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Twenty-five years of organic chemistry with diiodosamarium: an overview

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1. Introduction

In 1977 we published our first article on diiodosamarium,[1] followed three years later by a full paper.[2] Why did this new development in our research activity come about, which at that time was mainly oriented towards asymmetric synthesis? In 1969, I was interested to read the publication of Hinckley[3] who discovered that simple europium(III) chelates could be used as shift reagents to simplify the ^1H NMR spectra run at 100 MHz. We applied this method to ^1H NMR spectroscopy of sugars, in some collaborative works.[4,5] However, the explosion of the number of papers in that area, combined with the need for a strong background in physical organic chemistry, persuaded me to change the research topic of a Ph.D. student, Pierre Girard, who was involved in

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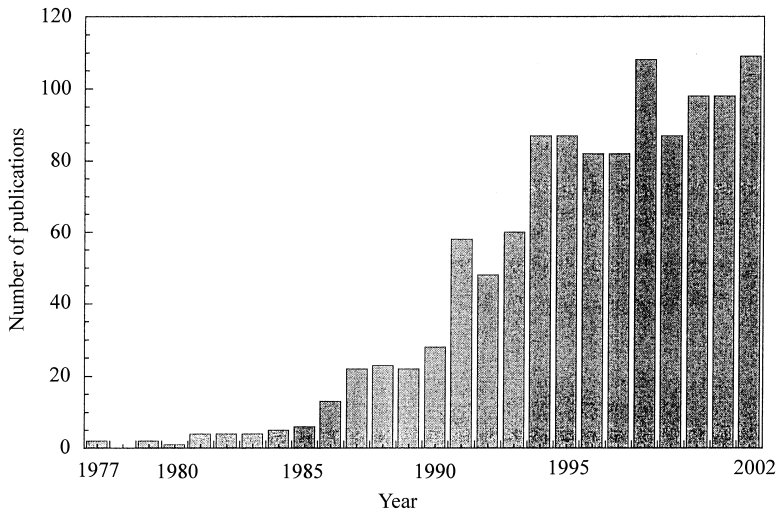


Scheme 1.

that research. I decided to keep the keyword *lanthanide* for the thesis, but with an orientation toward organic reactions. We set up first an air oxidation system for the conversions of benzoins to benzils, with $Yb(NO_3)_3$ as the catalyst.[6] Some organoytterbiums and organosamariums (lanthanide Grignards) had been recently described at that time.[7] In my laboratory, some of these experiments were reproduced, giving a mixture of divalent and trivalent organolanthanides. Then we moved to the poorly known field of divalent lanthanides, with the expectation of realizing some new types of reduction of organic compounds. Divalent europium salts are easy to prepare and to handle. It has been described that a water solution of $EuCl_2$ could reduce isonicotinic acid into the corresponding aldehyde.[8] We were not able to extend this chemistry to other classes of compounds. We hypothesized that more promising reducing agents (monoelectronic donors) could be found by using another lanthanide. At that time the following E^0 values of normal reduction potential (in water) were reported (Ln^{3+}/Ln^{2+}):[9] Eu: −0.43 V, Yb: −1.15 V, Sm: −1.55 V, Tm: −2.3 V. Because of the high price of thulium we concentrated on ytterbium and samarium. We decided to prepare inorganic salts of Yb(II) and Sm(II), and succeeded in obtaining THF solutions of SmI_2 and YbI_2, by treating 1,2-diiodoethane with samarium or ytterbium powder.[1] This approach was inspired by the classical procedure in organic chemistry for preparing diethyl ether solutions of MgX_2 from 1,2-dihalogenoethane and magnesium. The promising reducing properties of diiodosamarium encouraged us to concentrate on this new reagent.

In this account are first summarized some of the main reactions obtained in our group, especially in the early developments. Then the general trends of the use of SmI_2 are presented. This article doesn't intend to make a full coverage of all the chemical transformations induced by SmI_2, since many reviews have been already published.[10–21] The strong impact of diiodosamarium in chemistry is well reflected by a recent literature search (SciFinder), as indicated in Scheme 1. After an induction period a fast growth started around 1985, the continuous interest for this reagent up to now is evidenced by the graph of Scheme 1.

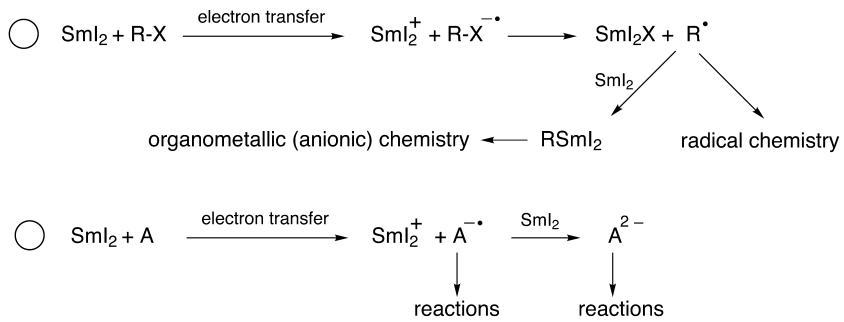
2. Diiodosamarium

Diiodosamarium was prepared for the first time in 1906 by Matignon and Caze, by disproportionation of triiodosamarium at 800°C.[22] Inorganic chemists devised alternative methods of preparation, because of the interest of this salt in solid state chemistry.[23] Until 1977 there were no uses in organic chemistry. From our mild procedure, one obtained a deep blue–green THF solution (0.1 M) of SmI_2, air-sensitive but stable under nitrogen or argon. Some physical properties of the solution have been measured:[24] strong absorptions at 617 and 525 nm,[25] magnetic susceptibility μ=3.52 μ_B. The electronic spectrum of SmI_2 was discussed by comparison with the spectrum of Sm^{2+} in some solid state compounds. In 1985, Sen et al.[26] established the X-ray structure of SmI_2/*t*-BuCN and SmI_2/diglyme complexes, while Evans et al.[27] later gave the structure of SmI_2/5 THF complex. The electrochemical properties of SmI_2 have been reinvestigated recently, and were found to be very sensitive to the nature of the solvents.[28] The reducing properties increase by going from THF to DMF and HMPA; they are highly dependent on the presence of additives, as already found in the transformations of organic substrates (see Section 8).

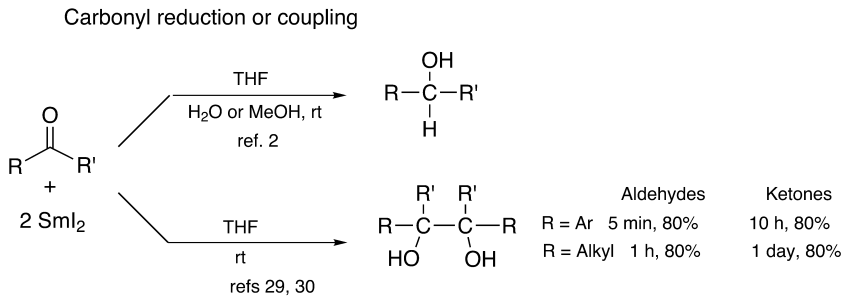
Diiodosamarium was expected to react as a one-electron donor towards suitable acceptors. This was easily confirmed by the visual inspection of solutions in THF (dark blue–green), which turned to yellow (Sm(III) state) after reduction of the substrate. Sometimes the reaction is fast at room temperature, sometimes a prolonged time or some heating is necessary. Since SmI_2 acts as a monoelectronic donor (Sm(II)→Sm(III)) one may assume that organic transformations will need a one-electron transfer or two consecutive one-electron transfers, according to the case. The principle of the transformations is described in Scheme 2.

3. The main reactions discovered in Orsay during the 1977–1985 period

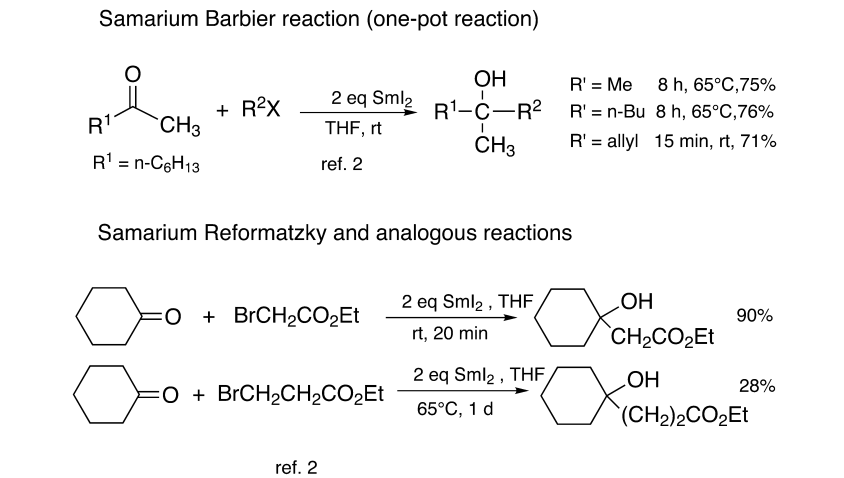
Several simple transformations of organic compounds have



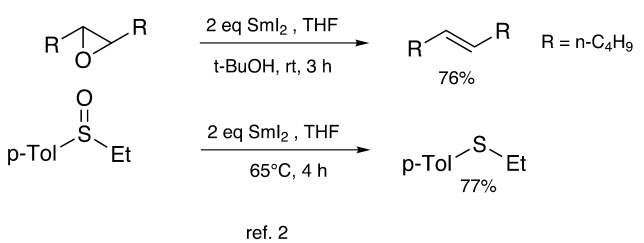
Scheme 2.



Scheme 3.

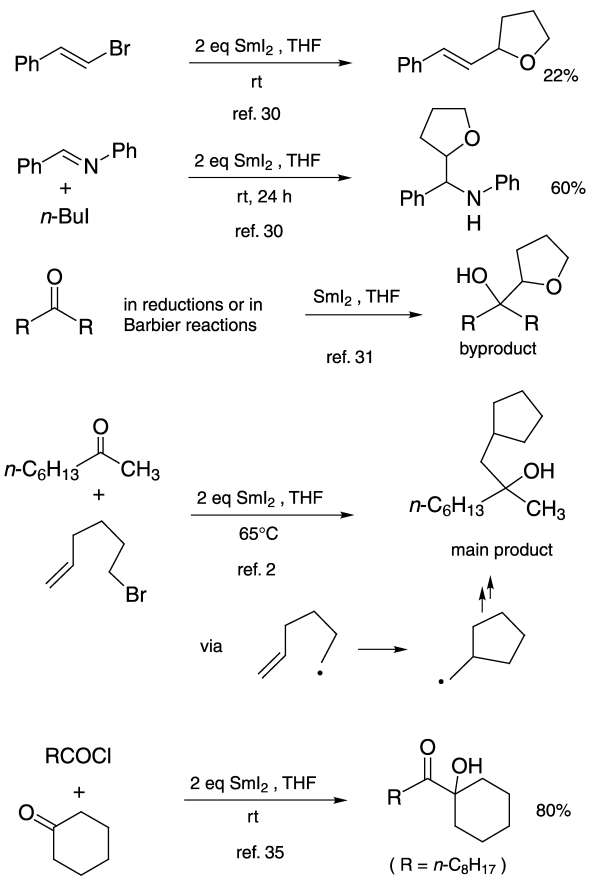


Scheme 4.



Scheme 5.

been identified.[1,2] These reactions were run in THF, usually at room temperature in the presence of two equivalents of SmI_2. The reactions are summarized in Schemes 3–5. Aldehydes and ketones were reduced into the corresponding alcohols, the reaction was especially fast with aromatic aldehydes or ketones in the presence of SmI_2 and a proton source (alcohols, water) (Scheme 3).[2] In a 1:1 mixture of *n*-octanal and 2-octanone there was almost exclusive selectivity in favor of the aldehyde reduction.



