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Samarium Diiodide

Samarium Diiodide Mediated Reactions in Total Synthesis

K. C. Nicolaou, Shelby P. Ellery, and Jason S. Chen*

Keywords:
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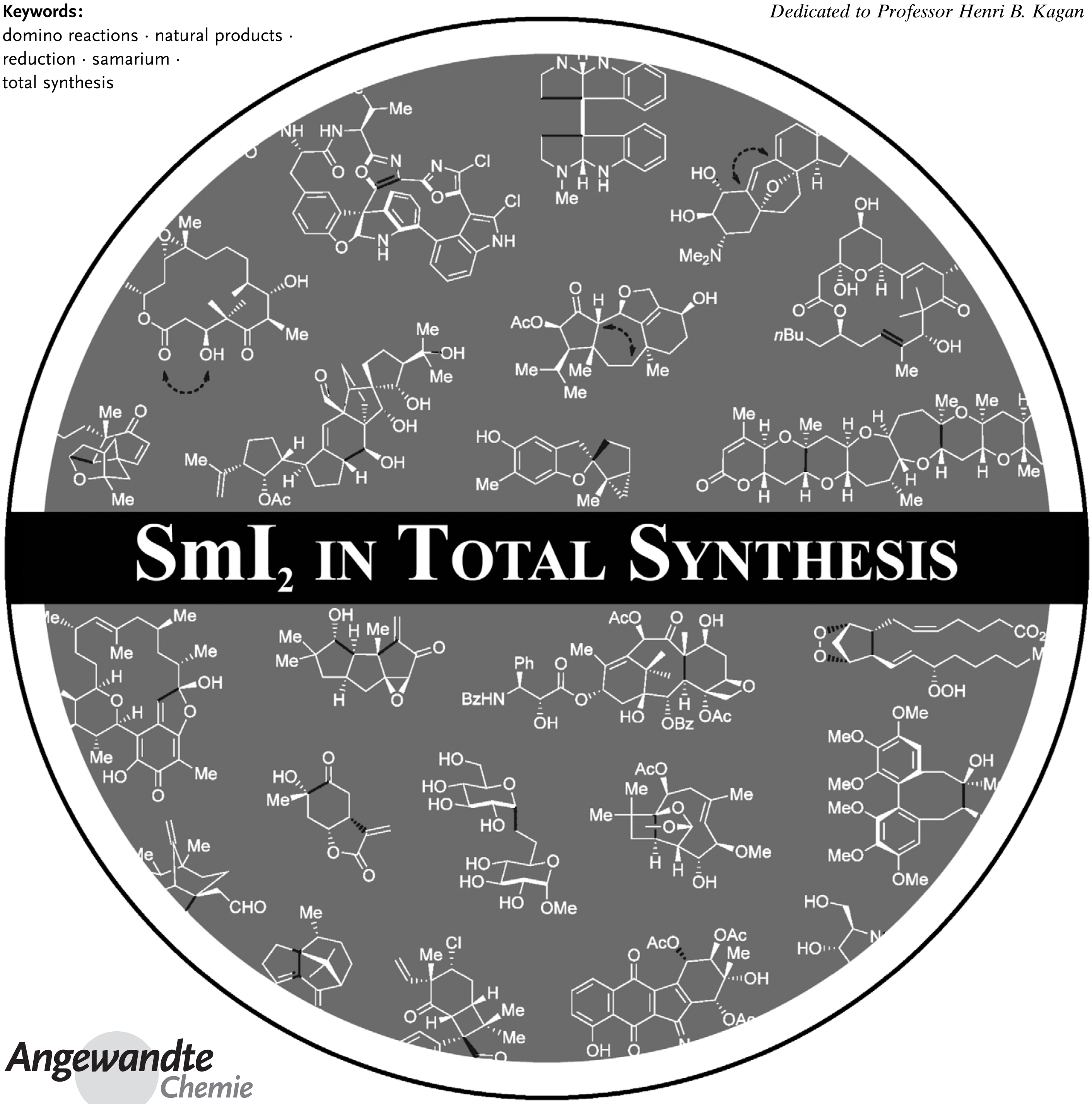
Dedicated to Professor Henri B. Kagan



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Introduced by Henri Kagan more than three decades ago, samarium diiodide (SmI_2) has found increasing application in chemical synthesis. This single-electron reducing agent has been particularly useful in C–C bond formations, including those found in total synthesis endeavors. This Review highlights selected applications of SmI_2 in total synthesis, with special emphasis on novel transformations and mechanistic considerations. The examples discussed are both illustrative of the power of this reagent in the construction of complex molecules and inspirational for the design of synthetic strategies toward such targets, both natural and designed.

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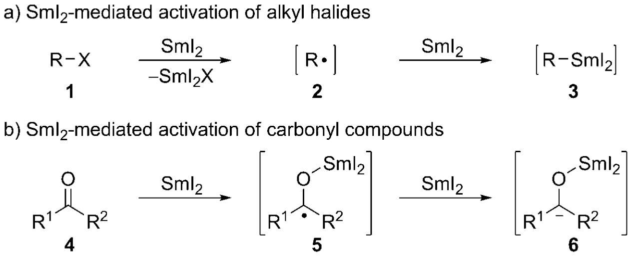
1. Introduction

The total synthesis of complex targets provides a compelling proving ground for promising new reagents and novel applications of existing reagents, some of which eventually become recognized as invaluable tools in the synthetic chemist's arsenal. Those that achieve this level of importance do so because of their useful reactivities, versatility, predictable selectivities, functional-group tolerance, and simplicity of handling, as demonstrated by a track record of successful applications in the synthesis of both simple and complex targets. First used in organic chemistry by Kagan and coworkers in 1977,[1] samarium diiodide (SmI_2) has since been employed in the development of a wide variety of reactions and has been featured in hundreds of syntheses.[2] The large reduction potential of SmI_2 (up to -2.05 V in the presence of HMPA)[3] allows access to a rich array of reactive intermediates. As shown in Scheme 1 a, the reduction of an alkyl halide **1** can generate either radical species **2** (through a single-electron reduction) or organosamarium intermediate **3** (through two successive single-electron reductions). Likewise, a carbonyl moiety (**4**; Scheme 1 b) can be reductively activated to form a reactive ketyl radical **5** which, under appropriate conditions, can be further reduced to provide access to carbanion **6**. Access to this diverse group of high-energy species allows for a broad range of reactivities. However, these possibilities do not render SmI_2 an indiscriminant reducing agent, since its powerful reactivity is highly tunable through careful optimization of the reaction conditions. Indeed, the ability to selectively access both radical[4] and ionic reactions, sometimes in the course of the same reaction,[5] makes SmI_2 particularly versatile in organic synthesis. As a result of this potent combination of useful reactivity and tunable selectivity, SmI_2 is widely employed and recognized as one of the premier single-electron reducing agents in synthetic chemistry.



Scheme 1. Common mechanisms of SmI_2-mediated activation of a) alkyl halides and b) carbonyl compounds.

This Review seeks to highlight the power and versatility of SmI_2 by examining selected examples of its elegant application in total synthesis, a topic not fully explored in previous reviews.[2] The featured examples are grouped according to the type of SmI_2-mediated reaction into the following categories: Barbier, radical–alkene/alkyne, Reformatsky and aldol-type, carbonyl–alkene/alkyne, pinacol-type, fragmentation, and elimination reactions (Scheme 2). Cascade sequences[6] will be discussed separately. It must be noted that the reaction classes depicted in Scheme 2 in no way cover all of the useful reactions of SmI_2; indeed, the deoxygenation of epoxides, cleavage of heterocycles, β- and 1,2-eliminations, and deprotection of nitrogen-containing functionalities are but a few of the many reactions that are not represented in Scheme 2.

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2. Barbier Reaction

The Barbier reaction (Scheme 2a) is a reductive addition of an alkyl halide or, more rarely, alkyl sulfone to a carbonyl group.[7] It is differentiated from a Grignard-type coupling by the presence of the reactive halide and the carbonyl coupling partner in the same reaction mixture. Kagan and co-workers discovered the intermolecular SmI_2-mediated Barbier reaction in 1977.[1] In 1986, Molander and Etter reported the intramolecular version.[8] Unlike other common variants of the Barbier reaction with metals such as magnesium, lithium, or zinc, the SmI_2-mediated variation occurs in a homogeneous reaction mixture and is often associated with superior chemoselectivity. Originally proposed to involve the coupling of an alkyl radical and a ketyl radical,[9] the SmI_2-mediated Barbier reaction is now believed to proceed both inter- and intramolecularly through the intermediacy of an organosamarium species formed through two successive single-electron reductions (see Scheme 2a).[10] The Barbier reaction is one of the most commonly employed SmI_2-mediated transformations, and the intramolecular variant in particular has proven to be popular for the formation of five- to eight-membered carbocycles.

Matsuda and co-workers employed the intramolecular SmI_2-mediated Barbier reaction in the construction of the synthetically daunting eight-membered ring within their vinigrol model **8** (Scheme 3).[11] Thus, advanced intermediate **7** reacted smoothly with SmI_2 in the presence of HMPA at room temperature to deliver cyclization product **8** in a highly satisfying 98% yield without any requirement for high dilution or slow addition. The use of HMPA as a means to enhance the reduction potential of SmI_2 was critical to the success of this transformation. In its absence, the desired product **8** was obtained in only 15% yield, and the major product was the primary alcohol resulting from direct reduction of aldehyde **7**. Although the reaction proceeded best at ambient temperature, smooth ring closure was observed even at −78 °C, with only a modest drop in yield. This surprisingly facile ring closure to give an eight-membered ring was attributed to a preference for intermediate **7** to adopt conformation **9**, a supposition that was supported by NMR spectroscopic analysis. This conformation places the reacting groups in axial positions of a chair cyclohexane system to avoid the significant $A^{1,3}$ strain that would otherwise exist, and, as a result, preorganizes them in proximity.

