups are present in the molecule.[51,52]

As far as the mechanism is concerned, it must be recalled that the organic halide as well as the carbonyl compound can be reduced by SmI_2. The results will depend on their nature, and this will be

Scheme 3

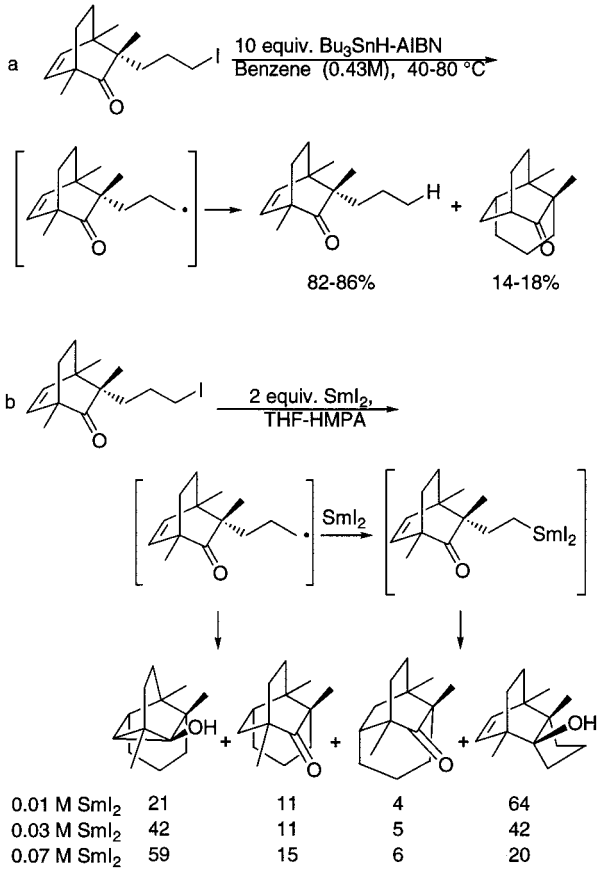


furthermore modulated by the experimental conditions used. Benzylic (as well as allylic) radicals are, for example, easily generated, and therefore aromatic carbonyl compounds as well as benzyl halides are much more easily reduced than their aliphatic counterparts. Thus, it will not be surprising to observe competing side reactions such as reduction of the carbonyl group (formal H_2 addition) or pinacol formation with the former compounds[25,37] and an increased aptitude to generate an organosamarium from the latter derivatives (section 3.2.1).

All the possible mechanisms have been postulated over the years,[7,24,29] and a consensus for an ionic addition mechanism began to merge after the seminal work of Curran.[9,38] This mechanism seems to be valid for all the reactions performed under SGR conditions.[9,29] In the other cases involving SBR and ISBR, there is no unambiguous evidence in favor of any of the obvious intermediates (free alkyl or alkoxy radicals, ketyls, organosamarium species) which can be postulated. In fact much of the evidence for the ionic addition mechanism supported by in situ trapping experiments, by D_2O for example, are compromised because it is now known that their presence can alter the reducing power of SmI_2 and therefore change dramatically the intimate process. It has been found, for example, that the reduction of a primary alkyl iodide was accelerated by at least a factor of 10 by performing the reaction in the presence of a ketone.[29]

Scheme 3 summarizes results for an organolithium (entry a), a Bu_3SnH (entries b−d), and some SmI_2 (entries e−i) reactions. The experiments were designed by Curran in order to get some insight on the intimate mechanism of the ISBR.[29] The δ-iodoketones described in Scheme 3 possess a quaternary carbon connected to an ω-alkenyl side chain susceptible to compete with the carbonyl group of the ketone in trapping the alkyl radical. The other group attached

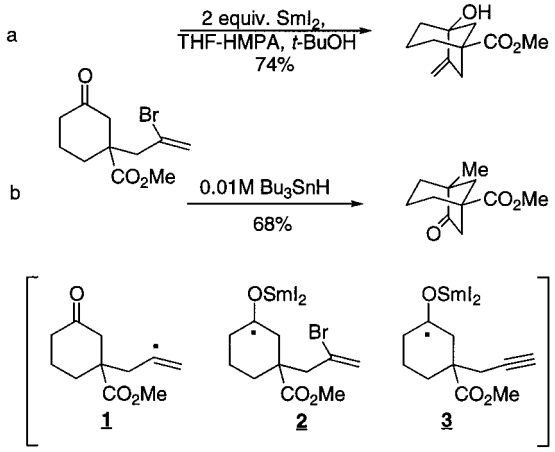
Scheme 4



to the carbonyl group is expected to slow its reactivity on going from methyl to *tertio*-butyl (Scheme 3, compare entry f to entry i) or to trap a transient ketyl radical by cyclopropyl ring opening[14] (Scheme 3, entry h). The only products observed for the SmI_2 reactions were the epimeric alcohols. These alcohols are formed independent of the reaction concentration and of the amount of HMPA used (Scheme 3, entries f and g). Even the addition of 10 equiv of MeOD or of H_2O prior the addition of SmI_2 had no effect on the outcome of the reaction. These results are remarkable since if the intermediate is a radical it would have been trapped by the C,C double bond (as when tributyl tin hydride is used; Scheme 3, entry d), if it is a ketyl, the cyclopropylcarbinyl fragmentation would have taken place (instead of the result disclosed in Scheme 3, entry h) and if it is an organosamarium it would have been trapped by protonation or deuteration (reaction performed with H_2O or MeOD).[29]

Results inconsistent with the predictions have been also described with the bicyclic unsaturated ketone bearing a 1-(iodopropyl) side chain α to the carbonyl group (Scheme 4).[29] As expected, cyclization takes place selectively on the C,C double bond with tributyltin hydride (Scheme 4, entry a), and substantial amounts of products resulting from cyclization onto the carbonyl group are formed when the reaction is carried out with SmI_2 in THF−HMPA (Scheme 4, entry b). It was expected that the percentage of the latter product would increase with increasing the SmI_2 concentration as the reduction of the radical resulting from the iodide to organosamarium becomes more efficient, but instead this ratio experimentally decreases significantly (Scheme 4, entry b).[29]

Scheme 5



The reaction between an organic halide and a carbonyl compound does not always follow the SBR or SGR type of reaction. For example highly chemoselective cyclization of the cyclohexanone bearing a vinylic bromide leads to the bicyclic alcohol whose structure is disclosed in Scheme 5 (entry a).[53] This reaction does not seem to proceed through the intermediate vinylic radical (Scheme 5, intermediate **1**) or the related anion but involves a ketyl (Scheme 5, intermediate **2**) which cyclizes to the bicyclic alcohol by a sequential exo-addition/β-elimination reaction on the vinyl bromide moiety.[53] The same compound is expected to be formed by addition of the same ketyl to terminal alkynes (Scheme 5, intermediate **3**). The reaction takes another course when carried out with tributyltin hydride and leads to a completely different product (Scheme 5, entry b). It probably arises by a series of reactions involving at first the cyclization of the vinylic radical onto the carbonyl group of the intermediate **1** (Scheme 5).[53]

2.1. About the Conditions

2.1.1. About the Solvent and the Additives

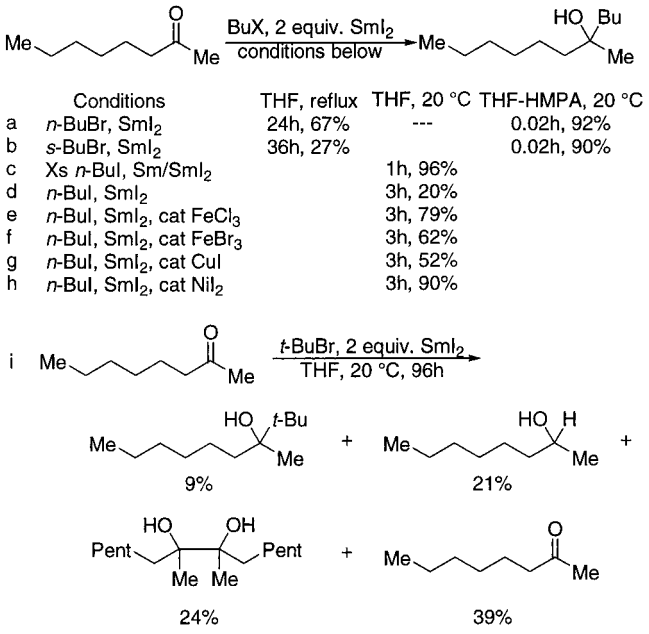
The reactions are in most cases carried out in THF and are quite slow unless a cosolvent such as HMPA or a transition metal salt is used as additive (Schemes 6 and 7).[1,25]

2.1.1.1. About the Solvent. Except in rare cases, described below, most of the reactions have been carried out in THF, the solvent in which SmI_2 is usually prepared and commercially available. In this solvent the SBR and SGR are relatively slow unless the organic halide is highly reactive such as allyl and benzyl halides and α-halocarbonyl compounds.

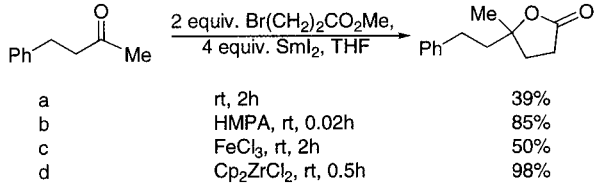
For other cases use of HMPA (5 equiv) dramatically improves the reducing ability of SmI_2 and increases the rate of the reaction (Scheme 6, entries a and b, and Scheme 7, compare entry b to entry a).[9,12,14,21,37,40,54] Surprisingly HMPA has no such effect when the reaction is instead performed in alkylnitriles.[20]

The effect of HMPA on the reduction of organic halides has been carefully studied.[21,55] It was found that the addition of HMPA to a THF solution of SmI_2 has a drastic effect on the redox potential (E°) of

Scheme 6



Scheme 7

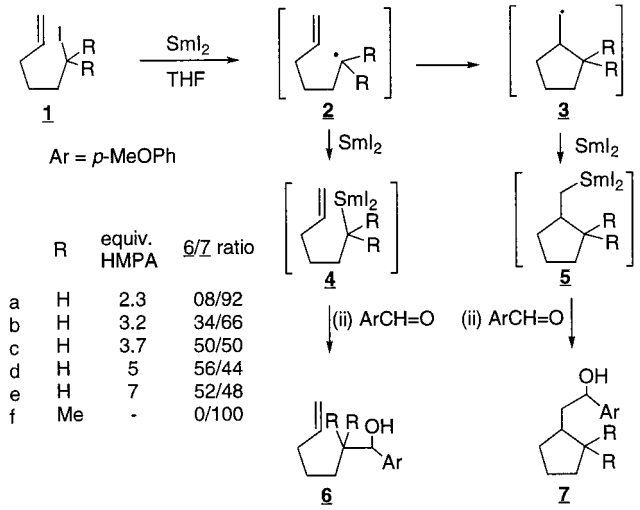


Sm^{2+}/Sm^{3+}. This increases from −1.33 V to −1.95 V with 3 equiv of HMPA, reaches −2.05 V with 4 equiv and remains constant with more equivalents.[55]

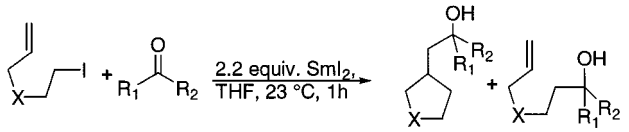
Some quantitative results have been obtained from 6-hexenyl iodide and a carbonyl compound under SGR[40] and SBR[29] conditions using the 6-hexenyl radical clock. The effect of HMPA proved to be quite different depending upon the experimental conditions used. The rate constants k_{Sm} for reduction of a *primary* alkyl radical by SmI_2 as a function of HMPA concentration has been estimated under SGR by quenching the reaction with *p*-methoxybenzaldehyde and measuring the ratio of unrearranged to rearranged products (Scheme 8, entries a−e).[9,40] Similar results were obtained with 2-octanone (Scheme 9, entries a and b).[9]

Reduction of 6-hexenyl iodide (Scheme 8, **1**, R = H) by SmI_2 in THF alone is too slow to measure; under SGR conditions, the rate measuring experiment ranges on the order of several hours to a day.[40] A reasonable reaction time (<0.1 h) is, however, attained when the reaction is performed with as little as 2 equiv of HMPA per SmI_2 ($k_{Sm} = 5 \times 10^5$ M^{-1} s^{-1}), leading mainly to the cyclized product (Scheme 8, **7**, R = H) after quenching with a *p*-methoxybenzaldehyde. The ratio of directly reduced product (Scheme 8, **6**, R = H) to rearranged product (Scheme 8, **7**, R = H) increases when the ratio of HMPA to SmI_2 increases from 2 to 4 equiv. Typical results are reported in Table 1. The unsaturated/saturated alcohol ratio as well as the calculated rate constant k_{Sm} increase by increasing the HMPA/SmI_2 ratio (Table

Scheme 8



Scheme 9



	X	R_1	R_2	conditions	yield	yield
a	CH_2	Me	Hexyl	2.8 equiv. HMPA, SGR	90%	10%
b	CH_2	Me	Hexyl	5 equiv. HMPA, SGR	56%	44%
c	CH_2	Me	Hexyl	SBR	61%	39%
d	CH_2	Me	Hexyl	3.2 equiv. HMPA, SBR	57%	43%
e	CH_2	Me	Hexyl	5 equiv. HMPA, SBR	60%	40%
f	O	Et	Et	HMPA	57%	
g	O	$(CH_2)_4$		HMPA	53%	
h	O	$(CH_2)_5$		HMPA	52%	

Table 1

entry	equiv HMPA/ SmI_2 ratio	unsatd/satd alcohol ratio	calcd rate constant k_{Sm} ($\times 10^6$ M^{-1} s^{-1})
1	2.3	8/92	0.5
2	3.2	34/66	2.8
3	3.7	50/50	5.3
4	5.1	56/44	6.8
5	7.0	52/48	6.2
6	13.5	45/55	4.8

1, entries 1−3) to reach a plateau around 4−5 equiv of HMPA (Table 1, entries 3−5, $k_{Sm} = 6 \times 10^6$ M^{-1} s^{-1}).[29,40] Increasing the amount of HMPA beyond 5 equiv resulted in a slow decrease of the unsaturated/saturated alcohol ratio (Table 1, entries 5 and 6, and Scheme 8, compare entry d to entries a−c). Under these conditions it was checked that no equilibration between the alkenylsamarium diiodide and methylene cycloalkylsamarium diiodide takes place.[9,38,40]

These results have been rationalized as follows: 6-iodohex-1-ene is rapidly reduced in the presence of SmI_2 to the 6-hexenyl radical which undergoes a carbocyclization reaction to the cyclopentylmethlyl radical faster than reduction to the corresponding unsaturated 6-diiodosamarium precursor of the unsaturated alcohol. Further reduction of the cyclopentylmethlyl radical by the remaining equivalent of SmI_2 leads to the cyclopentylmethyl diiodosamarium precursor of the saturated alcohol. Increasing the amount of HMPA greatly improves the production of the alcohol derived from the original iodide by

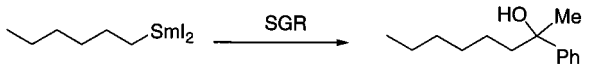
increasing the rate of reduction of the straight chain radical first formed (Scheme 2).

Surprisingly, when the ketone (2-octanone) is present in the medium, i.e., if the reaction is conducted under SBR conditions, not only the reaction is faster and occurs in reasonable time (much faster than under SGR conditions in THF) but also the ratio of directly reduced product to rearranged product remains constant independent of the presence of HMPA ($k_{Sm} = 6 \times 10^6$ M^{-1} s^{-1}) (Scheme 9, entries c−e).[29]

The reduction of tertiary alkyl ($k_{red} < 10^4$ $M^{-1}s^{-1}$),[1,9] aryl,[9] and vinyl[9] iodides to the corresponding radicals can be carried out with SmI_2 but further reduction to the organosamarium cannot be achieved in THF. Use of HMPA does not improve the SBR or SGR reactions. For example, aryl[9] and vinyl[9] iodides react faster with THF, even in the presence of HMPA, to abstract a hydrogen than they are reduced to the corresponding organosamariums,[9] and the reduction of the tertiary alkyl iodide (Scheme 8, **1**, R = Me) in the presence of an aldehyde gives exclusively the rearranged alcohol (Scheme 8, **7**, R = Me, entry f) with no trace of the directly reduced product (Scheme 8, **6**, R = Me).[9]

In some cases when HMPA alone did not give the expected rate acceleration, as with aryl ketones and enones, the addition of trimethylsilyl chloride proved to be particularly efficient (Scheme 10, compare entry b to entry a).[56]

Scheme 10



a	acetophenone, THF-HMPA, -78 °C	7%
b	acetophenone-TMSCl, THF-HMPA, -78 °C	65%

The reactions involving the most reactive allyl bromides and iodides do not usually need to be performed in the presence of HMPA (section 3.2.1). It has been nevertheless mentioned that the use of this additive is absolutely required for the successful synthesis of medium size cyclic ketones from ω-keto allylic halides (see Scheme 51, compare entry c to entry d).

The reactions have been carried out in other solvents or mixture solvents such as

• tetrahydropyran which was found to be the solvent of choice for allyl (see Scheme 17, entries k and l, and Scheme 18) and benzyl (see Scheme 19, entry c) samariums from the corresponding halides.[51] It allows, under SGR conditions, the synthesis of the corresponding alcohol with high regio- and stereocontrol (Scheme 17, entry k; Scheme 18, entries a and b) even from hindered carbonyl compounds (Scheme 18, entry b) and with complete chemoselectivity (Scheme 18, entry c).[51]

• alkylnitriles, especially pivalonitrile, in which SmI_2 is much less reactive than in THF but in which chemoselectivity is often improved.[20] For example, under SBR conditions, the reduction of allyl (see Scheme 17, entries f and g) and benzyl (see Scheme 19, entry b) halides takes place but not that of primary alkyl halides, such as iodododecane (compare section 3.1 to section 3.2.1).[20] Surprisingly, as already mentioned, HMPA does not enhance the reactivity of SmI_2 in alkylnitriles.[20]

• benzene−HMPA proved to be particularly valuable for (i) the arylation of ketones from aryl halides[57] (section 3.2.3.2) and for (ii) the alkynylation of aldehydes from iodoalkynes[52] (section 3.2.4). Those reactions do not properly proceed when carried out in THF or THF−HMPA[52] because the radical intermediates (which do not have a high propensity to be reduced to the organosamariums) instead abstract a hydrogen from THF. Benzene, which lacks radical-abstractable hydrogens, allows the synthesis of the corresponding organosamariums.

• THF in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*) pyrimidone (DMPU) (see Scheme 14, entry a, and Scheme 15)[42] or a polyether such as tetraethylene glycol dimethyl or dibenzyl ethers in order to favor the SBR with retardation of pinacol coupling products.[58]

2.1.1.2. About Metal and Metal Salts as Additives. The SBRs have been markedly improved if carried out in THF but in the presence of

• samarium metal (Sm°) (Scheme 6, entry c; see Scheme 35, entries a, b, d; Schemes 36 and 37).[59−61] Comparative results involving SmI_2 alone or Sm° with catalytic amounts of SmI_2 have been also reported.[59]

• catalytic amounts of SmI_2 (10%) in THF using mischmetall (a commercially available alloy of the light lanthanides (La 33%, Ce 50%, Nd 12%, Pr 4%, Sm and other lanthanides 1%) to regenerate SmI_2. This reducing agent is (i) cheaper than Sm°, (ii) able to quickly reduce Sm(III) species into Sm(II) ones, which implies the ability to cleave the Sm(III)−O bonds, (iii) unreactive to carbonyl compounds, and (iv) simple to use. Typical results reported on 2-octanone show that ethyl and allyl iodides and allyl and benzyl bromides react efficiently to produce the corresponding alcohols in good to very good yield (67%, 90%, 91%, and 91%, respectively, after 2−6.5 h of reaction in THF, at 20 °C), similar to or even better than those reported using stoichiometric amounts of SmI_2 (compare to Scheme 6, entries c and d; Scheme 17, entries b and c; Scheme 19, entry a),[135]

• catalytic amounts of transition metal salts such as $FeCl_3$, $FeBr_3$, FeI_3 (Scheme 6, entries e and f, and Scheme 7, entry c; see Scheme 70; Scheme 71, entry a; Scheme 72 and Scheme 87, entry a)[1,54,62,63] including $Fe(DBM)_3$ (iron tris(dibenzoylmethido) (see Schemes 44 and 45; Scheme 58, entries a−c; Scheme 59; Scheme 60; Schemes 63 and 64, Scheme 65, entry a; Scheme 66; and Scheme 83)[31] as well as copper(I)[62] (Scheme 6, entry g) or copper(II),[62] nickel(II)[17,50,62] (Scheme 6, entry h; see Scheme 12; Scheme 74; Scheme 75, entries b and d; Schemes 84−86)[33,50] and vanadium trichloride,[62] silver(I) halides,[62] cobalt dibromide,[62] or zirconium tetrachloride[62] as well as $Cp_2ZrCl_2$54 (Scheme 7, entry d).