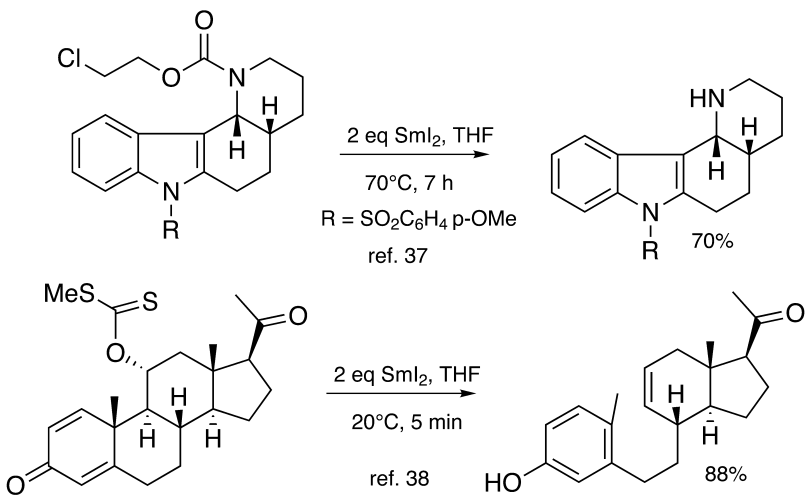
Scheme 6.

Several types of activated organic halides were easily reduced with simultaneous C–C couplings.[2] Alkyl halides were transformed into the corresponding alkanes, without coupling products. Another class of transformations of wide interest is the Barbier type reaction now often named the samarium Barbier reaction. In this one-pot procedure we mixed equimolar amounts of a ketone and an organic halide RX with two equivalents of SmI_2. After heating in THF, a C–C coupling occurred, producing a satisfactory yield of the product (Scheme 4). The aldehydes gave rise to a low yield of the expected product, because of some concurrent reactions. The main problem was the formation of tertiary alcohols bearing two R groups, instead of the expected secondary alcohol with one R group. A lot of the primary alcohol coming from the reduction of the initial aldehyde was also identified. The origin of this mixture of products was interpreted by an in situ Oppenauer oxidation of the initially formed Barbier product as a samarium alcoholate by the remaining aldehyde.[1] The samarium–Reformatzky reaction was found to occur very easily (Scheme 4). Finally, the deoxygenation of epoxides or sulfoxides was possible (Scheme 5), but phosphine oxides or sulfones were unreactive.

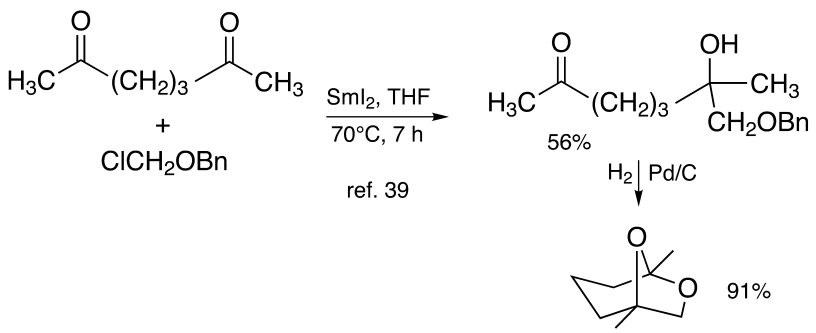
In conclusion, a large range of reactions were discovered, working in mild conditions and showing some chemoselectivity. It was also observed that the sluggish samarium–Barbier reaction could be strongly accelerated in the presence of 1% of an iron(III) salt. Thus the couple 2-octanone/*n*-iodobutane gave the tertiary alcohol after 10 h reflux in THF, while the iron catalysis allowed the reaction to proceed at room temperature for 2 h.[2] All the above results have been published in a full paper in 1980.[2]

During the next five years (1980–1985) we continued to look at the basic reactions induced by SmI_2, investigating intermolecular reactions and reductions of various functional groups.

The Barbier reaction was extended by the use of a variety of allylic and benzylic halides.[30] Interestingly, these halides, which are prone to give self-coupling products in the presence of SmI_2, are also excellent reactants in the Barbier reaction. In aprotic conditions, aldehydes and ketones generate pinacols, the reaction being very fast with aromatic aldehydes or ketones.[29,30] The reaction can be highly chemoselective, for example *p*-nitrobenzaldehyde is transformed quantitatively and almost instantaneously into the pinacol (*meso*/dl mixture) at room temperature without any reduction of the nitro group. The reactivity of nitrogen compounds was also screened. The reduction at room temperature in THF containing some methanol was very slow for nitrobenzene (with aniline formation), for benzaanilide (giving *N*-benzylaniline) and for diphenylhydrazine (giving aniline). Nitriles remained unchanged in the above conditions.



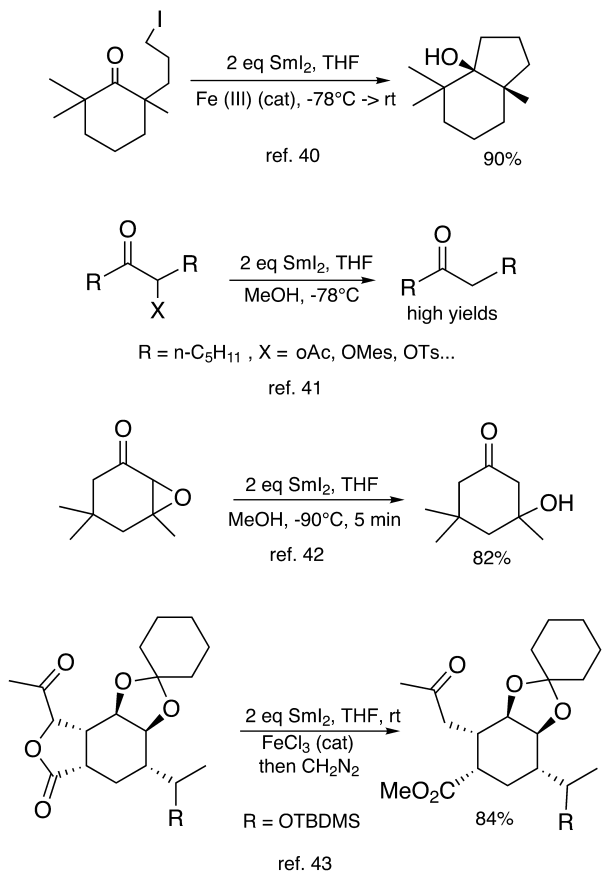
Scheme 7.



Scheme 8.

Some mechanistic studies have been performed for the reactions involving organic halides.[31] Final hydrolysis by D_2O did not give rise to deuterium incorporation in the alkanes. Then the formation of stable organosamariums was dismissed (see Section 6 for further developments). The transient formation of radicals was indirectly shown by the formation of products or by-products having incorporated the tetrahydrofuranyl fragment (Scheme 6). 6-Bromo-1-hexene gave rise to a cyclized product, an indication of the initial formation of radical R· species from RBr, which has time to cyclize before leading to the final product. In the Barbier reaction we envisaged a coupling between radical R· and a ketyl radical. However this hypothesis was later abandoned in favor of an organosamarium mechanism (see Section 6).

The reduction of various acid chlorides unexpectedly led to coupled products, benzoins or α-ketols.[32] The reductive coupling between acid chlorides and aldehydes or ketones was subsequently discovered, the product being an α-ketol (Scheme 6).[33–35] We proposed for these transformations an acylsamarium intermediate. Later, reactions of acid chlorides were extended (see Section 6).



Scheme 9.

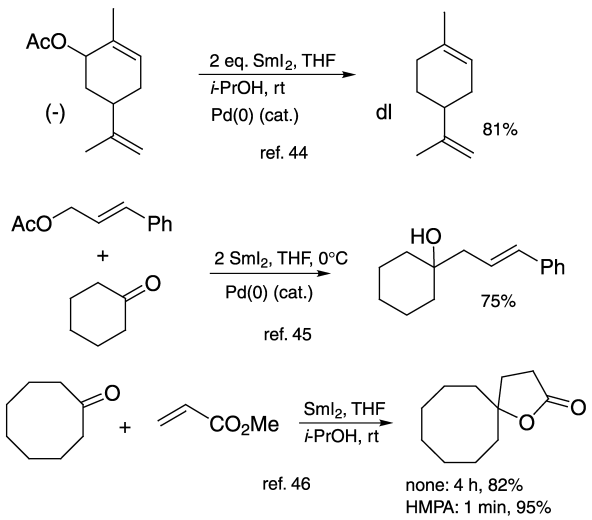
4. The first papers on SmI_2 external to Orsay (1982–1986)

Within a five-year period, six groups entered into the area of diiodosamarium chemistry. In 1982, Natale[36] cleaved the N–O bond of several isoxazoles by SmI_2, generating β-aminoketones. In 1982 and 1983, Magnus et al.[37,38] used SmI_2 in some fragmentation reactions (Scheme 7), after unsuccessful attempts with many other reducing agents.

In 1984, Imamoto et al.[39] performed some samarium Barbier reactions with $ClCH_2OBn$. In this way it was possible to create a dihydroxymethyl unit after debenzylation (Scheme 8).

In 1986, Molander et al.[40] extended the scope of the samarium Barbier reaction by the investigation of its *intramolecular* version. One example is shown in Scheme 9. In this systematic study, with variation on the ring size (five- and six-membered rings) and the side-chain length, a Fe(III) catalyst allowed the running of reactions at room temperature. In the same year, Molander et al.[41,42] described the easy C-heteroatom cleavage by SmI_2, when the bond to cleave is vicinal to a carbonyl group. The reactions were performed in THF/MeOH at low temperature. In these conditions only α-hydroxyketones provided low yields. White et al.[43] were able to reduce a complex ketolactone (Scheme 9) in excellent yield, after trying several reducing systems.

In 1986, Inanaga et al.[44,45] published their first papers on diiodosamarium reactions. They found that allylic acetates in the presence of a catalytic amount of a Pd(0) complex and two equivalents of SmI_2 in THF could be reduced (if there is some 2-propanol) or coupled to carbonyl compounds (Scheme 10). The same authors discovered that the reductive coupling of ketones with α,β-unsaturated esters was slow in THF, but was greatly accelerated by addition of HMPA (Scheme 10).[46] The following year, Fukuzawa et al. reported similar results.[47] It was also noticed that addition of 5% HMPA in THF induces a rapid reduction of many



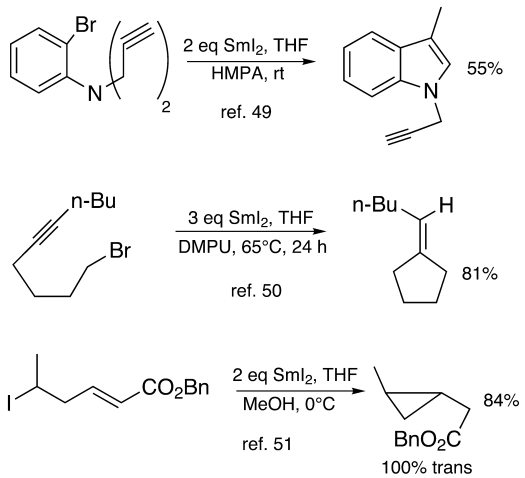
Scheme 10.

organic halides to the corresponding alkanes, in mild conditions.[48] The HMPA procedure became very popular, because it allows the acceleration of many reactions that are sluggish in the presence of SmI_2/THF only.