Carroll and Little employed two SmI_2-mediated transformations in their rather concise synthesis of phorbol system **11** (Scheme 4).[12] We shall return to their first use of SmI_2 later (see Scheme 18), but the second application is shown in Scheme 4. Under the initial conditions, iodide **10** underwent a SmI_2-promoted Barbier cyclization to give hemiketal **11** in only 43–68% yield. However, the addition of a catalytic amount of NiI_2, a modification to the SmI_2-mediated Barbier reaction which was first reported by the Kagan research group,[13] resulted in both an enhanced reaction rate and improved efficiency, providing phorbol model **11** in 82–88% yield. While NiI_2 and other transition-metal salts have been employed extensively to catalyze SmI_2-mediated reactions, the cause of the improvements to both the reaction rate and efficiency remains unclear.

One of the more complex examples of the use of the SmI_2-promoted Barbier reaction in total synthesis may be found in the synthesis of variecolin model **16** by Molander et al. (Scheme 5).[14] The sequence of events includes both inter-

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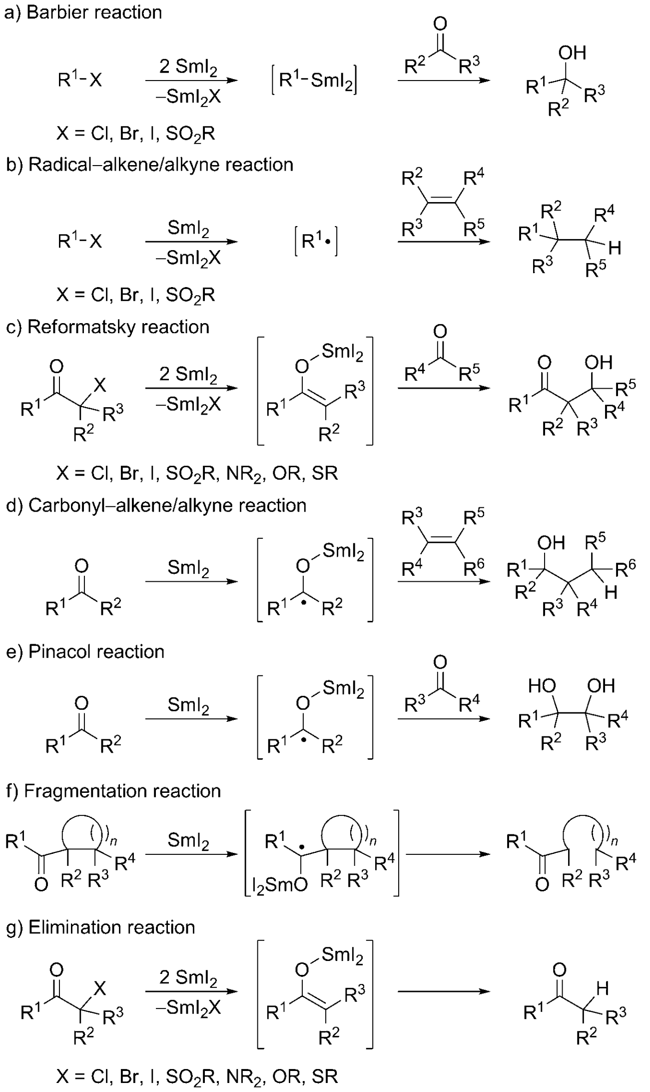
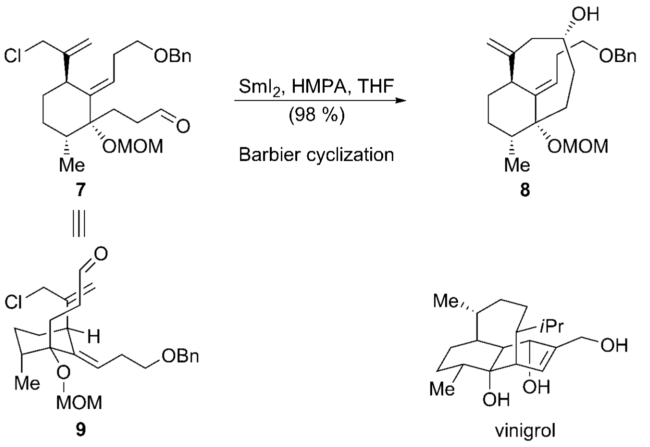
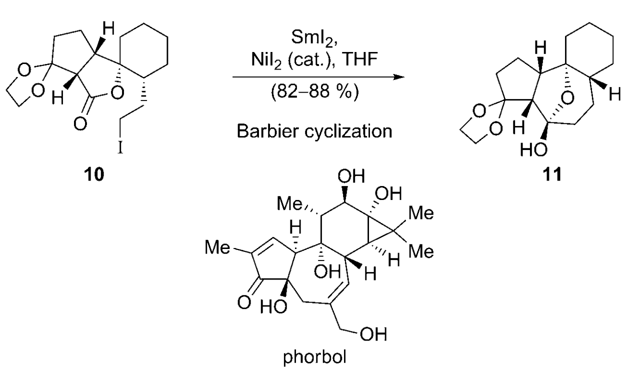


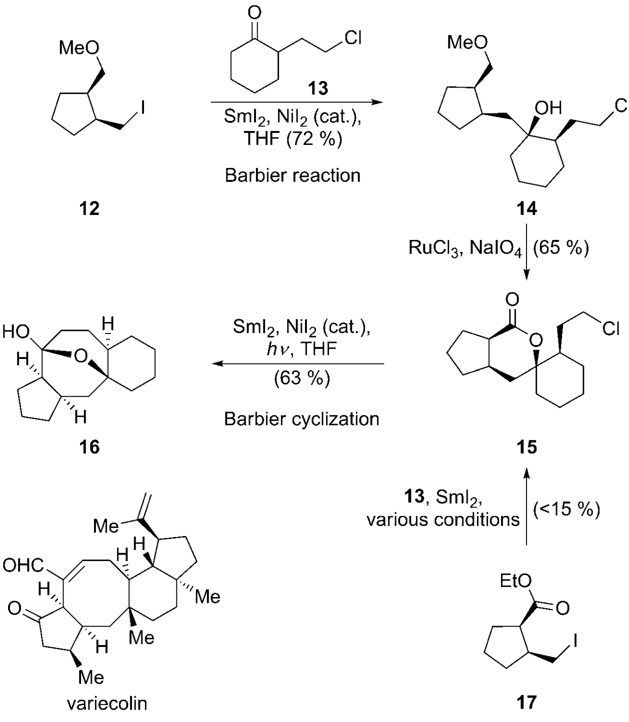
Scheme 2. Some representative SmI$_2$-mediated transformations.



Scheme 3. Formation of the eight-membered ring of vinigrol model **8** by a Barbier cyclization (Matsuda and co-workers, 1997).[11]



Scheme 4. Construction of phorbol system **11** by a Barbier cyclization (Carroll and Little, 2000).[12]



Scheme 5. Synthesis of variecolin model **16** through halide-selective Barbier reactions (Molander et al., 2001).[14]

and intramolecular Barbier reactions, and exploits the different reactivity of SmI$_2$ toward alkyl iodides and chlorides. The direct Barbier coupling of ester iodide **17** and chloro ketone **13** provided the desired coupling product **15** in less than 15 % yield under all reaction conditions screened. This low yield is presumably due to intramolecular attack of the intermediate organosamarium species generated from the primary iodide on the ester functionality of **17** and formation of the resulting cyclobutanone intermediate, which can decompose through various pathways. Therefore, methoxy iodide **12** was employed instead, and, pleasingly, the resulting Barbier reaction, promoted by a stoichiometric amount of SmI$_2$ and a catalytic amount of NiI$_2$,[13] gave tertiary alcohol **14** in 72 % yield. (The product was isolated as a 1:1 mixture of

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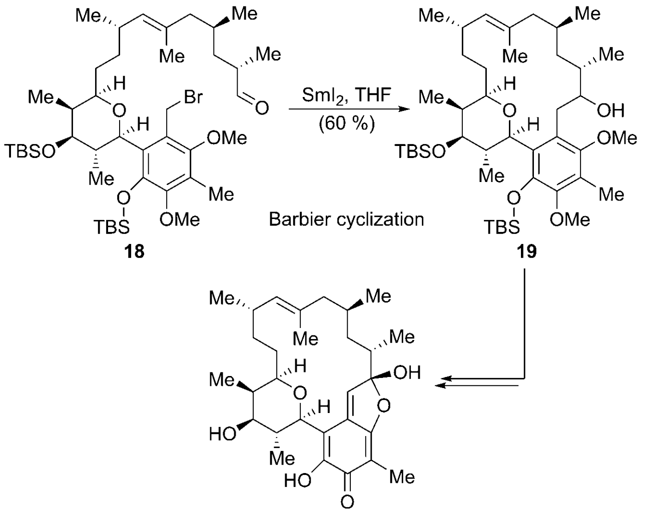
diastereomers since ketone **13** was employed in racemic form.) The primary chloride of **13** was untouched in this reaction, and, therefore, could be carried along in an unprotected form. The methyl ether of **14** was then oxidized by using the Sharpless procedure ($RuCl_3$, $NaIO_4$) to afford, after spontaneous lactonization, spirocycle **15** in 65 % yield. A photoactivated[15] SmI_2-mediated Barbier cyclization then formed the eight-membered ring of **16** in 63 % yield. This example highlights some of the many possible means of tuning both the substrate and the reaction conditions to achieve the desired outcome.