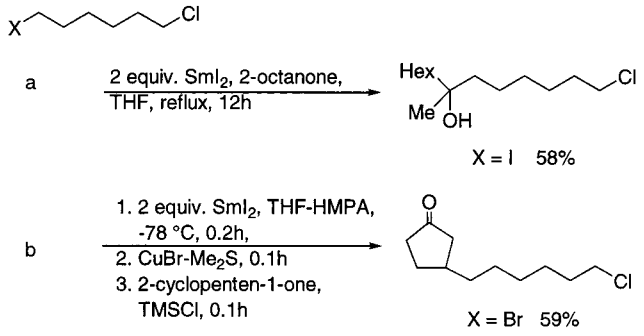
Ferric salts, which proved to be among the most efficient at allowing the intramolecular addition of alkyl iodides to esters, are believed to be reduced to low-valent iron species, that in turn are able to promote the desired coupling.[54] Nickel salts, and

especially nickel diiodide (1%), proved to be particularly efficient for promoting the intramolecular reactions (see Scheme 74)[33] as well as the addition of *n*-butyl iodide to 2-octanone under SBR conditions[62] (Scheme 6, entry h). The last conditions are so efficient that they allow, in THF, THP, or even in alkylnitriles, double addition of *n*-butyl iodide on esters and lactones, producing, in less than in 0.05 h, the corresponding alcohols in very good yield.[62] We have to recall that Barbier reactions between iodoalkanes and esters are very slow when carried out in THF and do not proceed at all in alkylnitriles.[20] Nickel iodide, however, promotes the addition of alkyl chlorides to ketones, which has been used for the sequential addition of dihalogeno alkanes to keto esters under visible light irradiation (see Scheme 12; section 5.3).[17,50] Zirconium tetrachloride and vanadium trichloride do not allow the alkylation of the ketones but instead promote the reduction of their carbonyl group to the corresponding secondary alcohol.[62]

2.2. About the Nature of the Halogen of the Organic Halide

The reaction occurs chemoselectively with organic bromides and iodides including functionalized ones but does not usually take place with chlorides.[4,7,14,25] Although it effectively occurs on allylic and benzylic chlorides the reduction is slower than that on the corresponding bromides or iodides.[1,25] Chemoselective reactions can be therefore carried out with ω-chloro alkyl iodides (Scheme 11).[1]

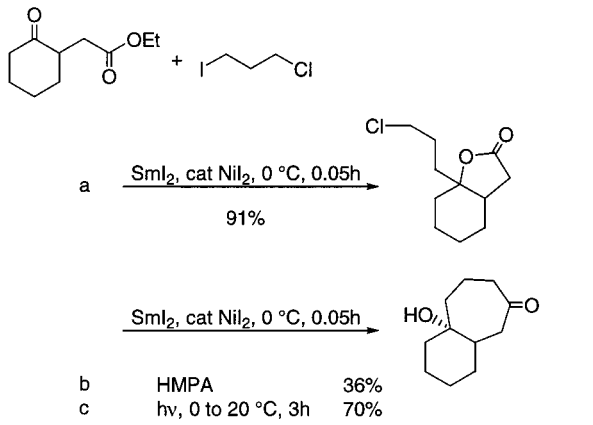
Scheme 11



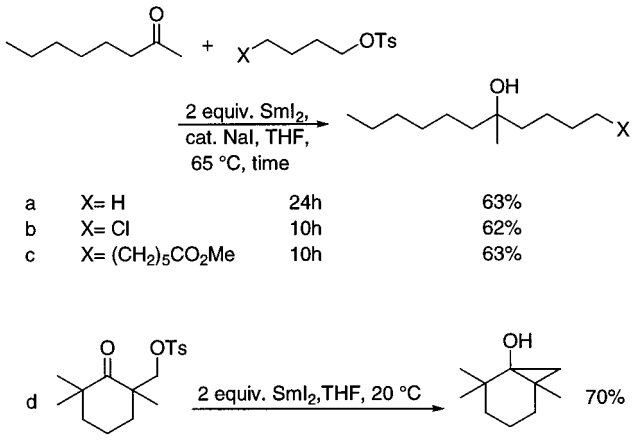
It has been nevertheless described that irradiation through Pyrex with visible light (560 and 700 nm, tungsten or krypton lamp) but not UV light (300−420 nm) enhances the reducing ability of SmI_2[50,64] and allows even the reduction of alkyl chlorides (primary to tertiary). These conditions have been successfully applied to the reductive alkylation of aldehydes, ketones, and lactones (Scheme 12),[50] as well as carbon monoxide,[64] the simplest carbonyl compound, from alkyl chlorides (section 5.3).[50]

Alkyl iodides have been in some cases prepared in situ from the corresponding tosylates and sodium iodide or SmI_2 in a Finkelstein-type reaction.[1] They have been directly used in intermolecular (Scheme 13, entry c, under SBR conditions)[1] as well as in intramolecular (Scheme 13, entry d)[10] reactions. It is interesting to notice that tosylates are reduced faster than chlorides, esters, and keto groups by SmI_2.[1]

Scheme 12



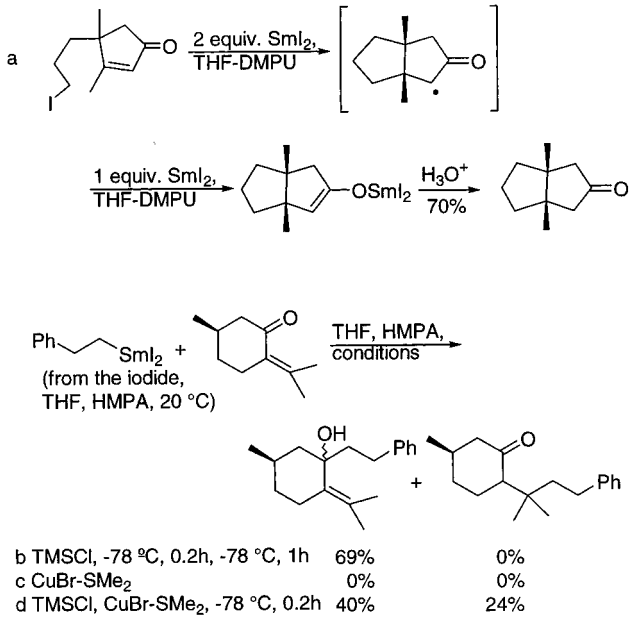
Scheme 13



2.3. 1,2- versus 1,4-Addition to Enones

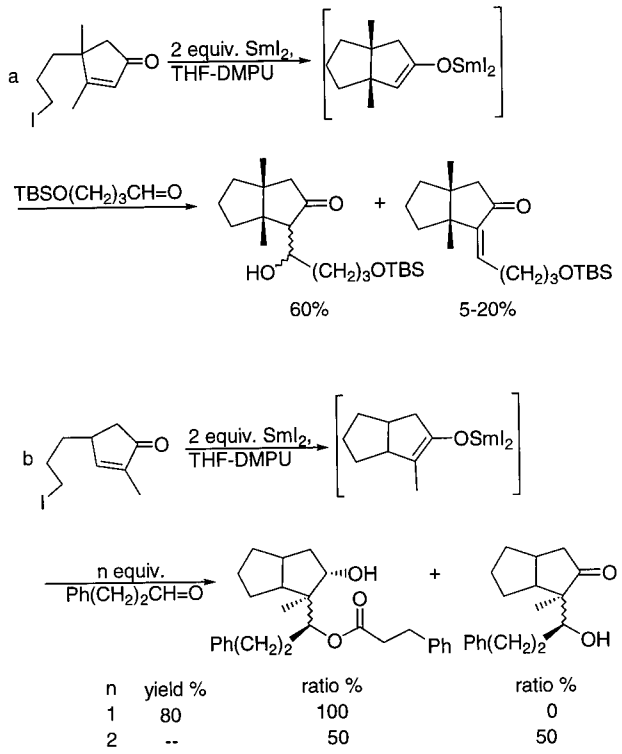
Except in the rare case of the intramolecular reactions disclosed in Scheme 14, entry a, and Scheme 15,[42] organosamariums add 1,2 to enones (Scheme 14, entry b).[56,65] However, 1,4-addition is feasible, if carried out under SGR conditions in the presence of CuI−$P(OEt)_3$,[66] CuBr-Me_2S, or CuBr-

Scheme 14



Me_3SiCl in THF−HMPA[56] (Scheme 11, entry b; Scheme 14, compare entry d to entries b and c; and Scheme 15). Intramolecular addition has been efficiently achieved, however, with α,β-unsaturated esters (section 5.1.2).

Scheme 15



3. SmI_2 Promoted Intermolecular Coupling of Organic Halides with Aldehydes and Ketones [3−5,7,9,10,12,13,15]

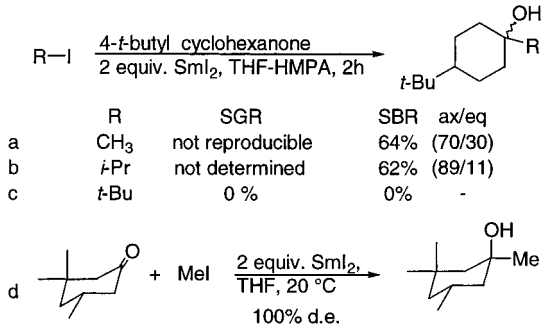
3.1. Reactions Involving Alkyl Halides

There is a great difference of reactivity between primary and secondary alkyl halides and their tertiary alkyl analogues toward SmI_2 and carbonyl compounds since only the two former allow the alkylation of the carbonyl compounds. All these organic halides (with the exception of chlorides) are, however, reduced by SmI_2. But whereas the reduction delivers organosamariums from primary and secondary alkyl halides, it is slower with their tertiary analogues which are reduced at the first radical stage. For example, the reaction of tertio-butyl bromide, SmI_2, and 2-octanone delivers only a few percent of the expected tertiary alcohol besides unreacted ketone, 2-octanol, and the related pinacol (Scheme 6, entry i).[1]

Nonfunctionalized primary alkyl, secondary alkyl,[1,9,30,37] and cycloalkyl,[37] iodides and bromides react, under SGR but better under SBR conditions with carbonyl compounds, especially dialkyl ketones, in the presence of SmI_2 to produce the corresponding alcohols in reasonably good yields.[1,9,30,37,43] The reaction of a series of isomeric butyl bromides with 2-octanone reveals a lower reactivity and decreasing yields in replacing primary (36 h, 96%) with secondary alkyl bromides (*s*-BuBr, 36 h, 27%; *i*-BuBr, 48 h, 33%).[1] We have to recall that although related organolithiums often behave efficiently, Grignard reagents of the same bromides lead mainly to reduction products.[1]

Exceptions to the above generalization include some of the simplest iodides, especially methyl and isopropyl iodides, which misbehave under SGR conditions[25,37] but efficiently react under SBR conditions (Scheme 16).[1,23,25,30,37]

Scheme 16



Quite good stereocontrol has been achieved from 4-*tertio*-butylcyclohexanone[37] (mainly equatorial attack) (Scheme 16, entries a and b) and 3,3,5-trimethylcyclohexanone (exclusive equatorial attack) (Scheme 16, entry d).[30] Although the reaction does not work properly with hindered or enolizable ketones,[37] it proceeds efficiently with cyclobutanone. Cyclobutanols are produced in high yields and products resulting from the cyclobutane ring opening (which would have been formed if a ketyl radical would have been instead involved) are not produced.[24,39] Another advantage in using SmI_2 is that organosamariums are far more selective than other organometallics because they selectively react with ketones in the presence of esters, alkylnitriles and amides.[9,26,54]

3.2. Reactions Involving Unsaturated Organic Halides

The structure of the product, resulting from the reaction of unsaturated alkyl halides, SmI_2, and carbonyl compounds, greatly depends on the position and the nature of the unsaturation:

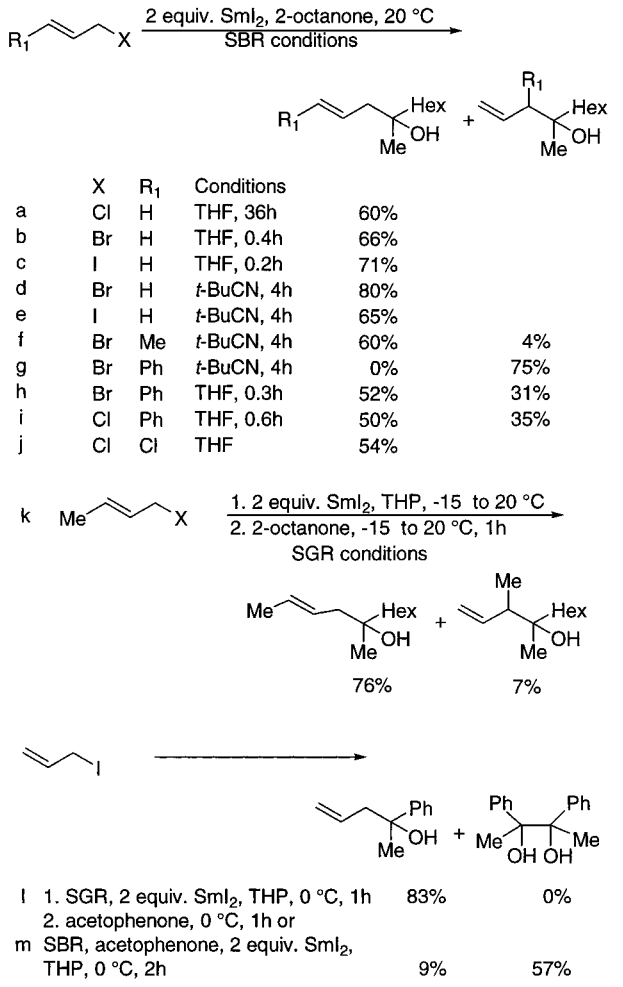
- higher reactivity is observed with allyl derivatives
- cyclization takes place, before the Barbier−Grignard reaction, if a five-membered ring compound can be produced
- successful reactions have been achieved with aryl halides when carried out in benzene−HMPA instead of THF−HMPA.

3.2.1. Reaction of Allyl, Propargyl, and Benzyl Halides [3−5,7,8,10,12,13,15,25,43]

In contrast to alkyl halides, the reaction of allyl or benzyl halides with SmI_2 in THF leads to the formation of products resulting from the coupling of two allyl moieties (Wurtz coupling). This of course precludes the use of SmI_2 in THF under SGR conditions.[1]

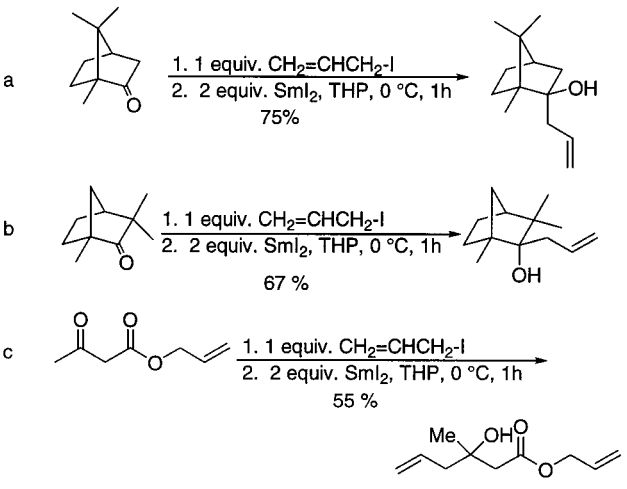
Allylation (Schemes 17 and 18) and benzylation (Scheme 19) of carbonyl compounds can nevertheless be successfully achieved in THF under SBR conditions[1,67] but is limited to aliphatic compounds because

Scheme 17



	X	R_1	Conditions		
a	Cl	H	THF, 36h	60%	
b	Br	H	THF, 0.4h	66%	
c	I	H	THF, 0.2h	71%	
d	Br	H	*t*-BuCN, 4h	80%	
e	I	H	*t*-BuCN, 4h	65%	
f	Br	Me	*t*-BuCN, 4h	60%	4%
g	Br	Ph	*t*-BuCN, 4h	0%	75%
h	Br	Ph	THF, 0.3h	52%	31%
i	Cl	Ph	THF, 0.6h	50%	35%
j	Cl	Cl	THF	54%	

Scheme 18

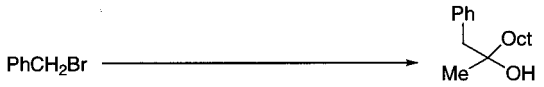


pinacols are instead produced from aromatic carbonyl compounds such as acetophenone.

The reaction occurs particularly rapidly with cinnamyl halides (Scheme 17, entries g−i) including the chloride (Scheme 17, entry i), and although it is quite slow with allyl chloride (Scheme 17, entry a), it works fine, attesting to the higher reactivity of the allyl derivatives as compared to the corresponding alkyl halides which are inert toward SmI_2 (section 3.1).

Related reactions allow the coupling, which is otherwise particularly difficult to achieve, of benzyl

Scheme 19



a	(SBR) 2-octanone, 2 equiv. SmI_2, THF, 20 °C, 0.5h	69%
b	(SBR) 2-octanone, 2 equiv. SmI_2, *t*-BuCN, 20 °C, 4h	85%
c	(SGR) 1. 2 equiv. SmI_2, THP, -15 °C, 0.2h 2. 2-octanone, -15 to 20 °C, 1h	85%

bromide to acetaldehyde (THF, 36%), of propargyl bromide to octanal (THF, 72% propargyl alcohol + 16% allenyl alcohol)[67] or to 2-octanone (THF, 37% propargyl alcohol + 36% allenyl alcohol),[1] and of $PhCF_2Cl$ to 2-octanone (THF−benzene−HMPA, see Scheme 40, entry a).[68]

At any rate, the SBR can be favorably compared to some known process when it works (see above-mentioned limitations) because of its smoothness, rapidity, and chemoselectivity. Selective reduction of the allyl chloride moiety in the presence of a vinylic chloride has been successfully achieved (Scheme 17, entry j).[7]

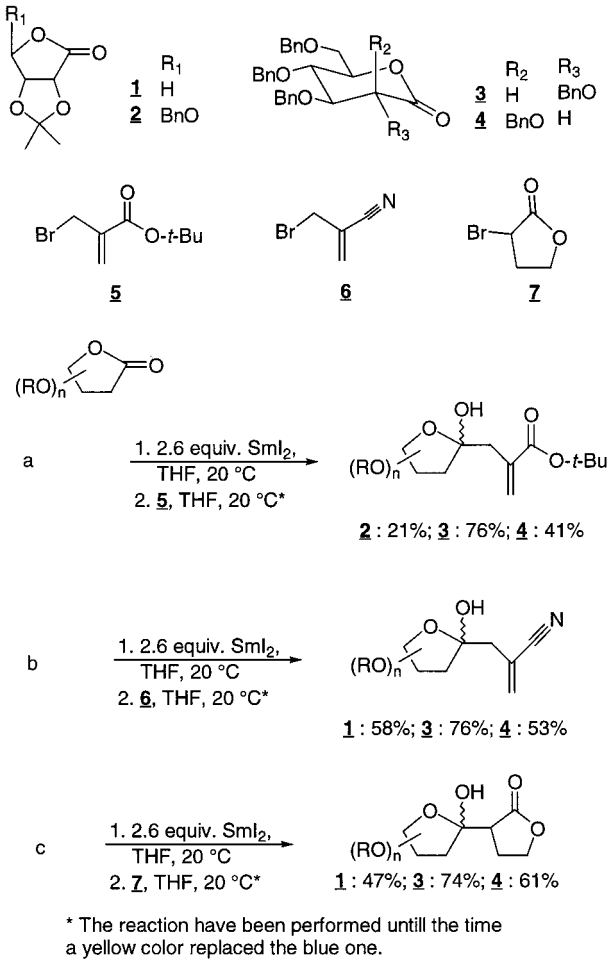
The reaction has been also carried out in alkylnitriles as well as in THP.[62] These solvents offer several advantages over THF that are disclosed below. For example, the reactions are slower in pivalonitrile and need several hours at room temperature to go to completion instead of a few minutes in THF.[67] The chemoselectivity is nevertheless improved since related alkyl halides such as iodododecane are inert under these conditions. Addition of NiI_2 greatly improves the rate of the SBR.[62]

Terahydropyran proved to be the solvent of choice for the allylation (Scheme 17, entries k−m; Scheme 18) and the benzylation (Scheme 19, entry c) of carbonyl compounds. It allows, more efficiently than in THF, the hydroxy-allylation under SBR conditions of several carbonyl compounds, including aldehydes, hindered carbonyl compounds, and allyl acetoacetate which is particularly prone to enolization (Scheme 18, entry c). It also permits under SGR conditions the hydroxy-allylation of aromatic ketones which otherwise are not properly allylated (Scheme 17, compare entry l to entry m).[51] In this solvent (i) allyl iodide reacts with exceptionally high stereocontrol with camphor (97% d.e. for the exo alcohol) and fenchone (92% d.e. for the endo alcohol) (Scheme 18, entries a and b),[51] and (ii) crotyl bromide reacts with 2-octanone with very high regioselectivity from its least substituted carbon (Scheme 17, entry k).[51]

Similar results have been obtained in the latter case if the reaction is performed in pivalonitrile under SBR conditions[20] but the regioselectivity is reversed with cinnamyl bromide, which reacts with the same ketone from its benzylic carbon (Scheme 17, entry g).[20] It is interesting to notice that a regioisomeric mixture (63/37; benzylic/allylic) of compounds is produced when the same reaction is carried out in THF (Scheme 17, entry h).[1]

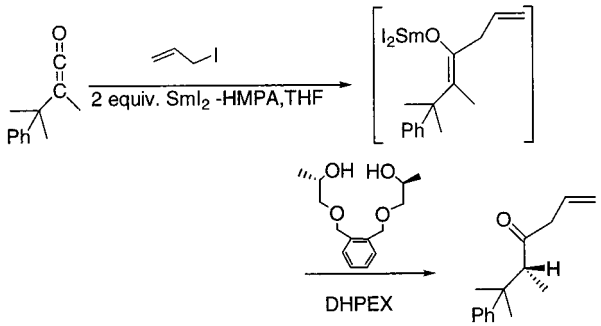
The reaction has been successfully extended to *tertio*-butyl bromomethyl-acrylate and aldonolactones or carbohydrates and to the related bromomethyl-acrylonitrile (Scheme 20, entries a and b).[69]

Scheme 20



* The reaction have been performed untill the time a yellow color replaced the blue one.

Scheme 21



a > 1 equiv. DHPEX, -78 °C to 20 °C --- (97% e.e.)
b 0.15 equiv. DHPEX, Ph_3COH, -78 °C, 26h 55% (93% e.e.)

Finally, the reaction of allylsamarium diiodide with unsymmetrical dialkylketenes has been disclosed and provides samarium enolates.[70,71] These have been enantioselectively protonated using (i) a stoichiometric amount of a C2-symmetric homochiral diol (DHPEX, Scheme 21, entry a) or (ii) a catalytic amount of the same diol but in the presence of stoichiometric amounts of triphenylcarbinol as a proton source (Scheme 21, entry b).

3.2.2. Reaction of ω-Alkenyl Halides

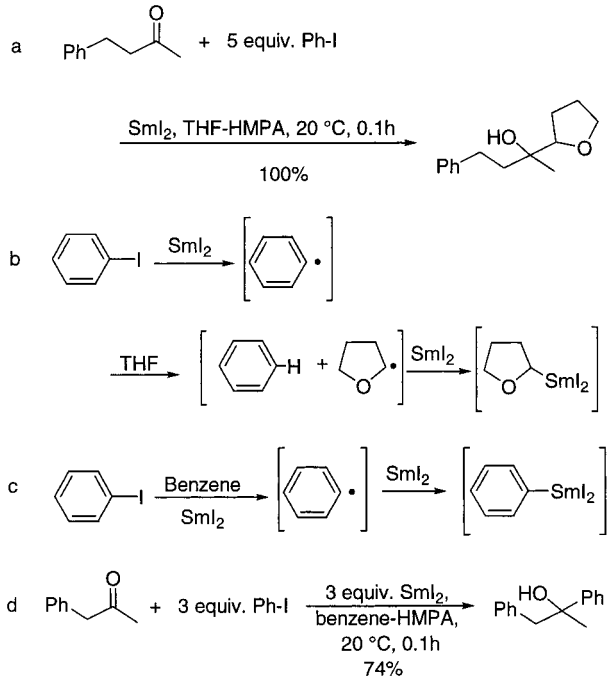
The reaction of ω-alkenyl halides[3,7,9,29,40] with SmI_2 and a carbonyl compound can produce, depending upon the structure of the alkenyl halide and the conditions used, the alcohol (i) derived from trapping of the original organosamarium or (ii) resulting from a cycloalkylmethylldiiodosamarium (Scheme 8, entry a−e and Scheme 9).[7,40] As already discussed in section 2.1.1.1, this reaction provides unsaturated alcohols along with the rearranged alcohol (55/45) under SBR conditions whether the reaction is carried out in THF or THF−HMPA,[29] whereas SGR conditions using as little as 2 equiv of HMPA proved to be best to produce the rearranged alcohol.[9,29,40] Unsaturated compounds bearing a tertiary instead of a primary iodide (Scheme 8, entry f),[9] an oxygen, or a nitrogen atom on the alkenyl or alkynyl side chain (Scheme 9, entries f−h)[72] possess an even higher propensity to produce the rearranged product via a radical process.

