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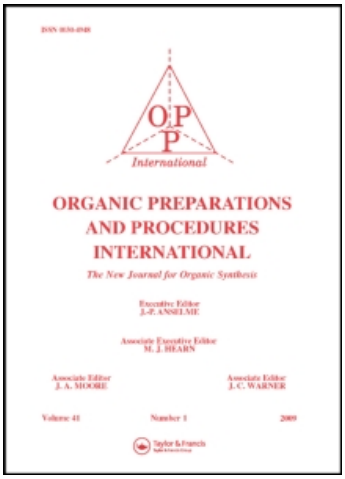

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FRAGMENTATION AND CLEAVAGE REACTIONS MEDIATED BY SmI_2. PART 1: X-Y, X-X AND C-C SUBSTRATES

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PREAMBLE AND INTRODUCTION 565
I. REACTIONS INITIATED AT C-X 566
II. REACTIONS INITIATED AT C=O 567
III. SIMPLE REDUCTION/BOND CLEAVAGE REACTIONS 567
1. Reduction of X-Y Species 567
2. Reduction of X-X Species 572
IV. CARBON-CARBON BOND FRAGMENTATION REACTIONS 575
1. C-C Fragmentation Reactions in 'no-strain' Systems 575
2. C-C Fragmentation Reactions in 'ring-strained' Systems 578
a. *Cyclobutane containing Substrates* 578
b. *Cyclopropane containing Substrates* 581
c. *1,4-Diketones in Non-strained and Strained Systems* 590
V. CONCLUSION 595
REFERENCES 596

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PREAMBLE AND INTRODUCTION

Samarium diiodide (SmI_2) was introduced by Kagan[1] in 1980 as a powerful, one-electron reductant of a variety of organic functional groups. While this salt had previously been prepared and fully characterized, its preparation was tedious and difficult.[2] Kagan's method provided a rapid methodology for its generation in an organic solvent making use of apparatus available to most synthetic chemists.

Since the seminal work of Kagan, many chemists have made use of this potent, yet highly selective reductant in manifold reactions. Indeed, there have been a number of excellent reviews on the more general types of chemistry and transformations that may be effected using SmI_2.[3] This reagent is useful not only for the simple reduction of organic moieties, but also in bond forming reactions. Such transformations make use of the fact that SmI_2 supports both radical and anionic chemistry depending upon the substrate and specific reaction conditions.

This review (which shall be presented in two parts; the second part focuses on C-X cleavage reactions) will focus on bond fragmentation and cleavage type reactions, which have also formed an important part of SmI_2-mediated chemistry. It is important at the outset to define the terms used in the previous sentence, and to describe the scope of the type of transformations on which we will concentrate. For the purposes of this review, fragmentation and cleavage reactions shall refer to those reactions in which a sigma bond is broken during the normal progress of the reaction. Many reactions are initiated at an aryl/alkyl halide moiety, which formally falls within our definition. We shall only briefly discuss this reaction and not fully describe the extent of its use, as this would detract from the main purpose of this review, and would lead to no new insights. The same holds true for the reduction of the various carbonyl moieties into their corresponding ketyl radicals: these intermediates are important in general SmI_2-promoted chemistry, but do not advance our present objectives.

From an organizational point of view, we have arranged the fragmentation/cleavage reactions into certain logical categories: simple reductions of various organic moieties (including deoxygenation reactions and heteroatom-heteroatom bond cleavage), and fragmentation of carbon-carbon bonds. These discussions will follow after a more general introduction to the types of chemistry supported by SmI_2.

As stated in the preamble, SmI_2 has become a popular and easily accessible reductant. The ease of its preparation and use has led to SmI_2 being used in many chemistry laboratories world-wide. This reagent is unique in that it displays a remarkable reduction potential (Sm^{2+}/Sm^{3+} = -1.55 V in water,[4] -1.33 V in THF[5a] *vs.* $Ag/AgNO_3$ [E° = -1.41 V *vs.* Fc^+/Fc according to Ref. 5b]), which is substantially enhanced by the presence of four equivalents of hexamethylphosphoric triamide (HMPA) as cosolvent (Sm^{2+}/Sm^{3+} = -2.05 V in THF, *vs.* $Ag/AgNO_3$),[5a,c] yet it can be used in reactions where a high degree of selectivity is required.

In general, SmI_2-mediated reactions fall into two categories: those being initiated at a C-X (X = halide) functional group and those being initiated at a C=O unit. Each of these two general types of reactions shall be briefly discussed in turn.

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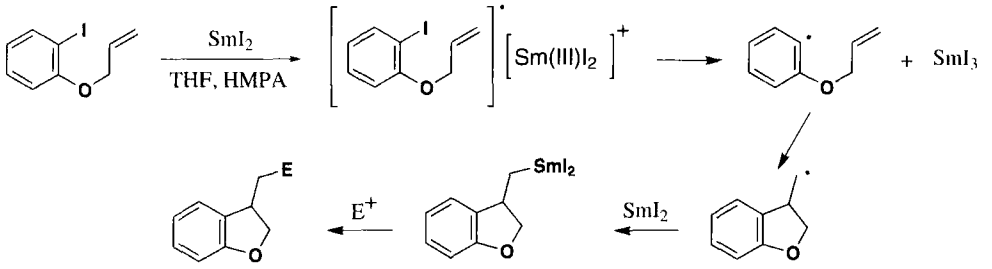
I. Reactions Initiated at C-X

In many cases, substrates for SmI_2-mediated reactions are so prepared that they contain a suitably disposed halide. Alkyl and aryl halides, notably the iodides, readily react with SmI_2 to produce the corresponding radical (*Scheme 1*). The reaction is believed to proceed *via* initial single electron transfer to the halide leading to a radical anion which decomposes to the alkyl/aryl radical and SmI_3.[6] There is substantial selectivity in reactions in which the substrate possesses multiple halogen atoms: iodides react faster than bromides, while chlorides react only sluggishly.[1,7]



Scheme 1

The aryl/alkyl radical that is formed is subject to further reaction. For example, *Scheme 1* shows that cyclisation takes place to afford the exocyclic methylene radical. This radical is reduced to the corresponding anion by a second equivalent of SmI_2, and quenched by the addition of a proton source or an electrophile such as a ketone or aldehyde.[8] In general, vinyl or aryl radicals require the presence of an intramolecular radical trap if they are to be

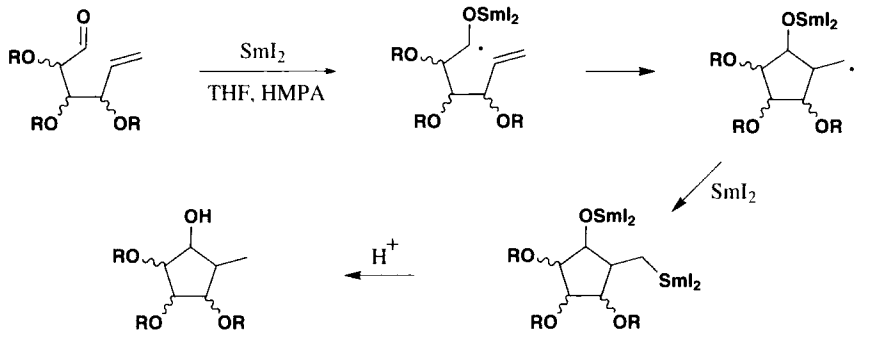
successfully employed in bond forming reactions.[9] Failing this, hydrogen atom abstraction from the solvent usually ensues due to the highly reactive nature of this type of radical.

Reactions of the type described in the preceding paragraph shall form the basis of and first step towards many cleavage/fragmentation reactions to be discussed later in this text.

II. Reactions initiated at C=O

Various carbonyl functions are susceptible to single electron transfer reactions from SmI_2. In general, it is only the ketone or aldehyde groups that are employed, but esters can be successfully employed under certain circumstances to be expanded upon later.

Treatment of an aldehyde or ketone with one equivalent of SmI_2 leads to the corresponding ketyl radical with concomitant breaking of the C=O pi bond (*Scheme 2*). The ketyl radical is highly reactive, and has been used in a variety of transformations, including cyclisation,[10] pinacol,[11] and in fragmentation/cleavage reactions.



Scheme 2

In the remainder of this review, the two methods of generating radicals mentioned in I and II, namely from organohalides or from ketones/aldehydes, shall not be treated as fragmentation reactions *per se*, but rather as the initiating step for same.

III. SIMPLE REDUCTION/BOND CLEAVAGE REACTIONS

1. Reduction of X-Y species

Numerous X-Y type cleavage reactions have been carried out on a variety of substrates. The first SmI_2-mediated reaction of this type was in the seminal paper of Kagan.[1] In that work, a small variety of simple aromatic sulfoxides were deoxygenated to the analogous sulfides in good yields (77-90%). For the first time, the difference in reactivity of SmI_2 at ambient temperature (reaction time = 3 days) and at elevated temperature (65°, reaction time 1-4 h) was noted. The same article mentions the deoxygenation reactions of various 1,2-epoxides to their corresponding alkenes. In that reaction set, the beneficial effect of added alcohol (*t*-

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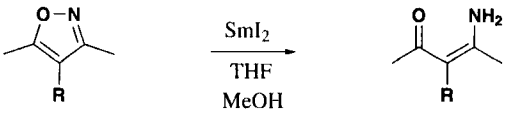
BuOH in that case) was noted. The exact reasons for this effect have been ascribed in another paper as an enhancement of the reduction potential of SmI_2.[12] Indeed, the cosolvent effect on the reduction potential of SmI_2 has been well documented.[5a,13]

At the time of Kagan's disclosure, the cosolvent effect was not known. As a result, the attempted reduction of phosphine oxides to phosphines failed under what were termed 'standard conditions', *i.e.* SmI_2 in THF in the presence/absence of added alcohol at ambient/elevated temperature. The work of Inanaga,[5c] in which he detailed the use of HMPA as cosolvent for SmI_2, paved the way to more rapid and selective reactions. In a later paper,[14a] this effect is clear: in the presence of HMPA, SmI_2 readily reduced triphenylphosphine oxide to triphenylphosphine in a yield of 75%. The same article shows that sulfoxides are reduced by the SmI_2-THF-HMPA system to the analogous sulfides within minutes at room temperature in yields of up to 99%. It was also displayed that a sulfone may be reduced to the sulfide in a low yielding reaction (26%), and that *bis*(tributyltin) oxide was reduced to hexamethylditin almost instantaneously in good yield (92%).

N-Oxides have been shown to be reduced to their amines (N-O cleavage) in very high yields (96-98%) within one minute at room temperature, in the presence of SmI_2-THF-HMPA,[14a] while nitro groups could be selectively reduced to hydroxylamines or to amines.[14b] An earlier disclosure had discussed the use of SmI_2 in THF for the reduction of isoxazoles to enamino ketones (N-O cleavage) in the presence of a proton source (*Scheme 3*).[15] α-Chloro and α-bromo derivatives additionaly offered alternative reactions due to competitive reduction of the C-halogen bond affording mixtures of products. At this early stage in the development of SmI_2 chemistry it was noted that organo bromides are more reactive than the corresponding chlorides.



R = H, CO_2Et, CH_2Cl, CH_2Br

Scheme 3

Various other N-O moieties have been reduced by SmI_2: pyridine type *N*-oxides have been reduced to pyridines, trioctylamine *N*-oxide to trioctylamine and nitrobenzenes to anilines.[16] It was also mentioned that triphenylarsine oxide can be readily reduced to triphenyl arsine, azobenzene to hydrazobenzene, and quinone to hydroquinone. In all cases, the yields were good to excellent.

The utility of SmI_2-THF in the reduction of N-O moieties was further extended to include hydroxamic acid and hydroxylamine derivatives (*Scheme 4*, *Scheme 5*).[17] This work is important in the light of the many synthetic procedures employing acylnitroso, nitrile oxides,

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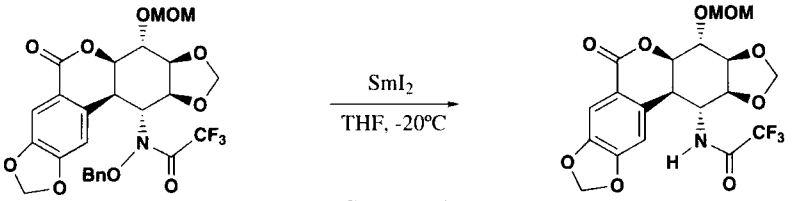
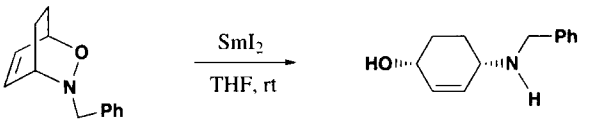
nitrones, nitroalkenes, and *O*-silyl nitronates as reactive intermediates. The products of reactions using these substrates invariably contain nitrogen in an higher oxidation state (*i.e.* containing at least one N-O bond), and it is often desirable to selectively reduce these moieties to lower oxidation states. While a number of other methods exist to effect the reduction of N-O bonds,[18] these often fail in highly functionalised molecules. In the example shown in *Scheme 4*, various other methods had failed to selectively reduce the N-O to the corresponding N-H group.