While the SmI_2-mediated Barbier cyclization is most commonly used to construct small- and medium-sized rings, Lowe and Panek recently reported a total synthesis of kendomycin (**20**; Scheme 6) in which this reaction was employed to forge a macrocycle for the first time in natural product synthesis.[16] Treatment of advanced intermediate **18** with a dilute solution of freshly prepared SmI_2 at room temperature led to a smooth macrocyclization and delivered the desired product **19** in 60 % yield. This intermediate was created as a single stereoisomer, but the configuration of the alcohol was inconsequential (and left unassigned) since it was subsequently oxidized to a carbonyl moiety in the course of elaborating **19** into kendomycin (**20**).



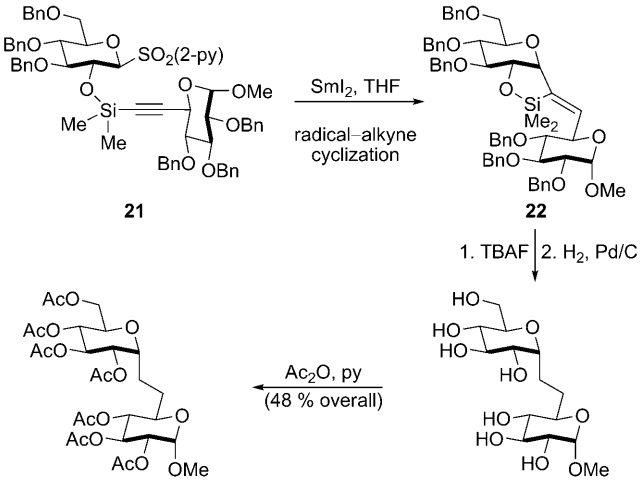
20: kendomycin

Scheme 6. Barbier macrocyclization in a total synthesis of kendomycin (**20**; Lowe and Panek, 2008).[16]

3. Radical–Alkene/Alkyne Reaction

The SmI_2-mediated radical–alkene/alkyne reaction (Scheme 2b) is initiated by a single-electron reduction of a halide or sulfone to generate a radical intermediate which undergoes subsequent addition to an alkene or alkyne. The first example of this transformation was reported in 1981 by Kagan et al. during a study on the mechanism of action of SmI_2.[9] As with other radical carbon–carbon bond-forming processes,[4] the SmI_2-mediated variant is best for the construction of five-membered rings and can employ activated[17] or unactivated alkenes and alkynes. This is a relatively uncommon use of SmI_2, and we shall highlight only one example in this section; however, others may be found as parts of cascade sequences (see Section 9). The use of SmI_2 offers some advantages over more popular reagents such as $n$$Bu_3SnH$/AIBN, including reduced toxicity and improved ease of separation from reagent by-products, which may be valuable in the synthesis of certain fine chemicals.

Beau, Skrydstrup, and co-workers reported the use of SmI_2 as an alternative to the more commonly employed tin hydrides in the construction of C-glycosides.[18] Following a modification of a procedure developed by Stork et al.,[19] a temporary silicon group was used to tether the two glycoside units, as shown in **21** (Scheme 7). Through the course of this project, it was discovered that the use of a 2-pyridinyl sulfone group, instead of the more commonly employed phenyl sulfone moiety, eliminated the need for HMPA. Previously, and in contrast to the above observation, only geminal bissulfones were susceptible to SmI_2 in the absence of HMPA.[20] Therefore, silicon-tethered intermediate **21**, containing a 2-pyridinyl sulfone functionality, was treated with SmI_2 in the absence of HMPA to effect a 5-*exo-dig* cyclization, which gave vinylsilane **22**. Cleavage of the temporary silicon tether (TBAF) and hydrogenation (H_2, Pd/C) with concomitant hydrogenolysis of the benzyl ethers gave methyl-α-*C*-isomaltoside (**23**), which was then masked (Ac_2O, py) as the more readily purified peracetylated disaccharide **24** in a pleasing 48 % overall yield from **21**. This is the first example of a stereoselective synthesis of a disaccharide through a 5-*exo-dig* radical cyclization reaction.



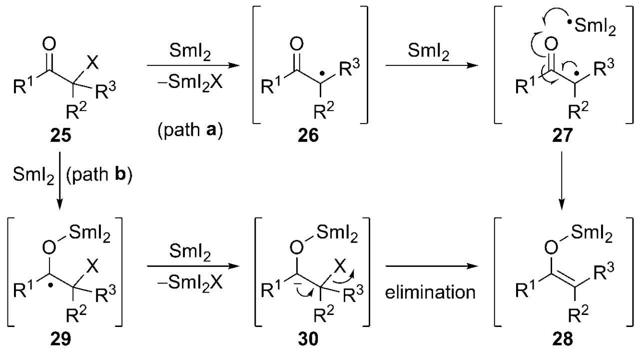
24: methyl-α-C-isomaltoside peracetate

23: methyl-α-C-isomaltoside

Scheme 7. Application of a radical–alkyne cyclization in the synthesis of methyl-α-C-isomaltoside (**23**) and its peracetate (**24**; Beau, Skrydstrup, and co-workers, 1994).[18]

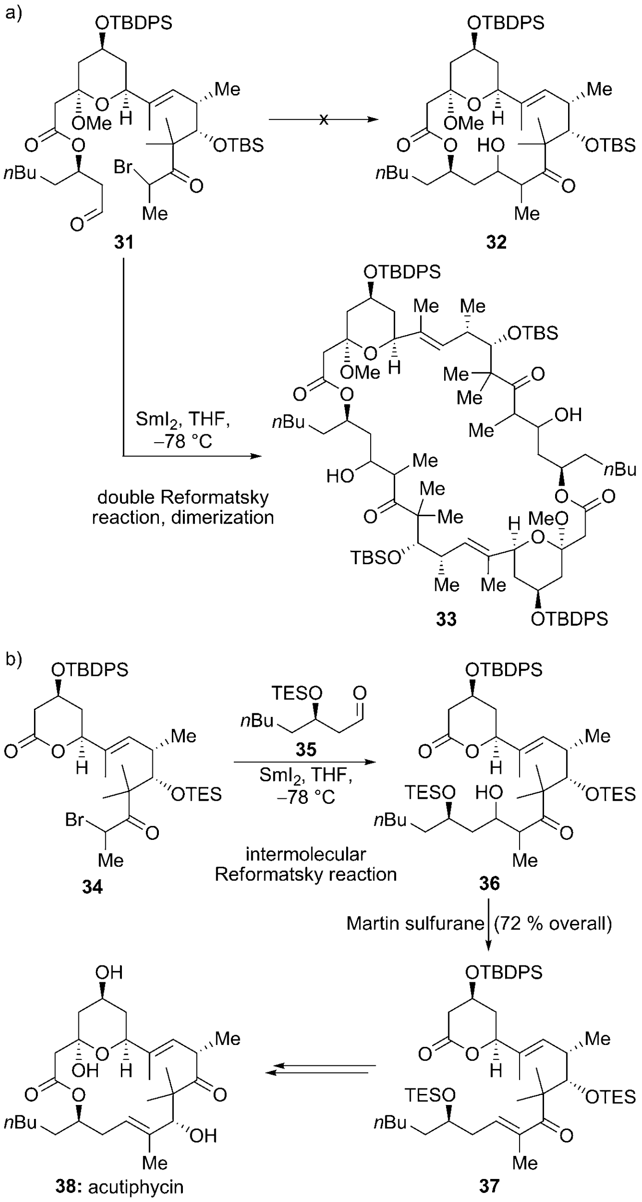
4. Reformatsky and Aldol-Type Reactions

First demonstrated by Kagan and co-workers in 1977,[1] the SmI_2-mediated Reformatsky reaction[21] proceeds through initial reductive cleavage of a heteroatom-containing substituent vicinal to a carbonyl group to form a Sm^{III} enolate, which then attacks a carbonyl functionality in an aldol fashion (Scheme 2c). Depending on the identity of the initial functional group, two possible mechanisms for the formation of the Sm^{III} enolate intermediate may be envisioned.[22] If the starting material (**25**; Scheme 8) possesses a moiety in the α position to the carbonyl or carboxyl functional group that is amenable to a direct reductive cleavage, such as a halide or sulfone, SmI_2 may induce a single-electron reduction to form stabilized radical **26** (path **a**, Scheme 8). A subsequent reduction (see **27**) then provides Sm^{III} enolate **28**, which contains an oxygen–samarium bond. Alternatively, if the vicinal group is not reductively labile, the reaction will proceed through initial formation of ketyl radical **29** (path **b**, Scheme 8), which then undergoes a second reduction to form carbanion **30**. Spontaneous elimination of the vicinal group then generates Sm^{III} enolate **28**. The intermolecular reaction is rarely employed because of the presence of many possible side reactions. In contrast, the intramolecular variant generally results in high yields and stereoselectivities, presumably as a consequence of chelation of the Sm^{III} ion with the two reacting functional groups. Although not as popular as traditional aldol reactions, the SmI_2-mediated Reformatsky reaction has featured prominently in several total syntheses, including instances where the zinc-promoted variant failed to provide the desired product.