3.2.3. Reactions Involving Aryl and Vinyl Halides[9,17,38]

3.2.3.1. Reactions Performed in THF or THF−HMPA. Aryl and vinyl halides react similarly to tertiary alkyl halides when the reaction is carried out in THF or THF−HMPA. They are less reactive than primary alkyl halides[1] and are reduced to the radical stage but are not further reduced to the carbanion stage.[1,7,9,37] They do not, therefore, add to carbonyl compounds whatever the conditions used (SBR or SGR). Nevertheless, the radical thus formed

(i) reacts intermolecularly with THF to produce, even in the presence of HMPA, the 2-tetrahydrofuranyl radical first, then the 2-tetrahydrofuranylsamarium (Scheme 22, entry b), which finally adds

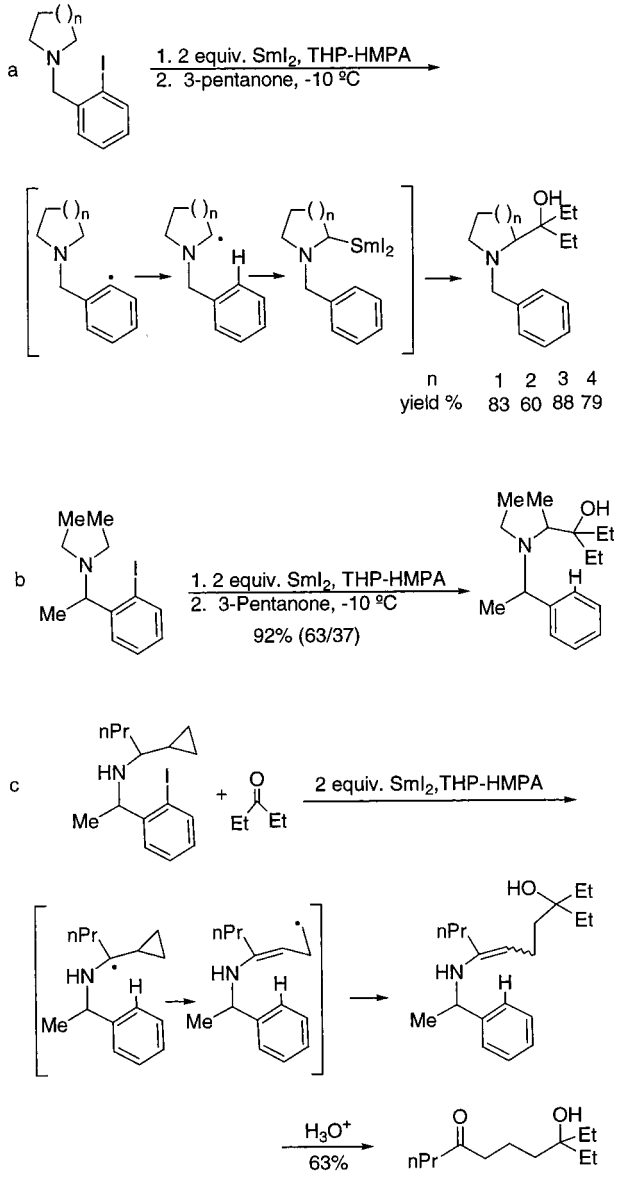
Scheme 22



to ketones and leads to tetrahydrofuranyl carbinols (Scheme 22, entry a).[7,9,73]

(ii) reacts intramolecularly in the case of *o*-iodobenzylamines to produce sequentially the aryl radical, the α-aminoalkyl radical and the α-amino carbanion which finally leads to the corresponding

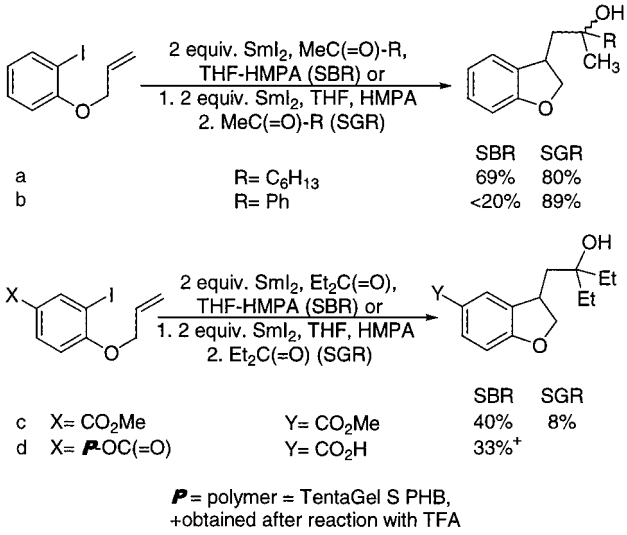
Scheme 23



β-amino alcohol on further reaction with a carbonyl compound (Scheme 23, entries a and b).[74−76] The reaction takes place on tertiary as well as secondary cyclic or alicyclic amines (Scheme 23, entries a and b)[74−76] and provides an original and efficient route to α-metalloamines that are otherwise difficult to synthesize. It takes another course with (1-cyclopropylbutyl)amine which, after aqueous workup, instead leads to a δ-hydroxyketone arising from the ring opening of the intermediate cyclopropyl radical (Scheme 23, entry c).[74]

(iii) adds intramolecularly on suitably positioned C,C double bonds to generate a novel radical by cyclization. This can be further reduced to a new alkyl samarium which has, in turn, been efficiently trapped with carbonyl compounds to provide the alcohols disclosed in Scheme 24. The reaction has been performed with aryl iodides in THF−HMPA, using SBR[7,9,37,38,66,72,77] as well as SGR conditions (Scheme 24).[9,37,38,66,77] The latter conditions are those recommended especially for aromatic carbonyl compounds (Scheme 24, entry b). The whole process

Scheme 24



P = polymer = TentaGel S PHB,
+obtained after reaction with TFA

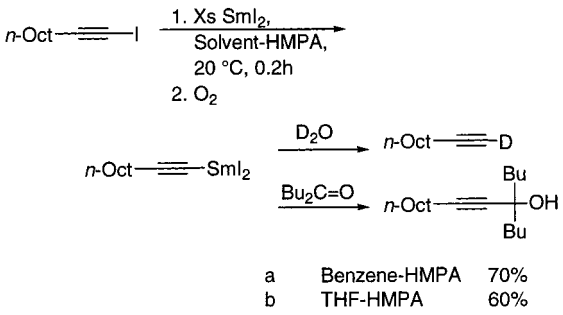
occurs on aromatic compounds with or without a heteroatom on the side chain and possessing a terminal or an α,β-dialkyl substituted C,C double bond.[9] The presence of an additional group on the aromatic ring (Scheme 24, compare entry c to entries a and b) slightly changes the figure. The alcohol resulting from trapping the cyclized organometallic with ketones is still formed when an ester group is present on the aromatic ring but in very poor yield under SGR conditions (8%) and in modest yields (40%) under SBR ones (Scheme 24, entry c).[77] It has been suggested that "the reductive species in this case is generated faster and had a shorter lifetime than allyloxy-2-iodobenzene".[77] This SmI_2-mediated sequential radical cyclization/ionic capture has been successfully extended to reactions on solid resin (TentaGel S PHB), with results similar to those described for the corresponding solution reactions (Scheme 24, compare entry d to entry c).[77] They are both highly substrate-dependent, which may limit generality in combinatorial construction.[77] The reaction has been extended to allyloxy-2-chlorobenzene[64] but requires being performed under irradiation (560−700 nm) and not with HMPA.

3.2.3.2. Reactions Performed in Benzene−HMPA. The reaction takes another course when carried out under SBR conditions with aryl iodide in benzene−HMPA because it now provides the corresponding alcohol in moderate yield (Scheme 22, entry d; compare to section 3.2.3.1).[57] In this mixture of solvents, the aryl radical first produced is further reduced to the arylsamarium diiodide (Scheme 22, compare entry c to b). The reaction is much more difficult with aryl bromides and does not take place with the corresponding chlorides.[57]

3.2.4. Reaction of Iodoalkynes

1-Iodoalkynes react, in the presence of SmI_2, with aldehydes, ketones, and enones to produce the corresponding propargylic alcohols in good to fair yields.[52] The reaction has been performed in benzene−HMPA (SBR, SGR) or THF−HMPA (SGR) (Scheme 25)[52] and takes place with high chemoselectivity on the keto group of ϵ-keto esters whatever the conditions (SBR,

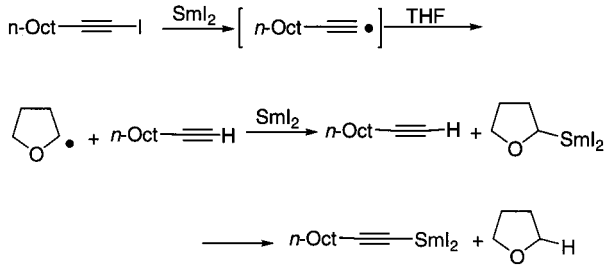
Scheme 25



SGR) used. An important difference of reactivity is nevertheless observed with γ-hydroxy ketones and enones which react cleanly to provide the corresponding alcohol under SGR conditions but lead to a complex mixture of compounds under SBR conditions.[52]

Although it has been clearly proved that alkynylsamariums are involved in this process, their formation is not straightforward and does not, for example, involve a direct halogen/metal exchange. There is, in fact, strong evidence that the reaction proceeds through an alkynyl radical either in benzene or THF (Scheme 26).[52] In the case of THF, for example, the

Scheme 26



alkynyl radical is expected to abstract a hydrogen atom from THF to afford an alkyne and the THF radical. The latter then would be reduced by SmI_2 to its anion which deprotonates the alkyne to lead finally to the alkynyl diiodosamarium (Scheme 26).[52]

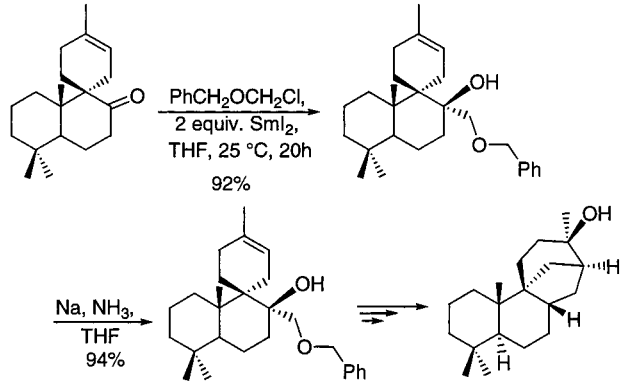
3.3. Reactions Involving α-Heterosubstituted Alkyl Halides[4,10,12]

SmI_2 reacts at room temperature, under SBR conditions, with α-heterosubstituted alkyl halides and carbonyl compounds to produce β-heterosubstituted alcohols. This reaction offers the advantage of simplicity and high yields and avoids the problems usually associated with the instability of the related organometallics which decompose via an α-elimination reaction.[58]

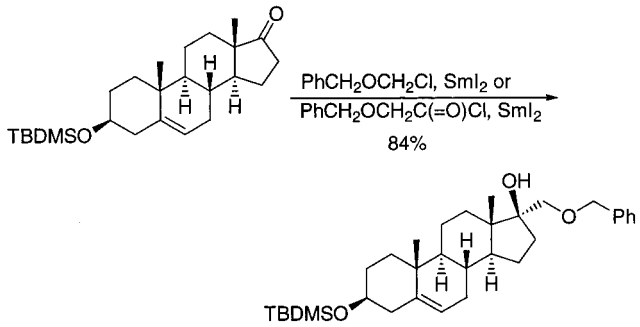
3.3.1. Reaction of α-Alkoxyalkyl Halides

α-Alkoxyalkyl halides[4,43,58,78,79] (e.g., methoxymethyl chloride[43] and benzyloxymethyl chloride[43,58,79,80]) react with SmI_2 under SBR conditions to allow the alkoxyalkylation of various aldehydes and ketones. Benzyloxymethyl chloride (Schemes 27−29) is particularly useful because the resulting β-benzyloxyalkyl alcohols give, after hydrogenolysis, 1,2-diols, and therefore the intermediate benzyloxymethyl samarium diiodide plays the role of a hydroxymethyl anion (Schemes 27 and 29).[43,58,79,80]

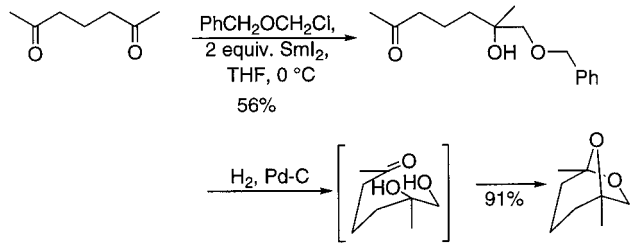
Scheme 27



Scheme 28



Scheme 29

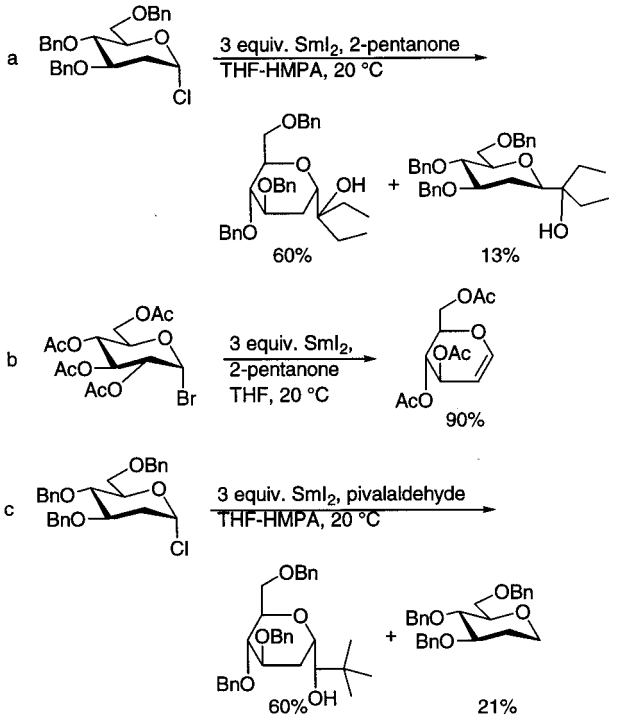


The reaction takes even place with the highly enolizable dibenzyl ketone[58] and with the highly hindered cyclohexanone precursor of (*d*,*l*)-2-desoxystemodinone, which, in turn, leads to a quantitative yield of the corresponding monoprotected diol (Scheme 27).[80] This is remarkable because this ketone is so hindered that it does not react even with methyllithium.[80] This reaction has also been successfully used for the particularly straightforward synthesis of frontalin (Scheme 29).[58,79]

The α-alkoxymethylsamarium has also been produced from the more stable and less toxic (i) α-alkoxyacetyl chloride and SmI_2 via the decomposition of the corresponding acyl radicals[43,81] (Scheme 28) or (ii) α-alkoxyalkylpyridylsulfone.[82] The latter reaction has been used efficiently for the synthesis of sugar derivatives.[83]

Applied to 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl chloride, the SBR produces the corresponding alcohols in quite good yield from ketones.[78] Unfortunately epimerization, which is due to the high temperature (20 °C) required for the reduction, takes place leading to a 82/18 mixture of α/β-stereoisomers (Scheme 30, entry a).[78] The reac-

Scheme 30

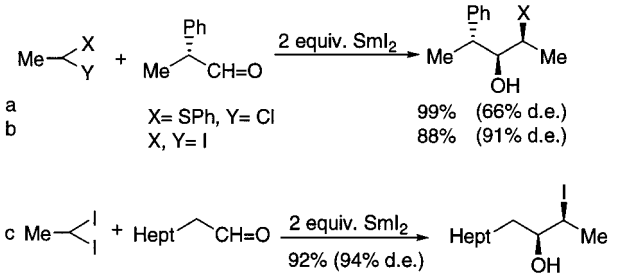


tion takes another course with the corresponding acetylated analogue (Scheme 30, entry b).[78] It probablyproceeds through the transient formation of an anomeric organosamarium species which undergoes fast β-elimination of an acetate to produce the unsaturated glycal instead.[78] In this case the bromine/samarium exchange takes place even in THF alone, and HMPA is not necessary. The reductive samariation proved to be much slower than the reductive lithiation (performed by lithium naphthalenide in THF) and is routinely and advantageously performed at room temperature.[78] In contrast with the related organolithium species, the anomeric organosamarium species is stable enough at 20 °C to be trapped by electrophiles. The condensation with aldehydes is more problematic and has been performed under SGR conditions. The aldehyde has to be added to the chloride shortly (30 s) after SmI_2 in order to avoid the fast reduction of the carbonyl group (Scheme 30, entry c).[78] The production in these cases of a single α-*C*-glycoside of unknown stereochemistry at the hydroxyl carbon has been accounted for the trapping of the kinetic α-samarium species by the more reactive aldehyde.[78]

3.3.2. Reaction of α-Thioalkyl and of α-Selenoalkyl Halides

α-Phenylthioalkyl chlorides react in THF−HMPA with aldehydes under SBR conditions and produce β-hydroxyalkyl sulfides[84] with quite good stereocontrol (Scheme 31, entry a). The same reaction when applied to β-hydroxyalkyl sulfoxides works fine but takes place with no stereocontrol.[43] The reaction between 1-phenylthio-1-ethyl chloride and α-branched aldehydes is particularly valuable because it provides the corresponding β-hydroxyalkylsulfides in high yield and quite high control on the three stereogenic centers (Scheme 31, entry a).[84,137]

Scheme 31

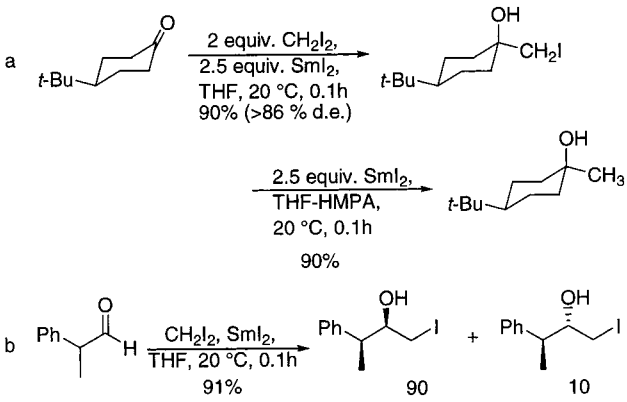


Reaction of related phenylselenomethyl chloride, which has been performed in THF alone, is much less general since it is strictly limited to ketones and does not apply to aldehydes, which instead lead to alcohols or to pinacols by direct reduction or reductive dimerization.[136]

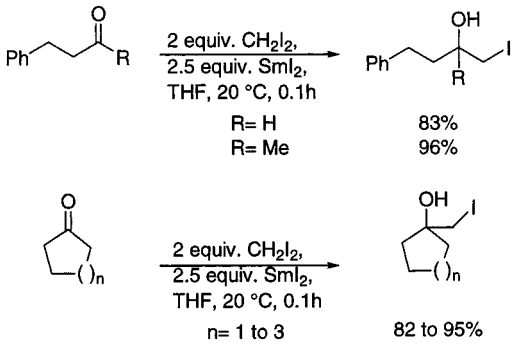
3.3.3. Reaction of α-Halogenoalkyl Halides

Kagan's reagent proved to be useful for the monohaloalkylation of aldehydes and ketones under SBR conditions (2 equiv SmI_2, THF, −78 °C, −20 °C, or 0 °C). The reaction has been efficiently achieved with diiodo-[61,85,86,137] and dibromoalkanes,[60,85,87] producing usually the corresponding β-iodohydrins in high yields (Scheme 31, entries b and c; Schemes 32 and 33).