5. The cyclization reactions

5.1. Cyclization via alkyl or aryl radical intermediates

Many reactions with SmI_2 involve a carbon radical intermediate that attacks C=C or alkynes systems. Some examples are reported in Scheme 11, including the cyclization of an aryl radical on a triple bond to generate an indolic compound.[49] The formation of nitrogen- and oxygen-based heterocycles by SmI_2 is possible when an aryl radical (produced by reduction of bromo or iodoaromatics) has the opportunity to react intramolecularly with an alkene or alkyne moiety. The same principle can be applied to alkynyl halides: the alkyl radical adds intramolecularly on the triple bond and gives a cyclic structure.[50] Similarly a secondary radical can add intramolecularly on an unsaturated ester (Scheme 11).[51] In that case, a proton source (methanol) is needed to overcome competitive reactions by quenching



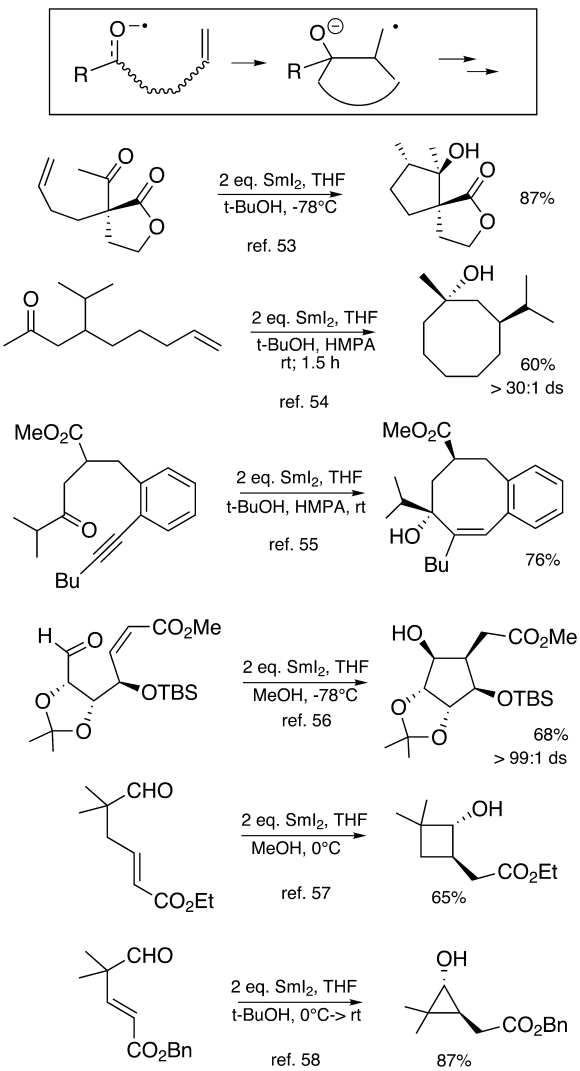
Scheme 11.

the intermediate enolate. Curran et al.[52] studied many radical cyclizations by SmI_2 both from the synthetic and mechanistic points of view.

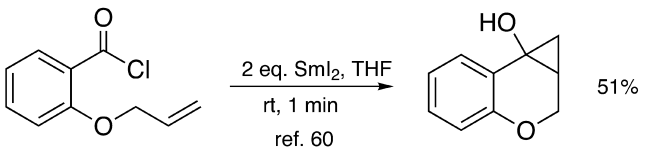
5.2. Ketyl radical: alkene or alkyne cyclizations

This is a wide area, where ω-unsaturated aldehydes or ketones give rise to a large range of structures. The ketone–olefin coupling reactions were pioneered by Molander et al.[53] for a large number of different substrates, often affording products with a high diastereoselectivity. Five-membered rings are easily formed in absence of HMPA (Scheme 12).[53]

Interestingly, Molander et al.[54] found that SmI_2 (with HMPA, *t*-BuOH in THF) promotes a radical cyclization to eight-membered rings (usually difficult to achieve by cyclization), as illustrated in Scheme 12. The reaction works also on an alkyne; one case studied by Reissig et al.[55] is described in Scheme 12. Cyclization often occurs between a carbonyl group (transformed into a ketyl radical) and a conjugated double bond (usually in α,β-unsaturated esters). Rings of various sizes have been obtained in the presence of an alcohol as a proton source. Examples of five-, four- and



Scheme 12.



Scheme 13.

three-membered rings are indicated in Scheme 12.[56–58] *exo-trig* Cyclizations characterized all the examples of Scheme 12, except in the eight-membered ring formation. A small number of 5-*endo-trig* cyclizations are known.[59]

5.3. Cyclization via acyl radicals

We described the reduction by SmI_2 of some ω-unsaturated acid chlorides into cyclopropanols (Scheme 13).[60] The reaction was interpretated by the internal trapping of the acyl radical intermediate by the terminal double bond.

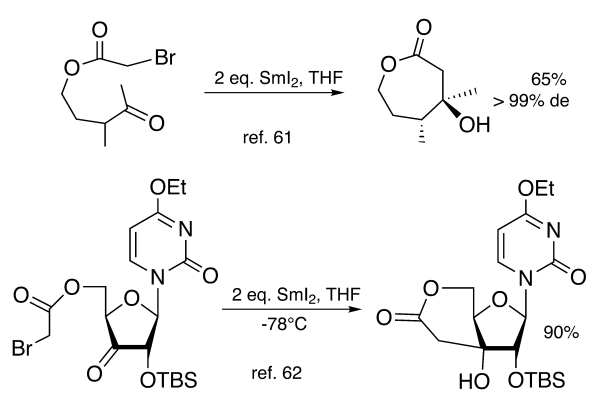
5.4. Cyclization via samarium enolates intermediates

These reactions involve the reduction by SmI_2 of precursors such as α-heterosubstituted aldehydes or ketones or α-bromo-esters. The samarium enolate is trapped by a carbonyl group located in another part of the molecule. Two examples of intramolecular Reformatsky reactions are listed in Scheme 14.[61,62]

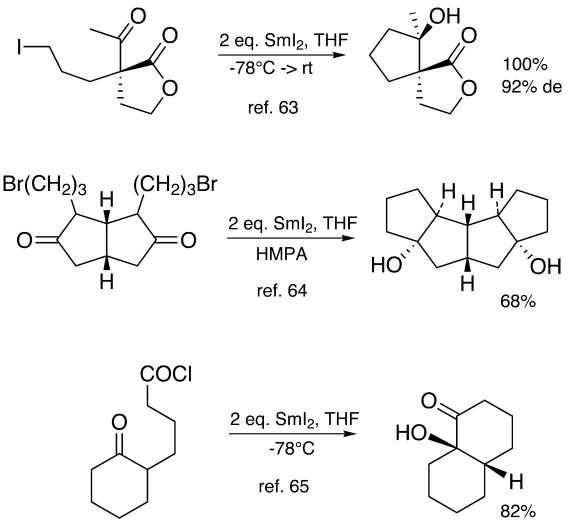
5.5. Intramolecular samarium Barbier reaction

Since the first report of Molander in 1986 (vide supra), the intramolecular samarium Barbier reaction has given rise to many developments. It is impossible to detail here the various cyclic structures that are available using this approach. In the review of Krief and Laval in 1999,[18] a section is devoted to the intramolecular Barbier reaction. The SmI_2 promoted cyclization of ω-halogeno aldehydes and ketones as a way to achieve the synthesis of a multitude of monocyclic and bicyclic compounds, sometimes densively functionalized. It is interesting to note that often the cyclization is highly diastereoselective (Scheme 15).[63] Polyquinanes have been prepared by a bis-Barbier reaction (Scheme 15).[64]

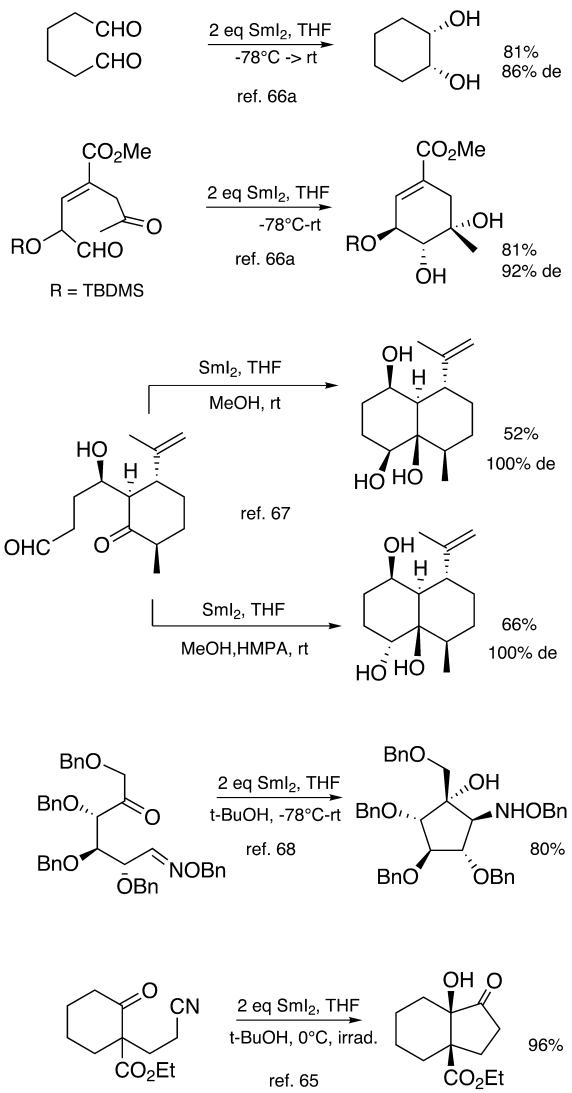
Acylsamariums can be obtained by the in situ reduction of acid chlorides, and may give an intermolecular Barbier type



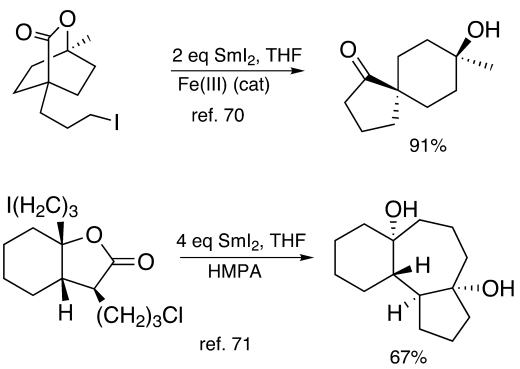
Scheme 14.



Scheme 15.



Scheme 16.



Scheme 17.

reaction (see Section 6). The intramolecular version has been described in a few cases (Scheme 15).[65]

5.6. Intramolecular pinacol formation and analogous reactions

Hanessian et al.[66a] discovered that SmI_2 transformed aliphatic 1,5- and 1,6-dialdehydes into *cis*-diols. The *cis*-stereoselectivity is retained in many cases, including cross-coupling between aldehydes and ketones.[66] Moreover, a chelation control often introduces useful additional diastereoselectivities in complex systems (Scheme 16).[66,67] Cyclizations by coupling between carbonyl and C=N functionalities (hydrazones, oximes) have been described. One example involving an oxime derivative is indicated in Scheme 16.[68] Mixed couplings with nitriles as one of the components are rare.[69] Quite good yields can be obtained in the reductive cyclization of keto nitriles by the use of visible light, as indicated in Scheme 16.[65]

5.7. Cyclization by nucleophilic acyl substitution

The reduction by SmI_2 of some halogenoesters generates in situ an organosamarium, which reacts intramolecularly to give a ketol, as shown in Scheme 17.[70] This interesting transformation has been also applied to esters bearing two halides.[71] The keto group produced in the first step enters into a subsequent intramolecular Barbier reaction (Scheme 17).