Scheme 4

Another example of the utility of this method is seen in *Scheme* 5, which depicts the preparation of a stereodefined aminoalcohol (the authors made use of racemic starting material). The reactivity of these substrates is such that the addition of HMPA is not necessary to promote a successful reaction. In most instances, the reactions proceeded within a few hours at or below room temperature, and afforded, from a variety of substrates, products in yields of up to 95%. This protocol has also been successfully applied as a key step in the synthesis of aminocyclopentitols from carbohydrate derivatives.[19]



Scheme 5

A similar but chiral substrate afforded remarkably different results to those shown above: low temperature promoted the standard N-O cleavage reaction (*Scheme 6*), while higher temperatures selectively afforded a cyclised cyclobutane or cyclopentane product.[20]

It is possible that the fact that the substrate is *N*-acylated is determinative of the mechanism and hence the outcome of the reaction (*vis-à-vis* the reaction depicted in *Scheme 5*). One result that remains unexplained is that the des-methyl substrate fails to undergo any rearrangement whatsoever, and affords instead the cyclohexan-aminol derivative only. One explanation might be that the initially formed radical anion is reduced only slowly to the dianion due to the added steric constraints of the methyl group. This would engender sufficient lifetime to the oxygen radical to allow C-C fragmentation to be effected in preference to further reduction, as depicted by the proposed mechanism (*Scheme 7*).

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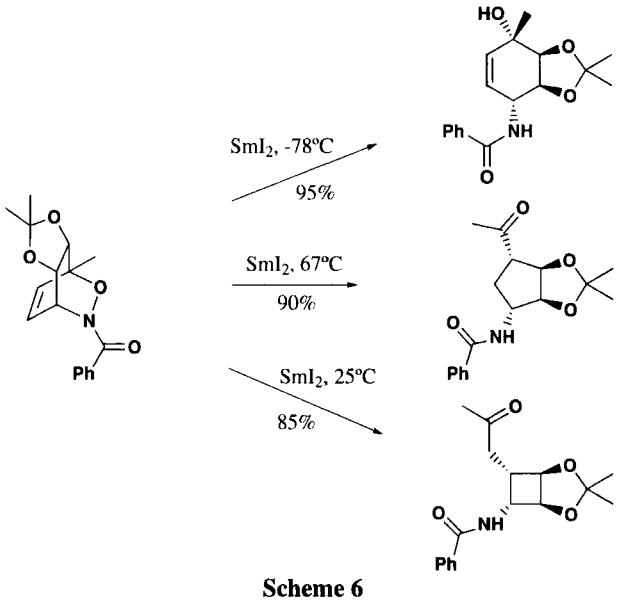
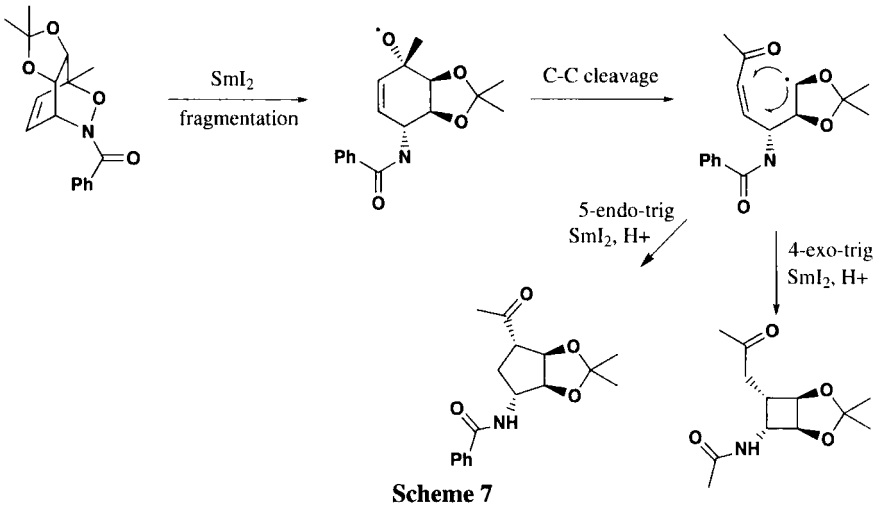


Scheme 6



Scheme 7

Somewhat rarer than the N-O cleavage reactions is the cleavage of N-S bonds. Here, an *N*-protected sulfonamide is reductively deprotected to the corresponding amine in the presence of SmI_2-THF (*Scheme 8*).[21,22] In some instances,[21] 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU)[12] was added to the reaction mixture as cosolvent to enhance reaction rates and selectivity. However, this was found to be unnecessary in cases where the protecting group was a pyridine-2-sulfonyl or a *N*-acylphenylsulfonamide group.[22a,b,c] In the latter cases, it seems that the substrates were possessed of sufficient reactivity in the absence of this cosolvent to not require the inclusion of DMPU, possibly because the reaction is initiated at the amide carbonyl.

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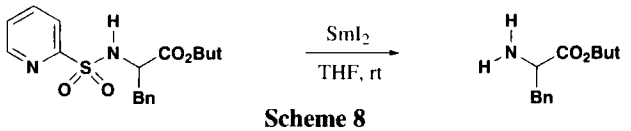
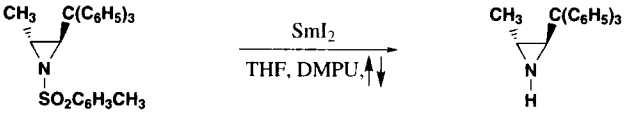


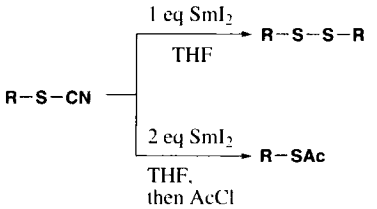
Scheme 8

However, *N*-(toluenesulfonyl)aziridine[21b] derivatives required both the use of DMPU as cosolvent *and* heating the reaction mixture under reflux for a successful reaction (*Scheme 9*). The toxicity and carcinogenicity of HMPA originally brought about the employment of DMPU as a cosolvent.[12] While DMPU does not suffice in all instances as cosolvent, it does in general exert a sufficiently positive influence on the reactivity of SmI_2 to warrant its use instead of HMPA.



Scheme 9

An isolated report in which the reaction of thiocyanates with SmI_2 results in disulfides appeared in the literature some time ago (*Scheme 10*).[23] While this might seem anomalous in the light of the ability of SmI_2 to reduce disulfides to the analogous thiols (see Section 2.2.), it should be kept in mind that the present case made use only of one equivalent of SmI_2 with respect to thiocyanate. Under these conditions, it is believed that the initially formed thiocyanate radical anion decomposes to cyanide anion and thiolate radical. Two of the latter would combine to afford the observed product. When the same substrates were subjected to reaction with two equivalents of SmI_2 and subsequently with acyl chlorides, the corresponding thiolesters were isolated. This experiment showed that an excess of SmI_2 would rapidly reduce the thiolate radical to the samarium thiolate, which would subsequently be trapped by the added acyl chloride.



Scheme 10

Depending on the particular substrate, 1,1-dibromo compounds have been known to generate carbenes when allowed to react with SmI_2.[24] The carbenes have been used in Simmons-Smith type cyclopropanation reactions as well as in 1,3-dipolar addition reactions. In an unusual turn of events, a rearrangement product, namely an alkyne, was observed as a by-product of the reaction of a 1,1-dibromo-1-alkene with SmI_2-THF-HMPA (*Scheme 11*); the main product was that of hydrodebromination.

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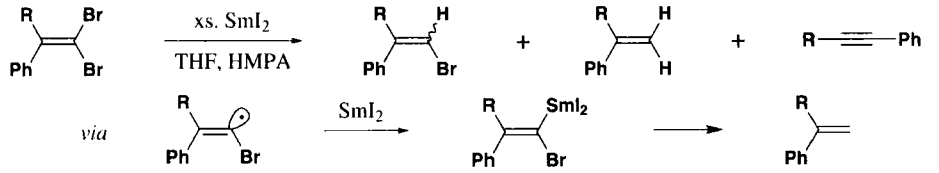

Scheme 11

The authors reasoned that a vinyl radical is formed upon reaction of the substrate with one equivalent of SmI_2. This reactive intermediate would abstract an hydrogen atom from the THF solvent, affording the main product, while the by-product was formed by further reduction of the vinyl radical to the samarium species which underwent α-bromo elimination to afford an alkylidenecarbene. This carbene underwent rearrangement to afford the alkyne by-product that they observed. In order to favor the production of the vinylsamarium intermediate and to suppress hydrogen atom abstraction, the workers carried out the reaction in the unusual benzene-HMPA solvent system, which represents the first mention of the preparation of SmI_2 in such a system. It was found that this change of solvent dramatically altered the fate of the reaction, in that the alkyne became the main product of the reaction (up to 90% yield). This observation bodes well for other chemistry in which *intermolecular* vinyl/aryl radical addition reactions are the subjects of experiment.

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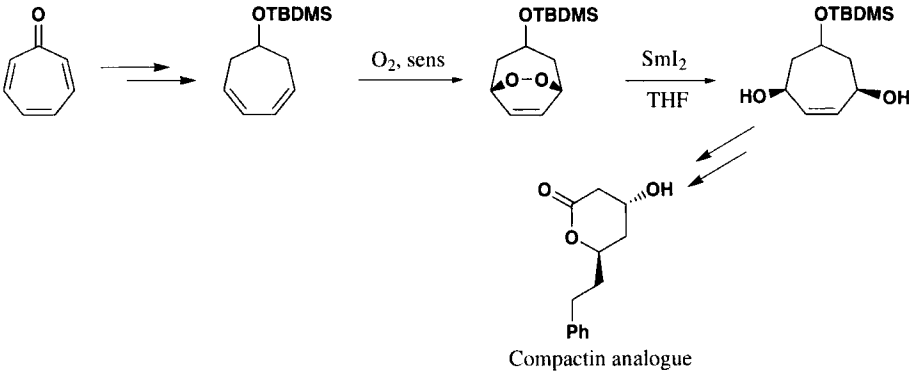
2. Reduction of X-X species

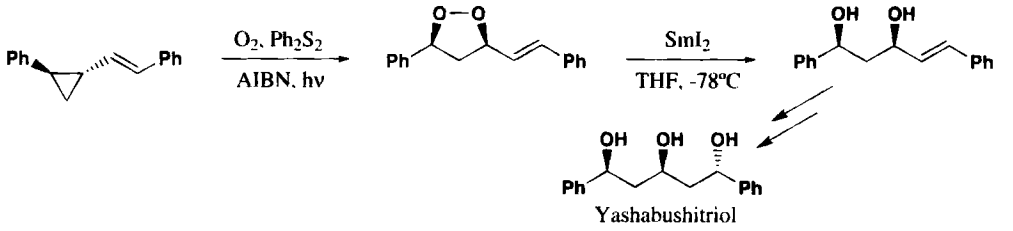
As with the X-Y type cleavages, there are various X-X type systems that undergo reductive cleavage in the presence of SmI_2. One of the earliest mentions of an X-X type cleavage reaction was in a 1,2-dioxane species that had been obtained *via* a sensitized addition of O_2 to a tropone derivative (*Scheme 12*).[25] It was established that Zn/AcOH was found to effect the same reductive cleavage. The *meso* product was subsequently subjected to an enzymatic resolution, and the product was converted in a few steps into Compactin analogues.



Compactin analogue

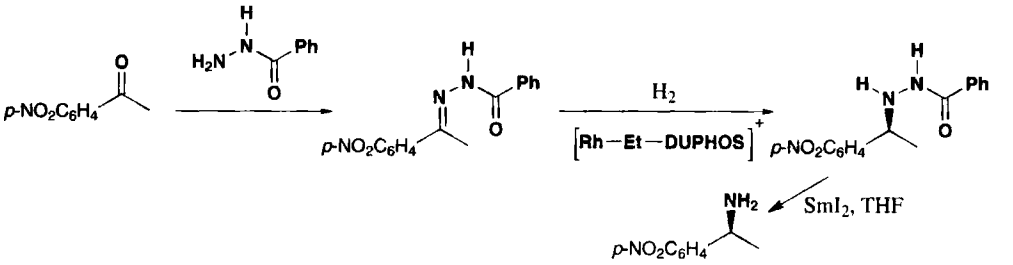
Scheme 12

Analogous work on 1,2-dioxolanes, synthesized by an (*E*)-selective radical catalyzed oxygenation of alkenylcyclopropanes, showed similar results and proved that SmI_2 was superior to a variety of other reducing agents for the reductive cleavage of the O-O bond.[26] The range of products subjected to this reaction also showed that the reduction progresses with retention of the stereochemical integrity of the molecule (*Scheme 13*), in contrast to some hydride reductants which caused stereochemical scrambling or isomerisation products. At least one of the *syn* diols thus formed was useful in the synthesis of the plant metabolite Yashabushitriol.



Scheme 13

The use of SmI_2 has also enabled the synthesis of chiral amines from ketone starting materials in a reductive amination procedure (*Scheme 14*).[27] In this elegant process, an *N*-benzoylhydrazone was prepared in the first step. This product was reduced to the hydrazine (C=N reduction), using H_2 in the presence of a chiral Rh catalyst, which was subjected to N-N cleavage in the presence of SmI_2. In the present case, the reaction of the *N*-benzoylhydrazine with SmI_2 proceeded at ambient temperature almost instantaneously without loss of optical purity of the product. This is in contrast to 1,2-diphenylhydrazine which reduces only slowly and inefficiently with SmI_2.[28] The difference between these two substrates and their reactivity presumably lies in the activating effect of the *N*-benzoyl group.