Scheme 32

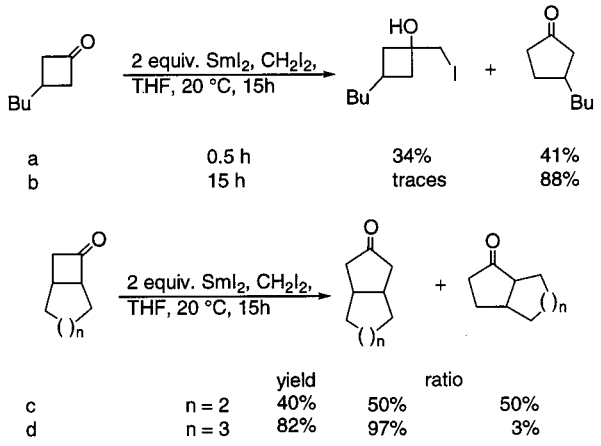


Scheme 33



The mono-iodomethylation of carbonyl compounds can be carried out with similar success either from diiodo- or dibromomethane.[85] It is very fast in the former case (THF, 20 °C, <0.1 h) but takes a longer time with dibromomethane. The formation of an iodohydrin instead of the expected bromohydrin from dibromomethane implies that bromine−iodine ex-

Scheme 34



change has taken place. This process could has been achieved via the intermediate formation of an epoxide.[85]

The reaction takes place at room temperature, without appreciable decomposition of the organic halide, on a large variety of carbonyl compounds including aldehydes and straight chain and cyclic (C-5 to C-7) ketones. It produces the corresponding iodohydrins in very good yields (Schemes 32 and 33).[85] We have to recall that very low temperatures (−78 °C or −115 °C) are required when the reactions are carried out with other metal counterions.[85]

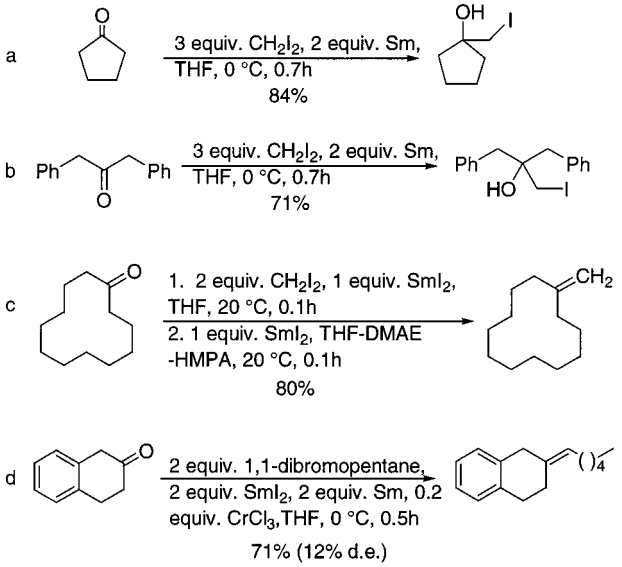
The reaction takes a slightly different course when performed on cyclobutanone since it delivers, even after a short time (THF, 20 °C, 0.5 h), not only the expected iodohydrin but also a five-membered ring-enlarged ketone (Scheme 34, entry a).[88] The latter is exclusively formed if the reaction is performed for a longer period of time (15 h) (Scheme 34, entry b).[88]

The reaction involving diiodomethane is highly chemoselective toward ketones and leaves untouched the ester group of ethyl levulinate.[85] It proved to be highly stereoselective in the case of 4-*tertio*-butylcyclohexanone (Scheme 32, entry a) and 2-phenylpropionaldehyde (Scheme 32, entry b), which led mainly to the axial alcohol and to the iodohydrin resulting almost exclusively from the "Cram-Felkin" type of approach.[85]

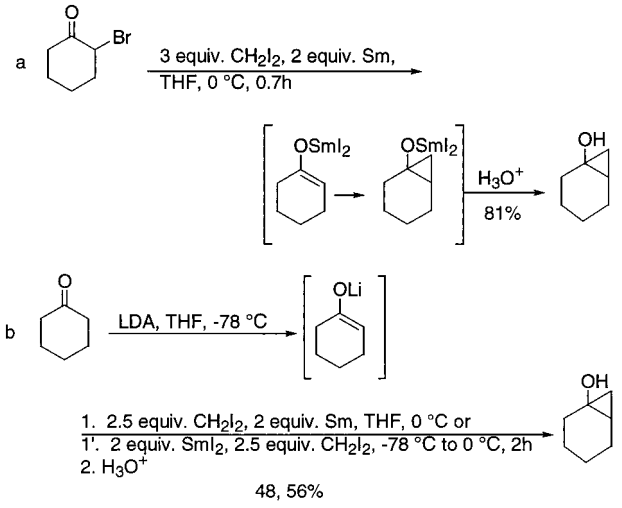
Even more spectacular stereocontrol has been achieved from 1,1-diiodoethane and aldehydes (Scheme 31, entries b and c), especially α-branched ones (Scheme 31, entry b), which leads to the corresponding iodohydrins with almost perfect control of the stereochemistry at the three stereogenic centers.[86,137] Production of a single diastereoisomer, in optically pure form, from 1,1-diiodoethane and an optically active α-amino-aldehyde rules out a kinetic resolution and probably implies a rapid racemization of the α-iodoalkylsamarium.[86]

The mono-iodomethylation can be efficiently performed in a more expeditious way by simply mixing the carbonyl compound, diiodomethane, and samarium (1:3:2) at room temperature in THF (Scheme 35, entries a and b).[58,61] Although the intermediate formation of SmI_2 from Sm and CH_2I_2[14] cannot be ruled out, there is some evidence that ICH_2SmI or ICH_2SmI_2 species are involved in the process.[58] In

Scheme 35



Scheme 36



any case, iodohydrins are produced from aldehydes and ketones, even from the highly enolizable dibenzyl ketone (Scheme 35, entry b), in yields similar to or a little lower than those reported from CH_2I_2 and SmI_2.[58]

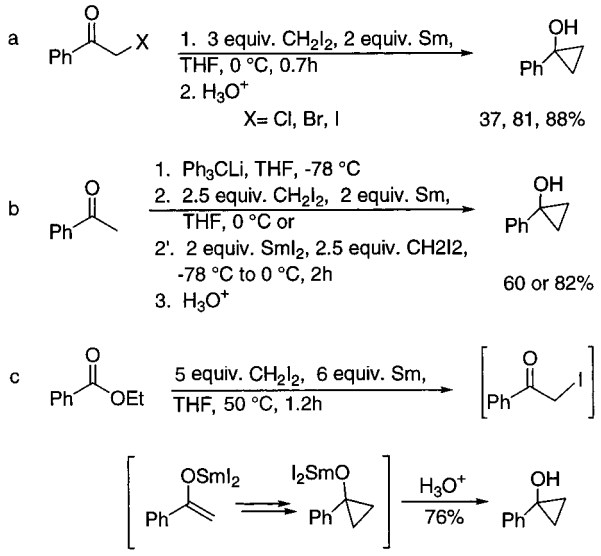
The reaction takes another course with α-halogeno ketones and instead leads to cyclopropanols (Scheme 36, entry a, and Scheme 37, entry a).[58,61] These are expected to be formed[58] by cyclopropanation of the samarium enolates resulting from the reduction of the α-halogeno ketones by the CH_2I_2−Sm reagent which also acts as a carbene source.[14,58] The same products are obtained when

(i) CH_2I_2−Sm or CH_2I_2−SmI_2 mixtures are reacted with the lithium enolate arising from the same ketones and LDA (Scheme 36, entry b)[58,89] or triphenylmethane (Scheme 37, entry b, compare the two methods described there).[58]

(ii) CH_2I_2−Sm is reacted with esters (Scheme 37, entry c)[58] or lactones.[69] The intermediate formation of an α-iodoketone has been postulated in this process.

Iodohydrins proved themselves valuable precursors of (i) alcohols from SmI_2−THF−HMPA for a short

Scheme 37



reaction time (Scheme 32, entry a),[85] (ii) epoxides on further reaction with NaOH−MeOH,[85] and (iii) olefins from SmI_2−THF−HMPA[85] or SmI_2−DMAE-HMPA (Scheme 35, entry c).[90] Alkylidenation of carbonyl compounds has been also achieved in one pot from SmI_2, Sm, and catalytic amount of $CrCl_3$ (ketone/dibromoalkane/SmI_2/Sm/$CrCl_3$: 1/2/2/2/0.1) (Scheme 35, entry d).[60] Note the particularly efficient formation of a new C,C bond formation from 1,1-dibromopropane and the highly enolizable β-tetralone (Scheme 35, entry d).[60]

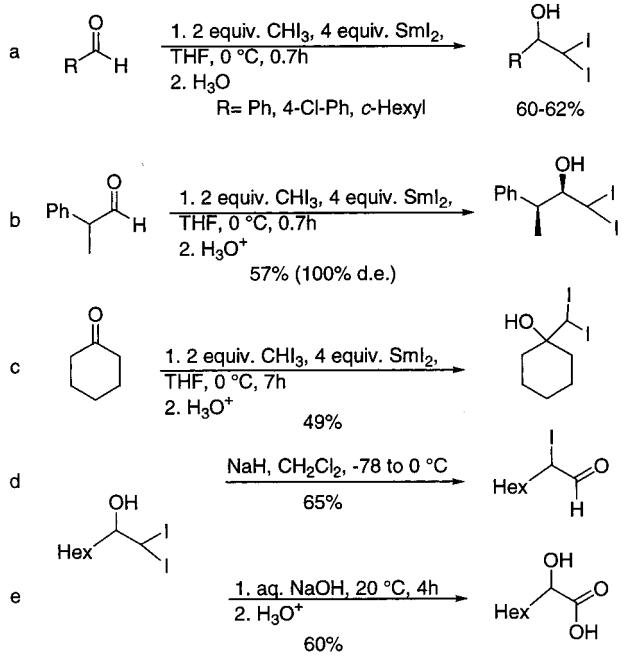
Diiodomethylation of carbonyl compounds, which has been very rarely described[91] compared to reactions involving CH_2I_2 instead, has been successfully achieved by iodoform and SmI_2 in THF under SBR conditions (Scheme 38, entries a−c).[92] β,β-Diiodoalkanols are produced in yields ranging from 40 to 60% from various aldehydes (Scheme 38, entries a and b) and ketones (Scheme 38, entry c).[92] Very high stereocontrol has been achieved with 2-phenyl propanal[92] which produces the iodohydrin resulting exclusively from the "Cram-Felkin" type of approach (Scheme 38, entry b)[85] (see Scheme 32, entry b, for related results).

A related process, involving the in situ synthesis of SmI_2 from metallic samarium and iodoform, has some drawbacks over the former process: aldehydes gave lower yields, and ketones are recovered.[92] Performing the latter reaction in the presence of HMPA does not improve the yields of β,β-diiodoalkanols but affords a complex mixture of products.[92]

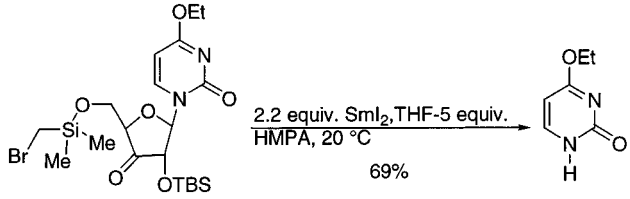
β,β-Diiodoalkynols proved to be valuable precursors of α-iodoaldehydes (Scheme 38, entry d) or of α-hydroxy carboxylates (Scheme 38, entry e) when reacted with sodium hydride or aqueous base, respectively.[92]

The reaction has been extended to 1-silyl-1,1-dibromoalkanes[87] and to carbon tetrachloride.[43] However, it has been observed that SBR conditions fail to give the expected tertiary alcohols from dibromodifluoromethane (Br_2F_2C)[43] and that an elimination takes place in THF−HMPA with the uridine derivative disclosed in Scheme 39 which leads to 4-ethoxy-2-pyrimidinone instead of the silyl protected alcohol expected from an ISBR.[36]

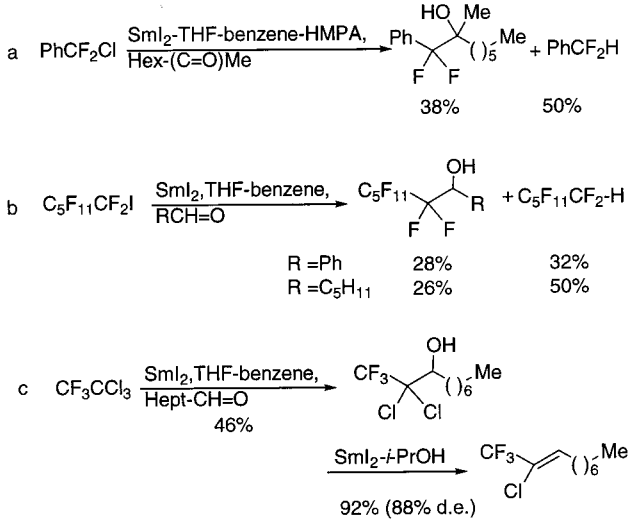
Scheme 38



Scheme 39



Scheme 40



Fluorinated organic groups such as C_6F_{13}, CF_3CCl_2, $PhCF_2$, and CF_2CO_2Et have also been introduced as nucleophilic species into aldehydes and ketones from fluorinated alkyl halides and SmI_2 under SBR conditions (Scheme 40).[68,93]

The reaction of $PhCF_2Cl$ is particularly slow in THF−benzene, requires the use of HMPA (Scheme 40, entry a),[68,93] and does not occur with aromatic aldehydes and ketones. These are, in fact, reduced faster by SmI_2 and deliver the corresponding alcohol in low yields.[93] This is also the case with $C_6F_{13}I$ (Scheme 40, entry b) which otherwise is efficiently

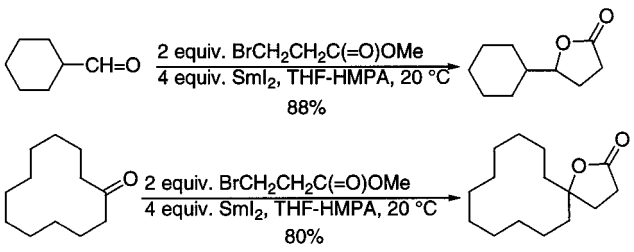
and quantitatively reduced, in the absence of the carbonyl compound, when the reaction is carried out in the presence of a proton source. The yields are, however, higher with CF_3CCl_3 (Scheme 40, entry c) which is more reactive and does not require the use of HMPA.[68]

Finally, some of the fluorinated β-chloroalkyl alcohols described above have been successfully transformed, on further reaction with SmI_2 in 2-propanol, to the corresponding α-trifluoromethyl vinyl chlorides in reasonably good yields and good diastereoselection (Scheme 40, entry c).[68]

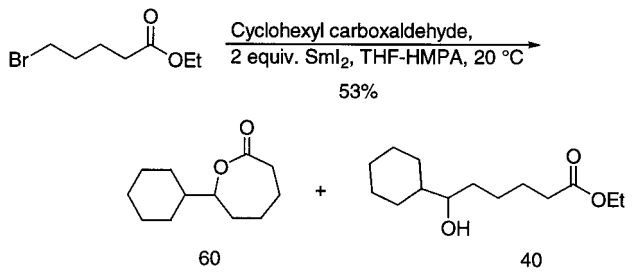
3.4. Reaction Involving ω-Halogeno Esters

Although reactive toward esters and lactones, organosamariums proved to be less reactive toward these functional groups than toward aldehydes and ketones. It is therefore possible to perform, under SBR conditions, the selective (i) intermolecular reaction of ω-halogeno esters with aldehydes or ketones, thus avoiding side reactions such as intramolecular cyclization of the ω-halogeno esters or competing intermolecular reaction of the organosamarium formed onto the carbonyl group of another molecule of ω-halogeno ester (Scheme 7, Schemes 41 and 42)[1,54]

Scheme 41



Scheme 42



and (ii) cyclization on to the carbonyl group of ω-halogeno aldehydes and -ketones bearing a carboxyl group in the α-position (section 4.2; see Scheme 52 for example).

β-Bromo esters, as well as γ- and δ-bromo esters have been successfully reacted, under SBR conditions, in THF−HMPA with carbonyl compounds to produce within minutes at room temperature γ- and δ-lactones in good yields (Scheme 7 and Scheme 41).[54]

Large ring lactones are somewhat more difficult to form and therefore appreciable amounts of uncyclized hydroxyesters can be also obtained (Scheme 42).[1,54] The reaction also works in THF alone or when carried out with transition metal salts such as $FeCl_3$ or Cp_2ZrCl_2, but use of HMPA as cosolvent proved to be by far superior (Scheme 7).

The case of β-bromo esters is particularly interesting because it gives rise very cleanly to homoenolates (Scheme 7 and Scheme 41),[54] which are otherwise difficult to prepare[94] and require special procedures including the masking of the ester group. (See Scheme 102, entries e and f, for an example of unsuccessful reactions.)

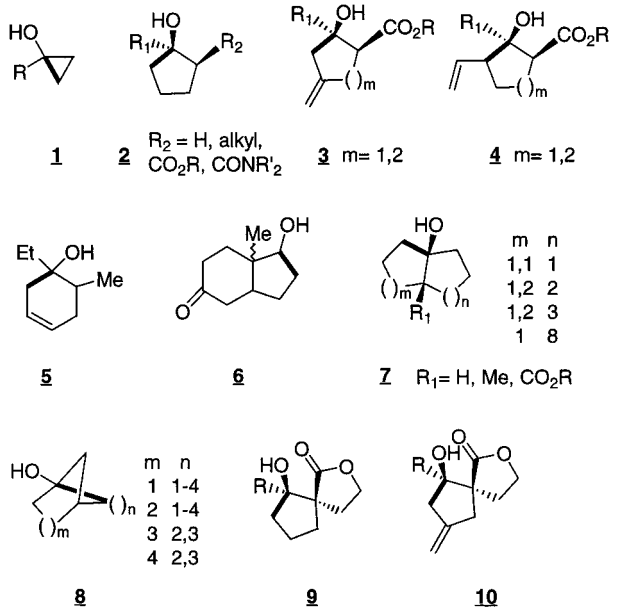
Unprecedented SmI_2 mediated Dreiding−Schmidt reactions involving 2-bromomethyl acrylates and the related nitrile have been used for the chain extension of aldonolactones (Scheme 20, entries a and b).[69]

4. SmI_2 Promoted Cyclization of ω-Halogeno Aldehydes and Ketones (ISBR)

SmI_2 promotes efficiently the cyclization of ω-halogeno carbonyl compounds. This is due to the homogeneity of the medium and the high chemo- and stereocontrol often unavailable with other metals.[12] This reaction proved to be, for the synthesis of five-membered cycles, by far superior to those involving instead Mg(Hg) in THF[27] and unique for the synthesis of six-membered cycles which cannot be produced by halogen/main group metal exchange.[30,31]

SmI_2 promoted cyclization of ω-halogeno carbonyl compounds leads, under very mild conditions, to a large variety of cycloalkanols (Scheme 43,

Scheme 43

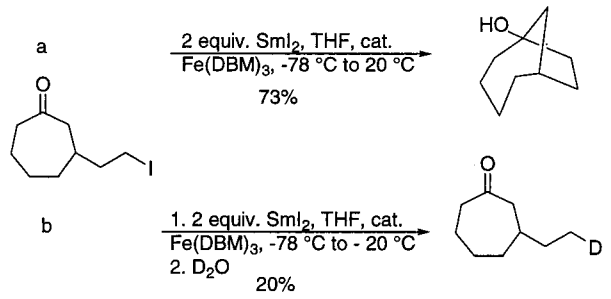


1−**10**)[26−28,30,41,95,96] including cyclic **1**−**5**, bicyclic (*m.n*.0) **6**, **7**, bicyclic (*m.n*.1) **8**, and spiro **9**, **10** derivatives. The reaction has been performed on aldehydes (**1**, **2**, **4**)[41] as well as on ketones (**1**−**3**, **5**−**10**)[26−28,30,96] bearing an alkyl[26,30] or an allyl iodide (**1**−**6**)[26] or in rare cases a bromide in proper position (**7**−**10**)[26] (the emboldened bond in Scheme 43 is the one formed in the process).

The reaction often occurs with extremely high stereocontrol especially if an extra carboxyl group is present in the β-position to the former[26] and even allows the synthesis of surprisingly strained alcohols such as cyclopropanols (Scheme 43, **1**)[97] or the bicyclo-[2.1.1]hexan-1-ol (Scheme 43, **8**).[31] The reaction is

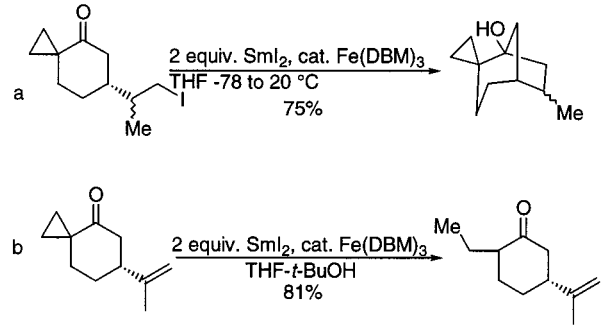
expected to take place via a halogen/samarium exchange followed by addition of the resulting species to the carbonyl function. This, although very difficult, has been proved in few instances (for related results and restrictions, see Section 2).[29] For example, the intermediate formation of a ketyl radical can be ruled out in the $SmI_2-Fe(DBM)_3$ catalyzed cyclization of 3-(ω-iodoalkyl)-cycloheptanone (Scheme 44) and of

Scheme 44



3-(ω-iodoalkyl)-cyclohexanone bearing a three-membered spirocycle in the α-position disclosed in Scheme 45 because

Scheme 45



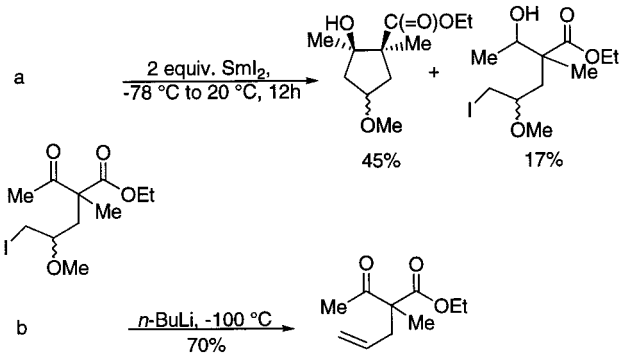
• quenching the former reaction with D_2O water, before completion, leads to deuterated 3-ethylcycloheptanone besides the unreacted iodo derivative and the bicyclo[4.2.1] cyclanol (Scheme 44, entry b compare to entry a)

• the tricyclic derivative is formed from the cyclopropyl ketone shown in Scheme 45, entry a. We have to recall that cyclopropane ring opening would have taken place if the reduction had instead led to a ketyl radical as disclosed in a related example involving the reduction by SmI_2 of a cyclopropyl ketone missing the halogen (Scheme 45, entry b).[31]

On the other hand, reaction of SmI_2 with the δ-iodo-γ-methoxy ketone shown in Scheme 46, entry a, leads after cyclization to substantial amounts of 2-carbethoxy-4-methoxy-cyclopentanol (Scheme 46, entry a)[31] rather than to the unsaturated β-keto ester which is in fact formed when the reaction is instead carried out with butyllithium (Scheme 46, entry b).[31] These results tend to suggest that an organosamarium has not been formed and that a ketyl radical is an intermediate in this and related reactions[26].

In several instances the reactivity of SmI_2 has been compared to that of lithium, Mg or Mg(Hg),[26,27] alkyllithiums,[27,30,31] or tributyltin hydride[41] and has been proven to be far superior not only because it

Scheme 46



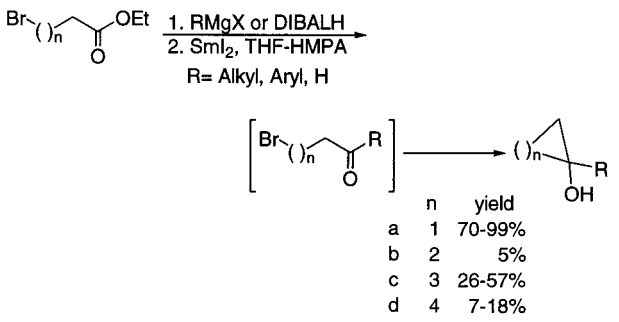
delivers a better yield of alcohol but also because it leads to a much higher diastereoselection.