6. The intermolecular reactions of organic halides on various substrates

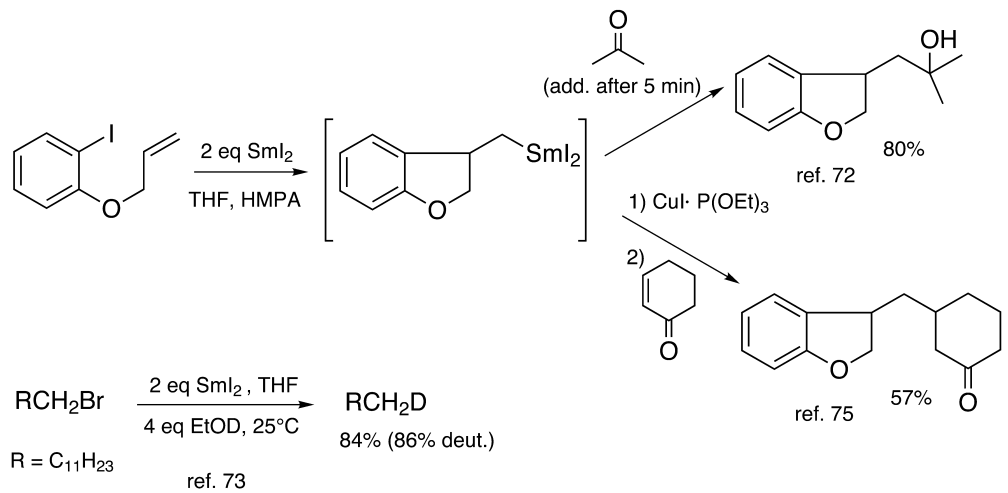
The samarium Barbier reaction was a cornerstone of our first investigations on the use of SmI_2 in organic chemistry. The reaction remains important for C–C bond formation. A mechanism was initially believed to likely involve a coupling between a radical and a ketyl.[31] The organosamarium route was eliminated because there was no deuterium incorporation in the alkane (RH) resulting from the deuterolysis of reaction mixture ($RX+SmI_2$) maintained in the conditions of the Barbier reaction. Later, the possibility of quenching the product of cyclization of some unsaturated halides by an electrophile[71,72] (Scheme 18) gave a clear indication that organosamariums may survive in THF. We reexamined the mechanism of the Barbier reaction, by using EtOD as an internal quench of C–Sm bonds (Scheme 18).[73] The deuterium incorporation was noticed, establishing the formation of an alkylsamarium intermediate. Such organometallics are highly reactive and survive in THF only at low temperature. Curran et al.[74] discussed in detail all the aspects of the Barbier reaction. The important conclusion is that two procedures are now available: the one-pot procedure (samarium Barbier) and the two-step procedure (samarium Grignard). The second one has some advantages, if the aldehyde or ketone is very reactive versus SmI_2 giving by-products such as pinacols.

Organosamariums add only in a 1,2-fashion to conjugated ketones. The transmetallation by Cu(I) salts of the organosamariums species (generated from R–X or by cyclization processes on C=C bonds as above) allow the performance of 1,4-additions, as described in Scheme 18.[75]

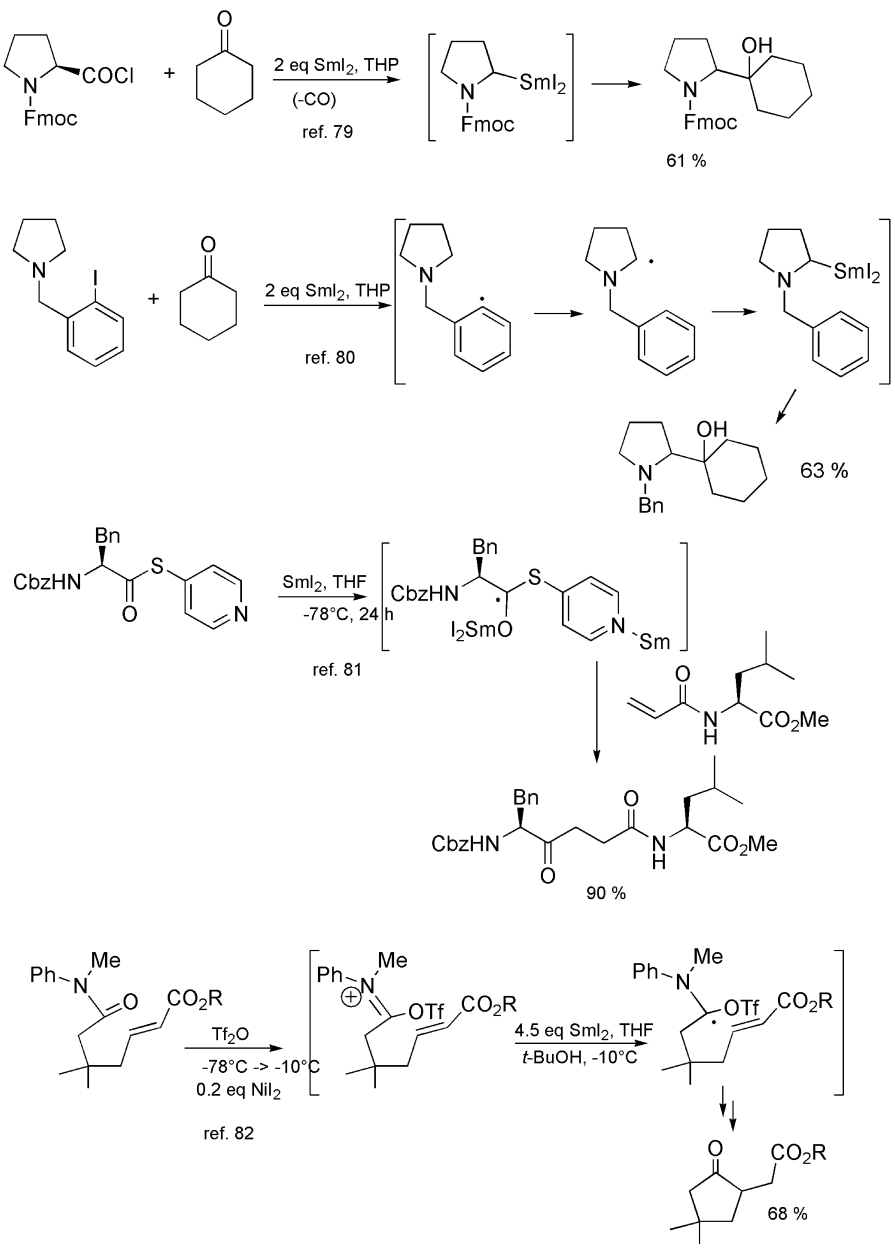
A benzyl or allyl halide can react with an imine by the samarium Grignard procedure, when THF was replaced by THP.[76] The Barbier or Grignard procedure has been successful when the imine carries a chelating group.[77]

Geminal diiodo- or triiodoalkanes undergo excellent Barbier reactions on alkyl aldehydes to generate iodohydrins or 2-hydroxydiodoalkanes, respectively.[78]

The case of acylsamarium produced by the two-electron



Scheme 18.



Scheme 19.

reduction of acid chlorides (vide supra) can be included here. The acylsamariums prepared by a Barbier procedure react on aldehydes or ketones to provide a variety of products, according to the experimental conditions (Scheme 6).[35] α-Heterosubstituted acid chlorides react with SmI_2, with decarbonylation. The example of the acid chloride of a protected proline is indicated in Scheme 19.[79] The coupling reaction with a ketone involves an *α*-aminosamarium species. It is interesting to notice that Ito et al.[80] prepared a related compound from *N*-2-iodobenzyl pyrrolidine, through a radical intermediate (Scheme 19).

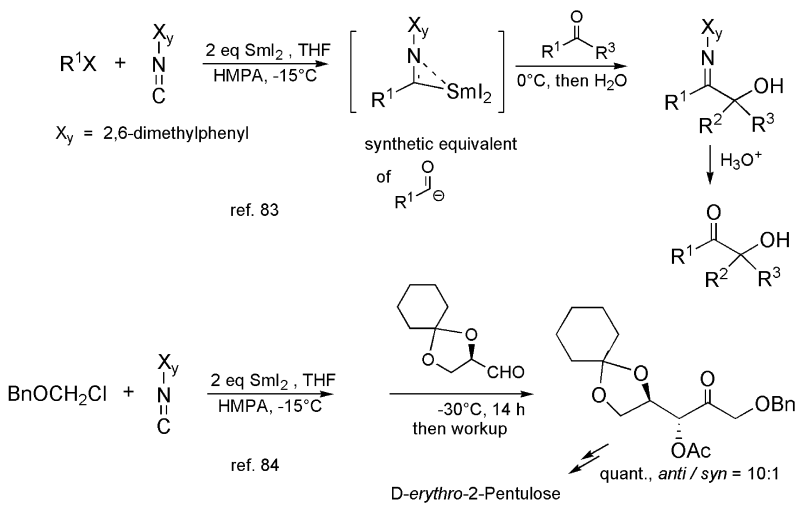
Recently Skrydstrup et al.[81] have been able to produce acyl radical equivalents by the SmI_2 reduction of α-aminothioesters. These acyl radical equivalents could be intercepted by α,β-unsaturated amides or esters, one example of which is shown in Scheme 19.

Acyl radical equivalents could be generated by the SmI_2 reduction of iminium salts produced in situ.[82] In this way, ω-unsaturated amides have been transformed into cyclic ketones of various sizes (Scheme 19).

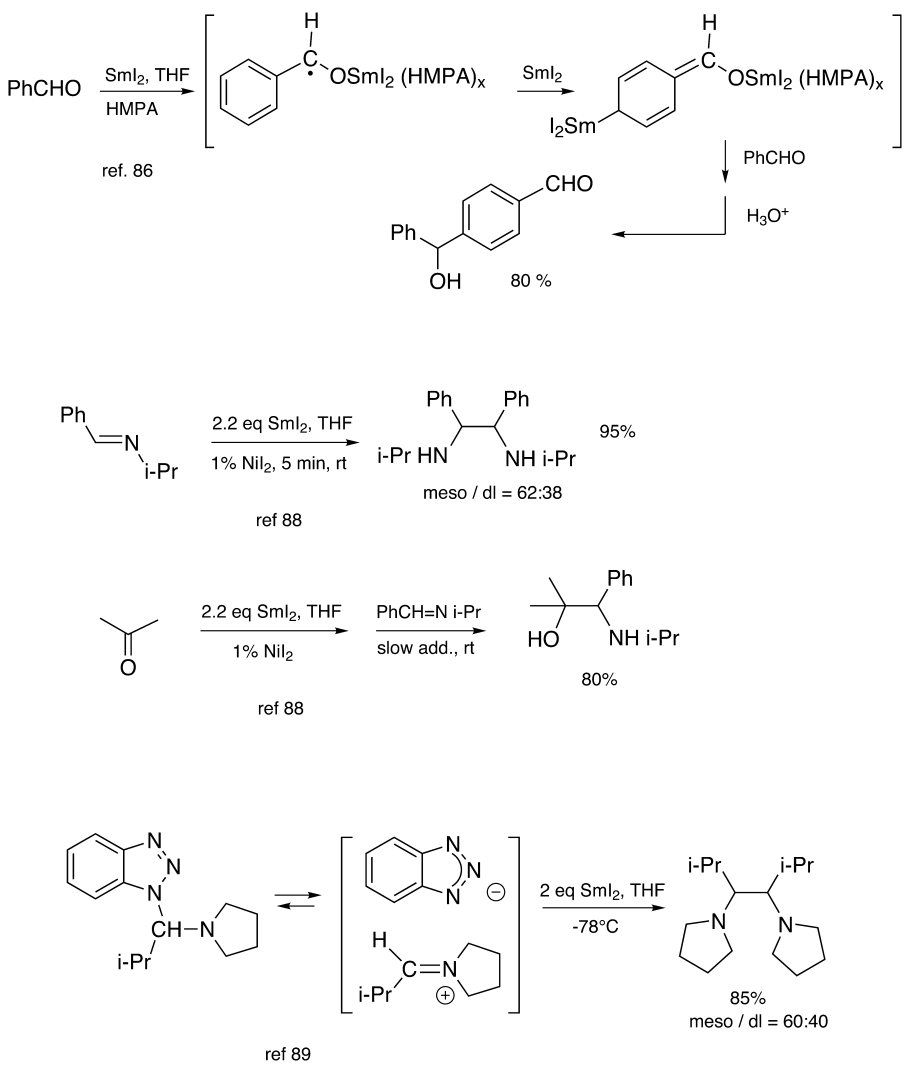
Acyl anion equivalents have been designed by Ito et al.[83,84] from the coupling mediated by SmI_2 (THF, HMPA) between an isocyanide and an organic halide (Scheme 20). The iminoalkyl samarium that is produced can react with aldehydes or ketones, affording an α-ketol after acidic hydrolysis. This method is quite general with alkyl halides.