Scheme 14

Recall that SmI_2 is readily capable of reducing nitro and other N-O functional groups to amines (see section III.1.). It is of particular interest to note that there is a nitro group in the example shown, and that no reduction of the nitro group in favor of reduction of the hydrazine was mentioned. Once again, this is testimony to the delicate selectivity of which SmI_2 is capable in multifunctional compounds.

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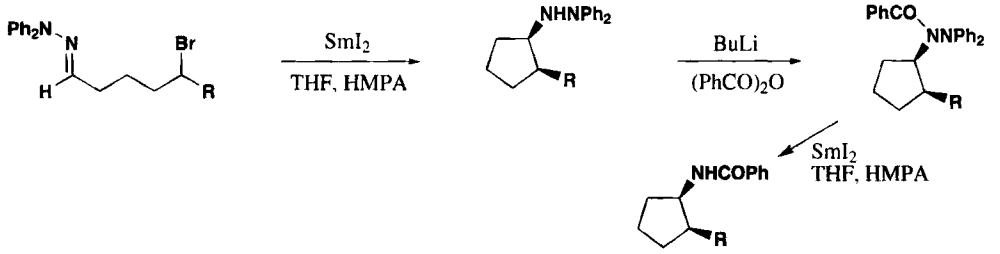
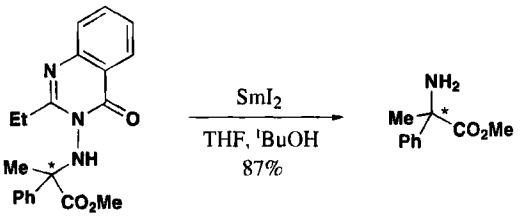
A similar approach was followed by Fallis,[29] who studied cyclisation-deprotection sequences of hydrazones/hydrazines. In that work, the lack of reactivity of the N-N bond in an hydrazone/hydrazine facilitated the cyclisation step (*Scheme 15*). The resulting 1,1-diphenylhydrazine was subsequently converted into a 2-benzoyl-1,1-diphenylhydrazine derivative, which allowed cleavage of the N-N bond under the action of SmI_2.



Scheme 15

In a similar vein, a variety of quinazoline derivatives were readily and directly reduced in the presence of SmI_2-THF-*t*-BuOH (*Scheme 16*).[30] In these cases, it was unnecessary to further acylate in order to achieve reactivity with SmI_2, due to the presence of the ring 'amide' already present in the quinazoline moiety. This method was employed in the synthesis of some α-amino acid esters.



Scheme 16

We would like to conclude this section with some miscellaneous reactions in which X-X species have been cleaved and have in many cases been used in sequential reactions, including:-

1. disulfides to sulfides; trapping with acid chlorides to furnish thiolesters,[31]
2. sodium alkyl thiosulfates ($RSSO_3Na$) to disulfides,[32]
3. diaryl diselenides and -ditellurides to samarium selenides and -tellurides, respectively, followed by nucleophilic aromatic substitution,[33]
4. diaryl diselenides and -ditellurides to samarium selenides/tellurides; trapping with acid chlorides to afford seleno- and telluroesters or with alkyl halides to provide unsymmetrical alkylphenyl selenides and -tellurides,[34]

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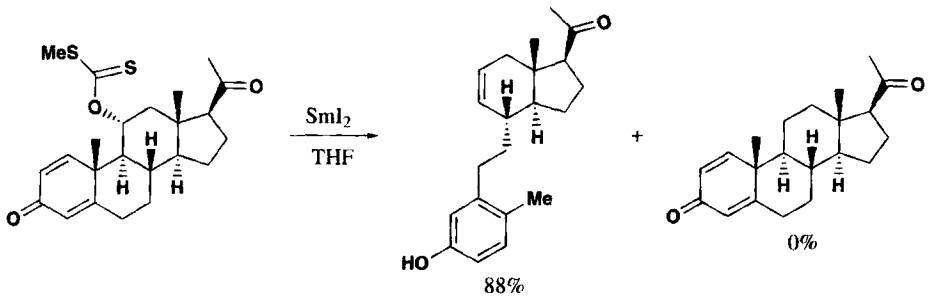
5. arylsulfanyltrimethylsilanes to samarium arylthiolates; trapping with alkyl halides to afford unsymmetrical sulfides,[35]
6. arylselenotrimethylsilanes to samarium arylselenolates; trapping with alkyl halides[36a] or acyl halides[36b] to yield unsymmetrical selenides and selenoesters, respectively.

IV. CARBON-CARBON BOND FRAGMENTATION REACTIONS

1. C-C fragmentation reactions in 'no-strain' systems

Although various dehalogenation and deoxygenation reactions of α-hydroxy, α-alkoxy, or α-acyloxycarbonyl compounds utilizing samarium(II) iodide have been extensively investigated, comparatively little work has been done on C-C bond fragmentation reactions.

Magnus and coworkers published one of the first C-C bond fragmentation reactions promoted by SmI_2 (*Scheme 17*).[37] The reagent was resorted to after a reaction with Bu_3SnH in toluene (40 h at reflux) yielded a mixture of the desired fragmentation product and the product of simple reduction in modest yield. Upon subjecting the steroid derivative to SmI_2 in THF at room temperature, the C-C cleaved product was isolated in 88% yield in only five minutes; none of the reduced product was detected. The authors suggested that a plausible explanation for the success of the reaction using SmI_2 where the tin reagent failed was the ability of the Sm(II) to rapidly reduce a radical to an anion. The radical mechanism can, however, not be discarded, nor indeed can one in which the initial electron transfer is to the conjugated ketone (leading to a delocalised radical).



Scheme 17

Honda and coworkers[38] have successfully prepared physiologically active, chiral, natural products using a carbon-carbon bond cleavage reaction as the key step. Starting from a chiral cyclopentane derivative, they were able to regioselectively cleave the α,β-C-C bond with respect to the ester functionality (*Scheme 18*). Since SmI_2 can complex both the halogen atom as well as the carbonyl moiety γ to the C-Cl, forming a seven-membered ring transition state, a concerted fragmentation mechanism was proposed in converting the carbocycle into the acyclic alkene. The reaction was successful using both the bromo and chloro substrates.

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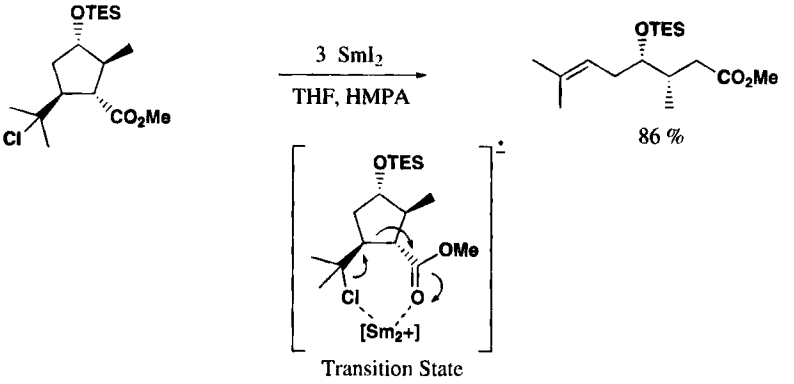


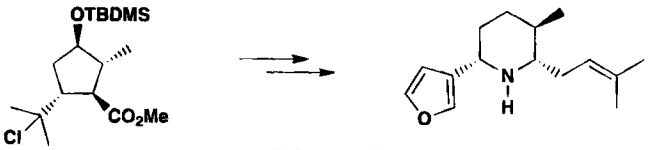
Scheme 18

In the absence of HMPA, none of the fragmented product was isolated: reductive dehalogenation took place in good yield. The reactions were shown to be SmI_2 specific with no fragmentation taking place under other standard reducing conditions. These included the treatment of the ester with tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN) in refluxing benzene under radical-initiating reaction conditions, and the reduction of the substrate with zinc powder in acetic acid.

The authors were cautious in proposing a mechanism for the observed fragmentation. However, they speculated that the results suggest that the reaction would occur *via* a two-electron reduction process, involving further reduction of the initially formed radical anion prior to either proton abstraction or a radical-induced fragmentation (see transition state).

Reaction of the ketone analogue of the ester, *i.e.* the γ-halo ketone, also yielded the bond cleaved product. In contrast, treatment of open-chain γ-halo ketones (halogen = Cl, Br) with SmI_2 under the same conditions has been known to yield cyclobutanols, *via* the ketyl radical.[39] The structural *bias* or inherent strain in forming a bicyclo[3.2.0]heptane ring system is probably the deciding factor which promotes the fragmentation over cyclisation.

Honda has used the SmI_2 promoted fragmentation of γ-halo esters for the synthesis of a number of enantiomerically pure natural compounds including alkaloids (*Scheme 19*), terpenes and antibiotics.[40]



Scheme 19

The fragmentation reaction of an ε-halo-α,β-unsaturated ester, where a similar cleavage reaction involving the fragmentation of the carbon-carbon bond between the γ and δ

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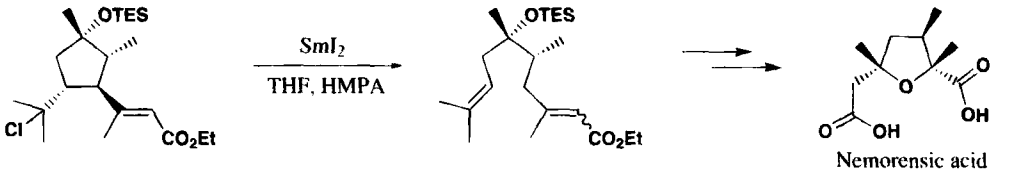
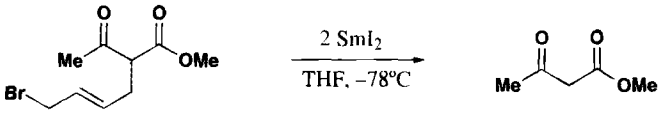
positions of the carbonyl group, was also investigated (*Scheme 20*).[41] The substrate underwent bond scission at room temperature upon treatment with SmI_2-HMPA to give a 2:1 ratio of stereoisomers (*E*:*Z*), in 91% yield.



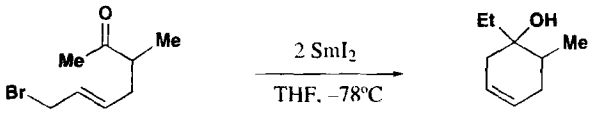
Scheme 20

Molander has described stereocontrolled cyclisation reactions of a number of substrates mediated by SmI_2.[42] Intramolecular cyclisation of allylic halides of varying chain lengths onto β-keto esters successfully provided vinyl-substituted cyclopentanes and cyclohexanes in good yields as a mixture of isomers. However, the attempted cyclisation of ethyl 2-methyl-2-(*trans*-4-bromo-2-butenyl)-3-oxobutanoate produced ethyl 2-methyl-3-oxobutanoate instead of the desired cyclobutane or cyclohexane derivative. The authors suggested that loss of butadiene as required for this transformation is facilitated by the ability of a β-keto ester stabilized (anion or radical) intermediate to serve as an effective leaving group in the reaction (*Scheme 21*). This result implied that the rate of fragmentation is substantially faster than that of cyclisation, which would normally first require reduction of the radical intermediate to the corresponding anion.



Scheme 21

This theory is supported by the outcome of the reaction shown below (*Scheme 22*). In this case, fragmentation would result in a less stabilized anion/radical species than that of the previously mentioned reaction; treatment of *trans*-8-bromo-4-methyl-6-octen-3-one with SmI_2 afforded 1-ethyl-6-methyl-3-cyclohexen-1-ol in 91% isolated yield.



Scheme 22

Samarium(II) iodide has been successfully used to promote reductive decyanation of malonitrile derivatives (*Scheme 23*).[43] The decyanation was achieved using a range of either monosubstituted (R^1 = alkyl, R^2 = H) or disubstituted (R^1 = alkyl, R^2 = alkyl) malonitriles in good yield. It was found that HMPA was essential for the success of the reaction. In the

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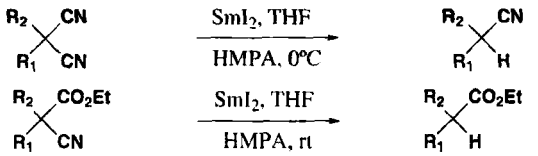
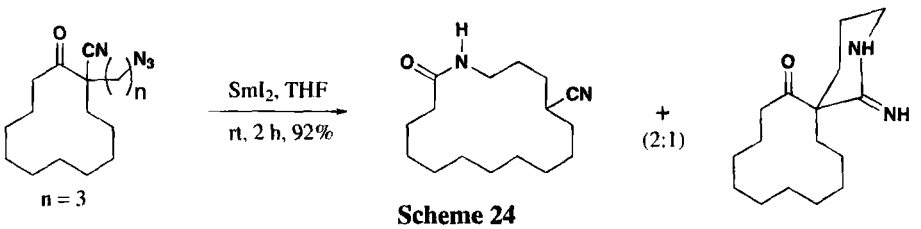
substrates where one of the alkyl groups contained a C=C, no cyclisation occurred where either a five- or seven membered ring could have formed.

The authors expanded on this work and were able to apply this new methodology to decyanate α-alkoxycarbonyl substituted nitrile derivatives. Again, the addition of HMPA was critical for the reaction pathway to proceed. Although Bu_3SnH can be used for the decyanation of malonitrile derivatives, the decyanation of the α-alkoxycarbonyl nitrile compounds seemed to be SmI_2 specific.