4.1. Cyclization of Acyclic ω-Halogeno Aldehydes and Ketones

4.1.1. Reactions Involving Saturated Derivatives

Acyclic ω-halogeno ketones of various length have been cyclized, in THF−HMPA, with variable efficiency to the three corresponding six-membered cyclanols (Scheme 47).[97] The formation of cyclopro-

Scheme 47



	n	yield
a	1	70-99%
b	2	5%
c	3	26-57%
d	4	7-18%

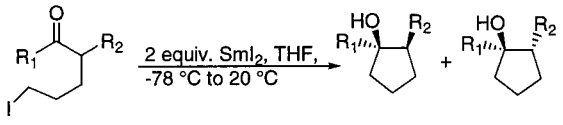
panols in exceedingly good yields from β-bromo ketones or aldehydes is particularly impressive,[97] especially if one knows that they can be generated in situ from 3-bromopropionates, Grignard reagents, or DIBALH, respectively (Scheme 47, entry a).[97]

The reaction is far more difficult when applied to the synthesis of cyclobutanols, cyclopentanols, and cyclohexanols which are delivered in quite poor yields (Scheme 47, entries b−d).[97] Nevertheless, cyclopentanols bearing two contiguous groups are formed in very high yield from 2-alkyl- and 2-aryl-5-iodo-acyclic ketones and SmI_2 (Scheme 48).[27] The diastereoselection (in favor of the *trans*-relationship between the two groups) is quite poor for methyl- and isopropyl ketones (Scheme 48, entries a−c) but is much higher for *tertio*-butyl- and phenyl ketones (Scheme 48, entries d and e).[27]

Comparative results involving butyllithium as the reagent are presented in Scheme 49.[27,32]

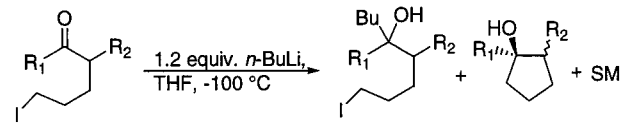
Cyclization also occurs on simple ketones incorporating a secondary alkyl halide (Scheme 50, entry a) or an allyl bromide (Scheme 50, entry b) moiety. The yields are good in both cases, but the former reaction lacks stereoselectivity (Scheme 50, entry a).[26]

Scheme 48



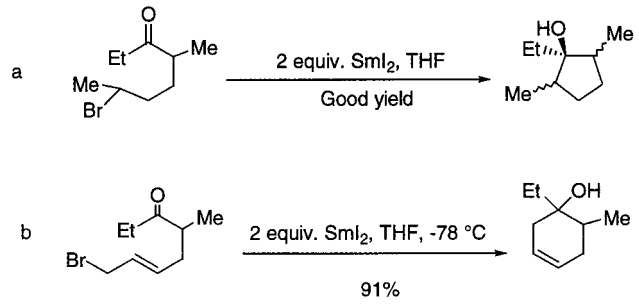
	R_1	R_2	yield %	ratio	ratio
a	Et	Me	92	47	53
b	*i*-Pr	*n*-Pr	78	80	20
c	*i*-Pr	Ph	99	82	18
d	*t*-Bu	Me	92	96	03
e	Ph	Me	54	97	06

Scheme 49



	R_1	R_2	ratio	ratio	ratio
a	Me	H	35%	21%	34%
b	*i*-Pr	Ph	0%	100%	0%

Scheme 50



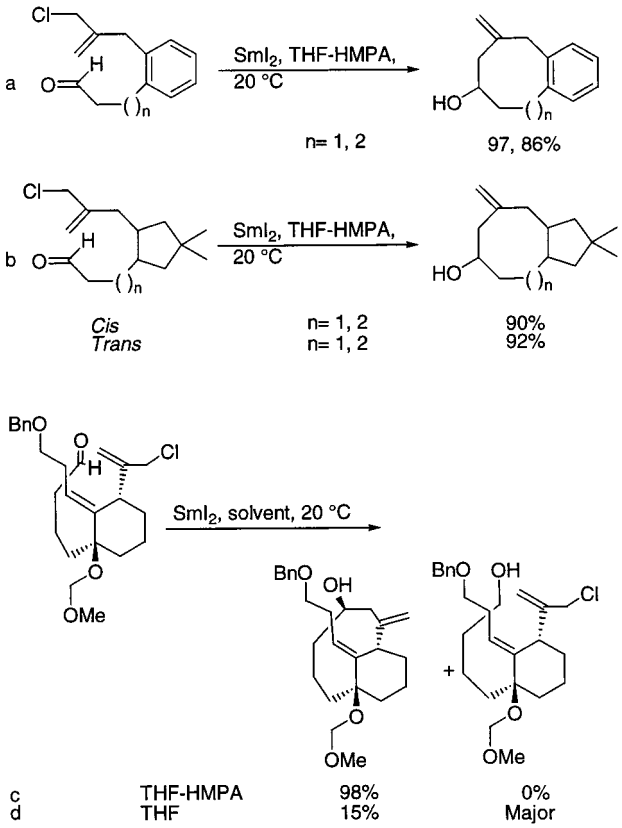
4.1.2. Reactions Involving Unsaturated Derivatives

Cyclization of aldehydes bearing an allylic chloride appendage in suitable position has been extremely efficiently achieved with SmI_2 in THF−HMPA (Scheme 51).[98,99] It allows, *without resorting to high dilution*, the synthesis of a series of methylenecyclooctanols and of methylenecyclononanols relevant to the 8-6(aromatic) and 9-6(aromatic) fused rings disclosed in Scheme 51, entry a, and to the most flexible 8-5, 9-5 fused rings shown in Scheme 51, entry b.[99] This reaction has been also used for the synthesis, in almost quantitative yield, of the 9-6 fused ring system of vinigrol (Scheme 51, entry c).[98] Use of HMPA is required since it has been, for example, found that reduction of the carbonyl group to the corresponding primary alcohol takes place rather than cyclization leading to the 9-6 fused ring system of vinigrol if HMPA is omitted (Scheme 51, entry d, compare to entry c).[98]

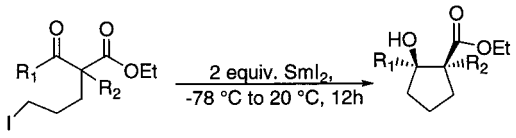
4.2. Cyclization of Acyclic ω-Halogeno Ketones Bearing an Ester or Amide Group in the α-Position

The presence of an ester (Scheme 52), an amido (Scheme 53) group, or a lactone ring (Scheme 54, entry a) β to the carbonyl group of ω-iodoalkyl carbonyl compounds allows the synthesis of β-hydroxy esters, amides, and spirocyclic derivatives with very high control of diastereoselectivity in a predictable sense.[26] The best results have been observed in

Scheme 51

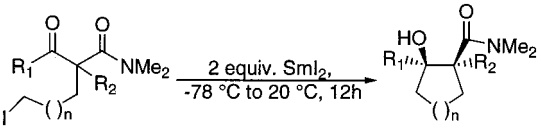


Scheme 52



	R_1	R_2	yield	d.e.
a	H	Me	96%	89
b	Me	Et	78%	91
c	*t*-Bu	Me	83%	100
d	Ph	Me	39%	100
e	Me	*i*-Pr	74%	87
f	Me	Ph	83%	100

Scheme 53

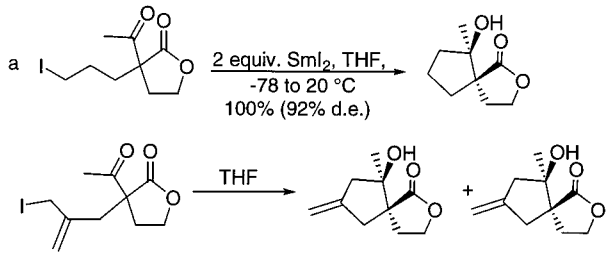


	R_1	R_2	n	yield	d.e.
a	H	Me	1	72%	90
b	Me	Et	1	89%	100
c	*t*-Bu	Me	1	77%	100
d	Ph	Me	1	49%	100
e	Me	Et	2	49%	100
f	*t*-Bu	Me	2	62%	100

THF. Use of additives such as $Fe(DBM)_3$ (5%), *N*,*N*-dimethylacetamide (10%), tetraglyme, or 18-crown-6 (1 equiv each) or performing the reaction in DME alone leads to lower yields and dramatic decrease in stereoselectivity. Even more interestingly it has been reported that magnesium, even when activated, is unable to promote this cyclization.[26]

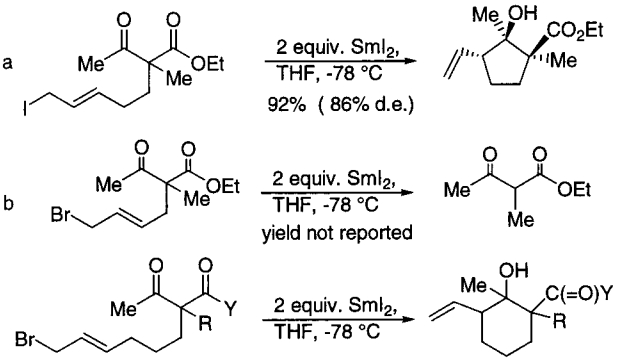
The reaction affords, from ketones, highly substituted *cis*-2-hydroxycyclopentanecarboxylates and the

Scheme 54



	reagent	yield	ratio	ratio
b	SmI_2	94%	86	14
c	$CrCl_2$	84%	87	13
d	Mg	71%	83	17
e	SnF_2	76%	3	97
f	Zn	71%	9	91

Scheme 55



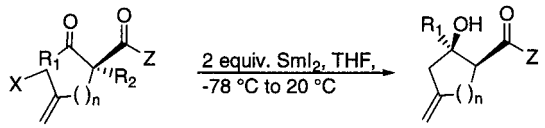
c R = Me, Y = OEt, 58% mixture of steroisomers
d R= H, Y = NEt_2, 43% (12% d.e.)

related amides and lactones in very good yield and complete or almost complete control of the relative stereochemistry (Scheme 52; Scheme 53, entries a−d; Scheme 54, entry a).[26] Unlike intermolecular SBR induced reactions, it is still effective with aldehydes but is less stereoselective (Scheme 52, entry a; Scheme 53, entry a).[26] The synthesis of higher homologues proved to be successful, and the stereochemical control is still very good (Scheme 53, entries e and f). However, the yields are modest due to competing reduction of the carbonyl group by SmI_2, leading to substantial amounts of uncyclized ω-iodo alcohols resulting from the direct reduction of the keto group.[26] Reduction of the ketone carbonyl group rather than the alkyl iodide is also observed when SmI_2 is reacted with a ω-iodoketone bearing the chiral Evans oxazolidinone in place of the amido group.[26]

The reaction has been successfully extended to compounds bearing an allylic halide moiety (bromides, and iodides) (Scheme 54, entry b; Scheme 55, entries a, c, d and Scheme 56).[26] It provides 2-vinyl cycloalkanols (Scheme 55, entries a, c, d) or 3-alkylidene cycloalkanols (Scheme 54, entry b, and Scheme 56) in good to very good yields and often with good stereochemical control especially from keto amides (Scheme 56, entries a−c). However, the nature of the product formed depends strongly upon the nature and the length of the alkenyl chain.

For example, whereas 8-iodo-3-carboethoxy-3-methyl-oct-6-en-2-one cleanly cyclizes to the vinyl-

Scheme 56



	X	R_1	R_2	Z	n	yield	d.e.
a	I	Me	H	NEt_2	1	80%	100
b	Br	*t*-Bu	H	NMe_2	1	43%	100
c	I	Me	Me	NEt_2	1	91%	90
d	I	Me	Me	OMe	1	91%	74
e	I	Me	Me	O-*t*-Bu	1	76%	32
f	I	*t*-Bu	Me	OEt	1	83%	100
g	I	Me	Me	OEt	2	73%	28
h	I	Me	Me	OEt	3	64%	00
i	I	Me	*i*-Pr	OEt	1	77%	-10

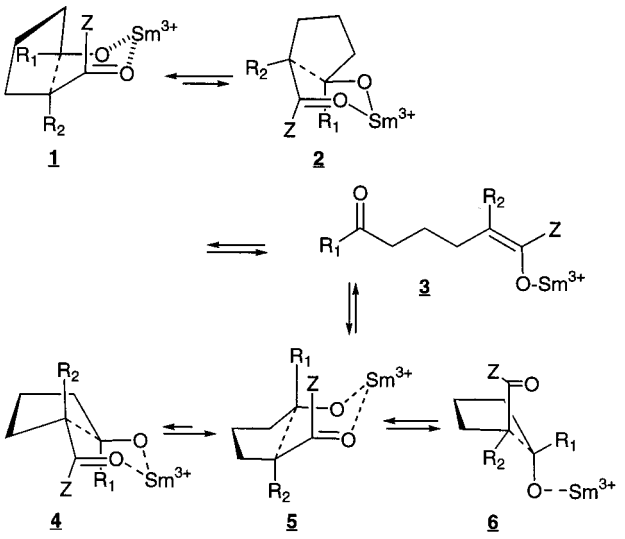
cyclopentanol disclosed in Scheme 55, entry a, its lower homologue (Scheme 55, entry b) is decomposed to ethyl 2-methyl-3-oxo-butanoate and butadiene,[26] and the related 8-bromo-4-methyl-oct-6-en-3-one missing the carbethoxy group cyclizes cleanly to the 2-methylcyclohexenol whose structure is disclosed in Scheme 50, entry b.[26] The high aptitude of 7-bromo-3-carboethoxy-3-methyl-hept-5-en-2-one to lose butadiene has been ascribed to the high ability of the β-keto ester function to stabilize a radical or an anion and to act as an effective leaving group (Scheme 55, entry b, compare to Scheme 50, entry b).[26] These results appear to rule out cyclization via S_N2 displacement of the halide by a samarium ketyl.

Related keto esters (Scheme 55, entries a and c) and keto amides (Scheme 55, entry d), which are unable to lose butadiene, cyclize to the related 2-vinyl cycloalkanols. Stereochemical control is poor except with those compounds which lead to a five-membered cycle (Scheme 55, compare entry a to entries c and d).[26]

The other allylic arrangement produces methylene cycloalkanols in very good yields. Ketoamides (Scheme 56, entries a−c) lead to consistently higher stereoselectivity, in favor of the products possessing *cis*-arrangement, than esters (Scheme 56, entries d−i). Poorer stereoselectivity is observed in the latter case when (i) the substituent α to the carbonyl group is larger: especially with compounds bearing a bulky *tertio*-butoxy instead of a methoxy group (Scheme 56, compare entry e to entry d) and a 2-isopropyl instead of a 2-methyl group (Scheme 56, compare entry i to entry d) or (ii) a ring larger than a five-membered one is formed (Scheme 56, compare entries g and h to entry d).[26] Interestingly, the larger group directly attached to the reacting carbonyl group leads to increased stereoselectivity (Scheme 56, compare entry f to entry d).

Although not firmly established, the reactions are believed to proceed under kinetic control at least with carboxamides. Nevertheless, invocation of a retro-aldol−aldol process which serves to equilibrate initially formed aldolates has been proposed especially for β-keto esters.[26] The preferred formation of the *cis*-adducts has been rationalized by consideration of the structures depicted in Scheme 57. Of the two *cis*-chelated conformations, Scheme 57, **1**, probably more accurately reflects the reality.[26] It rationalizes the increase in diastereoselectivities when the R_1 sub-

Scheme 57



stituent attached to the carbonyl group becomes bulkier (Scheme 53, entry f, and Scheme 56, compare entry f to entry d) and the decreased diastereoselectivity when R_2 becomes larger (Scheme 56, compare entry i to entry d). The higher propensity of *tertio*-butyl esters to lead to *trans*-esters might be attributed to a retroaldol−aldol reaction which prevents the 1,3-diaxal interactions present in the *cis*-stereoisomer.[26]

The reaction has been also carried out with other metals or metal salts on the unsaturated derivative bearing a lactone ring shown in Scheme 54 (entries c−f). It was found that whereas samarium diiodide, chromous dichloride, and magnesium (Scheme 54, entries b−d) favor the formation of one stereoisomer, SnF_2 and zinc favor the opposite diastereoisomer (Scheme 54, entries e and f).[26]

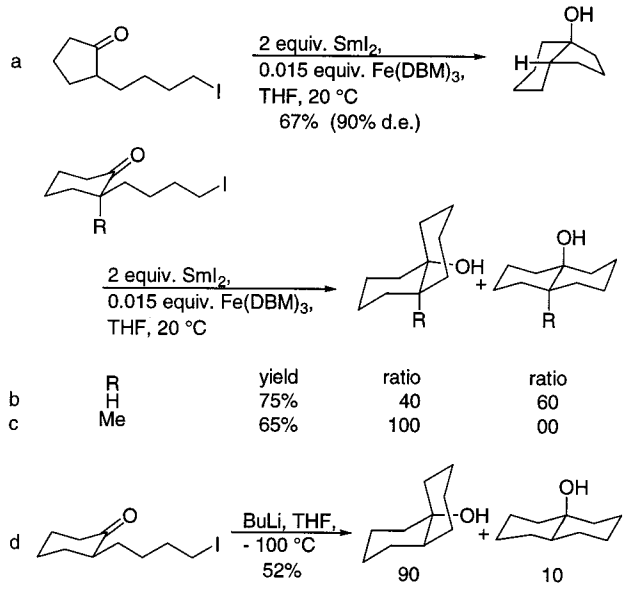
4.3. Cyclization of 2-(ω-Iodoalkyl)cycloalkanones

When applied to 2-(ω-iodoalkyl)cycloalkanones, the ISBR allows, in THF alone,[65] in THF−HMPA[28] (Scheme 4, entry b),[29] in the presence of catalytic amounts of $Fe(DBM)_3$[30,96,100] or in the presence of zinc,[100] the high yield synthesis of [*m*.*n*.o]-bicyclanols shown in Schemes 58−60.

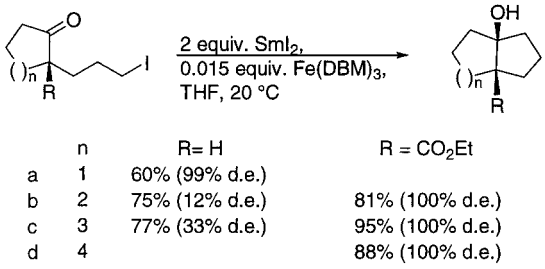
Very high stereocontrol in favor of the *cis*-stereoisomer has been achieved with cycloalkanones disubstituted in the α-position regardless of the nature of these substituents (R = Me or CO_2Et) (Scheme 58, entry c, and Scheme 59, entries b−d).[30] Similar results have been achieved from monosubstituted analogues which led to [3.3.0][30] and to [4.4.0] derivatives,[30,100] but much poorer stereoselectivities were observed in the case of [4.3.0], [5.3.0], and [4.4.0] derivatives bearing a hydrogen at the ring junction (Scheme 58, entry b; Scheme 59).[30,96] Comparative results disclosed in Scheme 58 clearly show that halogen−lithium exchange leads to the bicyclic [4.4.0] derivative in much lower yield but with better stereocontrol (Scheme 58, compare entry d to b).[30]

The lack of stereoselectivity in the synthesis of bicyclo[4.3.0]decan-9-ol has been demonstrated to result from the attack of an equatorial side chain with comparable ease from both the equatorial and

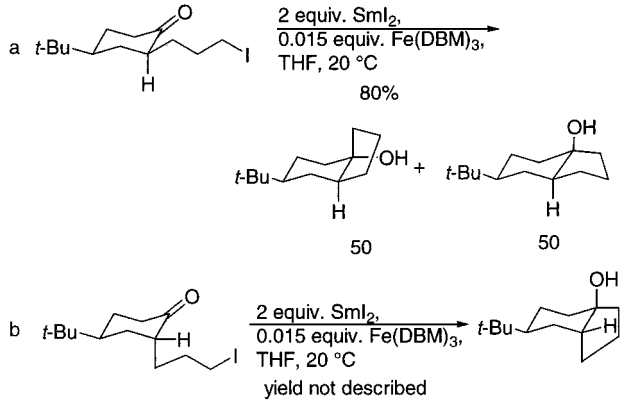
Scheme 58



Scheme 59



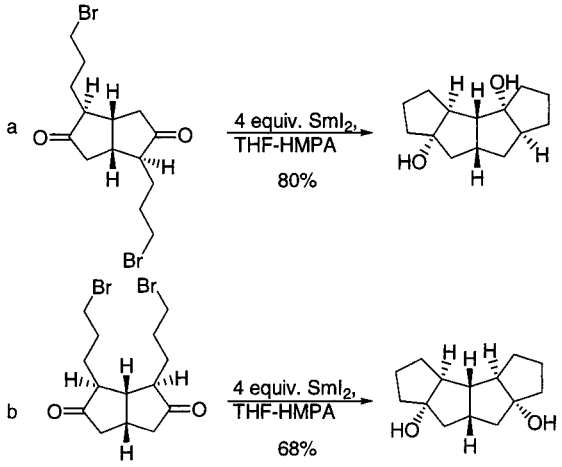
Scheme 60



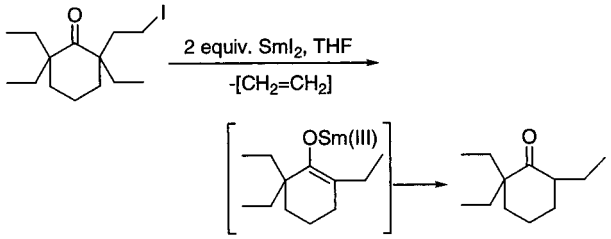
axial direction from the *cis*-2-(3-iodopropyl)-4-*tertio*-butylcyclohexanone (Scheme 60, entry a).[96] The other stereoisomer, *trans*-2-(3-iodopropyl)-4-*tertio*-butylcyclohexanone, only leads to the *cis*-ring fused compound, indicating that no epimerization is taking place (Scheme 60, entry b). Comparative results from other lanthanides and lanthanide salts and from reaction performed without catalysts have been disclosed. The stereoisomeric ratios change depending upon the conditions used but usually not very significantly.[30,96]

Otherwise, this reaction has been successfully used for the synthesis of (i) tetracyclic polyquinenes by bisannulation of appropriate di-halogenoalkyl-substituted bicyclic diketones, which occurs with impressively high yield and very high stereocontrol (Scheme

Scheme 61



Scheme 62



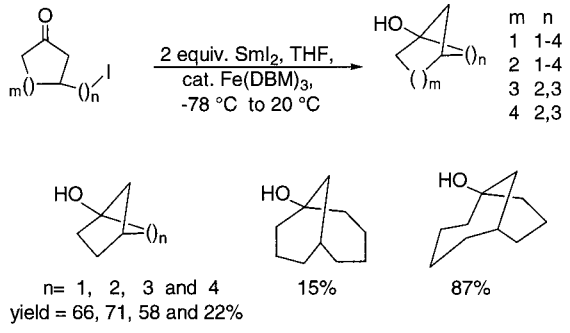
61)[101,102] (for a related example, see Scheme 79),[63] and (ii) exaltone and (*d*,*l*)-muscone natural products.[28]