7. Pinacol couplings and analogous reactions

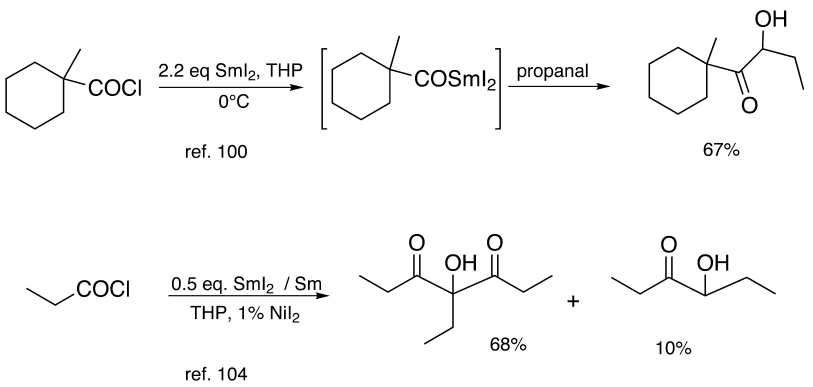
The pinacol coupling of aldehydes or ketones is a very important intermolecular transformation that has been also



Scheme 20.



Scheme 21.



Scheme 22.

realized intramolecularly (vide supra). The stereochemical control is usually poor, giving a *meso*/dl mixture close to the 1:1 composition. However, addition of polyethers promotes the diastereoselective pinacol formation of aryl aldehydes into *meso*-diols, and of alkyl aldehydes, into dl-diols.[85]

Addition of HMPA inhibits the coupling of the ketyl radical by subsequent reduction to a samarium dianion. The intermediate is able to react intra- or intermolecularly (Scheme 21).[86]

Imines can be dimerized into vicinal diamines, but very often with low diastereoselectivity.[87,88] Imine dimerization by SmI_2 is accelerated by catalytic amounts of diiodonickel.[88] The reduction by SmI_2 of iminium salts produced in situ from a benzotetriazole precursor (Scheme 21) created bis(*N*, *N*-dialkyl)diamines.[89]

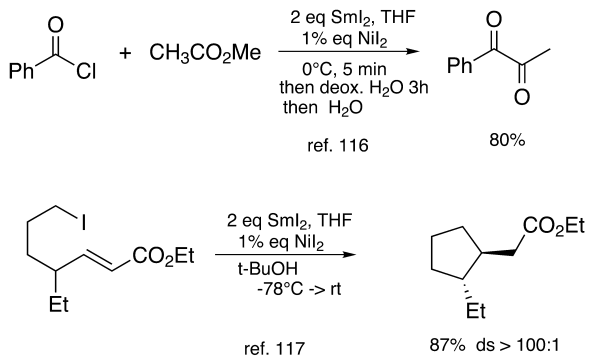
The coupling of conjugated esters, amides or ketones is similar to the pinacol coupling. It is a hydrodimerization process.[90] For example, chalcone gives a substituted cyclopentanol in the presence of HMPA, through a β,β-coupling followed by cyclization. [90a]

8. Influence of additives

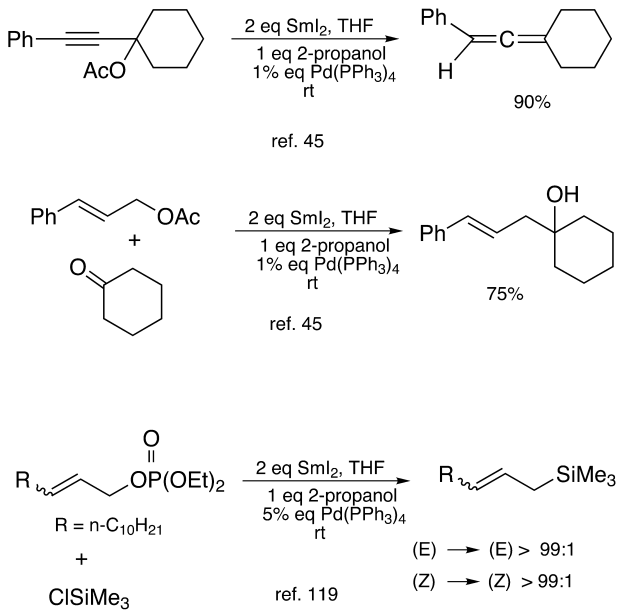
The influence of solvents or additives on the organic chemistry mediated by diiodosamarium was extensively reviewed in 1999.[20] In this section only the main trends will be summarized.

8.1. Cosolvent effects in THF

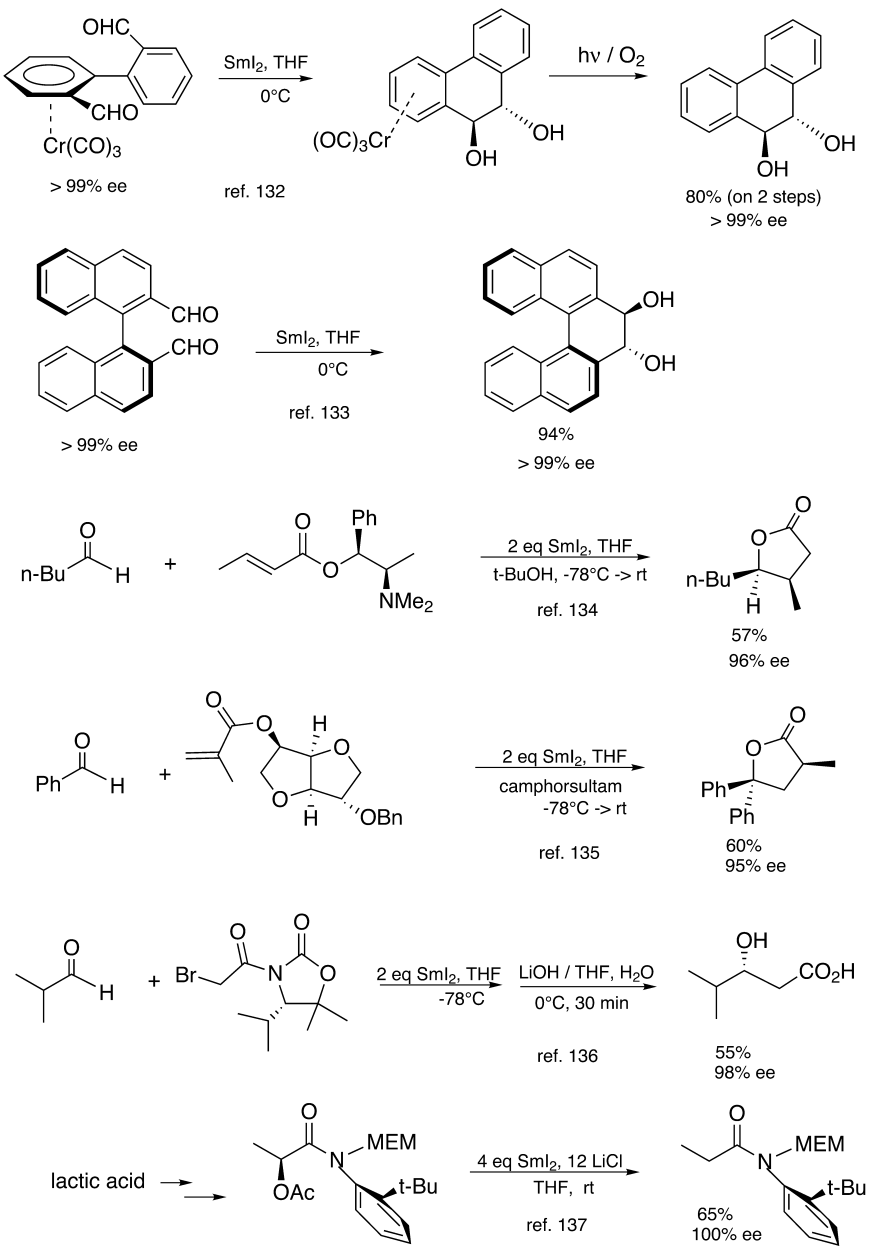
In 1987, Inanaga et al.[46,47] noticed the beneficial influence of HMPA on some reactions mediated by SmI_2. The authors found that samarium Barbier reactions in THF were much faster in the presence of some HMPA, allowing the use of room temperature instead of THF reflux.[91] The Inanaga procedure has been widely used in SmI_2 chemistry; many examples are quoted in the present article. Electrochemical and chemical studies have shown that only four equivalents of HMPA with respect to SmI_2 are needed to reach the maximum rate of reaction.[92–95] The structure of the complex $SmI_2(HMPA)_4$ has been characterized by Hou et al.[96] However, recent electrochemical and spectroscopic studies have shown that the main species in THF solution is not $[SmI_2(HMPA)_4]$ but the ionic cluster $[Sm(HMPA)_4(THF)_2]^{2+}$ 2 I^-, when four equivalents of HMPA were used.[28b] The less toxic DMPU may replace HMPA in some reactions.[97] TMU (1,1,3,3-tetramethylurea) has also been employed.[98] The influence of the addition of various cosolvents to THF on the reducing power of SmI_2 has been studied by Flowers et al.[92] These authors used linear sweep voltammetry and established the importance



Scheme 23.



Scheme 24.