Scheme 23

Although several methods of producing macrocyclic lactams have been forthcoming, the construction of these large ring systems still presents a significant challenge because ring closure is difficult to achieve.[44] With the discovery that alkylazides are reactive towards reduction by SmI_2 came an investigation into the ring enlargement of readily available azidocyclododecanones to large-ring lactams (*Scheme 24*).[45] Although the exact mechanism of the reaction is unknown, the synthetic route is mild yet efficient in producing 16- and 17-membered lactams. Attempts to synthesize larger ring systems by this route failed.



Scheme 24

2. C-C fragmentation reactions in 'ring-strained' systems

a. *Cyclobutane containing substrates*

A more common form of C-C cleavage is that of strained ring systems, including compounds that contain a cyclobutane moiety. The initial fragmentation of the following cyclobutane substrate led to an allylic radical, which upon further reduction and protonation yielded an isomeric mixture of fragmented products (*Scheme 25*).[46] The exact ratio of the mixture was shown to be dependent on the nature of the reducing agent employed. The reagents used were *n*-Bu_3SnH, $(C_6H_5)_3SnH$ and SmI_2, with AIBN used as the initiator for the former two reagents.

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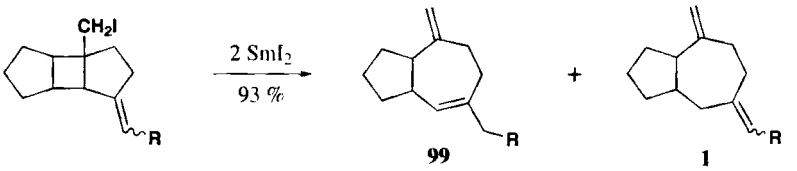

R = H, Me, CO_2R' (R' = Me, *t*Bu)

Scheme 25

With the hydride reagents the exocyclic double bond isomer predominated while with SmI_2 the endocyclic double bond product was favored. It was established that activation of the double bond was not necessary for the success of the reaction as displayed by the two cases where R = H and R = Me. SmI_2 was determined to be the reagent of choice in these transformations with the fragmentation yields being in excess of 90% in all four cases.

The reactions were assumed to proceed *via* a radical pathway forming the allylic radical after fragmentation of the strained cyclobutylcarbinyl system (*Scheme 26*). This radical was then reduced to the carbanion by a second equivalent of SmI_2, and finally protonated. Support of this theory is provided by the fact that quenching with excess MeI gave only the α-methylated product when making use of the ester substrates. While the latter result certainly proves the intermediacy of a carbanion, it does not exclude an anionic *fragmentation* pathway.

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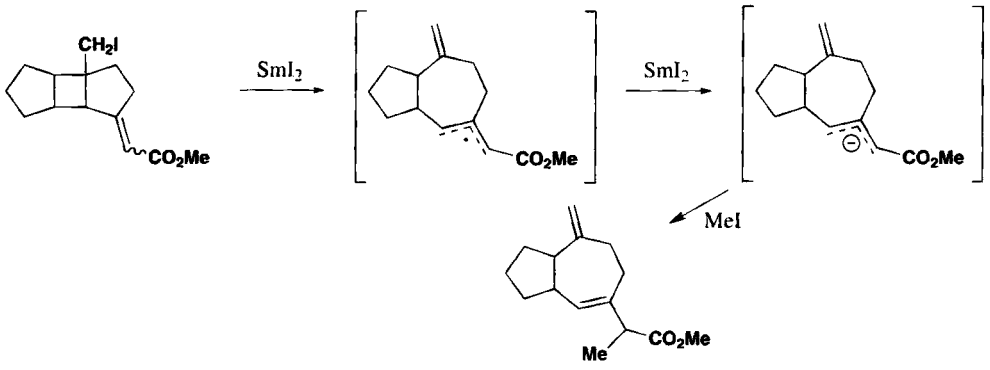

Scheme 26

Fragmentation of appropriate [2+2] photoadduct derivatives led to bicyclo[m.n.0]carbon skeletons that are present in a wide range of natural products. This methodology has been used in the synthesis of Dictamnol, a trinor-guaiane (*Scheme 27*).[47] The key step involves the initial reduction of a diiodo compound and a subsequent free radical fragmentation. Reduction of one iodo moiety initiates the reaction while the other iodide serves as a leaving group in the last stage of the fragmentation sequence. Treatment of the substrate with SmI_2 in THF and DMPU provided the ring expanded 5,7 fused ring diene in good yield. Apart from the generally higher yield offered by SmI_2, this reagent is preferable to *n*-Bu_3SnH as the radical initiator because of the convenience, lower toxicity, and the ease of product purification.

Scheme 27

A very similar methodology has been used to synthesize the 5,7 ring system and the strained cyclopropane moiety of the aromadendrane family of sesquiterpenoids (*Scheme 28*).[48] Again, the driving force for the reaction is the cleavage of the cyclobutane C-C bond of the [2+2] photoadduct. After fragmentation the radical is trapped by a pendant α,β-unsaturated ester moiety, leading to the formation of a cyclopropane ring. The stabilized radical (or anion?) intermediate allows this contra-thermodynamic process to take place. Although the cyclopropane was the major product isolated, a small amount of an isomeric mixture of α,β-unsaturated compounds was formed by fragmentation/cyclisation followed by opening on either side of the cyclopropyl carbinyl system.

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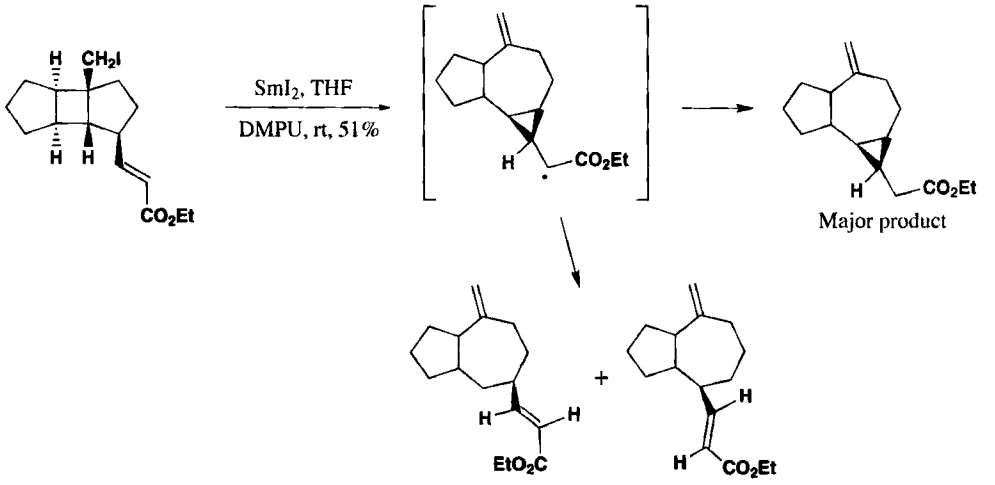
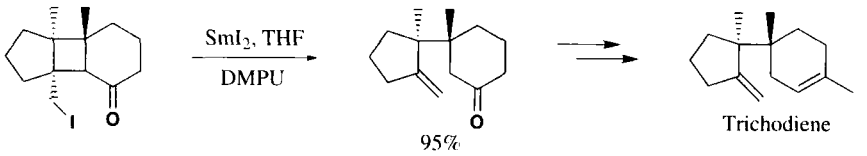


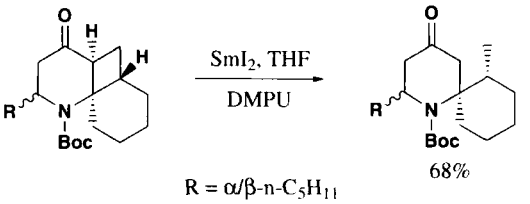
Scheme 28

The examples discussed above describe the synthesis of a number of terpenoids in which the critical step is the fragmentation of the "internal" cyclobutane bond. The cleavage of the "external" cyclobutane bond, however, allows the formation of a key intermediate in the preparation of the sesquiterpenoid Trichodiene (*Scheme 29*).[49] In the critical step of the synthesis, SmI_2 facilitated the desired cleavage of the external cyclobutane bond, to give the fragmented product in 95% yield. This fragmentation not only formed the cyclopentylcyclohexane system needed, but also introduced the exocyclic methylene group which is a structural feature found in the natural product.



Scheme 29

A number of physiologically active alkaloids contain a spirocyclic skeleton. This moiety is easily accessed by a novel cyclobutane ring cleavage (*Scheme 30*).[50] The regioselective ring opening was effected after treatment of the tricyclic precursor with SmI_2 in THF-DMPU, to give the desired spirocyclic ketone in 68% yield. The unique biological activity (*e.g.* compounds of this structure have been used in probing the mechanisms involved in transsynaptic transmission of neuromuscular impulses) of these alkaloids has stimulated considerable interest in their synthesis.



Scheme 30

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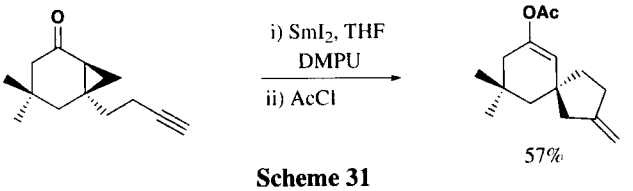
b. ***Cyclopropane containing substrates***

Alkyl radical cyclisations and tandem cyclisations are powerful aspects of the synthetic chemist's arsenal. The corresponding ring-opening fragmentation reactions, which in most cases are disfavored from both a kinetic and thermodynamic viewpoint, are, however, more scarce. An exception to this rule of thumb is the cyclopropylcarbinyl-homoallyl radical rearrangement, which is both fast and thermodynamically favoured as a direct consequence of the cyclopropyl ring strain, as is neatly shown by the work of Motherwell.[51] The beauty of the reaction is that ring opening occurs under stereoelectronic control, leading to the fragmentation of the exocyclic C-C bond. The regio- and stereochemistry of the intermediate is thus determined by the initially constructed cyclopropyl ketone.

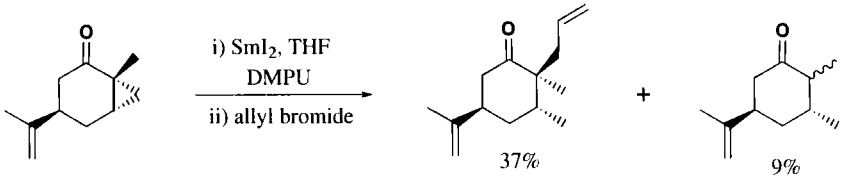
If no radical trap is incorporated into the molecule or added to the reaction mixture, only the fragmented methyl substituted derivative is formed. If a radical acceptor is present, the radical cascade reaction will dominate and allows entry into either spirocyclic ketones (*Scheme 31*) or fused bicyclic systems depending on the connective placement of the radical accepting chain. The reaction proceeds with alkenes and alkynes, and activating electron-withdrawing groups enhance the yield of the reaction.



Scheme 31

The reaction sequence, mechanism and intermediates allow not only tandem radical cyclisation reactions, but also allow capitalization of the enolate anion chemistry through trapping of the intermediate samarium enolates with electrophiles in cases where carbonyl-type alkene activating groups are present.

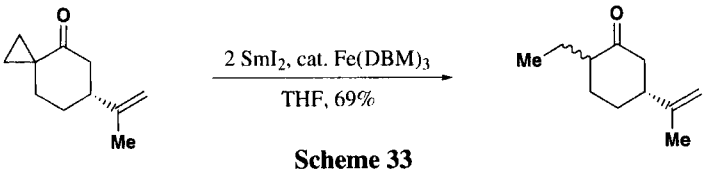
Attempted trapping with allyl bromide gave the allylated product in 37% yield and the epimeric ketone products of simple ring fragmentation in a combined 9% yield (*Scheme 32*). These experiments showed that it is possible to trap the Sm enolates with allyl bromide after a radical reaction sequence had taken place, in somewhat diminished yields.



Scheme 32

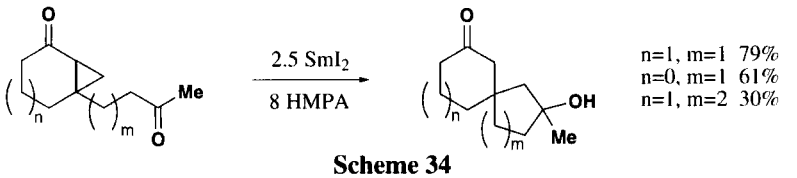
While other reagents (Bu_3SnH or sodium naphthalenide) can be used for this type of chemistry, the SmI_2/DMPU system was the most useful in terms of avoiding the problems of reagent basicity and second electron transfer associated with these reducing agents.

Subsequent to his first example of a simple cyclopropane ring cleavage (*Scheme 33*),[39] Molander has further developed the cyclopropyl ring cleavage reaction by taking advantage of the reducing strength of SmI_2 for further transformations.[52]



Scheme 33

The initially formed methylene radical can be further reduced to the corresponding carbanion and be trapped intramolecularly by a number of electrophiles (*Scheme 34*). These include ketones, esters, epoxides and aldehydes and lead to the formation of a variety of functionalised spirocyclic, bicyclic and tricyclic ring systems.