Scheme 8. Two possible mechanisms of Sm^{III} enolate formation.

In the original strategy developed by Moslin and Jamison toward acutiphycin (**38**; Scheme 9b),[23] a late-stage intramolecular Reformatsky reaction was envisioned to close the macrocyclic ring of the molecule. However, they discovered that slow addition of α-bromoketone **31** to a dilute solution of SmI_2 yielded not the expected monomeric macrocycle **32**, but the dimeric product **33** (Scheme 9a). Although intramolecular Reformatsky reactions to form medium and large carbocyclic rings were reported to be favored over dimerizations,[24] in this case, dimerization evidently prevailed. This occurred because of various steric interactions, notably at the geminal dimethyl group, conspiring to reduce the rate of the competing cyclization. In their revised strategy (Scheme 9b), enone **37** was targeted. However, common methods of coupling fragments **34** and **35** (or their derivatives) were unsuccessful. For example, a base-promoted aldol reaction favored reaction at the lactone ring system of **34**, and attempts at a Mukaiyama aldol, Horner–Wadsworth–Emmons olefination, or zinc-promoted Reformatsky reaction yielded only starting materials. Inspired by their earlier undesired dimerization (Scheme 9a), Moslin and Jamison proposed a bold intermolecular SmI_2-mediated Reformatsky reaction to couple their fragments. Gratifyingly, α-bromoketone **34** and aldehyde **35** were smoothly joined through the action of SmI_2 at −78 °C to give the expected product **36**, dehydration



Scheme 9. a) An unexpected intermolecular Reformatsky reaction/dimerization and b) an intermolecular Reformatsky reaction used in the total synthesis of acutiphycin (**38**; Moslin and Jamison, 2006).[23]

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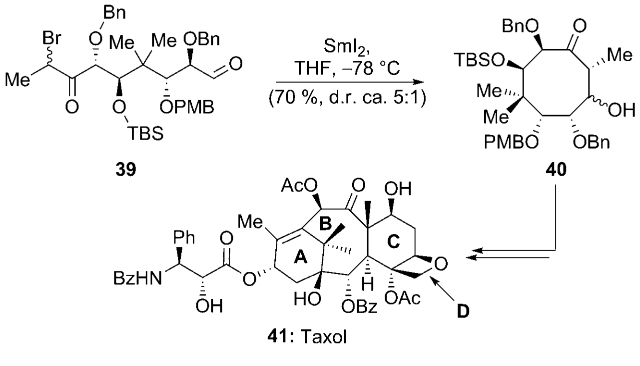
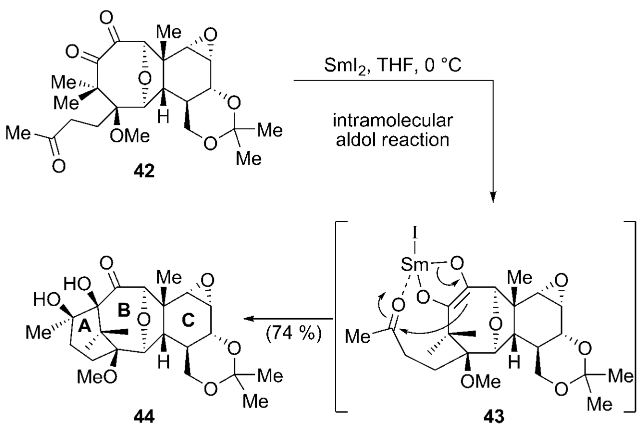
(Martin sulfurane)[25] of which afforded the target enone **37** in 72 % overall yield for the two steps. The latter compound was successfully elaborated to synthetic acutiphycin (**38**).

Another interesting application of the Reformatsky reaction may be found in the total synthesis of Taxol by Mukaiyama et al. (**41**; Scheme 10).[26] They first targeted the formation of the highly congested B-ring precursor **39** as an inconsequential mixture of bromide epimers. An intramolecular SmI_2-promoted Reformatsky reaction then delivered the highly substituted cyclooctane system **40** in 70 % yield, and as an approximately 5:1 ratio of inconsequential epimers at the newly formed secondary hydroxy group. The high efficiency of this process is impressive in light of the heavily functionalized nature of the product and the general difficulty of synthesizing eight-membered carbocyclic rings. Compound **40** was a critical building block for the total synthesis of Taxol (**41**) by Mukaiyama et al.



Scheme 10. An intramolecular Reformatsky reaction to form B-ring system **40** during the total synthesis of Taxol (**41**; Mukaiyama et al., 1997).[26]

Arseniyadis and co-workers also employed a SmI_2-mediated aldol-type reaction in their synthesis of Taxol ABC ring model system **44** (Scheme 11).[27] Thus, treatment of α-diketone **42** with SmI_2 led to the rapid formation of Sm^{III} enediolate **43**,[28] which underwent an intramolecular aldol reaction to give diol **44** in 74 % yield. The observed stereochemistry is proposed to be the result of chelation of the methyl ketone of **43** to the samarium counterion.

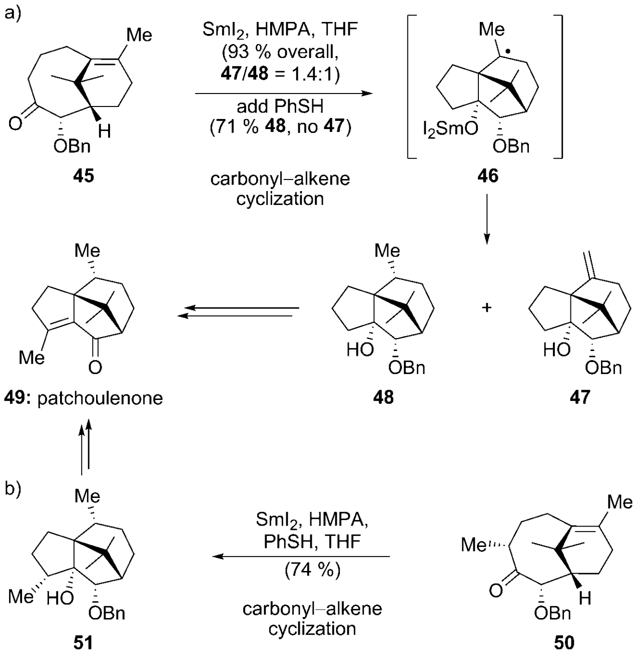


Scheme 11. Formation of the A ring of Taxol ABC model compound **44** through an aldol-type reaction (Arseniyadis and co-workers, 2005).[27]

5. Carbonyl–Alkene/Alkyne and Related Reactions

The carbonyl–alkene/alkyne reaction is arguably the most important SmI_2-mediated reaction in total synthesis. The carbonyl moiety is initially reduced to generate a ketyl radical, which then attacks an unsaturated system (Scheme 2 d). The ketyl–olefin coupling was first described by Molander and Kenny,[29] and variations of this reaction have been explored in many laboratories. As with the radical–alkene/alkyne reaction, the carbonyl–alkene/alkyne reaction may be performed with both activated[30] and unactivated alkenes and alkynes. When the alkene/alkyne partner is part of an α,β-unsaturated carbonyl moiety, alternative reaction pathways such as reductive enolate formation from the α,β-unsaturated system and subsequent aldol coupling may be operative.[31] Intramolecular cyclizations to form four- to eight-membered rings are the most common, but both inter- and intramolecular variants are routinely employed. We shall highlight some particularly elegant and innovative reactions of this general class as applied to targets of varying degrees of complexity, but with so many examples from which to choose our survey is necessarily of rather limited scope.

Banwell et al. commenced the construction of patchoulenone (**49**; Scheme 12 a)[32] with an anion-accelerated oxy-Cope rearrangement to give bridging bicycle **45**. The latter compound was a substrate for an acid-catalyzed Prins reaction which delivered the tricyclic skeleton of patchoulenone in high yield. Although this sequence was rather



Scheme 12. Carbonyl–alkene cyclizations in the a) first- and b) second-generation total syntheses of patchoulenone (**49**; Banwell et al., 1998).[32]

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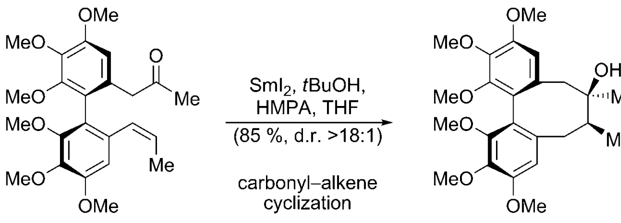
efficient, a challenging hydrogenation was required for the completion of the synthesis and prompted an evaluation of alternative strategies. In particular, they explored a SmI_2-mediated carbonyl–alkene reaction (a reductive process) as a potential replacement for the Prins reaction (a redox-neutral process) in the hope that it might circumvent the problematic hydrogenation. Initially, this route was rather disappointing; although the desired tricyclic core, found in both products **47** and **48**, was formed in 93 % overall yield upon treatment with SmI_2 and HMPA, the reaction gave a 1.4:1 ratio of alkene product **47** (which requires the problematic hydrogenation step) and the desired reduction product **48**. Apparently, formation of a ketyl radical and subsequent ring closure generated tertiary radical **46**, which proceeded to disproportionate under the reaction conditions to give both alkene **47** and the desired product **48** in comparable amounts. With this mechanistic rationale in mind, PhSH was added as a hydrogen-radical donor, and this operationally simple modification resulted in exclusive formation of the reduced product **48** in 71 % yield.