Scheme 25.

of the nature and concentration of various cosolvents on the properties of SmI_2. The inner-sphere versus outer-sphere electron transfer mechanism for various substrates and Sm(II) reductants is under investigation and discussion.[28,99]

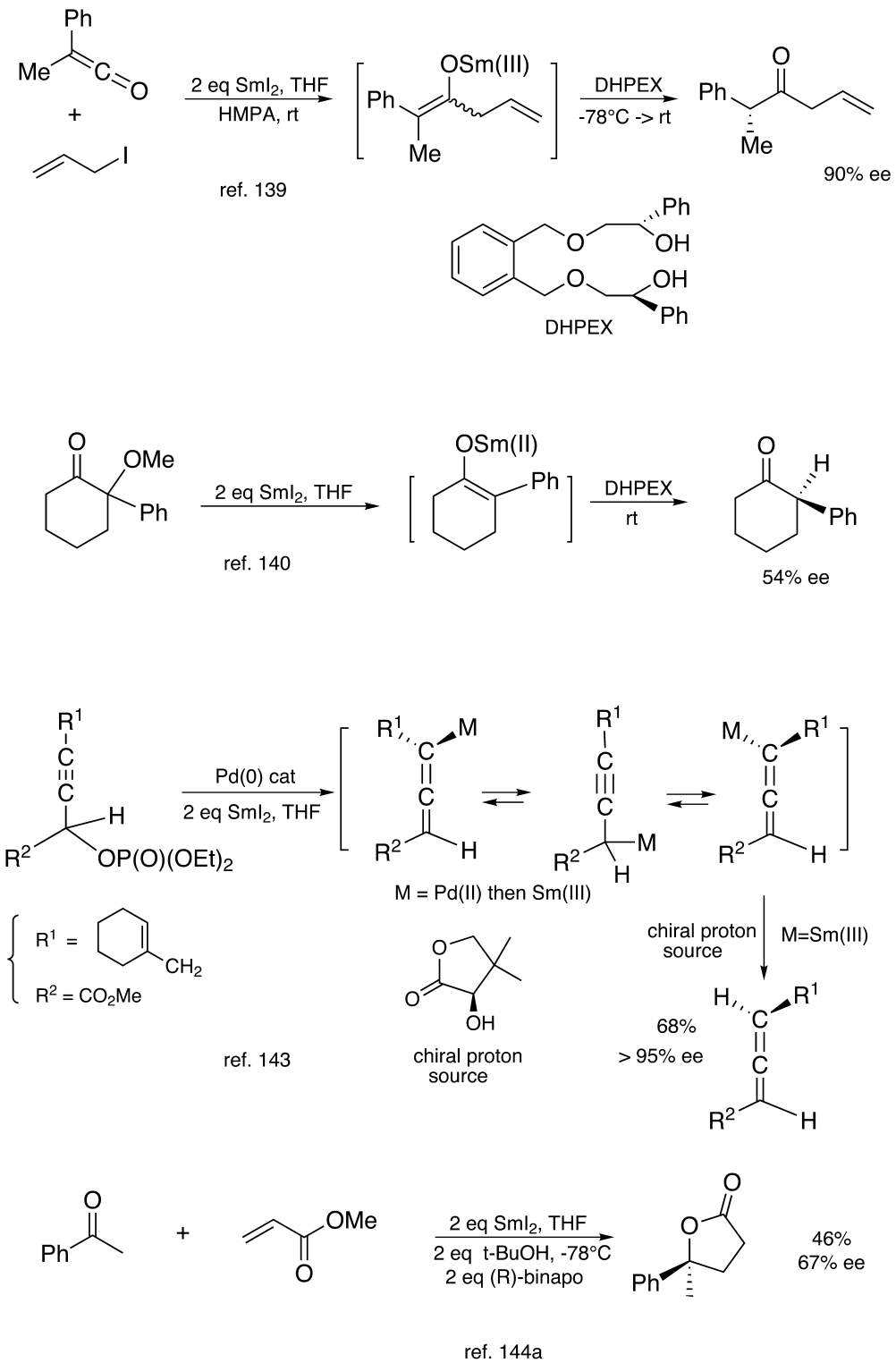
8.2. Solvent effects

Solvents have a crucial influence in diiodosamarium chemistry. Some reactions can be accelerated or made more selective, and also some organosamarium species can be stabilized.

There are only a small number of solvents where SmI_2 can be directly prepared from samarium metal and 1,2-diiodoethane. This is possible in tetrahydropyran (THP),[100] acetonitrile,[101,102] pivalonitrile[102] and octanenitrile.[102] A preparation of SmI_2 in a mixture of benzene and HMPA has been reported.[103]

The interest of THP as a solvent in place of THF is illustrated in Scheme 22. The acylsamarium can be prepared from tertiary acid chlorides, and then transferred on aldehydes or ketones.[100] The byproducts arising from the ring opening of THF or from hydrogen abstraction of THF occur no more. A coupling reaction using three equivalents of alkanoyl chloride was observed in THP (Scheme 22).[104] The three-unit compound arose from the C-acylation of a samarium enolate intermediate. In Scheme 19 we have already mentioned the interest of THP in the formation of a α-aminosamariums through a radical process initiated by the one-electron reduction of a *N*-iodobenzyl moiety.[80] Allyl or benzylsamariums have been prepared in THP at 0°C, and are able to add on ketones or imines.[105]

Addition of tetraglyme to THF solutions allowed the control of a Barbier reaction on aldehydes by preventing the competitive pinacol formation.[39] The beneficial effect of



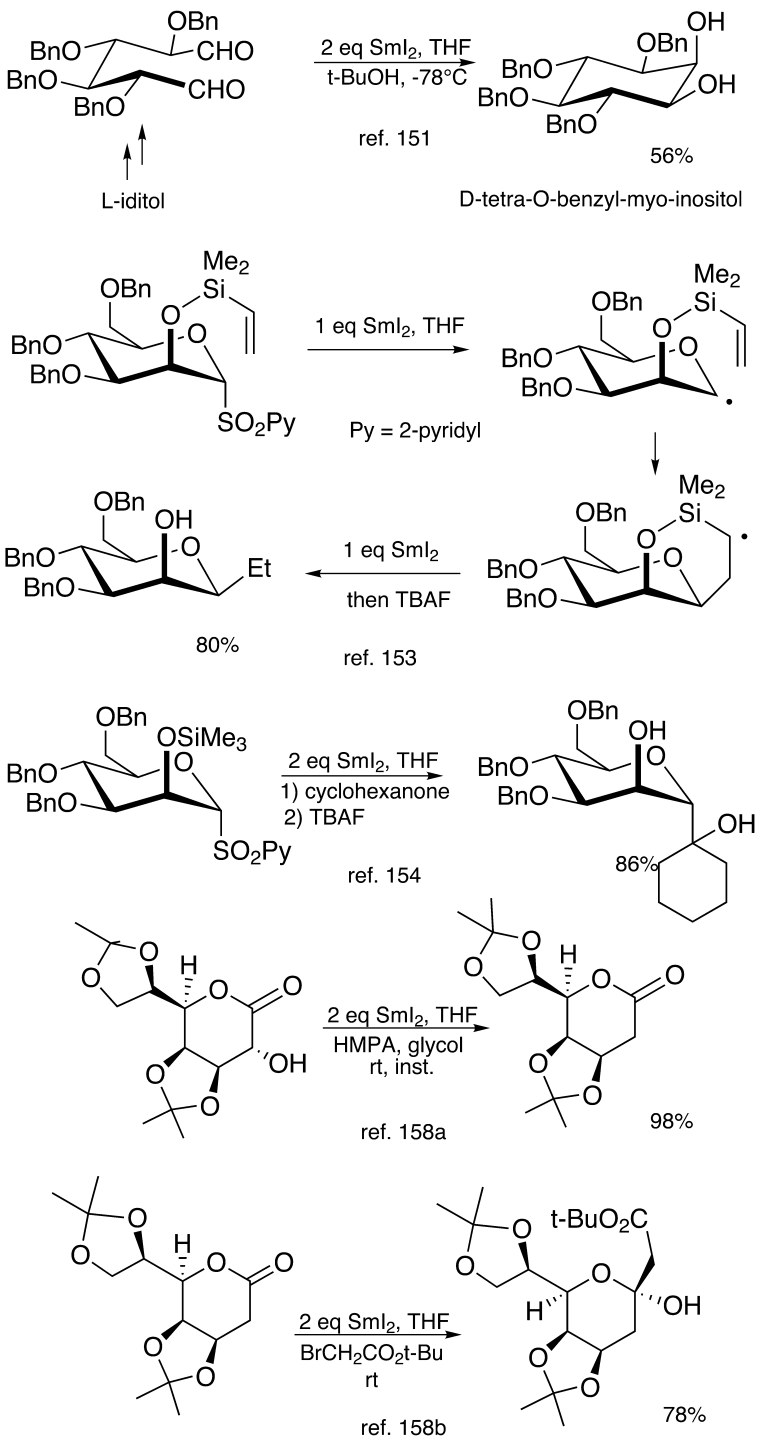
Scheme 26.

poly-ethers in the control of the diastereoselective formation of pinacols of aryl aldehydes has been noticed.[83]

8.3. Protic additives

Addition of an *alcohol* (usually MeOH or *t*-BuOH) is often essential to get the desired reaction (for examples, see Schemes 5, 9–12, 16 and 23–28). The marked differences between product distribution in protic conditions compared with aprotic conditions, arise from the in situ protonation of key intermediates or end products. Kinetic stabilization of SmI_2/THF solutions may also have happened.[106,107]

Water is an interesting additive that often accelerates some reductions. We established in 1980 that it was the additive of choice in the ketone or aldehyde reductions.[2] Many types



Scheme 27.

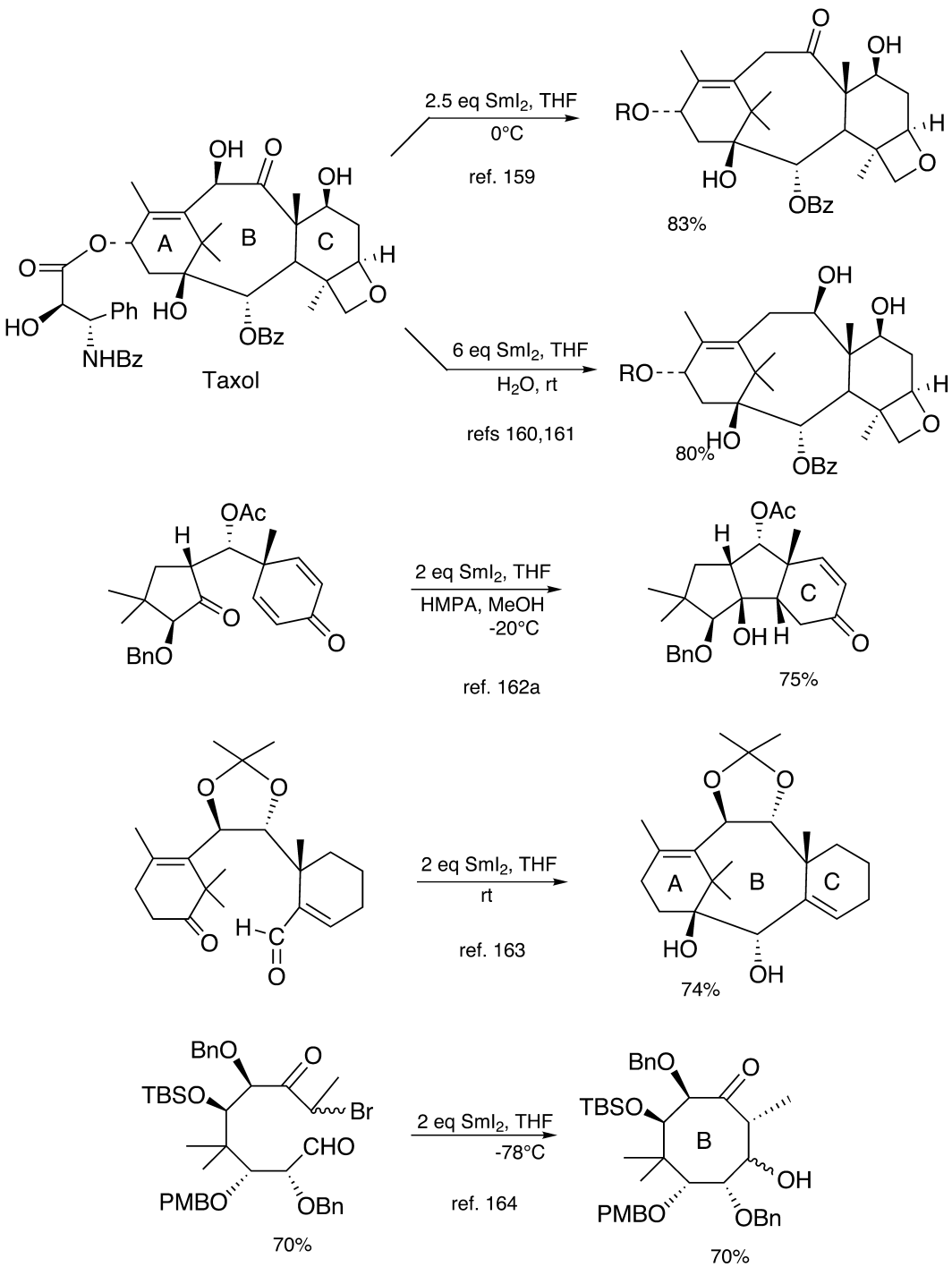
of reduction are accelerated by water.[108,109] Reduction of carboxylic acids to primary alcohols was obtained with SmI_2 in a THF–H_2O–NaOH mixture.[110]