Scheme 34

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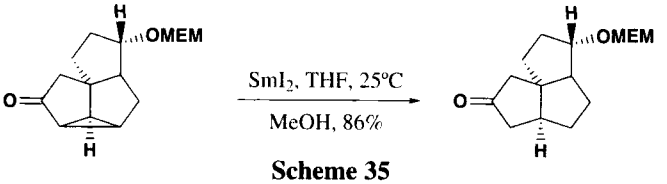
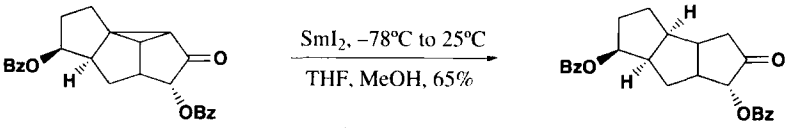
The reductive ring opening of α-cyclopropyl ketones with SmI_2 has been used in the key step for the preparation of angular and linearly fused triquinanes (*Scheme 35* and *Scheme 36*). The ring cleavages were effected by a SmI_2-THF-MeOH system in good yield.[53]

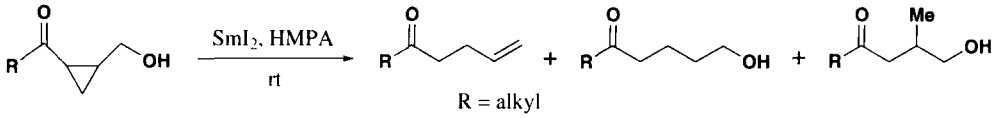


Scheme 35



Scheme 36

The samarium(II) iodide promoted ring opening of cyclopropyl-derivatised γ-hydroxy carbonyl compounds has been investigated as a possible strategy in the ongoing search for new syntheses of the tricyclo[5.3.1.$0^{1,7}$]undecane system of taxanes.[54] Two types of substrates were used in the study: a range of *cis*-substituted cyclopropanes (*Scheme 37*) and compounds



Scheme 37

containing a bicyclo[3.1.0]system ring (*Scheme 38*). The reaction with substrates containing aldehyde moieties were carried out in THF at room temperature in the absence of HMPA, while for reactions with ketones, the addition of 8-10 equivalents of HMPA was necessary. The former set of substrates formed a range of fragmentation products including homoallylic ketones, δ-hydroxy ketones and β-methyl-γ-hydroxy ketones in various amounts depending on the R group. The mechanism of the reaction was proposed to proceed *via* the ketyl radical. This radical then undergoes one of two different rearrangements depending on which C-C bond of the cyclopropane ring cleaves. Further reduction and, in one case, a sequential β-elimination afforded the three different fragmentation compounds.

The results of the reactions of the bicyclic compounds with SmI_2 were of greater interest. The regioselectivity of the reaction depended on the nature of the carbonyl group present: aldehydes underwent an *endo* bond cleavage followed by a β-elimination of the hydroxy group to give cyclohexenes, whereas ketones formed their respective cyclopentanols due to simple *exo* C-C bond fragmentation (*Scheme 38*). The rationalization of these findings relied either on a steric repulsion argument or one based on Frontier Molecular Orbital theory.

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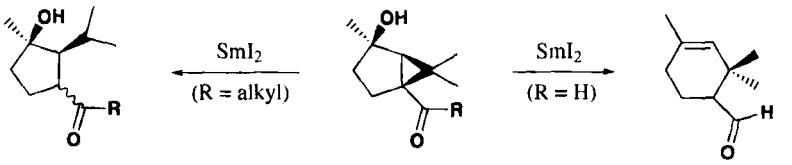
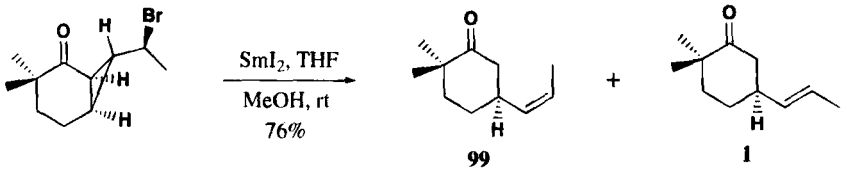


Scheme 38

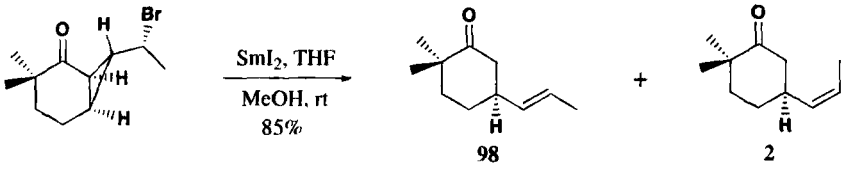
The reduction of both α-haloketones to the corresponding enolates and the ring opening of α-cyclopropyl ketones have both been investigated independently. Beerli *et al.* have studied the effect of having both these functionalities present under reducing conditions (*Scheme 39* and *Scheme 40*).[55] Although a ring opening and elimination sequence took place



99 **1**

Scheme 39

with a variety of reducing agents, only SmI_2 and NaHTe gave good stereochemical control. With systems such as Li/NH_3, Zn/AcOH, Cr(III), and Bu_3SnH/AIBN, mixtures of the subsequent keto-alkene isomers were obtained, with the thermodynamically favored *trans* product dominating.



98 **2**

Scheme 40

The fact that the reduction with SmI_2 is highly stereoselective (selective production of the *cis* or *trans* product, depending on the stereochemistry at the halogenated carbon atom), in contrast with other reducing agents like Bu_3SnH, led the authors to suggest a concerted reaction pathway, which would be similar to a Grob fragmentation.[56] Whether the reaction starts at the halogen or at the ketone is unclear, and it is possible that the mechanism resembles that proposed earlier for the ring scission of γ-haloesters (see section IV.1).[38]

The reduction and subsequent ring opening of α-halo-oxirane rings has been well studied. These reactions are generally selective for carbon-oxygen bond cleavage, although carbon-carbon bond fragmentation does occur when the oxirane ring possesses a vinyl or aryl substituent, which would lead to a resonance stabilized carbon radical (*Scheme 41*).[57] Treatment of a bromomethyl epoxide with 2.2 equivalents of SmI_2/THF in the presence of HMPA and MeOH at ambient temperature afforded the analogous allyl alcohol, as well as the vinyl ether as a by-product.

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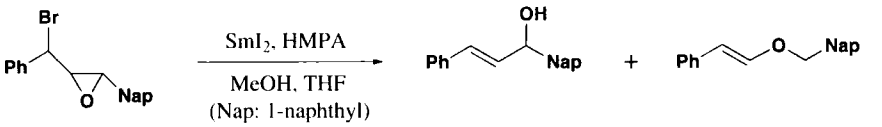
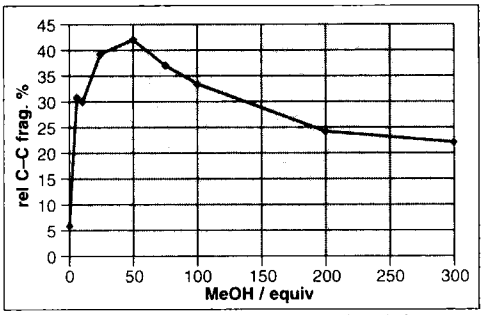


Scheme 41

The presence of the vinyl ether was indicative of a radical fragmentation reaction. The ratio of the fragmentation products was dependent upon a number of factors. These included the ratio of HMPA to SmI_2, the amount of methanol used, the concentration of the reaction mixture *i.e.* THF volume, the number of equivalents of SmI_2 added and the reaction temperature. Dilution of the mixture favored the C-C bond cleavage, as did an increase in reaction temperature; at –78°, no C-C fragmentation product was detected and 94% of the alcohol was produced, while the highest percentage of C-C fragmentation took place at 50°. The total product yield did, however, suffer at elevated temperatures.

The authors suggested that the reaction is initiated by reduction of the carbon-bromine bond to produce the oxiranylmethyl radical. Two pathways then become available. The first is a further reduction by a second equivalent of SmI_2, followed by C-O cleavage to afford the Sm-alkoxide. The second possibility is a C-C radical fragmentation to give the vinyl ether radical intermediate. Further reduction yields the anion which either protonates to give the vinyl ether or it can recyclise and undergo C-O cleavage.

The timing of the anionic quenching is critical in determining the product distribution. This is illustrated in the graph shown in *Figure 1*. If a proton source is present in the solution it is possible to rapidly trap the carbanion formed after reduction of the C-C fragmentation intermediate (radical) to yield the vinyl ether before it can recyclise and eliminate oxygen.



Effects of added MeOH on the relative ratio of C–C fragmentation

Fig. 1

The effect of added HMPA is difficult to rationalize. Intuitively one would think that the increase in reducing potential with increasing HMPA concentration would favor the reduction of the initially formed oxiranylmethyl radical, and yield an increasing amount of C-O cleaved product. This is opposite to experimental facts. The relative C-C fragmentation product increases with increasing HMPA concentration up to a maximum at 8 equivalents of

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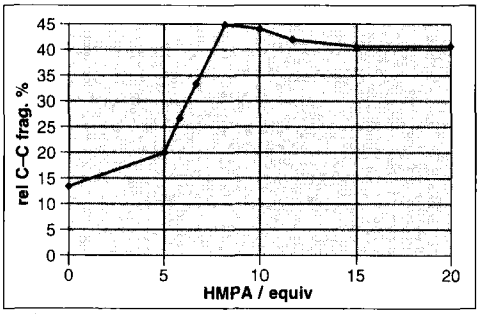
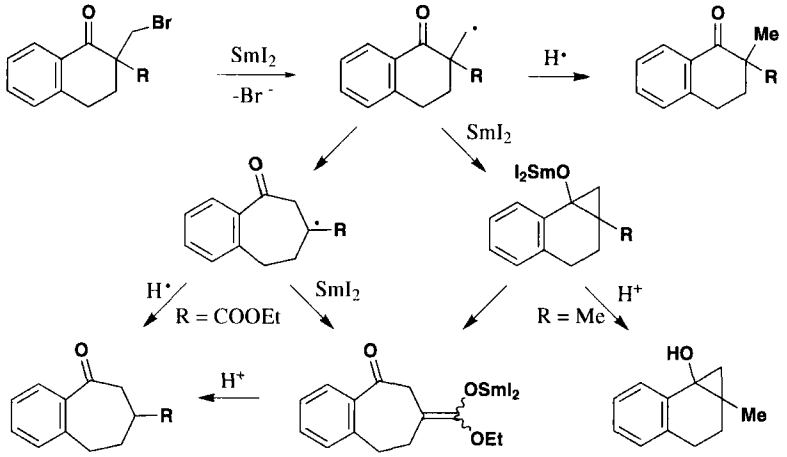
HMPA (*Figure 2*). Although SmI_2 with 4-5 equivalents of HMPA is considered to be most effective for the reduction of primary alkyl radicals,[5a,13] the initial radical formed in this reaction is benzylic and hence somewhat delocalised. The authors tentatively rationalized the observation by concluding that the reduction of the carbon radical possessing bulky aryl substituents may be sensitive to steric factors if the process involves the formation of a carbon-Sm bond similar to that of primary alkyl radicals. As the amount of HMPA increases so does the size of the co-ordination complex, and thus the reduction of the initial radical would slow down. This would allow the C-C fragmentation pathway to compete with the further reduction.



Effects of added HMPA on the relative ratio of C–C fragmentation

Fig. 2

SmI_2 is able to promote the conversion of α-bromomethyl cyclic β-keto esters to the corresponding ring-expanded one-carbon homologated γ-ketoesters in good yields.[58] The approach involves an intramolecular samarium Barbier reaction followed by a ring expansion sequence. The mechanism proposed is depicted below (*Scheme 42*). Deuterium labeling experiments showed a large amount of deuterium incorporation in the ring-expanded product. This



Scheme 42

lends credence to the reaction pathway that involves a reduction of the radical intermediate, rather than hydrogen abstraction from the solvent. With R = Me, the cyclopropanol was recov-

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ered in 98% yield. The presence of the ester moiety is, therefore, crucial for the ring expansion which leads to a carbanion intermediate. When the ring size of the substrate was reduced to the cyclopentane derivative, the addition of HMPA and a proton source were necessary for the ring expansion. In their absence, a naphthalene derivative was formed.

The literature on bicyclo[n.1.0] radicals reveals a preference for stereocontrolled exocyclic radical ring opening as opposed to the thermodynamically favored endocyclic ring opening.[59] Exocyclic ring opening has been achieved utilizing a variety of electron transfer techniques, including reagents such as SmI_2. The selectivity of the reaction can be altered to favor the endocyclic C-C fragmentation reaction if an appropriately situated radical/anion stabilizing group, such as an ester moiety, is incorporated into the substrate (*Scheme 43*).[60] Thus, when a solution of the cyclopropyl compound (below) is treated with SmI_2 in THF, the ring-expanded product is isolated in 44% yield. It was found that HMPA and DMPU were ineffective as additives in increasing the yield. However, when a proton source such as methanol was added, the reaction proceeded smoothly and the yield increased two-fold. This work contrasts that of the exocyclic ring opening, in which no stabilizing group is present on the substrate molecule.