Although the desired product **48** was successfully converted into patchoulenone (**49**), a further refinement allowed a simpler end game. Thus, bicyclic intermediate **50**, which differs from **45** by the presence of an additional methyl group, underwent the same carbonyl–alkene reaction promoted by SmI_2 and PhSH to give the desired product **51** in 74 % yield (Scheme 12 b). Only cleavage of the benzyl ether, oxidation, and dehydration were required for the completion of this second-generation synthesis of patchoulenone (**49**).

The Molander research group employed an 8-*endo-trig* carbonyl–alkene cyclization for the final step of their total synthesis of isoschizandrin (**53**; Scheme 13).[33] The final intermediate, optically active biaryl compound **52**, was treated with SmI_2 in the presence of *t*BuOH and HMPA to provide isoschizandrin (**53**) in 85 % yield as a > 18:1 mixure of diastereomers. The presence of the biaryl moiety is proposed to facilitate this ring closure by both lowering the SOMO/LUMO energy gap and reducing the entropic cost of ring closure by preorganizing at least four of the carbon atoms in the required conformation. The remarkable stereocontrol observed in this reaction is attributable to three factors:

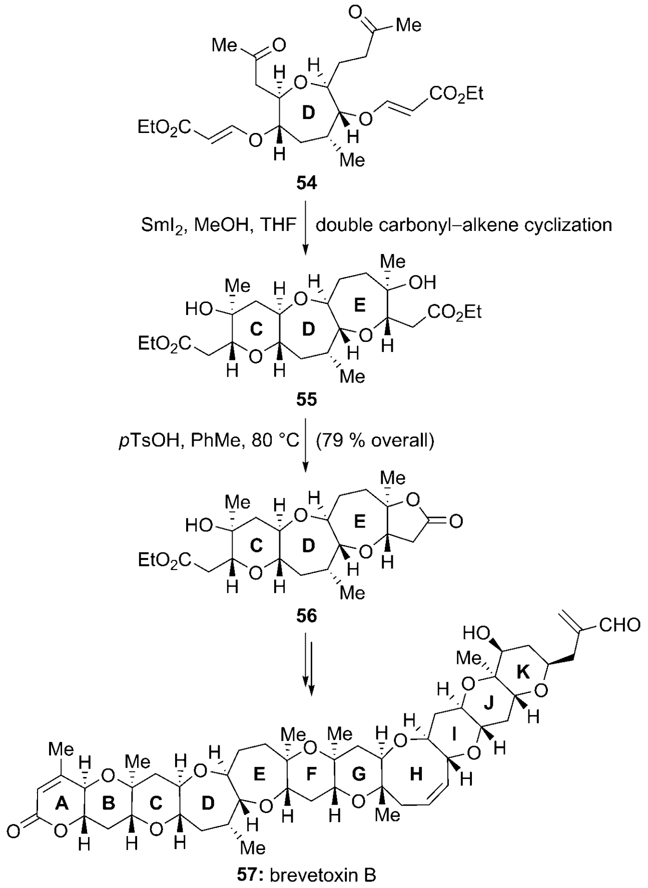
1. Dibenzocyclooctadiene systems normally exist in either the twist-boat-chair or twist-boat conformations, and the presence of the *Z* olefin prevents the adoption of a twist-boat-like conformation in the precursor, thus effectively prescribing the relative stereochemistry of the methine stereocenter.
2. The steric demand of the bound HMPA ligands forces the Sm^{III} ion to adopt a pseudoequatorial position and, therefore, enforces the relative stereochemistry at the newly formed quaternary center.
3. Finally, the preset absolute configuration of the biaryl ring system forces the ketone to approach from above the alkene, thus establishing the absolute sense of stereochemistry observed in isoschizandrin (**53**).



52 **53:** isoschizandrin

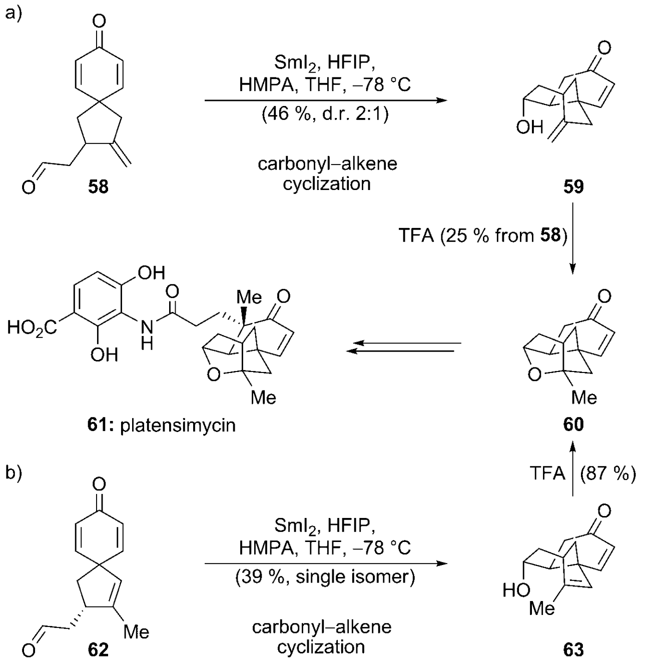
Scheme 13. A carbonyl–alkene cyclization to complete the total synthesis of isoschizandrin (**53**; Molander et al., 2003).[33]

In 1999, Nakata and co-workers reported[34] the use of a SmI_2-mediated carbonyl-α,β-unsaturated ester cyclization reaction for a high-yielding and stereoselective formation of *trans*-fused polytetrahydropyran ring systems, a structural motif that is common in polyether marine natural products. This useful method was soon expanded to the synthesis of *trans*-fused cyclic ethers of other sizes[35] and has been applied by many research groups toward the total synthesis of many natural products, including the marine polyether compounds gambierol,[36] brevetoxin B (**57**; Scheme 14),[37] and brevenal.[38] Nakata and co-workers used this SmI_2-mediated formation of a cyclic ether for the formation of four rings in the synthesis of brevetoxin B (**57**);[37] one example is shown in Scheme 14. Thus, D-ring fragment **54** was treated with SmI_2 in the presence of MeOH to effect concomitant formation of



Scheme 14. A double carbonyl–alkene cyclization in the total synthesis of brevetoxin B (**57**; Nakata and co-workers, 2004).[37]

both the six- and seven-membered cyclic ether rings (the C and E rings, respectively) and give tricyclic intermediate **55** in high yield and with complete stereocontrol. Although the nearly identical nature of the functional groups attached to the C and E rings might have been expected to pose a problem of chemoselectivity, treatment with *p*TsOH resulted in selective lactonization, giving tetracycle **56** in a pleasing 79% overall yield for the two-step process. The latter compound was an important building block for the synthesis of brevetoxin B (**57**) by Nakata and co-workers.

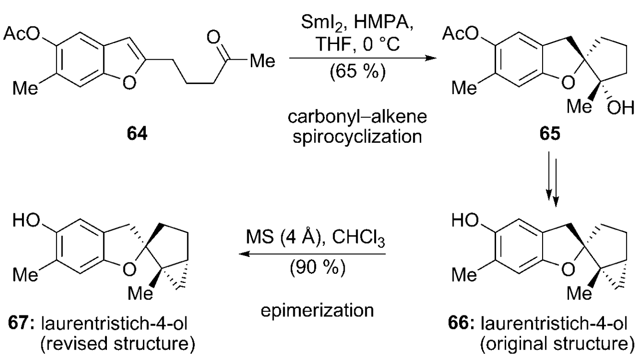


Scheme 15. Carbonyl–alkene cyclizations in a) racemic and b) enantioselective total syntheses of platensimycin (**61**; Nicolaou et al., 2006, 2007).[39,40]

An intramolecular cyclization of an aldehyde onto an enone was employed in the first synthesis of (±)-platensimycin [(±)-**61**; Scheme 15a], disclosed by Nicolaou et al. in 2006.[39] Spirocyclic aldehyde **58** was treated with SmI_2 in the presence of HFIP and HMPA to deliver tricyclic product **59** in 46% yield, and as a 2:1 mixture of epimers at the newly formed hydroxy group. HFIP is not commonly employed in SmI_2-mediated reactions, but it was essential in this reaction to obtain an acceptable yield of product **59**. This is believed to be due to its enhanced acidity ($pK_a = 9.3$) compared with more commonly used proton sources (for example, MeOH or *t*BuOH) and the resulting enhanced activation of the dienone system of **58**. Treatment of tricycle **59** with TFA resulted in intramolecular etherification, thereby completing the construction of the platensimycin core (**60**) in 25% overall yield from **58**. A short series of manipulations then provided (±)-platensimycin [(±)-**61**].