Dahlén and Hilmersson[111] recently discovered that the combination *SmI_2/H_2O/tertiary amine* is superior to SmI_2/HMPA in some reactions. Ketones, imines and α,β-unsaturated esters were reduced in less than 10 s at room temperature. The same system is also highly efficient in the reduction of alkyl halides. For example, 1-bromodecane was transformed into *n*-decane after 5 min (with NEt_3 as amine). The electrochemical properties of the SmI_2/H_2O/tertiary amine have been explored.[112]

Acids have been seldom used as additives in SmI_2 chemistry.[113,114]

8.4. Metal salts in catalytic amounts

It was discovered in 1980 that Fe(III) salts are excellent for accelerating samarium Barbier reactions and reductions of organic halides.[2] This procedure has been subsequently



Scheme 28.

used in many reductions mediated by SmI_2.[42,44,84] In 1996, we screened the catalytic behavior of various transition-metal salts.[115] Diiodonickel (1 mol%) was found to be an excellent catalyst for accelerating many reductions by SmI_2 in THF: samarium Barbier reactions (a few minutes at room temperature), epoxide deoxygenation, pinacols from ketones, etc. The intermolecular nucleophilic acylation of esters by acid chlorides is also possible in the presence of the nickel catalyst[116] as well as the coupling of imines into vicinal diamines or the cross coupling of a mixture of imine/ketone into β-amino alcohol (Scheme 21).[88] Some additional examples of the efficiency of the catalysis by NiI_2 are indicated in Scheme 23.[116,117]

Catalytic amounts of some palladium complexes in combination with 2 mol% of SmI_2 allowed Inanaga et al.[45,118] in 1986 to reduce allylic or propargylic acetates, or to realize some additions on ketones (Scheme 24). SmI_2 reacts with a transient π-allylpalladium species to give a

π-allylsamarium(III) complex with regeneration of the Pd(0) catalyst. The reductive silylation by TMSCl of allylic phosphates have been promoted regio- and stereoselectively by a SmI_2/HMPA/Pd(0) system (Scheme 24).[119]

9. Catalytic amounts of SmI_2

Because of the molecular mass of SmI_2 (M=404), a large amount of matter with respect to the substrate is required. For example, in the first transformation of Scheme 24 the formation of 1 g of the allenic product requires 4.8 g of SmI_2. Moreover, the samarium metal necessary for preparing SmI_2 is quite expensive. It is therefore highly desirable to reduce the amount of inorganic reagent by devising a catalytic process.

Two approaches have been published, involving magnesium or zinc as the co-reducing agent. Endo et al.[120] selected magnesium metal, combined with 10 mol% of SmI_2 and 1.5 mol. eq. of trimethylsilyl chloride (TMSCl), to prepare the bis-OTMS derivative of various 1,2-diols from aromatic or aliphatic aldehydes. For example *p*-methoxyacetophenone gave the corresponding pinacol at room temperature at 78% yield. The beneficial addition of TMSCl is related to the formation of SmI_2Cl and its subsequent reduction into a Sm(II) salt, which is easier than the corresponding reduction of the iodoalcoholates. The catalytic coupling of imines using magnesium has been published.[121] In 1997, Corey and Zhang[122] found conditions where amalgamated zinc reduced SmI_3 into SmI_2 in THF. Then they set up a procedure with 10 mol% SmI_2 for the realization of several types of transformation. For example, epoxystyrene gave styrene after 5 h at room temperature. When samarium iodoalcoholates are the end products, it is necessary to add LiI and TMSOTf for enhancing the formation of SmI_3, which is more easily reduced than $SmI_n(OR)_{3-n}$ species.

In 1999, Helion and Namy[123] proposed a new solution to the problem of the catalytic use of SmI_2. They selected mischmetall as the co-reducing agent for the in situ regeneration of SmI_2. Mischmetall is an alloy of approximate composition La (33%), Ce (50%), Nd (12%), Pr (4%) and other lanthanides (1%). It is very cheap (12 $ per 1 kg, Fluka). Catalytic Barbier reactions were run by the slow addition of a THF solution of the organic halide and the ketone to the THF/SmI_2 (10 mol%)/mishmetall (1.4 eq.) suspension. The slow addition is necessary in order to maintain the deep blue color of the solution. With this procedure, the Barbier reaction between 2-octanone and benzyl bromide or ethyl iodide gave the corresponding tertiary alcohols with 91% yield (after 3.5 h) and 67% yield (after 7.5 h). The pinacolic coupling of acetophenone provided (after 6 h) the mixture of diasteromeric diols at 70% yield, without the need to add TMSCl as in refs 120–122. The mischmetall method was applied as well in the samarium Barbier or samarium Grignard modes.[123–125] In the samarium Grignard case, the organic halide (allylic or benzylic) is first added to the THF/SmI_2 (cat)/mishmetall suspension and after 4 h at room temperature, the ketone or aldehyde is slowly introduced. The yields are slightly inferior in the samarium Grignard reaction. The authors checked that the mischmetall alone is unable to display the desired reactions. The in situ formation of a quite stable organosamarium reagent was established: it reacts with the substrate or gives a transmetallation with one (or several) of the components of the mischmetall. In support of this hypothesis, it was found that the combinations lanthanum/SmI_2, cerium/SmI_2 or Nd/SmI_2 gave results close to that of the SmI_2(cat)/mischmetall procedure. The latter remains much more attractive, because of its low cost.

An electrochemical process with catalytic amounts of a Sm(III) salt has been devised by Dunach et al.[126]

SmI_2 is able to play the role of a Sm(III) precursor, which itself acts as a Lewis acid or a base catalyst. In this way, various reactions have been catalyzed: MPV/O reactions, Tischenko reactions, epoxide rearrangements, Diels–Alder reactions, Mukaiyama Michael and aldol reactions, etc. This area has been reviewed by Collin et al.[127] and is not in the scope of the present article.

10. Asymmetric reactions

There are many diastereoselective transformations mediated by SmI_2, especially in intermolecular reactions; for some examples see Schemes 11, 12 and 14–17. The stereoselectivity originates from the ability of Sm(II) and Sm(III) centers to coordinate to one or several heteroatoms suitably located in the substrate, giving rise to a preferred transition state (for a review see ref. 16). Usually oxygen atoms of various natures are involved in the process. The stereodirecting effects of a hydroxyl group,[127] or other groups are well evidenced.[128–130] Even an OTBDMS group can give rise to some stereocontrol.[131]

The application of the two main strategies of asymmetric synthesis: the diastereoselective asymmetric synthesis and the enantioselective asymmetric synthesis are considered in this section. Surprisingly, only a limited number of examples are known at the moment.

10.1. Diastereoselective asymmetric synthesis

In this approach the chiral auxiliary is temporarily bound to a prochiral substrate, and is released or destroyed after the reaction.

Scheme 25 indicates the use of planar chiral $Cr(CO)_3$ biaryl complexes.[132] The planar chirality fully controls the stereochemistry of the intramolecular pinacol coupling into *trans*-diols. The photo-oxidative demetalation affords the diols enantiomerically pure with an excellent yield. The preparation of an enantiopure *trans*-diol from the enantiopure 2,2′-bis carboxaldehyde-1,1′-binaphthyl (Scheme 25) is also possible.[133] Here the axial chirality of the binaphthyl fragment has been retained intact in the product.

A formal enantioselective asymmetric synthesis is the formation of chiral γ-butyrolactone from aldehydes or ketones and chiral α,β-unsaturated esters in the presence of SmI_2.[134] The chiral auxiliary is released after the

heterocoupling stage, during the in situ lactonization. Scheme 25 shows the example of the condensation of the crotonate ester derived from *N*-methyl ephedrine on an aldehyde. This reaction has a wide applicability. This approach, pioneered by Fukuzawa et al.,[134] has been extended to the reductive coupling of ketones with methacrylates of various chiral auxiliaries.[135] Inexpensive isosorbide was especially useful, as indicated in Scheme 25. The best ees were observed in the presence of bulky protonating agents such as racemic camphorsultam.[135] The asymmetric center was created before the lactonization step, under the control of the isosorbide fragment.

Asymmetric Reformatsky reactions have been realized with α-bromoacetyl-2-oxazolidinones (Scheme 25).[136] The first step is the reduction of the α-bromoacetyl group into a samarium imide enolate, which reacts stereoselectively on the aldehyde.

Samarium diiodide has been used in many diastereoselective asymmetric syntheses to detach the chiral auxiliary or a protecting group from the product, by the reductive cleavage of a bond. It can also destroy an asymmetric center, which was at the origin of the construction of a chiral unit in the same molecule. For instance, in Scheme 25 is described the last step of an asymmetric synthesis of an atropoisomeric anilide from lactic acid,[137] where SmI_2 in the presence of LiCl deoxygenates the chiral product without racemization.

10.2. Enantioselective asymmetric synthesis

There are only a few reports of this category of asymmetric syntheses. The enantioselective protonation of prochiral enolates have been pioneered by Takeuchi et al. in 1992.[138] They reduced benzil by two equivalents of SmI_2 into a samarium (*Z*)-enediolate, which was enantioselectively protonated by quinine. In the optimized conditions (benzil//HMPA/quinine=1:2.3:1.5:3.0), with oxygen quenching of the unreacted enediolate, (*R*)-benzoin (91% ee) was isolated at 61% yield. The authors extended this approach by the generation of samarium enolates prepared from coupling between ketenes and organic halides in the presence of SmI_2.[139] They selected a chiral diol (DHPEX, Scheme 26) as an excellent enantioselective protonating agent. One experiment is shown in Scheme 26. Interestingly, the catalytic enantioselective protonation of samarium enolates has been obtained by 15 mol% DHPEX in the presence of one equivalent of trityl alcohol.[140] The experiment was performed at −45°C on the enolate prepared from methyl-(1-methyl-1-phenylethyl)ketene and allyl iodide. The product (93% ee) was isolated at 55% yield.

Takeuchi, Mikami et al.[141,142] produced regioselectively enolates of 2-substituted cyclohexanones by reduction of a 2-methoxy precursor, which were protonated (Scheme 26). The screening of a set of diols of C_2 symmetry as chiral protonating agents led to the use of a binaphthyl diol able to give 2-phenylcyclohexanone at 87% ee.[141]

The enantioselective dynamic protonation of racemic samarium allenic ester intermediates, produced by reduction of an acetylenic precursor, has been reported by Mikami et al.[143] These authors found that pantolactone is an excellent protonating agent, giving an allene with ee up to 95% (Scheme 26).

Enantioselective reductive coupling of α,β-unsaturated esters with ketones (lactone formation) was studied by Mikami et al.[144a] Two equivalents of the (1:1) combination *t*-BuOH/(*R*)-binapo gave 67% ee into a chiral lactone (Scheme 26). The reaction presumably involves an enantioselective ketyl addition on the conjugated double bond, with a chelation control involving samarium-bearing binapo as ligand. Some chiral sulfonamides induced enantioselective protonation of samarium enolates generated in the reaction of α,β-unsaturated esters with ketones.[144b]

The reductive coupling of β-monosubstituted acrylamides gave chiral 1,6-diamides with ees up to 85%, in the presence of (*R*)-binol and a tertiary amine.[90] The authors proposed that the asymmetric induction occurred in a samarium complex binding two binol molecules.