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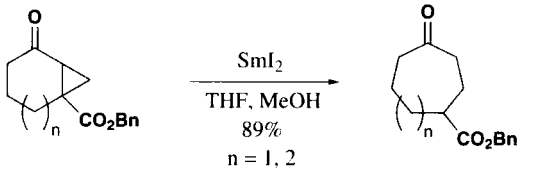
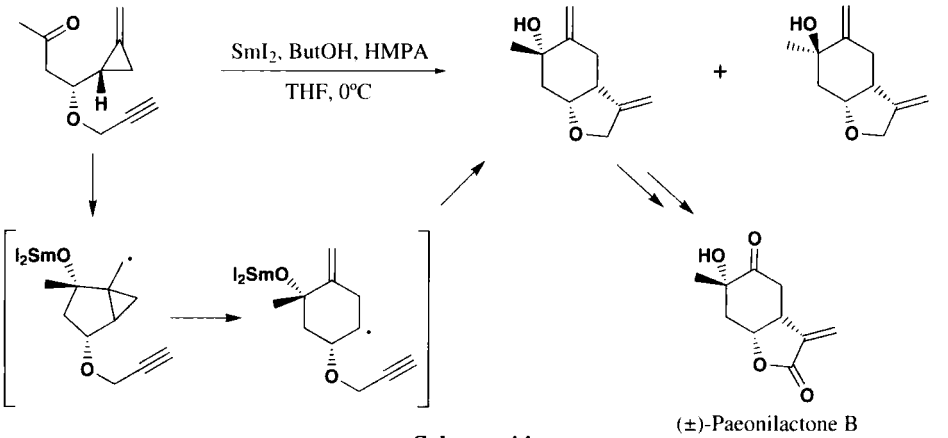


Scheme 43

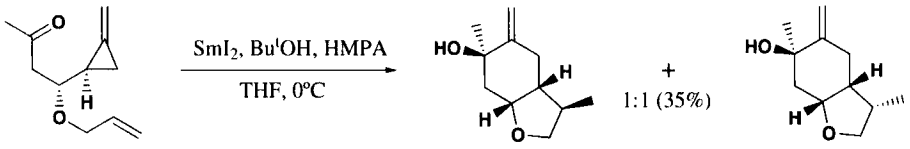
A number of natural products and key intermediates have been elegantly synthesized using SmI_2 radical cascade methodology. (±)-Paeonilactone B has been constructed utilizing such an approach (*Scheme 44*).[61] The mechanism presumably involves an initial cyclisation of



Scheme 44

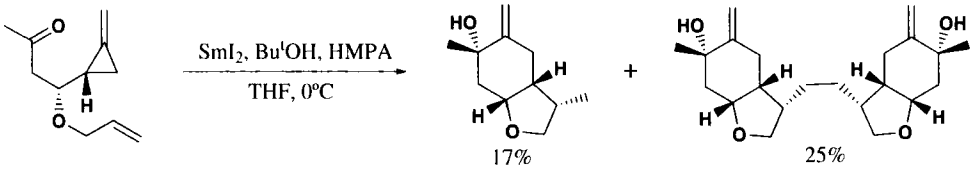
the ketyl radical onto a methylenecyclopropane unit with subsequent '*endo*' ring opening to give the methylene cyclohexyl radical. This then cyclises onto the pendant alkyne giving rise to a *cis*-fused bicyclic system. The authors found that the addition of HMPA or DMPU was imperative for a successful reaction, with HMPA far out performing DMPU with respect to both yield and diastereoselectivity. The observed diastereoselectivity (*cis*-hydroxy *vs. trans*-hydroxy, 10:1) is attributed to steric constraints in the transition state. The cyclisation is thought to proceed *via* a chair-like transition state, favoring the conformation in which both the bulky $SmI_2(HMPA)_n$ alkoxide and the prop-2-ynyl ether adopt a pseudo-equatorial position.

A similar methodology was applied to the corresponding allyl ethers in the hope of synthesising Paeonilactone A. When the keto-diene substrate was subjected to SmI_2 / HMPA (*Scheme 45*) the fragmentation reaction proceeded as before, but the yield as well as the stereoselectivity at the newly formed chiral center were reduced with respect to the analogous propargyl ether.



Scheme 45

Subjecting the diastereomer to the same reaction conditions, however, yielded a single diastereomeric bicyclic product (17% yield) accompanied by its dimer as a single diastereomer in 25% yield (*Scheme 46*). Although this particular reaction sequence was highly diastereoselective, it did not give the correct stereochemistry for the desired natural product. As noted before, the use of DMPU as a substitute for HMPA led to a loss of diastereoselectivity in the cyclisation step. Although the cyclisations of the allyl ethers failed to provide the correct stereochemistry for Paeonilactone A, the conversion of the bicyclic ethers formed to diastereomers of the natural product was investigated. This allowed for the efficient and stereoselective synthesis of (±)-6-epi-paeonilactone A.



Scheme 46

Walborski and Topolski[62] studied the reaction of chiral cyclopropyl halides with SmI_2 in the presence of HMPA (*Scheme 47*). The major product was the racemic reduced cyclopropyl compound, with the alkene and dimeric product being only minor components. By

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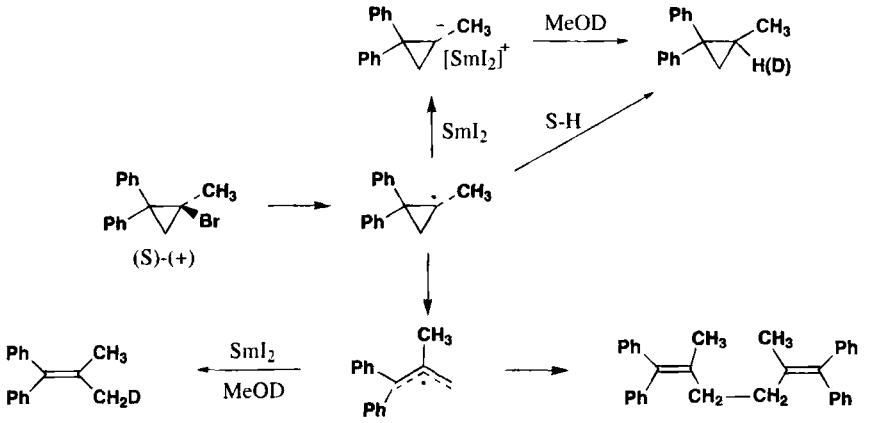
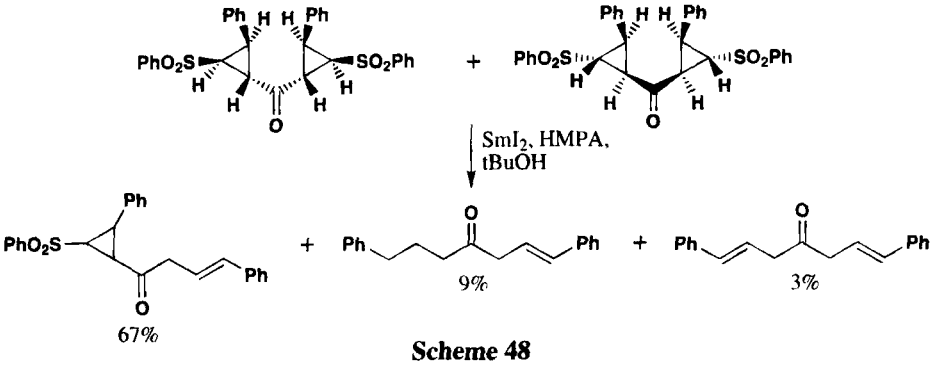
carrying out these reactions in the presence of deuterated methanol, the authors were able to deduce which products were formed *via* a radical process and which were formed *via* an anionic sequence. Their experiments showed only a 15% deuterium incorporation into the cyclopropyl derivative, implying that ring opening or H-atom abstraction from the solvent occurs before the radical can be further reduced. The alkene, however, possessed one deuterium atom per molecule, proving that it was formed after the radical had been reduced by a second equivalent of SmI_2.



Scheme 47

SmI_2 can also induce the regioselective cleavage of phenylsulfonyl activated cyclopropyl ketones.[63] The cleavage of these cyclopropanes followed by β-elimination of phenylsulfonyl radical leading to β,γ-unsaturated ketones has been demonstrated (*Scheme 48*).



Scheme 48

The SmI_2-$Fe(DBM)_3$ [*tris*(dibenzoylmethido)iron(III)] reagent system has been used successfully to promote the ring opening reaction of a number of cyclopropane-1,1-dicarboxylic esters (*Scheme 49*).[64] Excellent yields were achieved in a relatively short period of time with a number of different ester moieties. When the same reactions were carried out at reflux temperature in the presence of an aliphatic ketone, the respective 5-pentanolide deriva-

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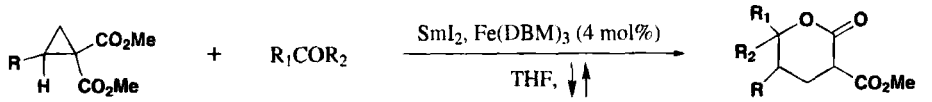
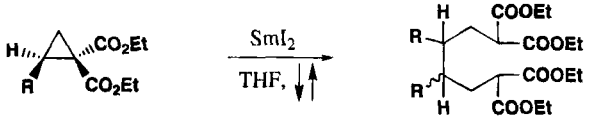
tives were isolated. The addition of aldehydes or aromatic ketones resulted in a significant amount of pinacol products with low yields of the desired 5-pentanolides. *S,S'*-Diphenyl cyclopropane-1,1-dicarbothioate was allowed to react with carbonyl compounds under similar conditions, giving δ-hydroxy esters in moderate yield.



Scheme 49

Yamashita and coworkers have expanded on the ring opening of cyclopropanecarboxylic esters and cyclopropane-1,1-dicarboxylic esters with a SmI_2-HMPA-THF system in the presence of *tert*-BuOH as a proton source to give 4-substituted butyric esters and (2-substituted ethyl)malonic esters (*Scheme 50*).[65] In the absence of a proton source however, they were able to reductively dimerize several 2-substituted cyclopropane-1,1-dicarboxylic esters.[66] The initial yields were poor, but were increased by the omission of HMPA from the system. The yield was further improved by conducting the reactions in a refluxing solution of SmI_2-THF.



Scheme 50

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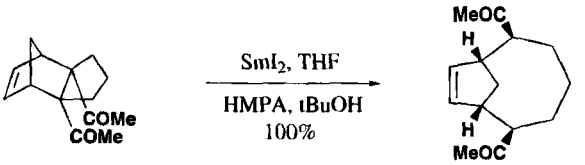
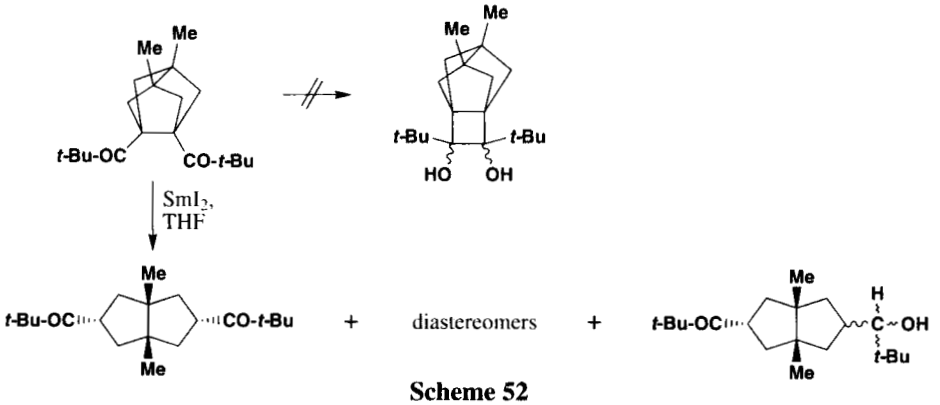
c. 1,4-*Diketones in non-strained and strained systems*

Hoffmann and coworkers[11] have recently described a 1,4-pinacolisation methodology utilising SmI_2 that is useful for the production of highly strained systems containing a 1,2-cyclobutanediol moiety. Ghosh anticipated that this methodology would be useful for gaining easy access to [3.3.2]propellanes. Thus, bicyclo[2.2.1]heptane derivatives bearing a 1,4-dicarbonyl moiety were prepared and subjected to reaction with SmI_2 (*Scheme 51*).[67] Contrary to expectations of cyclisation of the substrate, fragmentation to macrocyclic compounds was observed. Although the pinacol reaction is a possible reaction outcome, it would lead to an increase in strain of an already strained norbornene system: the more facile C-C fragmentation pathway is, therefore, followed. Relieving some ring strain by prior reduction of the double bond did not alter the outcome of the reaction.



Scheme 51

Camps has recently reported a similar experience in the fragmentation of a 1,4-diketone while trying the Hoffmann pinacol methodology.[68] Upon subjecting the strained bisnoradamantane system to SmI_2, it readily underwent fragmentation to give a mixture of three stereoisomeric bicyclic diketones in 80% yield (*Scheme 52*). A mixture of stereoisomeric alcohols (16% yield) derived from further reduction of the diketones was also isolated.



Scheme 52

A molecular mechanics (MM2 and MM3) investigation was carried out on the substrate, the possible cyclobutanediol isomers, and the fragmented diketones giving the formation enthalpies as well as the strain energies of the individual molecules. The calculations confirmed natural intuition, showing an enormous increase in strain energy for the pinacol products, while the strain energy of the products after fragmentation was considerably reduced. The authors went further and stated that it was reasonable to assume that the transition-state for the conversion of the diketyl radical derived from the bisnoradamantane diketone to the bis-enolate derived from the fragmented product is of much lower energy than the corresponding transition-state for its conversion to the diolate derived from the pinacol product. The fragmentation pathway *via* the diketyl radical is therefore more facile than that of its pinacol counterpart.