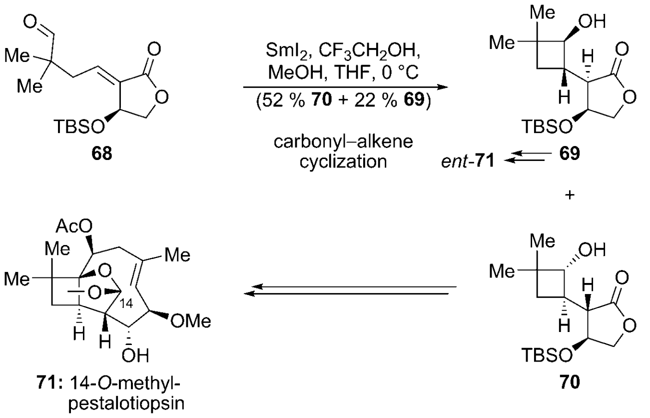
Interestingly, in one of the two asymmetric routes published shortly afterward by Nicolaou et al.,[40] a similar SmI_2-mediated ring closure of dienone **62** (Scheme 15b), which differs from **58** only in the transposition of one olefin, proceeded in 39% yield to deliver the desired product **63**, now as a single stereoisomer. As before, TFA-promoted ring closure gave **60**, and, thereby, platensimycin (**61**), but now in an optically active form. This change in stereoselectivity, presumably caused by subtle differences in the conformations of the substrates **58** and **62**, points to the potentially fickle nature of the stereocontrol in these reactions and the need for thorough experimentation to uncover the optimal substrate and reaction conditions.

Li and co-workers developed a method for the stereoselective formation of 1-oxaspiro[4.4]nonanes, which they employed in their total synthesis of laurentristich-4-ol (**67**; Scheme 16).[41] Thus, benzofuran **64** was treated with SmI_2 and HMPA to afford spirocycle **65** in 65% yield as a single stereoisomer. Cyclopropanation and cleavage of the acetate yielded compound **66**, which possesses the originally proposed structure of laurentristich-4-ol. However, the ^1H NMR spectrum of this substance did not match the published data and, furthermore, the compound was observed to undergo a slow isomerization in chloroform. This isomerization gave the epimeric substance **67**, which was found to be identical to natural laurentristich-4-ol. This epimerization process presumably proceeded by way of a transient benzylic carbocation, and could be accelerated by the addition of 4 Å molecular sieves.

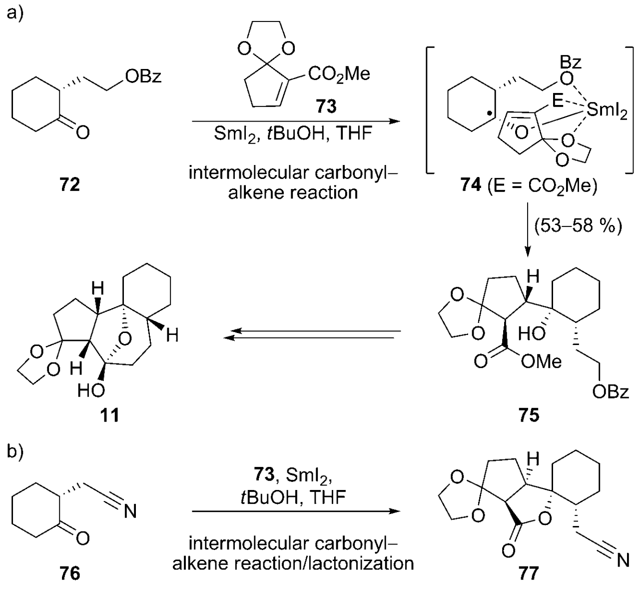


Scheme 16. Application of a carbonyl–alkene cyclization to a total synthesis and structural revision of laurentristich-4-ol (**67**; Li and co-workers, 2008).[41]

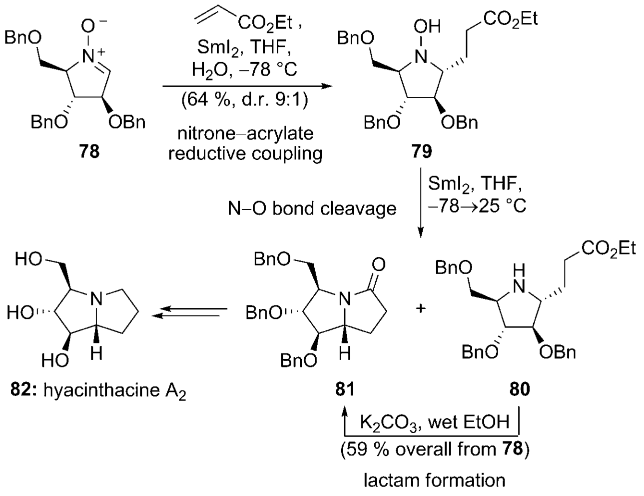
Procter and co-workers employed a carbonyl–alkene cyclization in their total synthesis of both enantiomers of 14-*O*-methyl pestalotiopsin A (**71**; Scheme 17).[42] Thus, aldehyde **68** underwent a SmI_2-mediated cyclization in a THF/MeOH/CF_3CH_2OH mixture to give cyclobutane derivative **70** and the stereoisomeric product **69** in yields of 52 and 22%, respectively. The use of CF_3CH_2OH as a cosolvent was critical to the success of this reaction, and in its absence only a 25% yield of **70** was obtained. This effect was attributed to the ability of CF_3CH_2OH to both moderate the reduction potential of SmI_2 and, by virtue of its greater acidity, rapidly quench the enolates corresponding to the products, thus avoiding the formation of elimination by-products. Since the



Scheme 17. Synthesis of both enantiomers of 14-*O*-methyl pestalotiopsin (**71**) through a carbonyl–alkene cyclization (Procter and co-workers, 2001, 2008).[42]



Scheme 18. a) Carbonyl–alkene fragment coupling in the synthesis of phorbol system **11** and b) a stereochemically distinct coupling result (Carroll and Little, 2000).[12]



Scheme 19. SmI_2-mediated nitrone–acrylate reductive coupling in the total synthesis of hyacinthacine A_2 (**82**; Py and co-workers, 2005).[44]

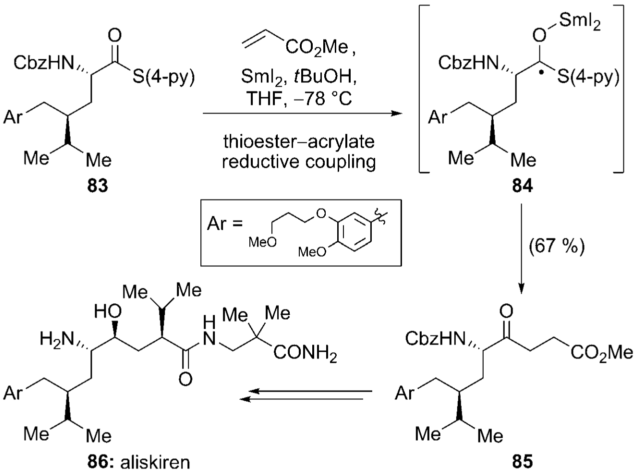
absolute configuration of natural pestalotiopsin A was not known at the onset of this campaign, the formation of diastereomeric products **69** and **70** was viewed as an opportunity to access both antipodes of the pestalotiopsin structure from one starting material. Indeed, **70** was advanced to 14-*O*-methyl pestalotiopsin A (**71**), and **69** to its enantiomer (*ent*-**71**). Unfortunately, the methyl mixed acetal at C14, installed subsequent to the aforementioned SmI_2-mediated ring closure, has proved so far to be resistant to cleavage.

The final step in the synthesis of phorbol system **11** (see Scheme 4) by Carroll and Little was already discussed in Section 2,[12] but we now return to an earlier stage of this synthesis in which an intermolecular carbonyl–alkene addition is employed. Thus, cyclohexanone system **72** and α,β-unsaturated ester **73** were coupled through the action of SmI_2 to give hydroxyester **75** as a single stereoisomer in 53–58% yield (Scheme 18a). The exclusive formation of this sterically congested product is proposed to be due to the ability of the Sm^{III} ion, which is bonded to the initially formed ketyl radical species, to chelate with oxygen atoms of the benzoate ester, methyl ester, and ketal ring as shown in putative intermediate **74**. It is worth noting that a seemingly innocuous change of the side-chain benzoate to a nitrile group, as in **76** (Scheme 18b), led to formation of **77** possessing a different relative stereochemistry, presumably because of the preference to adopt a less-hindered transition state because of a lack of chelation between the Sm^{III} ion and the nitrile group. This result was highly desirable since, unlike **75**, the resulting product **77** possesses the desired relative stereochemistry, and, therefore, does not require a later-stage epimerization for the construction of phorbol system **11**. However, difficulties in manipulating the nitrile moiety ultimately led to the decision to employ the route shown in Scheme 18a.