Skrydstrup et al.[145] attempted to convert carbonylhydrazones into cyclic aminodiols, but unfortunately ees were no higher than 10%.

Sometimes, diiodosamarium can be useful for generating *in situ* a chiral Sm(III) catalyst (vide supra, Section 8). This is well examplified by the asymmetric reduction of ketones by hydrogen transfer, as described by Evans et al.[146] The authors prepared a chelating chiral samarium (III) complex from a chelating chiral aminodiol and SmI_2, which was very efficient in the reduction of several ketones (ees up to 97%).

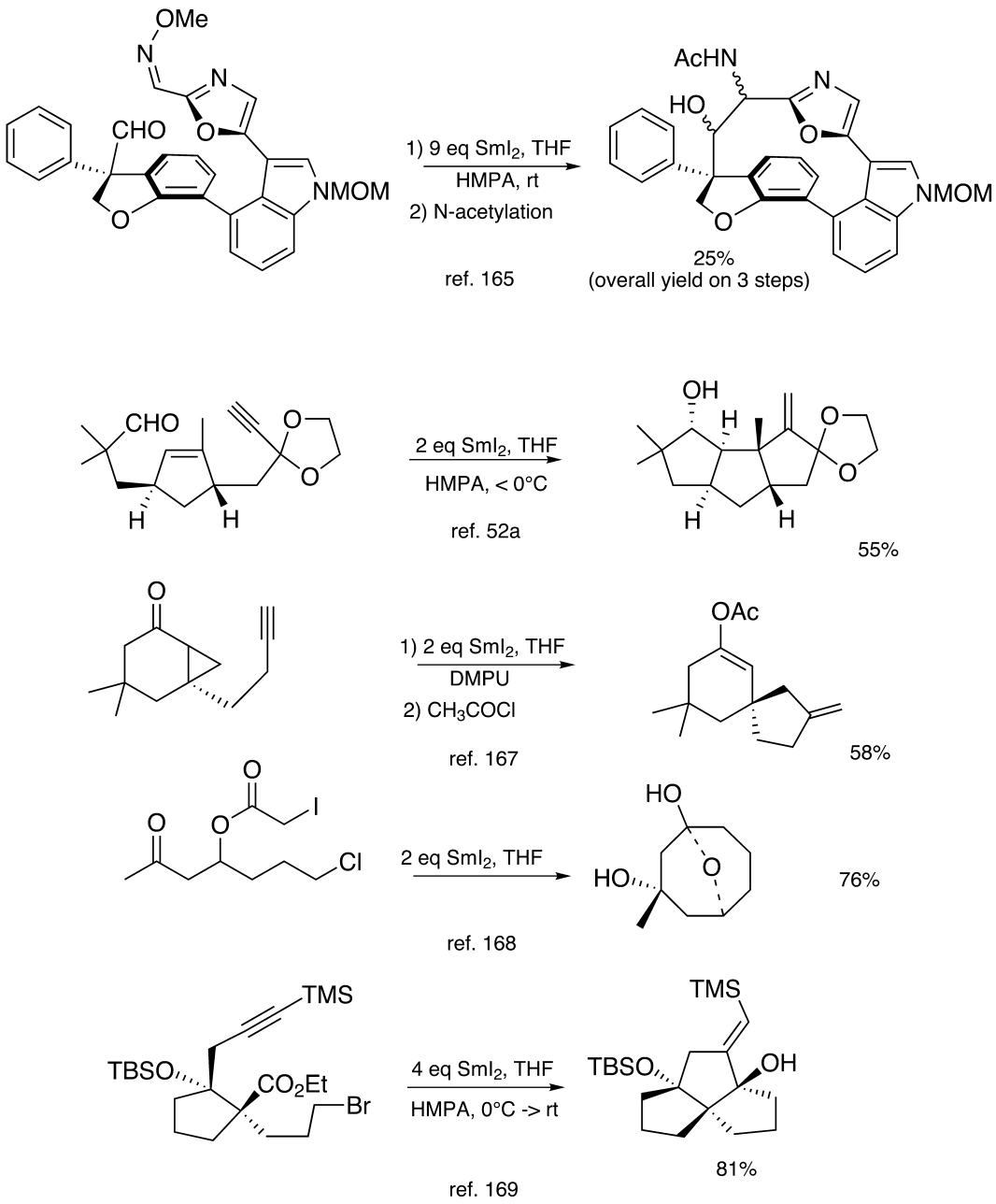
11. Natural product chemistry

SmI_2 was very useful for improving existing synthetic methodologies (such as Julia olefination)[147] or to give mild cleavages of various kinds of protecting groups.[148] Diiodosamarium chemistry has been also widely applied to the modification of some natural products, and to the preparation of intermediates of total syntheses. These two last aspects will be shortly discussed.

11.1. Carbohydrates

The *glycals* are easily obtained by reduction of acetobromoglucose and related compounds, the formation of an organosamarium at the anomeric center gives rise to a β-elimination with the vicinal OR group. The first examples have been published by Sinaÿ et al. in 1991–1992.[149,150]

Hanessian et al.[66] found that the reductive coupling of 1,5- and 1,6-dialdehydes by SmI_2 gave mainly *cis*-diols (see Section 5.6). In this way, the formation of carbocycles from sugars is easily accomplished by diol oxidation into dialdehydes followed by a *pinacol closure* with SmI_2. For example, D-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol has been prepared in a few steps from L-iditol (Scheme 27).[151] The same strategy allowed the preparation of L-*chiro*-inositol tetraacetate from D-sorbitol.[152]



Scheme 29.

The synthesis of a polysubstituted aminohydroxycyclopentane by *carbonyl oxime* cyclization.[68] has been seen already in Scheme 16. The *carbonyl ene* cyclization has been often used to produce polyhydroxycyclopentanes, as examplified in Scheme 12.[56] Samarium chemistry at the anomeric center was helpful not only for generating glycals, but also for preparing *C-glycosides*. Reductive cleavage of an arylsulfone group by SmI_2 can generate a radical at the anomeric center. This radical has the choice to attack a vicinal carbone–carbone double or triple bond, or to be further reduced into an anionic species (organosamariums). The radical cyclization was first reported for an *O*-allyl glucopyranosyl phenylsulfone,[150] and has been widely developed by Beau, Skrydstrup et al.[153,154] The authors selected the 3-pyridyl sulfone group, because it is easily cleaved by one equivalent of SmI_2 (without the need of addition of HMPA as for the phenylsulfone group). In the absence of HMPA, the radical is not easily reduced and is able to react intramolecularly on an alkene or acetylenic fragment. In Scheme 27 is indicated the β-functionalization of a glycoside thanks to the silicon-tethered approach.[152] It was also discovered that some Barbier type reactions on ketones or aldehydes are possible with 2-pyridyl sulfone, as shown in Scheme 27.[153] In this way, α–C-mannosides have been stereoselectively prepared. The yields in the *gluco* series are inferior and were discussed on the basis of the conformational analysis of the intermediate organosamarium species at the anomeric center.[153,154] Wong et al.[155] were able to synthesize C-glycosides by the coupling of pyranosyl or furanosyl phosphates with various aldehydes and ketones. The reaction was performed in mild conditions, in the

presence of diiodosamrium in THF. Another approach to C-glycosides has been devised by Chiara et al.[156] It was based on the stereocontrolled coupling of epoxides (obtained by epoxidation of glucals) on aldehydes or ketones. Interestingly, in this way C-glycosides with a free hydroxyl group in the C2 position were directly generated.

Deoxygenation mediated by SmI_2 has been widely applied very early to α-heterosubstituted ketones or lactones (see Section 4 and Scheme 9). Thus, 2-deoxy aldonolactones are produced from 2-hydroxylactones or their acetates by treatment with SmI_2 in the presence of HMPA and ethyleneglycol, as illustrated in one case in Scheme 27.[158a] The samarium enolate intermediate can be trapped by a ketone to give a branched chain carbohydrate lactone.[149] Many examples have been published based on this approach.

The samarium–Reformatzky reaction on aldonolactones allows the introduction of a side chain, and gives access to 3-ulosonic acid derivatives and homologues.[158b] One case is described in Scheme 27.

Most of the reactions mediated by SmI_2 have been applied to carbohydrates. It is impossible to quote here all the papers in that area.

11.2. Total synthesis

Diiodosamarium is increasingly used at some stages of the elaboration of complex molecules. Because of lack of space, it is impossible to cover fully this topic, therefore, only selected examples will be discussed.

We have already mentioned the selective deoxygenation by White et al.[43] of a ketolactone intermediate of the synthesis of (+)-pillaromycinone (Scheme 9).

Diiodosamarium chemistry has been widely applied to the taxol area. Taxol itself has been transformed into 10-deacetoxy-taxol derivatives (Scheme 28).[159–161] SmI_2 has been used for the ring formation of taxane compounds, by some intramolecular reductive couplings. Two examples are indicated in Scheme 28, a carbonyl/ene coupling[162] and a pinacol coupling.[163]

In their total synthesis of taxol in 1997, Mukaiyama et al.[164] constructed the 8-membered B ring in an intramolecular samarium pseudo-Reformatsky reaction (Scheme 28).

Nicolaou et al.[165] were able to form the aromatic core of diazonamide A by a reductive carbonyl oxime macrocyclization, as indicated in Scheme 29.

The stereoselective reduction of a keto group in a step of a total synthesis can be very helpful. For example, in their total synthesis of atractylgenine, Corey et al.[166] selected the combination SmI_2/H_2O in THF as the best reagent to achieve the highly stereoselective reduction of a cyclic ketone, after trying many other reducing agents.

Clearly, SmI_2 is becoming a valuable tool in total synthesis.

12. Conclusion

Diiodosamarium has been established as a major reagent in organic chemistry, as the result of 25 years of evolution and improvements. It is involved in many types of reactions, which are all included in the general mechanistic description of Scheme 2. SmI_2 is a powerful one-electron donor, which, surprisingly, reacts quite selectively with many complex molecules. There is a rich coordination chemistry around Sm(II) and Sm(III) centers, which give rise to *various types of selectivities*. The reducing properties of SmI_2 can be increased and *tuned by introduction of additives or cosolvents*, as discusssed in Section 8. Some rationalizations have been attempted by the combined use of electrochemistry and X-ray crystallographic data. The possibility to mix radical chemistry and organosamarium chemistry allows the performance of *sequential reactions* (reviews: refs 16, 17). Sequential reactions are one-pot reactions involving a set of consecutive reactions from a given reactant or a combination of intra- and intermolecular reactions. Some examples are given in refs 156, 157 and in Scheme 29.[167–169]

One severe limitation to the diiodosamarium chemistry is the price and the large molecular weight of SmI_2. Various solutions have been proposed to handle a *catalytic amount of SmI_2* with a suitable co-reducing agent (see Section 9); however, there is still room for improvement. Some very efficient Sm(II) derivatives have been discovered, such as $SmBr_2$[170] or $SmOTf_2$.[171] Other divalent lanthanide reagents have been recently prepared and checked for some organic reactions. Amongst them, TmI_2[172] and DyI_2[173] are very reactive, in agreement with the redox properties of Tm(II) and Dy(II) (E^0 (Ln^{III}/Ln^{II})=−2.3 and −2.5 V, respectively).[174] Nevertheless, SmI_2 represents at the moment the most convenient reagent for a large set of transformations. Especially impressive is the increasingly use of SmI_2 in the synthesis of complex molecules.[175]

We expressed a hope in the conclusion of our second publication in 1980:[2] "…results described in this publication lead us to hope that divalent lanthanide derivatives could form a novel class of useful reagents for organic synthesis." Twenty-three years later, it is obvious that this expectation has been realized.

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