Our own work in this regard has afforded several insights as to being able to predict the outcome of certain reactions of 1,4-diketone substrates with SmI_2. Treatment of aromatic 1,4-diketone substrates with a solution of SmI_2 in THF under the conditions specified by Hoffmann[11] readily allowed us to repeat those results: a range of cyclobutan-1,2-diols could readily be prepared in high yields. However, when HMPA was added to the reaction mixture, the outcome of the reaction was drastically altered. Instead of affording a pinacol product, various products of C-C fragmentation and sequential reactions were observed (*Scheme 53*).[69]

The exact product mixture could be determined by the specific reaction conditions employed. In this way, the extent of phenyl-carbonyl coupling, secondary reduction, *etc.* could be controlled. The selectivity for fragmentation over pinacol reaction in these reactions may be directly ascribable to the presence of HMPA. It is reasonable to assume that pinacol reactions

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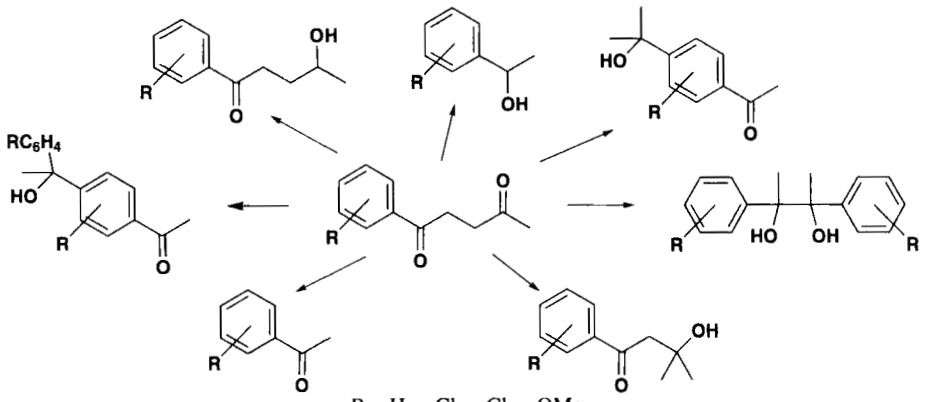
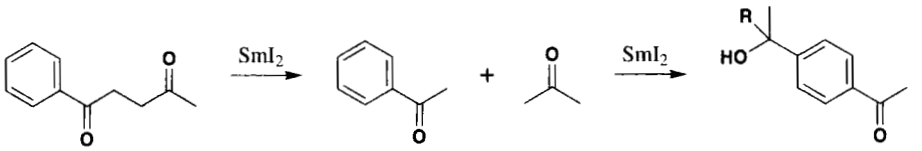


R = H, *o*-Cl, *p*-Cl, *p*-OMe

Scheme 53

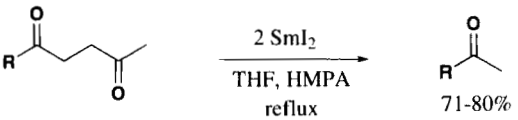
require chelate formation *via* the two carbonyl moieties onto the SmI_2 in order for C-C bond formation to be successful. The addition of HMPA could prevent or slow the chelation process to the SmI_2-$HMPA_n$ complex thereby favoring the observed fragmentation reaction (although the presence of HMPA does enhance the *rates* of reaction [*i.e.* electron transfer] of SmI_2 with carbonyl moieties).[70] This chelation process is normally facile when using only the SmI_2-THF_n complex, which is normally used for pinacol reactions.[71] In many cases, the fragmentation was the first step of a sequential reaction, most notable of which were the phenyl-carbonyl coupling reactions, which provided a variety of aromatic tertiary alcohols (*Scheme 54*). Others have speculated upon the mechanism of phenyl-carbonyl coupling.[72]



R = Me, Ph

Scheme 54

Follow up work investigated the outcome of similar reactions making use of aliphatic 1,4-diketones.[73] It was rapidly established that fragmentation to ketones or the corresponding alcohols could be effected at will (*Scheme 55* and *Scheme 56*), depending primarily upon the number of equivalents of SmI_2 added. In all cases, the reactions were high yielding.



R = n-C_5H_9, n-C_6H_{11}, n-C_7H_{13}, $C_6H_5CH_2CH_2$, $C_6H_5CH(CH_3)CH_2$, cyclo-C_6H_{11}

Scheme 55

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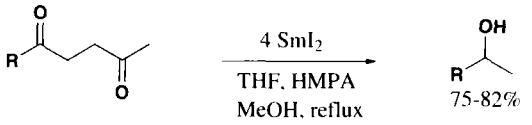
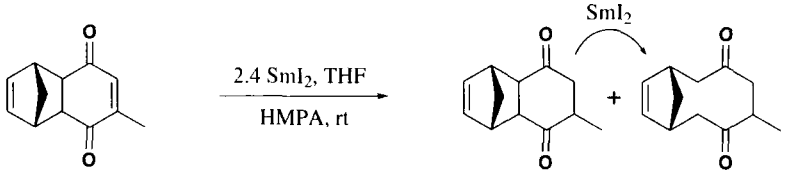


R = n-C_5H_9, n-C_6H_{11}, n-C_7H_{13}, $C_6H_5CH_2CH_2$, $C_6H_5CH(CH_3)CH_2$, cyclo-C_6H_{11}

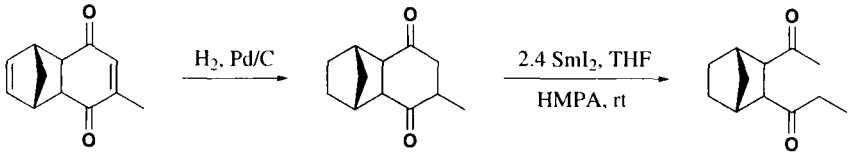
Scheme 56

We next turned our attention to norbornene (bicyclo[2.2.1]hept-2-ene) derivatives, with often surprising results.[74] *Scheme 57* shows that the 'internal' C-C bond of the 1,4-diketone fragmented upon treatment with SmI_2-THF, affording a macrocyclic diketone. It was interesting to note that both products of that reaction were mono-olefins. This demonstrated that the conjugated double bond was being reduced as a first step, preceding C-C fragmentation. It was shown that the reduced product was an intermediate towards the fragmented product, and that better selectivity for the fragmented product could be obtained by the addition of an excess (4.8 equivalents) of SmI_2.



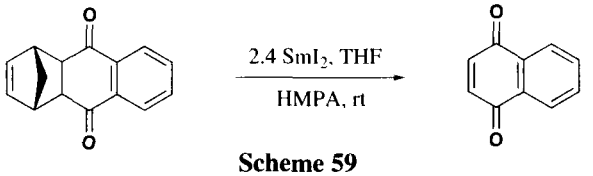
Scheme 57

The diolefin substrate could readily be saturated by reaction of that substrate with H_2 in the presence of Pd/C catalyst. Most interestingly, when the product was subjected to reaction with SmI_2, it was the 'external' C-C bond that fragmented, and no macrocyclic product was detected (*Scheme 58*). These results indicated that it was the presence or absence of the 'norbornene' double bond that determined which C-C bond fragmented.



Scheme 58

Another substrate of interest was the aromatic Diels-Alder adduct shown in *Scheme 59*. In this particular case, no fragmentation was observed; instead, a SmI_2-mediated retro Diels-Alder reaction was seen to take place. This particular reaction might prove to be an alternative means of protecting either naphthoquinones or cyclopentadiene moieties.



Scheme 59

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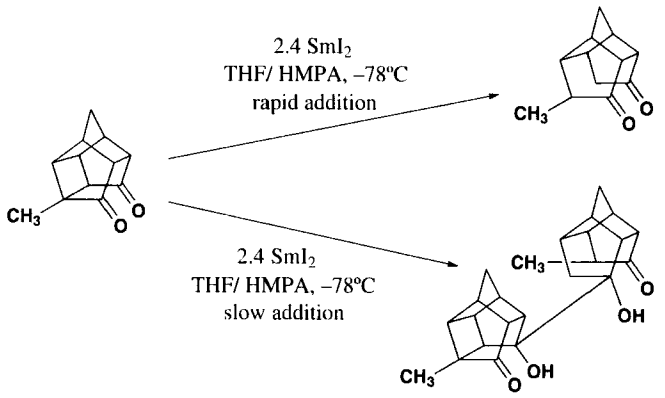
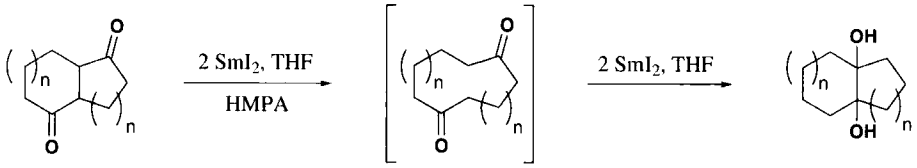
We finally turned our attention to cage compounds, and rapidly established that successful SmI_2-mediated reactions could only be carried out at low temperatures (-78°). At higher temperatures, an intractable multiple product mixture was obtained. This reaction was also found to be sensitive to the rate of addition of the SmI_2-THF-HMPA solution: at rapid rates of addition of the solution to the substrate, the C-C fragmented product was obtained (*Scheme 60*), while slow addition of the mixture afforded a mono-fragmented dimeric product. The latter product presumably arose from the fact that the ketyl radicals that formed upon reaction with SmI_2 were afforded sufficient lifetime by the slow rate of addition of the reductant to enable a pinacol-type combination to take place.



Scheme 60

We have also investigated the role of HMPA in determining the outcome of the reaction of 1,4-dicarbonyl substrates with SmI_2. As previously mentioned, 1,4-diketones readily cyclise to the corresponding cyclobutan-1,2-diols under the action of SmI_2 in the absence of HMPA,[11] while the same substrates fragment to the mono-ketones in the presence of HMPA. In line with our interest to convert, in one pot, a bicyclic 1,4-diketone into a 1,2-diol *via* an *in situ* fragmentation cyclisation sequence (*Scheme 61*, work in progress), we investigated the effect of added HMPA on the outcome of a specific reaction.



Scheme 61

We believed that it is possible to effect a fragmentation reaction with a minimum number of equivalents of HMPA present and to then effect a cyclisation reaction in the presence of an established maximum number of equivalents of HMPA present. The reaction employed is shown in *Scheme 62*,[73] and *Table 1* shows the results of this preliminary investi-

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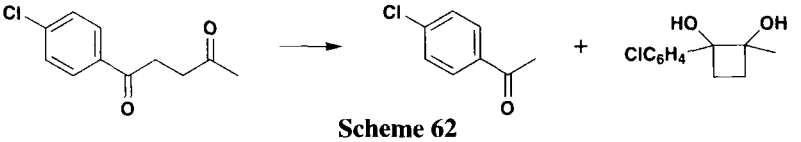
gation, which indicate that it should be possible to effect the desired two-step reaction (work still under investigation).



Scheme 62

Table 1. Effect of HMPA on 1,4-diketone reaction with SmI_2

Eq. HMPA	% Ketone	% Diol
8	100	0
4	100	0
3	70	30
2	50	50
1.5	1	99
1	0	100

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An insightful observation can be made when taking a bird's eye view of the fragmentation reactions of ring strained systems (see above, this section), pinacol-coupling reactions that afford ring strained systems,[11] and attempts at effecting pinacol coupling on substrates that contain ring strain.[67,68,69] The results indicate that it is possible to introduce large amounts of ring strain into systems that do not otherwise possess ring strain *via* the SmI_2-mediated pinacol reaction. However, when a substrate already contains a reasonably large amount of ring strain, *and* the two carbonyl moieties to be pinacolised have a 1,4-relationship, it seems that a pinacol reaction is kinetically disfavored. Instead, fragmentation reactions that lead to relief of ring strain predominate. The role of HMPA is also one of the primary determinative factors in the fragmentation *vs.* pinacolisation competition: the presence of HMPA in the reaction mixture favors fragmentation while its absence favors pinacol cyclisation.

V. CONCLUSION

SmI_2, either in the presence or absence of cosolvents, promotes manifold reactions, many of which are fragmentation reactions. In a number of cases, the fragmentation methodology has been put to good use in the preparation of highly functionalised products, which often are natural products or those that possess physiological activity. The fragmentation protocol has been found useful in a variety of transformations, and has been effectively applied to sequential reactions in which one or more transformations follow the initial fragmentation step.

SmI_2 is the reductant of choice for many reductive fragmentation reactions, and generally affords yields higher than those provided by other reducing agents, and in most

instances affords higher chemical and stereochemical yields. This being the case, SmI_2 should continue to find application in many synthetic sequences in more and more laboratories engaged in organic synthesis.

REFERENCES

1. P. Girard, J. L. Namy and H. B. Kagan, *J. Am. Chem. Soc.*, **102**, 2693 (1980).

2. a) C. A. Cooley and D. M. Yost, *Inorg. Synth.*, **2**, 69 (1946); b) D. A. Johnson, *Adv. Inorg. Radiochem.*, **20**, 1 (1970).