It has been reported, however, that the cyclization which would have led to the formation of a cyclobutanol from the particularly hindered carbonyl compound shown in Scheme 62 does not take place. The reaction takes another course and generates instead the samarium enolate disclosed in Scheme 62 resulting from a reductive elimination reaction.[10,14]

4.4. Cyclization of 3-(ω-Iodoalkyl)cycloalkanones

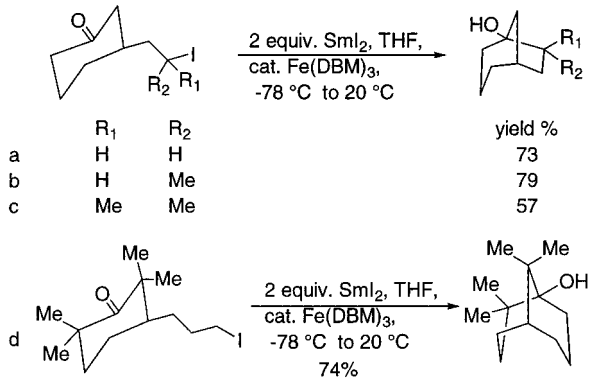
As shown in Scheme 44, entry a, in Scheme 45, entry a, and in Schemes 63 and 64, the reaction of

Scheme 63



SmI_2 with 3-(ω-iodoalkyl)cycloalkanones provides a quite general entry to a variety of bicyclo[*m*.*n*.1]-alkan-1-ols.[31] The reaction is best achieved at fairly high dilution (0.015 M) when initiated at low temperature (−78 °C) in the presence of catalytic amounts of iron complexes such as tris(dibenzoylmethido)-iron(III) ($Fe(DBM)_3$). Cyclopentanone through cyclooctanone substrates bearing a haloalkyl side chain

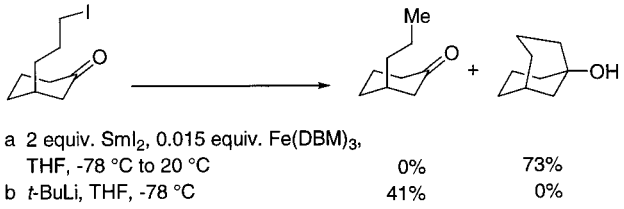
Scheme 64



whose length can be varied from one to three led to bicyclic derivatives with little if any differentiation in reactivity or yields.[31]

A bicyclo[2.1.1] derivative (Scheme 63; m, n = 1)[31] is produced in more than 60% yield although considerable strain (41 kcal/mol^{-1}) is engendered and a high energy of activation must be surmounted. Apparently the formation of the bicyclo [*m*.4.1] derivatives (Scheme 63, *m* = 1, *n* = 4, 22% yield) and (Scheme 63, *m* = 2, *n* = 4, 15% yield) defines the practical limit of side chain extension that can be tolerated. Cyclization still takes place efficiently when the halogen is attached to secondary (Scheme 64, entry b) and even tertiary (Scheme 64, entry c) carbon atoms and with ketones whose carbonyl is very hindered such as the fully α,α′-tetramethylated cyclohexanone disclosed in Scheme 64 (entry d).[31] The reactions disclosed in Scheme 65, compare entry a

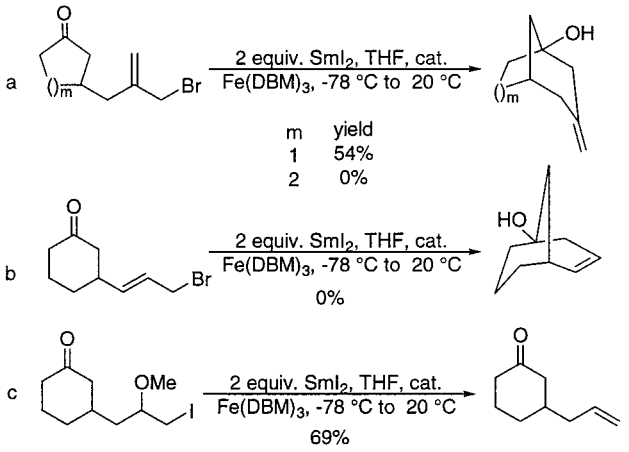
Scheme 65



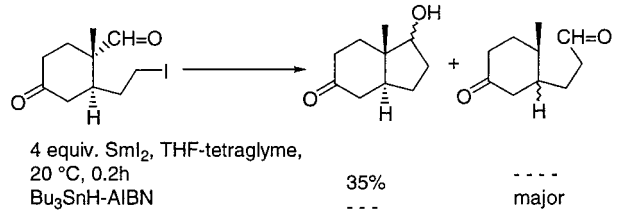
to entry b, clearly show the advantages of SmI_2 over the more conventional method using instead alkyllithiums as the reducing agent.[31]

Interestingly the reaction occurs on cyclopropyl ketones without cyclopropyl ring opening (Scheme 45, entry a) but elimination takes place on a related derivative bearing a β-methoxy-alkyliodide side chain (Scheme 66, entry c).[31] Allyl derivatives are much less prone to cyclize (Scheme 66, entries a and b),[31] probably due to the higher strain involved in the transition state. 1,4- rather than 1,2-addition takes place across the C,C double of a cyclopentenone bearing an ω-iodoalkyl side chain in the 4-position (Scheme 14, entry a, and Scheme 15),[42] and as expected addition occurs chemoselectively onto the aldheyde group of the δ-iodo aldehyde whose structure is disclosed in Scheme 67, entry a.[41] This reaction is by far superior to the one involving tributyltin hydride instead, which leads mainly to a rearranged compound (Scheme 67, entry b).[41]

Scheme 66



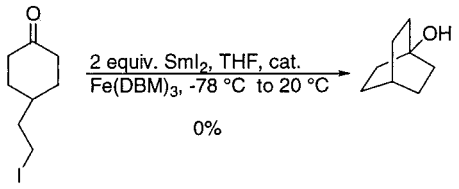
Scheme 67



4.5. Cyclization of 4-(ω-Iodoalkyl)cycloalkanones

Although the intramolecular SBR approach to bicyclo[*m*.*n*.1] alkanols proved to be extraordinarily general, it has not been possible to extend it to the construction of bicyclo[2.2.2]alkanols (Scheme 68).

Scheme 68



5. SmI_2 Promoted Cyclization of ω-Halogeno Esters and Related Derivatives

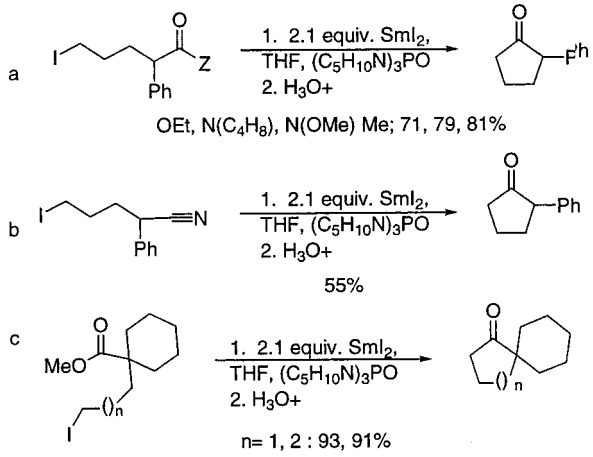
5.1. Cyclization of ω-Halogeno Esters

5.1.1. Cyclization onto the Carbonyl Group of Saturated Esters

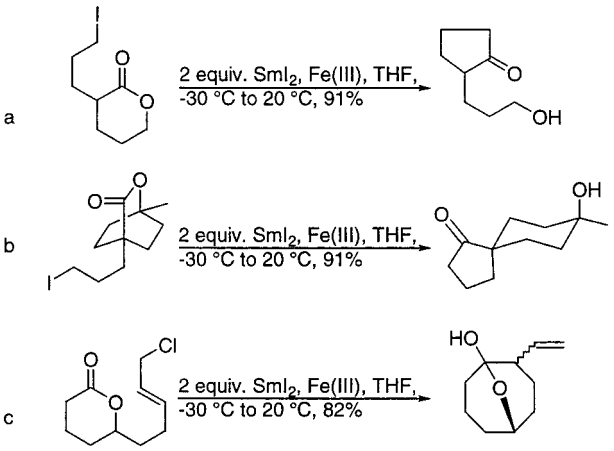
Samarium diiodide promotes, in the presence of Fe(III) salts or phosphoramides (especially tripiperidinophosphine oxide), the cyclization of ω-halogeno esters (Scheme 69, entries a and c)[103] and of ω-halogeno lactones (Scheme 70)[103] whose side chain is saturated (Scheme 70, entries a and b)[103] or unsaturated (Scheme 70, entry c).[103] This reaction leads to cyclic ketones (Scheme 69), 2-hydroxyalkyl cyclanones (Scheme 70, entries a and b) or lactols (Scheme 70, entry c), respectively.[103] Interestingly, samarium diiodide does not exhibit the aptitude to perform the double-addition reaction usually observed with organolithium or Grignard reagents.

Thus the δ-iodo ester bearing a γ-chloropropyl side chain in the α-position shown in Scheme 71[103]

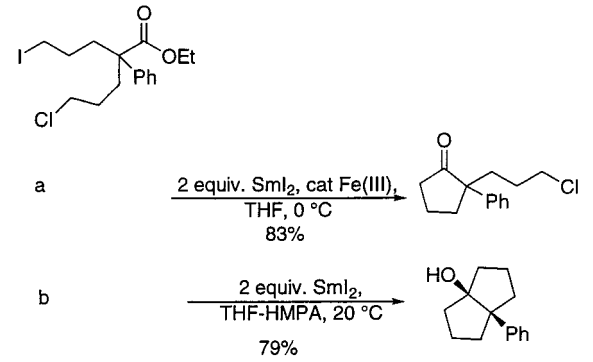
Scheme 69



Scheme 70



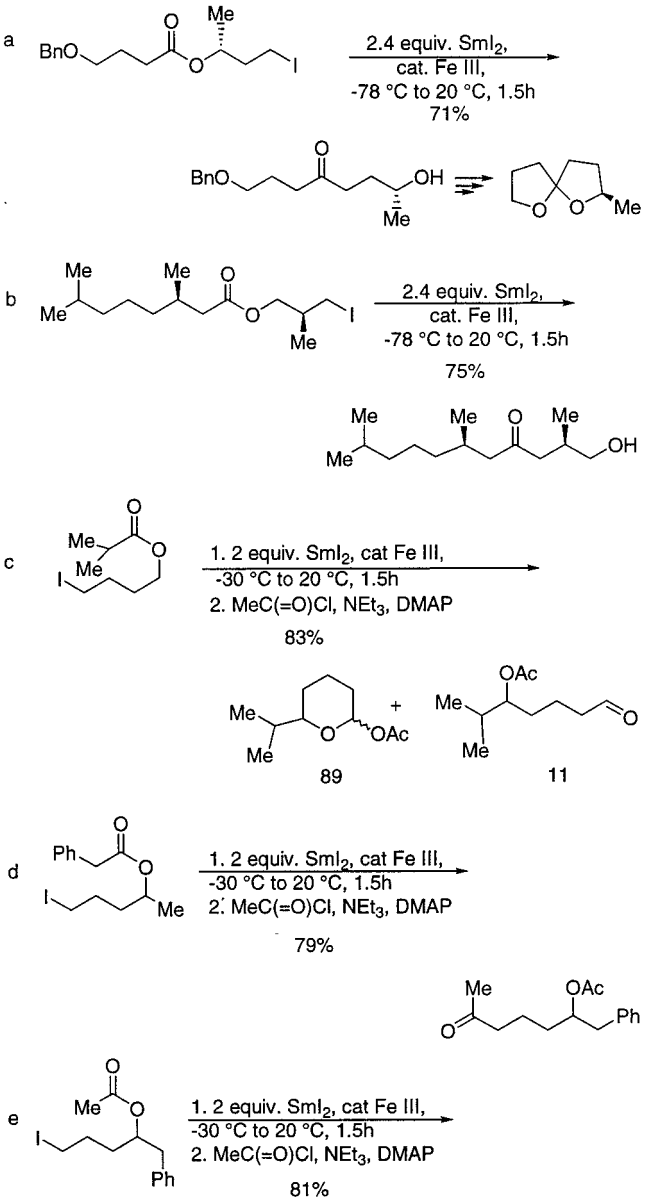
Scheme 71



selectively produces, on reaction with 2 equiv of SmI_2 and catalytic amounts of Fe(III) (THF, 0 °C), a 2(3-chloropropyl)cyclopentanone (Scheme 71, entry a)[103] or the bicyclic alcohol in very high yield (Scheme 71, entry b) under forcing conditions (2 equiv of SmI_2 in THF−HMPA).[103] Note that these reactions take advantage of the important difference of reactivity between the iodide and the chloride (section 2.2).

The reaction of γ-iodo-alkyloxy esters with SmI_2 in the presence of a catalytic amount of Fe(III) provides a good entry to γ-hydroxyketones via acyl substitution (Scheme 72, entries a and b).[104] It usually proceeds with excellent stereocontrol and has been used for particularly short and convergent syntheses

Scheme 72



of spiroketals (Scheme 72, entry a)[104] and of the vitamin E side chain (Scheme 72, entry b).[104]

This reaction is not general. It does not proceed as efficiently with esters bearing a heteroatom α to the carbonyl group, especially with α-alkoxy derivatives because of competing reductive elimination process,[104] and neither applies to iodomethyl-, 2-iodoethyl-, nor analogues higher than the 4-iodobutylcarboxylates.[104] In the latter case it proceeds via acyl substitution immediately followed by a highly stereospecific, Meerwein−Ponndorf−Verley/Oppenauer (MVP/O) intramolecular redox reaction as disclosed in Scheme 72 (entries c and d).[104,105] The results described in Scheme 72, entry c, are quite surprising since in this MVP/O redox process, the equilibrium favors the production of the secondary hydroxy aldehyde whereas it usually clearly favors the formation of 1° alcohols over 2° ones.[105] Finally, as expected from the equilibration process, the same compound is formed from both isomeric carboxylates disclosed in Scheme 72, entries d and e.[105]

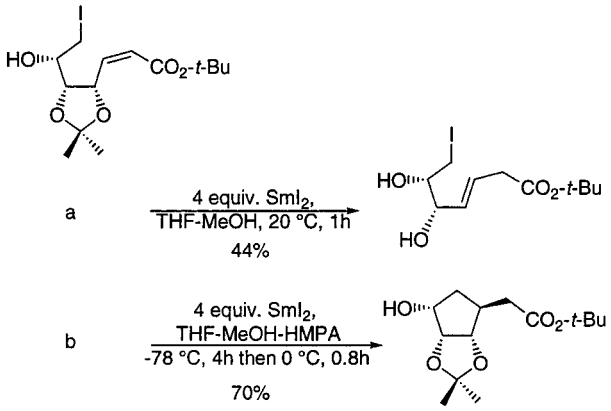
5.1.2. Cyclization onto the C,C Double Bond of α,β-Unsaturated Esters

Cyclization also occurs on ω-iodo-α,β-unsaturated esters and amides including the Weinreb amide, bearing a C,C double bond (Scheme 73, entry b; Schemes 74−76)[33,106] or a C,C triple bond (Scheme 77),[33] and is in such cases limited to the production of the alkylidene cyclopentane and does not give the alkylidene cyclohexane (Scheme 77, compare entry c to entry a).[33]

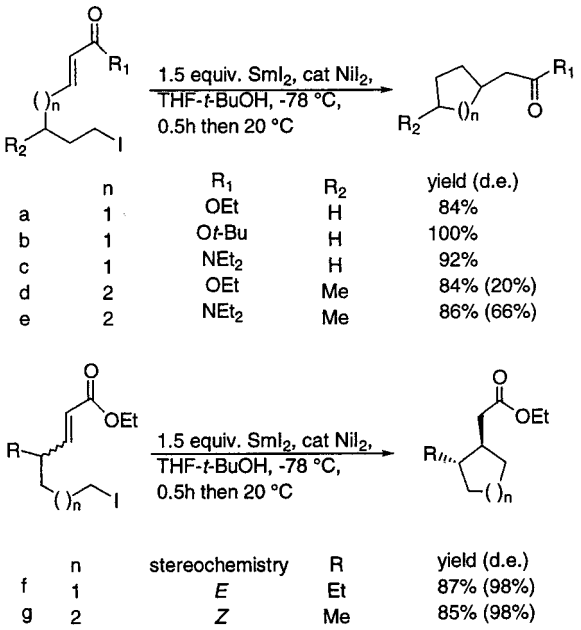
It takes place with primary alkyl iodides (Schemes 73−74; Scheme 75, entry d; Scheme 76) and secondary ones as well, but tertiary alkyl iodides provide a mixture of compounds in which the cyclized/uncyclized ratio is reasonably high (Scheme 78).[33]

The presence of an alcohol (MeOH or *tertio*-BuOH) and an additive such as HMPA (Scheme 73, compare entry b to entry a)[106] or a transition metal salt (NiI_2) (Scheme 74; Scheme 75, entries b and d; Scheme 76; Scheme 78) is important for its success.[33] Although the transition metal salts are not crucial, they enhance dramatically the rate of the reaction (1.5 h instead of 10 h).[33] The cyclization is believed to proceed through radical intermediates which cyclize and are then reduced to the corresponding enolates.

Scheme 73



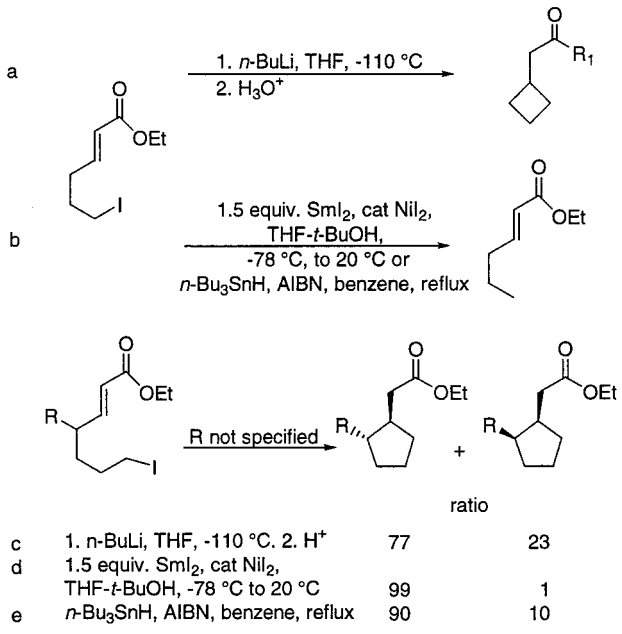
Scheme 74



	n	R_1	R_2	yield (d.e.)
a	1	OEt	H	84%
b	1	O*t*-Bu	H	100%
c	1	NEt_2	H	92%
d	2	OEt	Me	84% (20%)
e	2	NEt_2	Me	86% (66%)

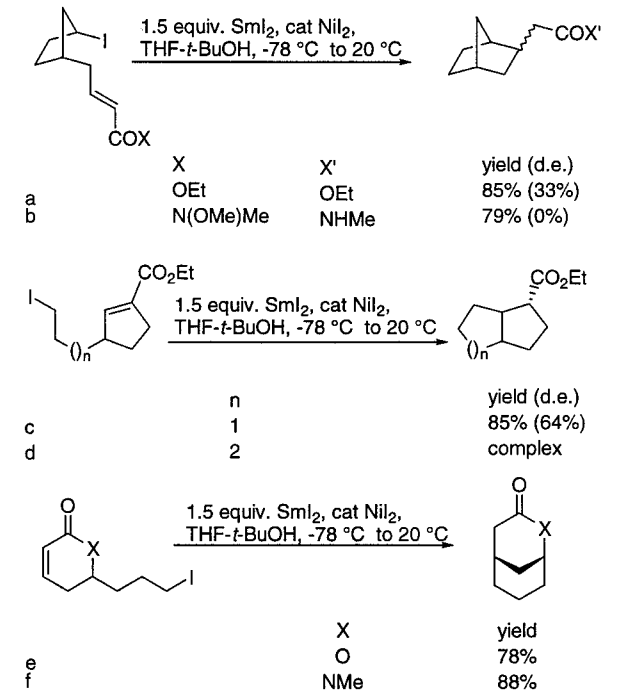
	n	stereochemistry	R	yield (d.e.)
f	1	*E*	Et	87% (98%)
g	2	*Z*	Me	85% (98%)

Scheme 75



c	1. n-BuLi, THF, -110 °C. 2. H^+	77	23
d	1.5 equiv. SmI_2, cat NiI_2, THF-*t*-BuOH, -78 °C to 20 °C	99	1
e	*n*-Bu_3SnH, AIBN, benzene, reflux	90	10

Scheme 76

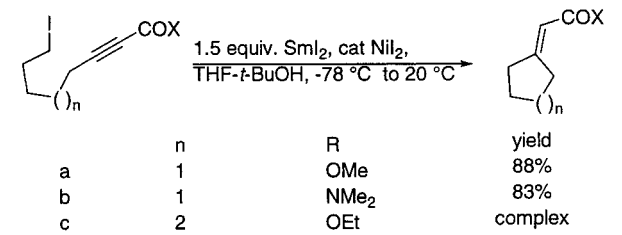


	X	X'	yield (d.e.)
a	OEt	OEt	85% (33%)
b	N(OMe)Me	NHMe	79% (0%)

	n	yield (d.e.)
c	1	85% (64%)
d	2	complex

	X	yield
e	O	78%
f	NMe	88%

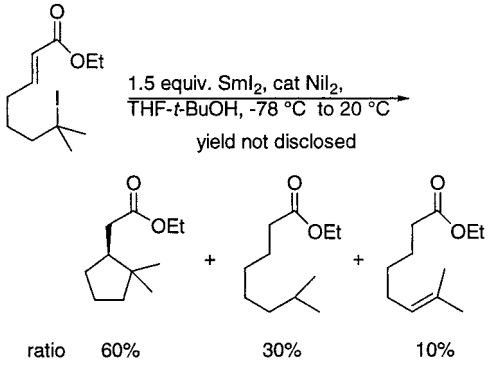
Scheme 77



	n	R	yield
a	1	OMe	88%
b	1	NMe_2	83%
c	2	OEt	complex

The reaction allows the synthesis of five- (Scheme 73, entry b; Scheme 74, entries a−c, f; Scheme 75, entry d; Scheme 76, entries a and c)[33,106] as well as six-membered (Scheme 74, entries d, e, g, and Scheme 76, entries e and f)[33] cycles. It proceeds with very high stereochemical control in some cases involving the formation of five-membered derivatives (Scheme 73, entry b; Scheme 74, entry f; Scheme 75, entry d).[33] Comparative results involving *n*-butyllithium (Scheme 75, entries a and c) or tributyltin hydride (Scheme 75, entries b and e) have been published for some specific cases.[33] The former reagent offers the advantage of allowing the formation of a four-membered cycle unavailable by the SmI_2 route (Scheme 75, compare entry a to entry b), but *n*-butyllithium as well as tributyltin hydride are far less stereoselective than SmI_2 for the construction of five-membered ring compounds (Scheme 75, compare entry d to entries c and e).