Carbonyl–alkene coupling has been extended to the use of related functional groups such as nitrones and thioesters. Py and co-workers reported in 2002 an umpolung reaction whereby nitrones attacked carbonyl groups and α,β-unsaturated esters.[43] The application of this reaction to their total synthesis of hyacinthacine A_2 (**82**)[44] is shown in Scheme 19. Thus, reductive coupling of cyclic nitrone **78** with ethyl acrylate, promoted by SmI_2 at −78 °C in the presence of water, gave *N*-hydroxypyrrolidine **79**. This reaction is thought to proceed through initial reduction of the nitrone to generate either a radical or an organosamarium species, which then undergoes conjugate addition with ethyl acrylate. *N*-Hydroxypyrrolidine **79** could be isolated in 64% yield, and as a 9:1 ratio of diastereomers; alternatively, subsequent warming of the reaction mixture in the presence of additional SmI_2 led to cleavage of the labile nitrogen–oxygen σ bond to give a mixture of reduced product **80** and its lactamized form **81**. Exposure of this mixture to K_2CO_3 in wet ethanol effected clean cyclization of amine **80**, thereby delivering lactam **81** in 59% overall yield from **78**. Reduction of the lactam group of

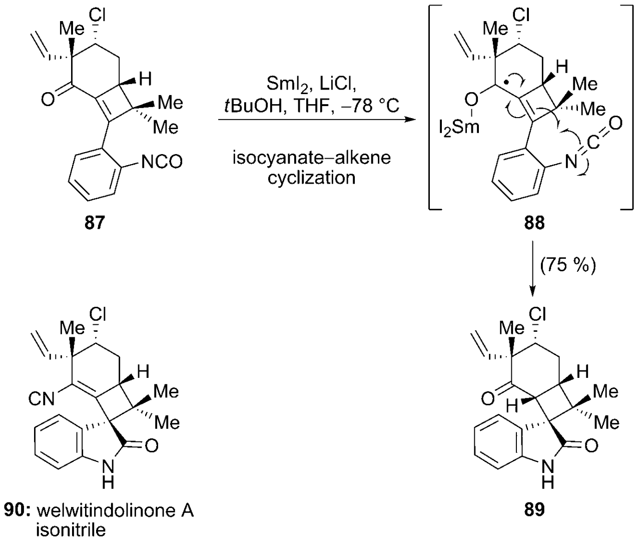
81 and cleavage of the benzyl protecting groups completed the total synthesis of hyacinthacine A_2 (**82**).

A novel thioester–acrylate reductive coupling was utilized as the key step in the total synthesis of aliskiren (**86**; Scheme 20) by Lindsay and Skrydstrup.[45] Thus, addition of SmI_2 to a mixture of thioester **83**, methyl acrylate, and *t*BuOH slowly gave, over the course of six days at −78 °C, coupled product **85** in 67 % yield. This remarkable process is equivalent to a conjugate addition of an acyl radical. However, as acyl radicals derived from α-amino acids are prone to rapid decarbonylation (a side reaction not observed in this process),[46] the intermediate in this transformation is proposed to be ketyl radical **84**, which undergoes conjugate addition and then eliminates a thiolate anion to yield the observed ketone **85**. The latter compound was successfully transformed into aliskiren (**86**).



Scheme 20. SmI_2-mediated reductive thioester–acrylate coupling in the total synthesis of aliskiren (**86**; Lindsay and Skrydstrup, 2006).[45]

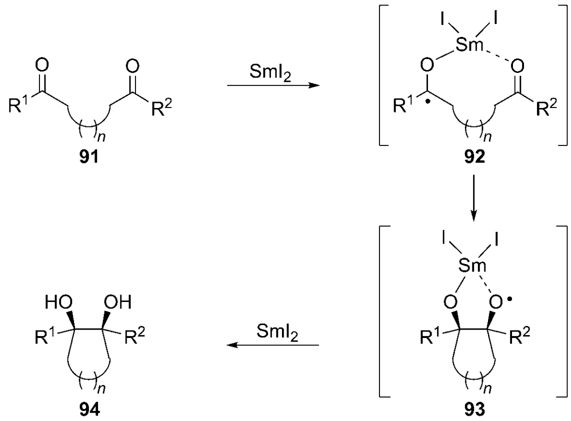
Wood and co-workers reported a novel SmI_2-mediated cyclization to construct oxindoles from isocyanates in the course of their studies toward the synthesis of welwitindolinone A isonitrile (**90**; Scheme 21).[47] Unlike a related intermolecular transformation,[48] this intramolecular variant required the addition of LiCl. This modification increases the reactivity of SmI_2 toward carbonyl compounds, possibly through in situ formation of $SmCl_2$ (a compound that is poorly characterized due to its low solubility), coordination of the chloride ion to SmI_2, and/or activation of the carbonyl group through chelation with the lithium ion.[49] In this manner, tricyclic enone **87** was converted into oxindole system **89** in 75 % yield. On the basis of earlier mechanistic studies, this reaction is believed to proceed by way of delocalized radical **88**, which may attack the neighboring isocyanate moiety. Subsequent reduction of the resulting tetracyclic radical generates, after protonation, oxindole **89**. Alternatively, radical **88** may first undergo a second reduction step to form a carbanion, which then attacks the isocyanate moiety. Despite this mechanistic uncertainty, this methodology was utilized in the construction of many advanced intermediates for the synthesis of welwitindolinone A isonitrile (**90**). However, the synthetic route that ultimately led to the natural product did not employ this route because of an inability to convert the ketone of **89** into the corresponding unsaturated isonitrile found in welwitindolinone A isonitrile (**90**).[50]



Scheme 21. Formation of the welwitindolinone A isonitrile model compound **89** through SmI_2-mediated isocyanate–alkene coupling (Wood and co-workers, 2004, 2008).[47,50]

6. Pinacol-Type Reaction

The pinacol reaction (Scheme 2e) is a reductive coupling of two carbonyl groups to form a diol or other related species.[51] The SmI_2-mediated pinacol reaction was first discovered by Kagan and co-workers in 1983,[52] and in 1988 Molander and Kenny described its application as a ring-closing reaction.[53] The generally accepted mechanism for this process is shown using an intramolecular example in Scheme 22.[53] Thus, reduction of dicarbonyl compound **91** initially results in formation of ketyl radical **92**, which attacks the other carbonyl compound to generate oxygen radical **93**. Rapid reduction of the latter species and quenching of the



Scheme 22. Mechanism of the SmI_2-mediated pinacol reaction.

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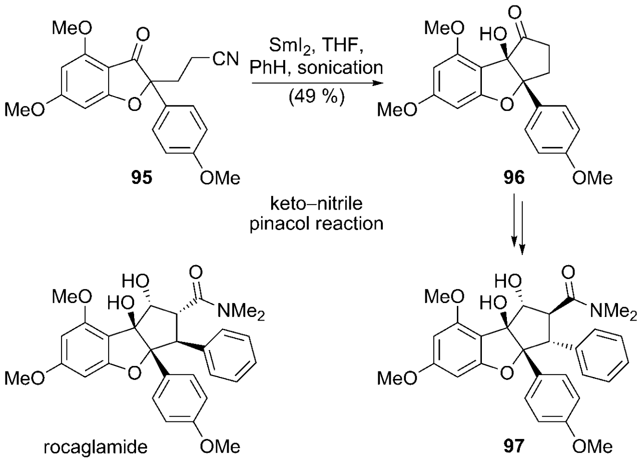
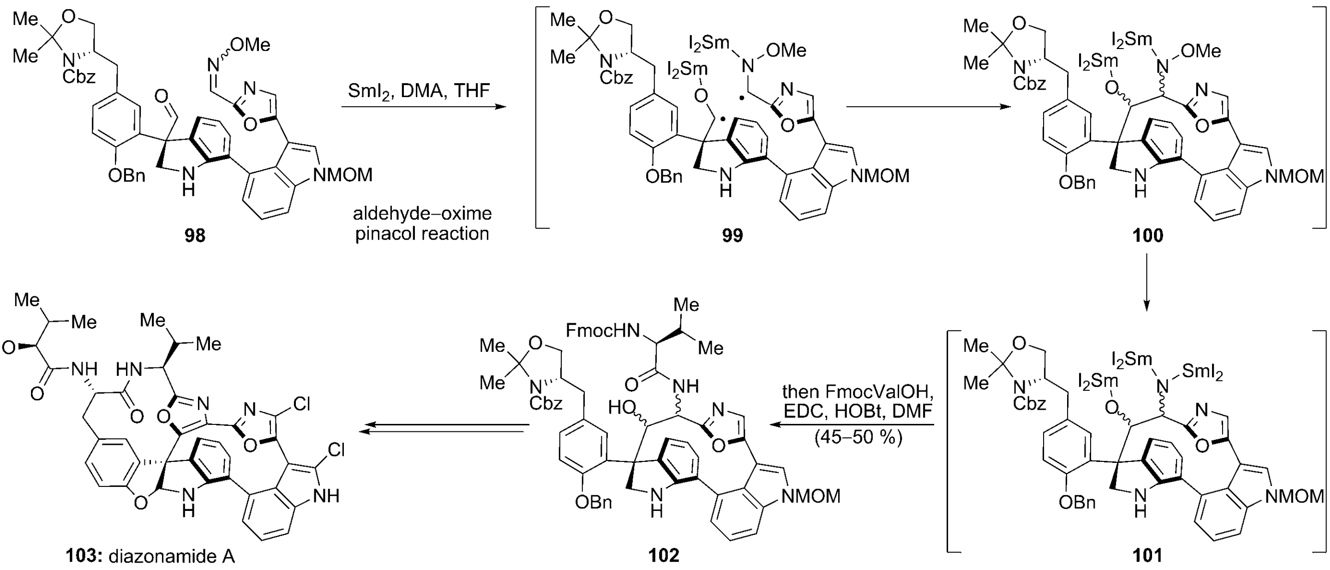
resulting alkoxide delivers pinacol product **94**. Whereas the intermolecular variant generally suffers from poor stereoselectivity, intramolecular examples generally provide a high degree of stereocontrol in favor of a *cis*-diol product as a result of chelation of the initially formed ketyl radical species **92** (see Scheme 22).[53] Additionally, if an alkoxy group is present vicinal to one of the two carbonyl moieties, then the newly formed diol is generally formed *anti* to this alkoxy substituent.[54] Both inter- and intramolecular variants are useful, and rings of various sizes, including macrocycles, may be formed through this process. Besides employing ketones and aldehydes, SmI_2-mediated pinacol-type reactions may also couple a ketone or aldehyde to an oxime,[55] nitrile,[56] or hydrazone.[57]