3. G. A. Molander, *Chem. Rev.*, **92**, 29 (1992).

4. a) D. A. Johnson, *J. Chem. Soc. Dalton Trans.* 1671 (**1974**); b) L. R. Morss, *Chem. Rev.*, **76**, 827 (1976).

5. a) M. Shabangi and R. A. Flowers, II, *Tetrahedron Lett.*, **38**, 1137 (1997); b) R. J. Enemærke, K. Daasbjerg and T. Skrydstrup, *Chem. Commun.*, 343 (**1999**); c) J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett.*, 1485 (**1987**).

6. D. P. Curran, T. L. Fevig, C. P. Jasperse and M. J. Totleben, *Synlett.*, 943 (**1992**).

7. H. B. Kagan and J. L. Namy, *Tetrahedron*, **42**, 6573 (1986).

8. D. P. Curran and M.J. Totleben, *J. Am. Chem. Soc.*, **114**, 6050 (1992).

9. a) M. Matsukuwa, J. Inanaga and M. Yamaguchi, *Tetrahedron Lett.*, **28**, 5877 (1986); b) T. L. Fevig, R. L. Elliott and D. P. Curran, *J. Am. Chem. Soc.*, **110**, 5064 (1988).

10. E. J. Enholm and A. Travellas, *J. Am. Chem. Soc.*, **111**, 6463 (1989).

11. a) H. M. R. Hoffmann, I. Münnich, O. Nowitzki, H. Stucke and D. J. Williams, *Tetrahedron*, **52**, 11783 (1996); b) O. Nowitzki, I. Münnich, H. Stucke, and H. M. R. Hoffmann, *Tetrahedron*, **52**, 11799 (1996).

12. E. Hasegawa and D. P. Curran, *J. Org. Chem.*, **58**, 5008 (1993).

13. M. Shabangu, J. M. Sealy, J. R. Fuchs, and R. A. Flowers, II, *Tetrahedron Lett.*, **39**, 4429 (1998).

14. a) Y. Handa, J. Inanaga and M. Yamaguchi, *J. Chem. Soc., Chem. Commun.*, 298 (**1989**); b) A. S. Kende and J. S. Mendoza, *Tetrahedron Lett.*, **32**, 1699 (1991).

15. N. R. Natale, *Tetrahedron Lett.*, **23**, 5009 (1982).

16. Y. Zhang and R. Lin, *Synth. Commun.*, **17**, 329 (1987).

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17. a) G. E. Keck, S. F. McHardy and J. A. Murry, *J. Am. Chem. Soc.*, **117**, 7289 (1995); b) G. E. Keck., S. F. McHardy and T. T. Wager, *Tetrahedron Lett.*, **41**, 7419 (1995); c) G. E. Keck, S. F. McHardy and T. T. Wager, *Tetrahedron*, **55**, 11755 (1999).

18. a) S. E. Denmark, A. Stolle, J. A. Dixon and V. Guagnano, *J. Am. Chem. Soc.*, **117**, 2100 (1995); b) S. S. Nikam, B. E. Kornberg, D. R. Johnson and A. M. Doherty, *Tetrahedron Lett.*, **36**, 197 (1995); c) A. R. Ritter, M. J. Miller, *J. Org. Chem.*, **59**, 4602 (1994); d) R. C. Larock, "*Comprehensive Organic Transformations*", p. 385, VCH Publishers Inc., New York, 1989.

19. a) J. Marco-Contelles, C. Destabel, J. L. Chiara and M. Bernabé, *Tetrahedron: Asymmetry*, **6**, 1547 (1995); b) J. L. Chiara, C. Destabel, P. Gallego and J. Marco-Contelles, *J. Org. Chem.*, **61**, 359 (1996).

20. B. J. McAuley, M. Nieuwenhuyzen and G. N. Sheldrake, *Org. Lett.*, **2**, 1457 (2000).

21. a) D. C. Hill, L. A. Flugge and P. A. Petillo, *J. Org. Chem.*, **62**, 4864 (1997); b) E. Vedejs and S. Lin, *J. Org. Chem.*, **59**, 1602 (1994); c) A. Batch and R. H. Dodd, *J. Org. Chem.*, **63**, 872 (1998).

22. a) C. Goulaouic-Dubois, A. Guggisberg and M. Hesse, *J. Org. Chem.*, **60**, 5969 (1995); b) H. S. Knowles, A. F. Parsons, R. M. Pettifer and S. Rickling, *Tetrahedron*, **56**, 979 (2000); c) H. Knowles, A. F. Parsons and R. M. Pettifer, *Synlett.*, 271 (**1997**).

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

24. M. Kunishima, K. Hioki, T. Ohara and S. Tani, *J. Chem. Soc., Chem. Commun.*, 219 (**1992**).

25. C. R. Johnson and C. H. Senayake, *J. Org. Chem.*, **54**, 736 (1989).

26. K. S. Feldman and R. E. Simpson, *Tetrahedron Lett.*, **30**, 6985 (1989).

27. M. J. Burk and J. E. Feaster, *J. Am. Chem. Soc.*, **114**, 6266 (1992).

28. J. Souppe, L. Danon, J. L. Namy and H. B. Kagan, *J. Organomet. Chem.*, **250**, 227 (1983).

29. C. F. Sturino and A. G. Fallis, *J. Am. Chem. Soc.*, **116**, 7447 (1994).

30. a) R. S. Atkinson, B. J. Kelly and J. Williams, *J. Chem. Soc., Chem. Commun.*, 373 (**1992**); b) R. S. Atkinson, B. J. Kelly and J. Williams, *Tetrahedron*, **48**, 7713 (1992).

31. X. Jia, Y. Zhang and X. Zhou, *Synth. Commun.*, **24**, 387 (1994).

32. X. Jia, Y. Zhang and X. Zhou, *Synth. Commun.*, **24**, 2898 (1994).

33. a) X. Jia, Y. Zhang and X. Zhou, *Synth. Commun.*, **24**, 1339 (1994); b) X. Jia, Y. Zhang and X. Zhou, *Synth. Commun.*, **25**, 1913 (1995).

Downloaded At: 20:23 26 January 2011

34. X. Jia, Y. Zhang and X. Zhou, *Synth. Commun.*, **23**, 189 (1993).

35. S. Zhang and Y. Zhang, *J. Chem. Res. (S)*, 48 (**1998**).

36. a) S. Zhang and Y. Zhang, *J. Chem. Res. (S)*, 350 (**1998**); b) S. Zhang and Y. Zhang, *Synth. Commun.*, **28**, 3999 (1998).

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

38. T. Honda, K. Naito, S.-i. Yamane and Y. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1218 (**1992**).

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

40. a) T. Honda, S.-I. Yamane., K. Naito and Y. Suzuki, *Heterocycles*, **37**, 515 (1994); b) T. Honda, F. Ishikawa and S-i. Yamane, *J. Chem. Soc., Chem. Commun.*, 499 (**1994**); c) T. Honda, S-i. Yamane, K. Naito and Y. Suzuki, *Heterocycles*, **40**, 301 (1995); d) T. Honda, F. Ishikawa and S-i. Yamane, *J. Chem. Soc., Perkin Trans. 1*, 1125 (**1996**); e) T. Honda, S-i. Yamane, F. Ishikawa and M. Katoh, *Tetrahedron*, **52**, 12177 (1996); f) T. Honda, M. Katoh and S-i. Yamane, *J. Chem. Soc., Perkin Trans. 1*, 2291 (**1996**).

41. T. Honda and F. Ishikawa, *J. Org. Chem.*, **64**, 5542 (1999).

42. G. A. Molander, J. B. Etter and P. W. Zinke, *J. Am. Chem. Soc.*, **109**, 453 (1987).

43. H-Y. Kang and W. Sang Hong, *Tetrahedron Lett.*, **42**, 7661 (1995).

44. Q. Meng and M. Hesse, *"Topics in Current Chemistry"*, Vol. 161, 107, Springer-Verlag, 1992.

45. C. Goulaouic-Dubois, A. Guggisberg and M. Hesse, *Tetrahedron*, **51**, 12035 (1995).

46. G. L. Lange and C. Gottardo, *Tetrahedron Lett.*, **35**, 6607 (1994).

47. G. L. Lange, C. Gottardo and A. Merica, *J. Org. Chem.*, **64**, 6738 (1999).

48. G. L. Lange and A. Merica, *Tetrahedron Lett.*, **40**, 7897 (1999).

49. G. L. Lange, L. Furlan and M.C. MacKinnon, *Tetrahedron Lett.*, **39**, 5489 (1998).

50. D. L. Comins and X. Zheng, *J. Chem. Soc., Chem. Commun.*, 2681 (**1994**).

51. a) R. A. Batey and W. B. Motherwell, *Tetrahedron Lett.*, **32**, 6211 (1991); b) R. A. Batey, J. D. Harling and W. B. Motherwell, *Tetrahedron*, **52**, 11421 (1996).

52. G. A. Molander and C. Alonso-Alija, *Tetrahedron*, **53**, 8067 (1997).

Downloaded At: 20:23 26 January 2011

53. J.-T Hwang and C.-C Liao, *Tetrahedron Lett.*, **32**, 6583 (1991).

54. a) A. Nivlet, V. Le Guen, L. Dechoux, T. Le Gall and C. Mioskowski, *Tetrahedron Lett.*, **39**, 2115 (1998); b) A. Nivlet, L. Dechoux, T. Le Gall and C. Mioskowski, *Eur. J. Org. Chem.*, 3251 (**1999**).

55. R. Beerli, E.J. Brunner and H.-J. Borschberg, *Tetrahedron Lett.*, **33**, 6449 (1992).

56. A. Grob, *Angew. Chem. Int. Ed. Engl.*, **8**, 535 (1965).

57. E. Hasegawa, M. Takahashi and T. Horaguchi, *Tetrahedron Lett.*, **36**, 5215 (1995).

58. E. Hasegawa, T. Kitazume, K. Suzuki and E. Tosaka, *Tetrahedron Lett.*, **39**, 4059 (1998).

59. a) S. Cristol and R. V. Barbour, *J. Am. Chem. Soc.*, **90**, 2832 (1968); b) A. L. J. Beckwith and G. J. Philliou, *J. Chem. Soc. Chem Commun.*, 658 (**1971**); c) A. L. J. Beckwith and G. J. Philliou, *Aust. J. Chem.*, **29**, 123 (1976); d) E. C. Friedrich and R. L. Holmstead, *J. Org. Chem.*, **36**, 971 (1971); e) K. U. Ingold and J. C. Walton, *Acc. Chem. Res.*, **19**, 72 (1986).

60. P. H. Lee and J. Lee, *Tetrahedron Lett.*, **39**, 7889 (1998).

61. a) R. J. Boffey, W. G. Whittingham and J. D. Kilburn, *J. Chem. Soc., Perkin Trans. 1*, 487 (**2001**), R. J. Boffey, M. Santagostino, W. G. Whittingham and J. D. Kilburn, *J. Chem. Soc., Chem. Commun.*, 1875, (**1998**); c) R. J. Bofey, W. G. Whittingham and J. D. Kilburn, *Tetrahedron Lett.*, **40**, 5625 (1999)

62. H. M. Walborsky and M. Topolski, *J. Org. Chem.*, **57**, 370 (1992).

63. V. Reutrakul, R. Saeeng, M. Pohmakotr and P. Kongsaeree, *Tetrahedron Lett.*, **40**, 1019 (1999).

64. T. Imamoto, T. Hatajima and T. Yoshizawa, *Tetrahedron Lett.*, **35**, 7805 (1994).

65. a) M. Yamashita, K. Okuyama, T. Ohhara, I. Kawasaki and S. Ohto, *Chem. Pharm. Bull.*, **43**, 708 (1995); b) M. Yamashita, K. Okuyama, T. Ohhara, I. Kawasaki, K. Sakai, N. Nakata, T. Kawabe, M. Kusumoto and S. Ohto, *Chem. Pharm. Bull.*, **43**, 2075 (1995).

66. M. Yamashita, K. Okuyama, T. Ohhara, I. Kawasaki and S. Ohta, *Synlett.*, 547 (**1996**).

67. A. Haque and S. Ghosh, *J. Chem. Soc., Chem. Commun.*, 2039 (**1997**).

68. P. Camps, A. E. Lukach and S. Vázquez, *Tetrahedron*, **57**, 2419 (2001).

69. D. B. G. Williams, K. Blann and C. W. Holzapfel, *J. Org. Chem.*, **65**, 2834 (2000).

70. Z. Hou, Y. Zhang and Y. Wakatsuki, *Bull. Chem. Soc. Jpn.* **70**, 149 (1997).

71. a) G. A. Molander, In "*Comp. Org. Synth.*", Trost, B. M.; Fleming, I., Eds., Vol. 1, p 251, Pergamon, Oxford, 1991; G. A. Molander and C. Kenny, *J. Org. Chem.*, **53**, 2132 (1988).

Downloaded At: 20:23 26 January 2011

72. a) J.-S. Shiue, C.-C. Lin and J.-M. Fang, *Tetrahedron Lett.* **34**, 335 (1993). b) J.-S. Shiue, C.-C. Lin and J.-M. Fang, *J. Org. Chem.* **62**, 4643 (1997).

73. D. B. G. Williams, K. Blann and C. W. Holzapfel, *Unpublished results.*

74. D. B. G. Williams, K. Blann and C. W. Holzapfel, *J. Chem. Soc., Perkin Trans. 1*, 219 (**2001**).

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