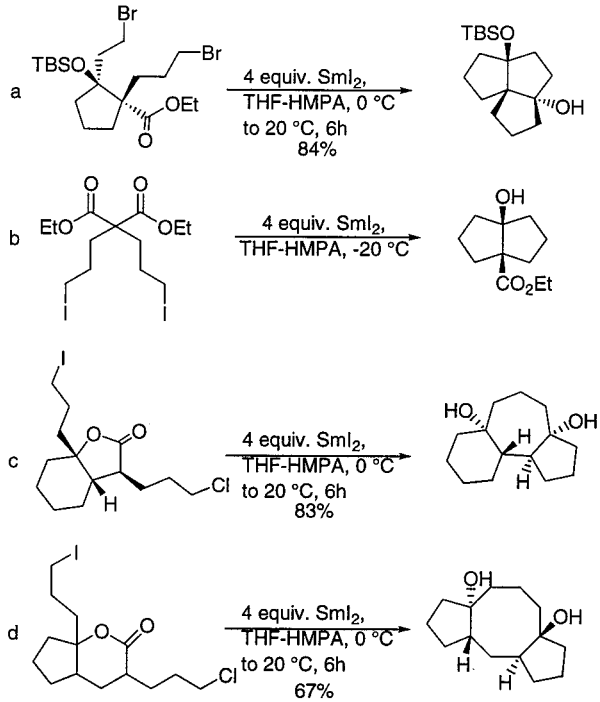
Scheme 78



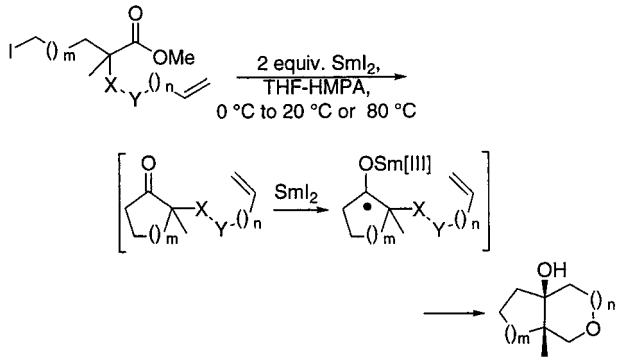
5.1.3. Sequential Nucleophilic Acyl Substitution/Keto Alkylation Reactions

Cyclization of ω-halogeno esters and lactones, used in an iterative process, allows the one-pot synthesis of complex molecules with excellent chemo-, regio-, and stereocontrol starting from esters (Scheme 79, entries a and b) and lactones (Scheme 79, entries c and d) bearing two different halogenoalkyl or halogenoalkenyl groups in suitable positions.[2,63] Libera-

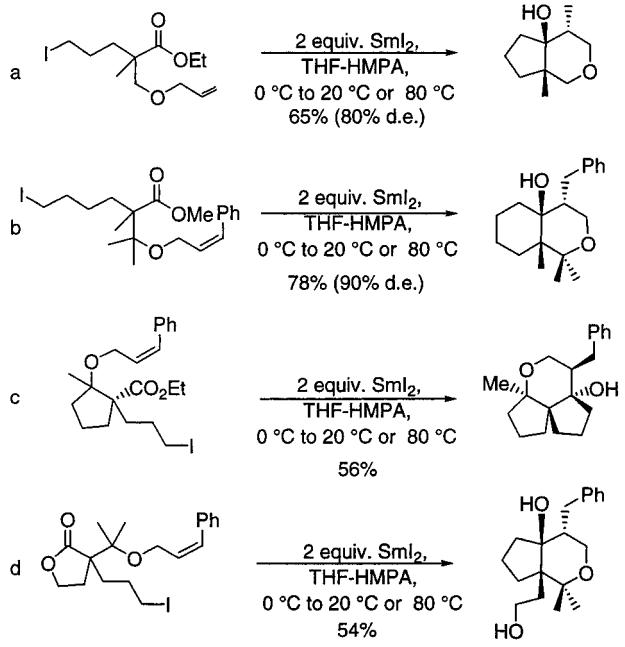
Scheme 79



Scheme 80



Scheme 81



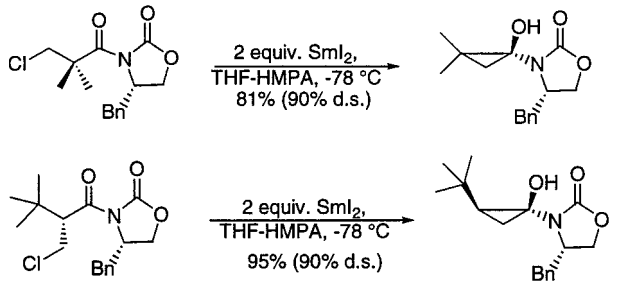
tion of the ketone is followed by the second intramolecular reaction (ISBR) upon reaction of the second alkyl halide. The sequential formation of the organosamarium intermediates is controlled by the different rates at which alkyl halides are reduced, and when the same halide is present in each of the two side chains, their length apparently determines the sequence of attack on the carbonyl group.[2,63] The diversity of the tricyclic structures shown in Scheme 79 (entries a, c, d) give an idea of the power of this approach.

If an unsaturated side chain is suitably positioned on the ω-iodo ester or lactone, the first cyclization leading to a cyclanone is followed by a second one involving intramolecular ketyl olefin coupling (Scheme 80).[107,108] These sequential nucleophilic acyl substitution/ketyl olefin coupling reactions allow in THF−HMPA the synthesis of carbobicyclic derivatives[107] as well as bicyclic, tricyclic, and spiro-fused oxygen heterocycles (Scheme 81)[108] in good yield and with high diastereoselection.

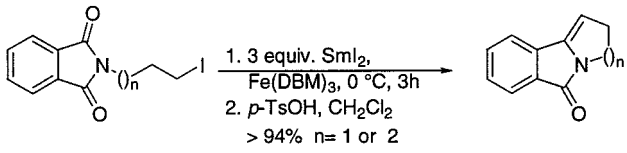
5.2. Cyclization of ω-Halogeno Amides, Oxazolidinones, Imides, and Alkylnitriles

Cyclizations have been also carried out on ω-halogeno amides (Scheme 69, entry a),[103] -alkylnitriles

Scheme 82



Scheme 83



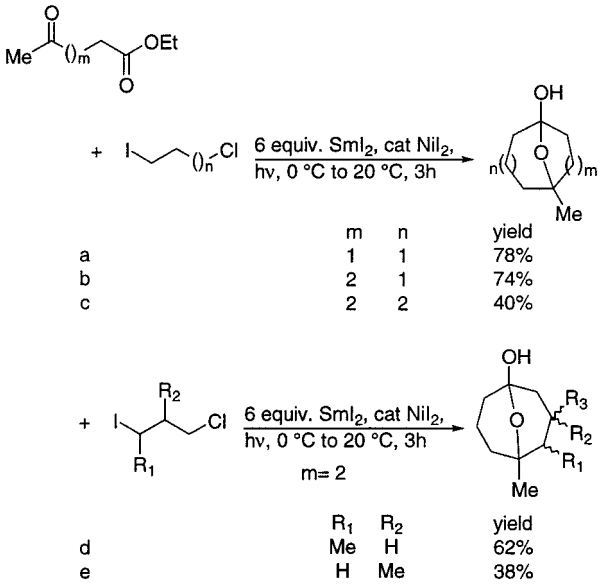
(Scheme 69, entry b),[103] -oxazolidinones (Scheme 82),[95] or -cyclic imides (Scheme 83).[109] They allow the synthesis of ketones or protected ketones resulting from the addition of the organosamarium intermediate to their carbonyl or nitrile groups. Optically active aminocyclopropanols have been synthesized from β-chloro oxazolidinones taking advantage of a precomplexation of their β-dicarbonyl moieties (Scheme 82),[95] and tricyclic amides have been produced from *N*-iodoalkyl phthalimides by acid-catalyzed dehydration of the α-amino alcohol intermediates (Scheme 83).[109]

5.3. Reaction of α,ω-Dihalogenoalkanes with Keto Esters

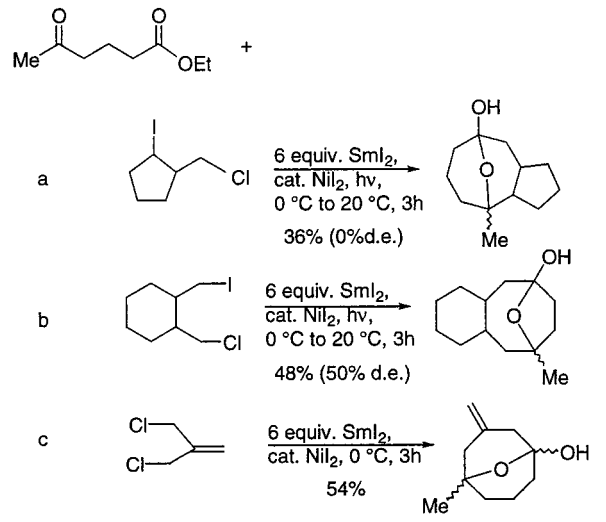
ω-Keto esters as well as related γ-aldehydo esters react under SBR with ω-chloro iodoalkanes in the presence of (i) an excess (6 equiv) of SmI_2, (ii) catalytic amounts of NiI_2 (2%), and (iii) under irradiation with visible light, to provide seven-, eight-, and nine-membered carbocycles in good to moderate yields.[17,50] Alkylation of the carbonyl group in THF proceeds very cleanly and leads chemo- and stereoselectively to the chloro lactone shown in Scheme 12, entry a, in almost quantitative yield. Intramolecular alkylation of the remaining carboxyl group is much difficult and requires the use of HMPA or better irradiation with visible light to take place (Scheme 12, compare entry c to entry a or b).[17,50]

The reaction has been successfully achieved on several γ- and δ-keto esters and γ-keto lactones bearing a methyl, primary alkyl, and secondary alkyl group attached to the carbonyl group as well as with compounds in which the keto group is part of a five- or a six-membered cycle (Schemes 12 and 84).[50] The reaction stops at the first stage with ϵ-keto esters, and complex mixtures of compounds are observed when the keto group is attached to an aromatic ring, to a C,C double bond, or when 1-acetyl-2-carbomethoxy cyclohexene is instead used.[50] Interestingly, the addition of the first formed 3-chloropropyldiiodosamarium chemoselectively occurs onto the keto group of the ketone rather than to produce a cyclopropane by an intramolecular substitution reaction.

Scheme 84



Scheme 85

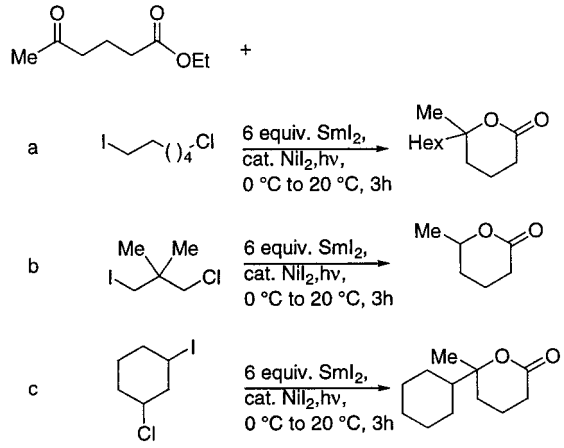


The reaction proceeds properly with γ-chloro-iodoalkanes bearing primary carbons at both ends such as 1-chloro-iodopropane (Scheme 12, entry c; Scheme 84, entries a and b) and 1-chloro-iodobutane (Scheme 84, entry c) and even with those compounds which bear a secondary alkyl center α (Scheme 84, entry d; Scheme 85, entry a) or β (Scheme 84, entry e and Scheme 85, entry b) to the carbon bearing the iodide.[17,50]

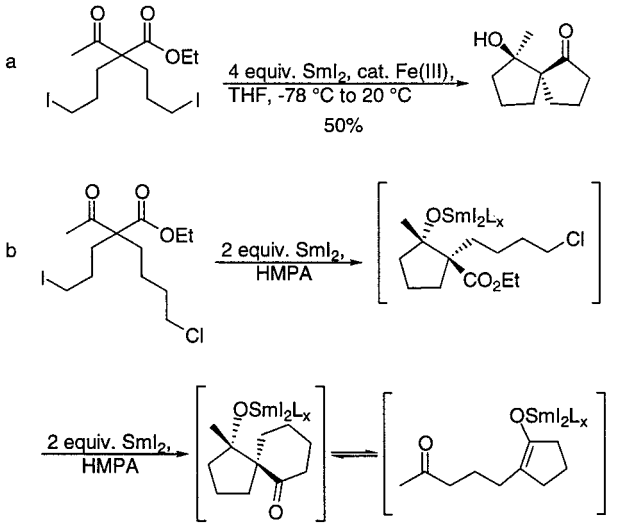
Nevertheless the second addition to the carbonyl group does not occur with long chain compounds such as 1-chloro-6-iodohexane (Scheme 86, entry a) and 1-chloro-3-iodocyclohexane (Scheme 86, entry c). In these cases the reduction, in the second step of the reaction, of the alkyl chloride to the alkyl substituent only takes place.[50] 1-Chloro-iodo-2,2-dimethyl propane does not add to the keto group of ethyl 2-oxohexanoate which is instead reduced by SmI_2 to produce the valerolactone shown in Scheme 86, entry b.[50]

Irradiation which induces the nucleophilic acyl substitution reaction of the less reactive chloride to the lactone intermediate (Scheme 12, entry c) is not

Scheme 86



Scheme 87



required for (2-chloromethyl)-2-chloropropene which exhibits, as expected, a higher reactivity (Scheme 85, entry c).[50]

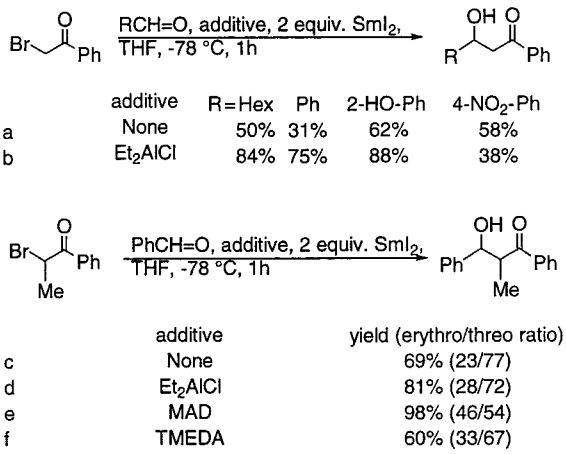
Reaction of the bis(diiodoalkyl)-substituted β-keto ester shown in Scheme 87 (entry a) with SmI_2 and catalytic amounts of Fe(III)[17] provides access, in fair yield, to a spirocyclic hydroxy ketone, as a single diastereoisomer. The chelation of the two carbonyl groups by SmI_2 which ensures the formation of the alkoxide is responsible for such unusual stereochemical control. The reaction is nevertheless limited since the homologous compound bearing a chlorine instead of an iodine on one of the two alkyl side chains provides the resulting hydroxy ester with good diastereoselectivity and in high yield (Scheme 87, entry b), but further reaction leads to complex mixture of products (Scheme 87, entry b).[63] This is probably due to the highly strained spirocyclic ring intermediate which suffers a retroaldol reaction.[63]

6. Intermolecular Samarium Diiodide Promoted Reformatsky Reaction

6.1. Reaction Involving α-Halogeno Ketones and Carbonyl Compounds

Only a few examples of the SmI_2 mediated intermolecular Reformatsky reaction involving α-halogeno

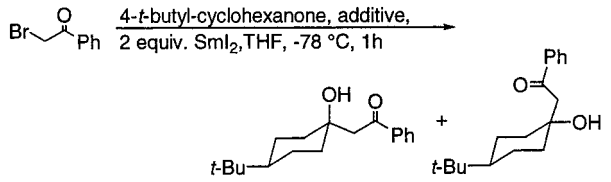
Scheme 88



	additive	R=Hex	Ph	2-HO-Ph	4-NO_2-Ph
a	None	50%	31%	62%	58%
b	Et_2AlCl	84%	75%	88%	38%

	additive	yield (erythro/threo ratio)
c	None	69% (23/77)
d	Et_2AlCl	81% (28/72)
e	MAD	98% (46/54)
f	TMEDA	60% (33/67)

Scheme 89



	Additive	yield (*cis/trans* ratio)
a	Et_2AlCl	98% (29/71)
b	TMEDA	85% (96/04)

ketones have been published. It has been nevertheless described that SmI_2 promotes the aldol reaction between α-bromoacetophenone or α-bromopropiophenone and various aldehydes and ketones (Schemes 88 and 89).[110] The reaction implying aromatic aldehydes and 2 equiv of SmI_2 (the usual amount required) provides, under SBR conditions, the aldols in quite modest yields (Scheme 88, entries a and c).[110]

The reaction between α-bromoacetophenone and aromatic aldehydes has been also successfully carried out under SBR conditions (THF, 20 °C), with only 1 equiv of SmI_2, and not 2, as usually required.[110] It does not provide the expected aldols but the enone resulting from their dehydration.[110] A mechanism involving SmI_2 and Sm(III)/I^- species has been proposed to account for the unusual ratio of substrates used.[110]

Performing this reaction in the same solvent but under SBR conditions and in the presence of additives such as Et_2AlCl, MAD (methylaluminum bis-(2,6-di-*tertio*-butyl-4-methylphenoxide)), or TMEDA[111] allows the formation of the aldol in reasonably good yields especially if the reaction is carried out at −78 °C in the presence of 2 equiv of both SmI_2 and Et_2AlCl[111] (Scheme 88, compare entry b to entry a). These conditions work fine on α-bromoacetophenone and a variety of aliphatic and aromatic aldehydes, including those bearing a free hydroxyl group on the aromatic ring (Scheme 88, entry b). This reaction has been successfully extended to α-bromopropiophenone and benzaldehyde (Scheme 88, entries c−f) and leads to aldols with modest diastereoselection (d.e. 40%). It has also been carried out under SGR conditions but is exclusively limited to aldehydes and leads to aldols in modest yields.[111]

The reaction also takes place with ketones but is more capricious, requiring, in some cases, Et_2AlCl to proceed (Scheme 89).[111] In the case of 4-*tertio*-butylcyclohexanone and phenacyl bromide, the *cis*/*trans* ratio of isomers can be reversed by use of the proper additive (Et_2AlCl or TMEDA) (Scheme 89) (for the related lithium enolate: *cis*/*trans* ratio = 77/23).[111]

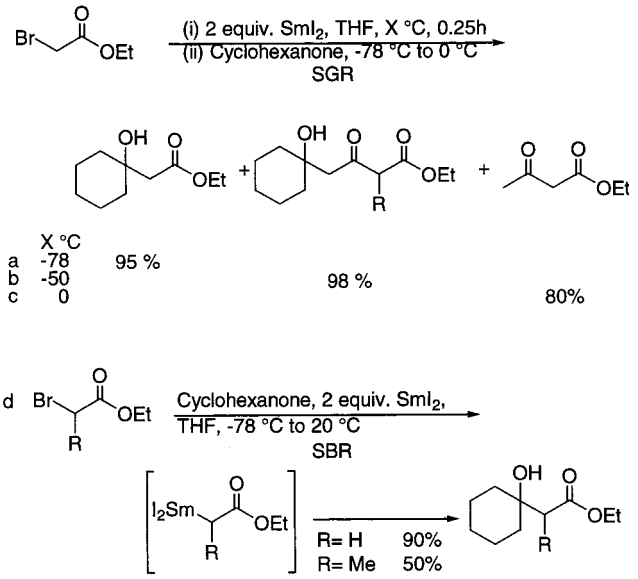
The reactions reported above imply the intermediate formation of ketone enolates which can also be synthesized by 1,4-addition of alkylsamariums to enones[42] (Scheme 14, entry a; Scheme 15). Although protonation of these enolates proceeds normally (Scheme 14, entry a), it has been found that reaction with aldehydes lead (i) to the expected aldols and/or the enones resulting from their dehydration (Scheme 15, entry a) and (ii) to alcohols resulting from a further Tischenko reaction (Scheme 15, entry b).[42] We have to recall that SmI_2 has a high propensity to favor the Tischenko reaction.[112]

Related 1,4-addition can also be efficiently achieved with tributyltin hydride in the presence of triethylborane, but interestingly the configuration at the carbon bearing the oxygen atom on the side chain is opposite to that disclosed in Scheme 15, entry b.[42]

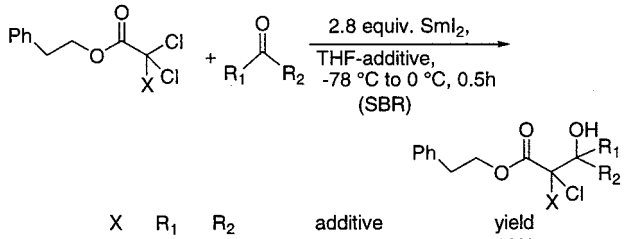
6.2. Reaction Involving α-Halogeno Esters, Lactones, Amides, and Alkylnitriles and Carbonyl Compounds[3,5,7,10,12]

SmI_2 efficiently promotes the Reformatsky-type reaction of α-halogeno esters (Scheme 90).[1,7,12,34,35,43,68,113−115] The reaction has been performed in one case under SGR but the nature of the product depends on the temperature at which the first reaction is performed.[137] Results disclosed in Scheme 90 (entries a−c) suggest that each intermediate generated at an individual reaction temperature is different (see below for discussion).[137] Such product−temperature dependence is not observed when the reaction is carried out under SBR conditions which constantly deliver the corresponding β-hydroxy ester (Scheme 90, entry d).[137]

Scheme 90

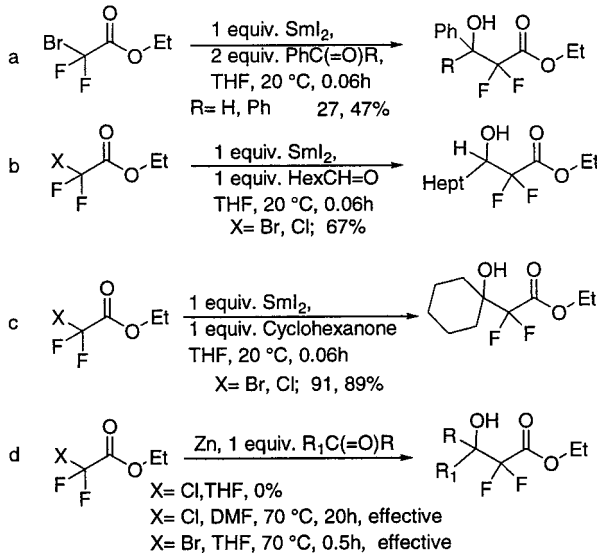


Scheme 91



	X	R_1	R_2	additive	yield
a	H	Me	Me	none	63%
b	H	Me	Me	2 equiv. HMPA	71%
c	H	Me	Me	8 equiv. HMPA	33%
d	Me	Me	Me	2 equiv. HMPA	55%
e	Cl	Me	Me	2 equiv. HMPA	65%
f	H	Me	Ph	2 equiv. HMPA	45%
g	H	H	Ph	2 equiv. HMPA	0%
h	H	Ph	Ph	2 equiv. HMPA	0%

Scheme 92

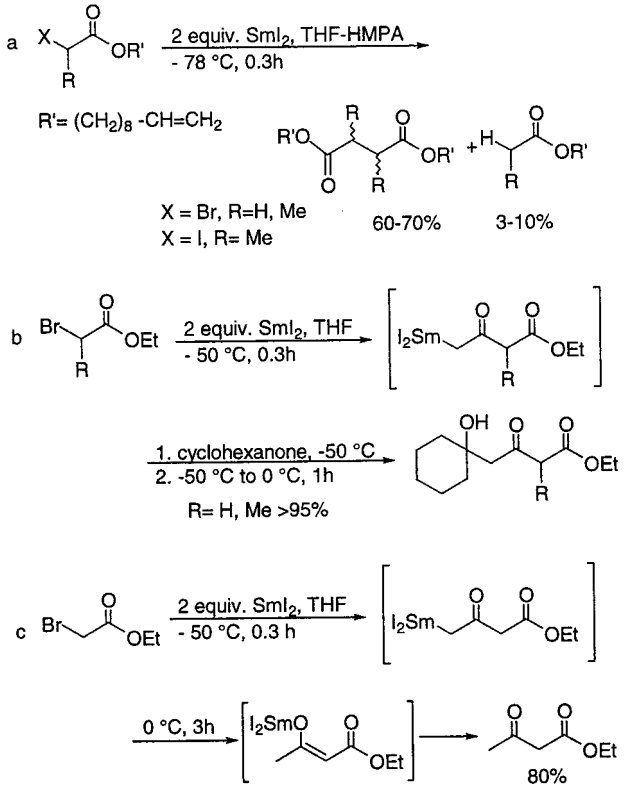


The reaction has been successfully extended to (i) α-bromo-*N*,*N*-dibenzylamides[116] which proved to be good substitutes to the related esters and provides, after SBR in THF and debenzylation, the related *β*-hydroxy carboxylic acids,[116] (ii) polyhalogeno derivatives such as dichloro and trichloro acetates as well as α,α-dichloro propionates (Scheme 91),[117] (iii) ethyl α-bromodifluoroacetate (Scheme 92, entries a−c),[68,115] and (iv) the related α-bromo-butyrolactone (Scheme 20, entry c).[69]

The reduction of α-halogeno esters is faster than that of the related alkyl halides, and therefore the SmI_2 promoted Reformatsky-type reactions have been successfully achieved on the bromides as well as on the chlorides. Furthermore, *β*-hydroxy esters are formed in good yields even when the reaction is carried out in THF alone (Scheme 90; Scheme 91, entry a; Scheme 92, entries a−c). In some cases similar or even better results are obtained from the chlorides (Scheme 92, entries b and c),[68,115] and although the use of HMPA proved to be in some specific cases beneficial, its amount has to be restricted (Scheme 91, compare entry b to entries c and a).[117]

The reactions usually proceeded properly with aliphatic aldehydes and ketones under SBR conditions (Scheme 91, entries a−e; Scheme 92, entries b and c) but with much poorer yields when carried out on aromatic carbonyl compounds (Scheme 91, compare entries f−h to entries a−e; Scheme 92, compare entry a to entries b and c).[68,115,117]

Scheme 93



The reduction of α-bromoesters by SmI_2 has been studied carefully. It has been described that it does not proceed at −78 °C, and that the SBR type reaction occurs during heating to 0 °C (Scheme 90).[1,34,137] It was also reported that a racemic *β*-hydroxyester is formed starting from an optically active α-bromopropionate and cyclohexanone[1] and that the reaction of phenethyl α,α-dichloroacetate (Scheme 91, entries f−g)[117] and ethyl α-bromodifluoroacetate (Scheme 92, entry a)[68] with aromatic carbonyl compounds does not proceed properly due to competing coupling or reduction.

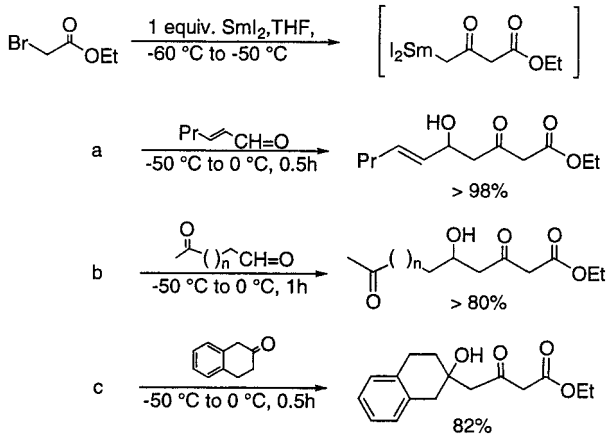
In many instances the advantages of the samarium Reformatsky reaction over the classical conditions have been pointed out (Scheme 92, compare entry d to entries b and c). The reaction (i) takes place in a homogeneous medium and (ii) proceeds with enhanced reactivity and reproducibility, (iii) under milder conditions, (iv) with similar or even better chemoselectivity, and (v) with high degree of diastereoselection in some of its intramolecular versions (ISBR).

Attempts to prepare organosamarium(III) species in order to perform the reaction stepwise (SGR) proved to be unsuccessful because of competing dimerization reactions that take place and afford, depending upon the conditions used, (i) succinates in modest to good yields when carried out in the presence of HMPA (Scheme 93, entry a)[118] or (ii) *β*-oxoester enolates in almost quantitative yield when performed in THF at low temperature (Scheme 90,

entry b).[119,120] β-Oxoester enolates are stable at −78 °C but isomerize at higher temperature (around 0 °C) to the low-reactive diiodosamarioacetylacetonate intermediates (Scheme 93, entry c) which then can couple with carbonyl compounds.[34,137]

β-Oxoester enolates are valuable synthetic intermediates, easily available from 2 equiv of α-bromoacetates and samarium diiodide. They react with various carbonyl compounds such as aldehydes, ketones (including α,β-unsaturated ones), aryl ketones, and aryl aldehydes to provide δ-hydroxyalkyl-β-oxoesters in one pot from the α-bromoesters (Scheme 93, entry b; Scheme 94).[34,119,137] The reaction exclu-

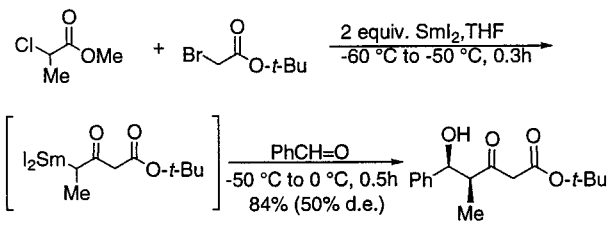
Scheme 94



sively occurs onto the aldehyde group of enals and ω-keto aldehydes, efficiently takes place with the highly enolizable β-tetralone (Scheme 94, entry c), and is highly stereoselective with 4-*tertio*-butylcyclohexanone.[34,119,137] It should be noticed that in comparison the dilithium salt obtained from acetoacetate and LDA reacts sluggishly with β-tetralone.[34,137]

The synthesis of α-bromoacetates enolates is, as expected, easier with α-bromo than with α-chloro esters, but both halides react with SmI_2. These results are particularly important not only because chlorides are much less expensive to use than bromides but also because it allows the synthesis of a large array of β-oxoester enolates from stoichiometric amounts of α-bromo and α-chloro esters of different structures.[119,137] For example, the enolate derived from methyl α-chloropropionate and *tertio*-butyl α-bromoacetate has been successfully trapped with benzaldehyde and leads to *tertio*-butyl 5-hydroxy-5-phenyl-3-ketopentanoate in 84% yield as a 75/25 mixture of stereoisomers (Scheme 95).[119,137] This accounts for the selective reduction of *tertio*-butyl α-bromoacetate and its selective reaction on the carbonyl group of

Scheme 95



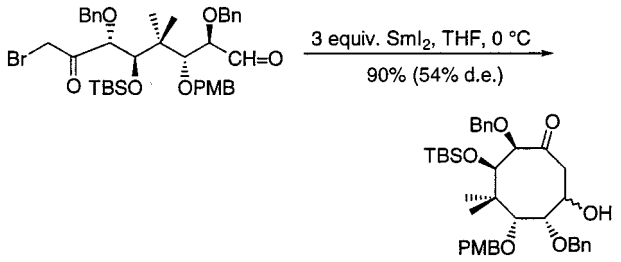
methyl α-chloropropionate leading to the intermediate *tertio*-butyl 4-chloro-3-oxo-butanoate, which is in turn reduced by SmI_2 to the ketone enolate.

7. Intramolecular Samarium Diiodide Promoted Reformatsky Reaction (ISRR)

7.1. Cyclization of α-Halogeno Ketones Bearing a Carbonyl Group in ω-Position

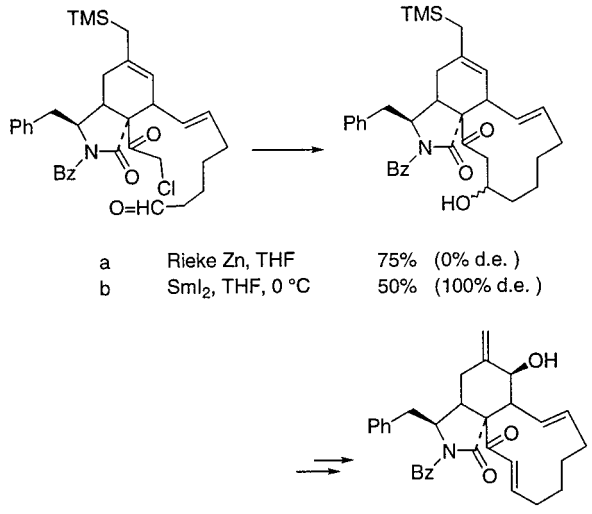
Intramolecular versions of the SmI_2 mediated Reformatsky reaction work fine. Cyclization of α-chloro or bromo ketones bearing an aldehydo group in suitable position takes place efficiently and allows the synthesis of the fully functionalized eight-membered B ring system of Taxol (Scheme 96)[121] and

Scheme 96



of an 11-membered ketone precursor of the cytochalasin ring system (Scheme 97, entry b).[35] In the latter case, remarkably high stereocontrol has been achieved which is unavailable under usual conditions involving, for example, zinc (Scheme 97, entry a).[35]

Scheme 97

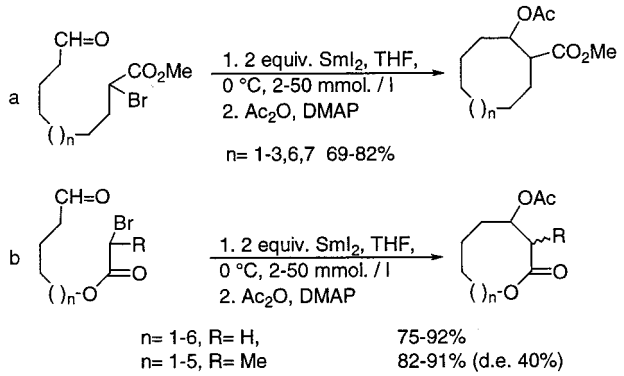


7.2. Cyclization of α-Halogeno Esters Bearing a Carbonyl Group in ω-Position

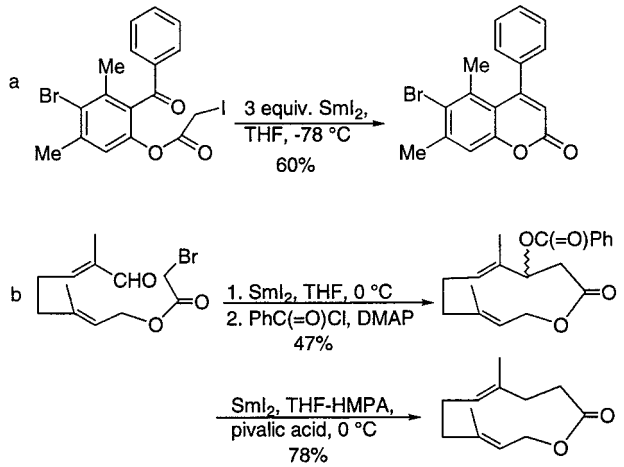
Two types of intramolecular SmI_2 mediated Reformatsky reactions involving esters have been described. They allow, depending upon the nature of the β-bromo ester, the synthesis of β-carbalkoxy cycloalkanols (Scheme 98, entry a)[113] or of β-hydroxy lactones (Scheme 98, entry b; Schemes 99 and 100).[12,114,122−124]

Both reactions have been performed in THF and used successfully for the synthesis of medium (6,7-

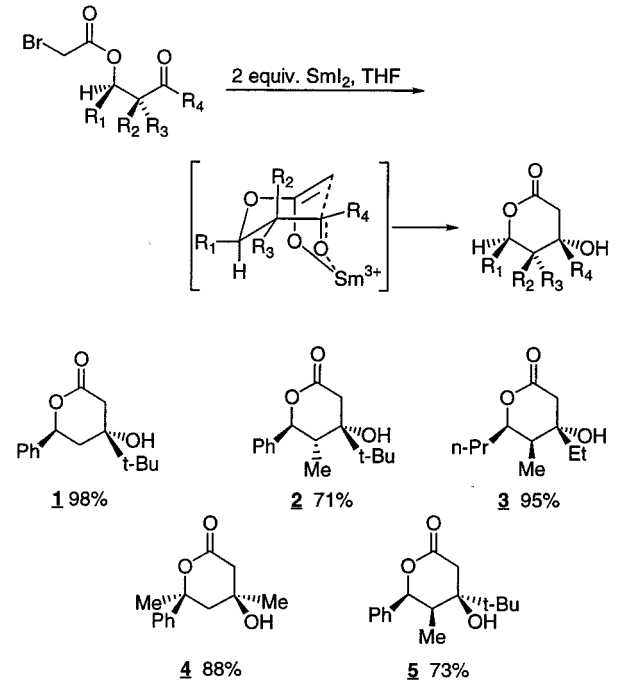
Scheme 98



Scheme 99

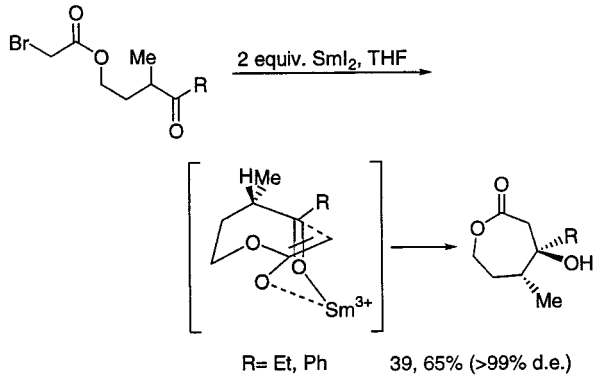


Scheme 100

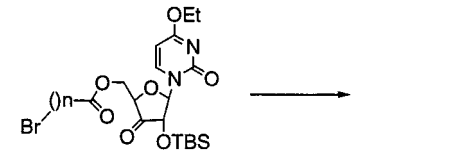


membered) and large ring (8−14-membered) carbocycles (Scheme 98, entry a) and macrocyclic lactones (Scheme 98, entry b). The reaction proceeds through an enolate in which the large ionic radius, the flexible coordination, and the high oxophilicity of samarium is playing an important role.[113] This

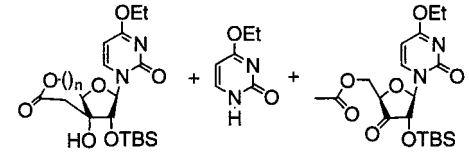
Scheme 101



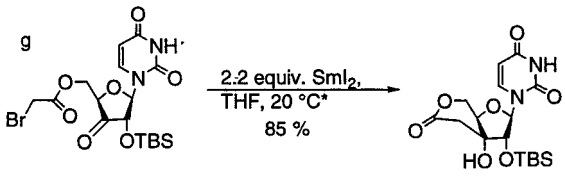
Scheme 102



	n	conditions
a	1	1 equiv. Zn, toluene, 20 °C
b	1	2 equiv. SmI_2, THF, -78 °C
c	1	2 equiv. SmI_2, THF-5 equiv. HMPA, 20 °C
d	1	2 equiv. SmI_2, THF-5 equiv. t-BuOH, 20 °C
e	2	2 equiv. SmI_2, THF, 20 °C
f	2	2 equiv. SmI_2, THF-5 equiv. HMPA, 20 °C



	n			
a	1	0%	0%	22%
b	1	90%	0%	0%
c	1	76%	11%	0%
d	1	61%	0%	0%
e	2	0%	0%	0%
f	2	0%	72%	0%



*The bromo ester must be added slowly to the medium

reaction has been successfully achieved for the synthesis of (i) neoflavonoids (4-arylcoumarins) (Scheme 99, entry a),[125] (ii) Ferrulactone 1 (Scheme 99, entry b),[124] and (iii) butyrolactones bearing a pyrimidinone or a uracil group (see Scheme 102).[36]

The stereoselectivity is poor with those ω-bromoacetoxy ketones which lead to large ring lactones (Scheme 98, entry b; Scheme 99, entry b)[122,124] but very high from those β-bromoacetoxy ketones which produce β-hydroxy valerolactones (Scheme 100)[114,123] and γ-bromoacetoxy ketones which lead to the related seven-membered lactones (Scheme 101).[123]

In contrast to previously reported 1,3-asymmetric inductions, aldehydes as well as ketones are suitable

substrates for these reactions.[114] The sense of 1,3-asymmetric induction in almost all cases (10 different examples, see for example Scheme 100, **1**−**4**) is consistent with that predicted by empirical models which derive from a chair transition structure with strong chelation between SmI_2 and the two carbonyl groups as disclosed in Scheme 100.

The formation of a single stereoisomer whose stereochemistry is the opposite of that described above at the hydroxyl carbon has been observed, however, in one case (Scheme 100, **5**) and might be due to unfavorable steric interactions forcing another transition state.[114]

The 1,2-asymmetric induction observed in the cyclization of γ-bromoacetoxy ketones has been rationalized by assuming Sm(III) coordination to both carbonyl functionalities affording the transition state shown in Scheme 101.[123] This leads then to the product (by placing the R group away and by allowing the attack of samarium enolate from the least hindered side of the carbonyl group (Scheme 101)).

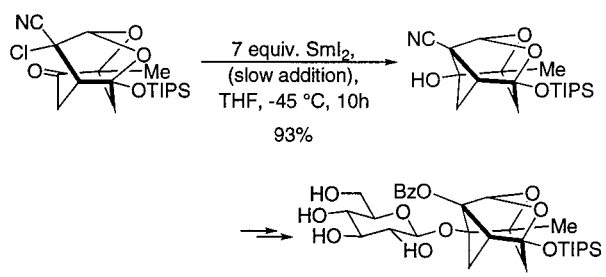
The reaction leading to the bicyclic β-hydroxylactone (Scheme 102, entry b) from the five-membered ketone bearing a α-(bromoacetoxymethyl) and a δ-pyrimidone moiety is valuable.[36] Under the usual conditions (Zn) the bromoacetate is effectively reduced, but the resulting enolate gives the acetate after protonation rather than cyclizing to the bicyclic β-hydroxylactone (Scheme 102, entry a).[36] Best results have been obtained when the reaction is carried out with SmI_2 in THF at low temperature (−78 °C) (Scheme 102, entry b). Performing the reaction in the presence of an additive such as (i) HMPA promotes the concomitant formation of 4-ethoxy-2-pyrimidone (Scheme 102, entry c) whereas (ii) *tertio*-BuOH (Scheme 102, entry d) lowers to a large extent the yield of the lactone.[36] Cyclization does not occur, however, with the higher homologue bearing a α-(β-bromopropionoxymethyl) moiety (Scheme 102, entries e and f).

Synthesis of the bicyclic β-hydroxylactone shown in the Scheme 102, entry g, has been achieved from related derivatives bearing an unprotected uracil derivative on the condition that the substrate is slowly added to the THF solution of SmI_2.[36]

7.3. Cyclization of α-Halogeno Alkylnitriles Bearing a Carbonyl Group in ω-Position

There are only a few examples involving α-halogeno alkylnitriles. The only example disclosed in this review is impressive because SmI_2 induces the cyclization of a nitrile enolate to a highly functionalized cyclohexanone (Scheme 103).[126] This is usually an unfavorable aldol cyclization which in fact proceeds in excellent yield to give the particularly strained four-membered β-cyanohydrin shown in Scheme 103. This polycyclic compound, which suffers a rapid retroaldol cleavage of the cyclobutane ring in the presence of bases such as triethylamine, is the precursor of the most complex part of paeniforin, a natural product belonging to the terpenoid and β-glucoside families. It has defied chemical synthesis for the last three decades (Scheme 103).[126]

Scheme 103



8. Conclusion

SmI_2 has been quite rapidly promoted as one of the most powerful reducing agents. Not only is its reducing ability particularly high but it can be modulated by the proper choice of the conditions. It is soluble in THF—a *nonprotic* solvent and commercially available. SmI_2 in THF solution is not toxic, it does not require tedious activation (like Rieke metals)[127] or special manipulations (like metals in liquid ammonia),[128,129] and it is indefinitely stable (in the absence of oxygen), which is not the case of dissolved metals (arenylmetals).[130,131] Although it is a very powerful reducing agent, SmI_2 is able to effect highly chemoselective reductions, often stepwise. Impressive advances have been made since the pioneer work of Kagan. Use of coadditives such as HMPA, a pallette of transition metal salts, or even visible light allows the proper tuning of its reducing ability. The reactions often imply radicals at one stage but offer the advantage of producing an organometallic in the end. It was the aim of this review to provide the state of the art in that series of fundamental "*Named*" reactions—the Barbier,[22,47,48] Grignard,[44,45] and Reformatsky[132−134] reactions—which all allow the formation of a new C,C bond. Particularly important are the intramolecular versions of these reactions which allow the construction of complex molecules and the formation of several cycles often in one single step with particularly high stereochemical control. SmI_2 is starting to be used more and more for the synthesis of natural products, and its use will surely increase.

9. References

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