Kraus and Sy reported one of the earliest examples of a SmI_2-mediated pinacol reaction between a ketone and a nitrile in the course of their total synthesis of the rocaglamide diastereomer **97** (Scheme 23).[58] Thus, treatment of ketonitrile **95** with SmI_2 under sonication provided α-hydroxyketone **96** in 49% yield. Interestingly, other methods for performing the same transformation were tried without success. For example, neither the method of Corey and Pyne (Zn and TMSCl)[59] nor that of Hutchinson and coworkers (Mg and TMSCl)[60] gave detectable amounts of the desired product **96**, with both procedures resulting, instead, in simple ketone reduction. Furthermore, the choice of solvent was critical to the success of this reaction. Under optimal conditions, a 1:10 THF/benzene solvent mixture was used and intermediate **96** was obtained in 49% yield, along with 10% of the secondary alcohol resulting from ketone reduction. However, when a higher percentage of THF was used, formation of the secondary alcohol was favored. α-Hydroxyketone **96** was advanced to compound **97**, a diastereomer of natural rocaglamide.



Scheme 23. Synthesis of rocaglamide diastereomer **97** through an intramolecular keto–nitrile pinacol reaction (Kraus and Sy, 1989).[58]

Nicolaou et al. employed a novel hetero-pinacol macrocyclization reaction as a key step in their second total synthesis of diazonamide A (**103**; Scheme 24).[61,62] This was the first aldehyde–oxime pinacol reaction reported to construct a ring containing more than seven atoms and the first SmI_2-mediated reaction in which the resulting organosamarium intermediate (that is, **101**) was trapped by something more complex than a simple acylating agent. Thus, nonmacrocyclic precursor **98** was treated with SmI_2 in the presence of DMA to forge macrocyclic pinacol product **101**, which was directly coupled (EDC, HOBt) with Fmoc-protected valine to deliver the desired product **102** in 45–50% overall yield as an inconsequential mixture of stereoisomers. This reaction was proposed to proceed through the intermediacy of diradical **99** because the products resulting from simple reduction of the aldehyde or the oxime are observed as by-products in this reaction. A large excess of both SmI_2 (9 equiv) and DMA (36 equiv) was required, and, in the presence of less DMA, the reduction of the N–O bond of intermediate **100** to afford **101** did not readily occur. The



Scheme 24. An aldehyde–oxime pinacol macrocyclization in the second total synthesis of diazonamide A (**103**; Nicolaou et al., 2001, 2003).[61]

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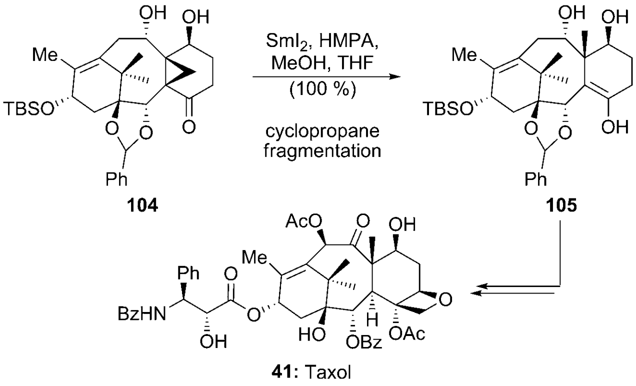
isolated product **102** was successfully transformed into diazonamide A (**103**).

7. Fragmentation Reactions

The fragmentation of cyclopropane and cyclobutane systems (Scheme 2 f) is a useful means of installing complex ring systems or congested substituents,[63] and SmI_2 has been employed for this purpose on several occasions. A different class of fragmentation reactions that has also been promoted by SmI_2 involves the cleavage of heterocycles containing weak heteroatom–heteroatom σ bonds, such as the N−O and N−S bonds in isoxazoles and isothiazoles.

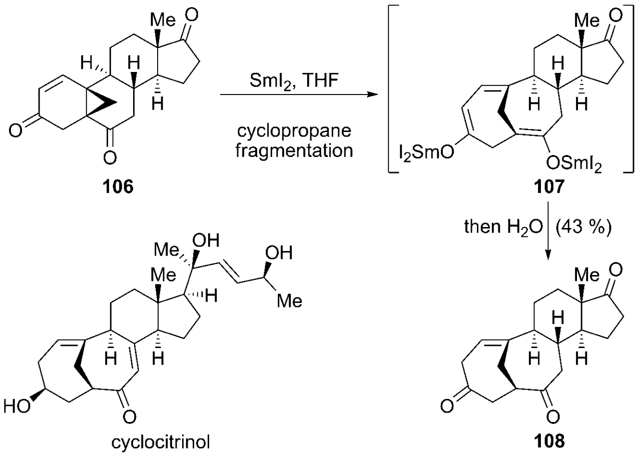
Kuwajima and co-workers used a SmI_2-mediated cyclopropane fragmentation reaction to install a methyl group during their total synthesis of Taxol (**41**).[64] Thus, the congested cyclopropane-containing intermediate **104** was treated with SmI_2 in the presence of HMPA and MeOH, a reagent combination which induced a cyclopropane fragmentation to deliver enol **105** in quantitative yield (Scheme 25).



Scheme 25. Cyclopropane fragmentation in the total synthesis of Taxol (**41**; Kuwajima and co-workers, 1998).[64]

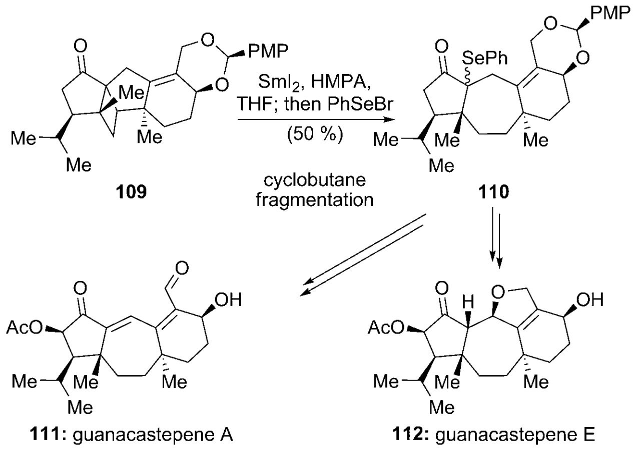
Interestingly, the enol group of the latter compound did not readily tautomerize to the corresponding ketone, presumably because protonation from the more accessible β face of the enol would generate a large amount of strain. Related enols were found to be unstable to air, and the presence of the silyl and benzylidene protecting groups on **105** was essential to stabilize the enol and allow subsequent manipulations to give Taxol (**41**).

Schmalz and co-workers called upon a SmI_2-promoted cyclopropane fragmentation reaction in their synthesis of cyclocitrinol system **108** (Scheme 26).[65] Cyclopropanated steroid **106** was treated with SmI_2 to effect a fragmentation, thus constructing the bridging ring system of **107**, which possesses two Sm^{III} enolate functional units. After quenching with water, cyclocitrinol system **108** was obtained as the only product in 43 % yield. It is interesting to note that although multiple products of this reaction may be envisioned, only one was observed to any appreciable extent, perhaps because of differences in the strain energies of the possible products.



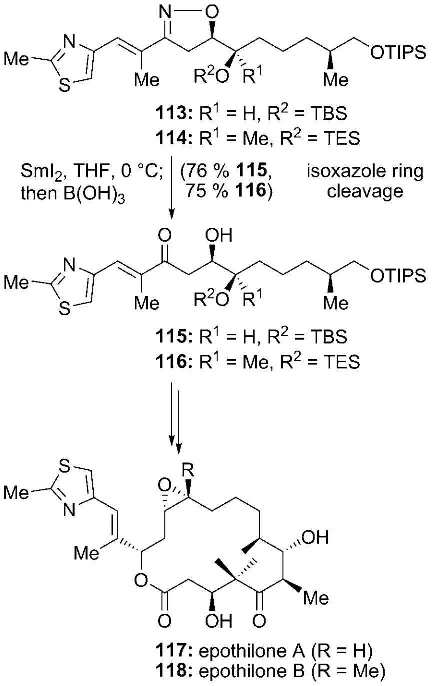
Scheme 26. Synthesis of cyclocitrinol system **108** through a cyclopropane fragmentation/ring expansion (Schmalz and co-workers, 2007).[65]

Shipe and Sorensen exploited a SmI_2-mediated fragmentation of a strained cyclobutane system to form a seven-membered ring during their synthesis of guanacastepenes A (**111**) and E (**112**; Scheme 27).[66] Cyclobutane system **109**, the product of an intramolecular [2+2] photo-cycloaddition, was treated with SmI_2 that was activated by HMPA, and the resulting Sm^{III} enolate was trapped with PhSeBr to give ring-expanded product **110** in 50 % yield as an inconsequential mixture of diastereomers. Alternatively, employing a dissolving metal reduction (Li/NH_3) with an isopropylidene acetal in place of the benzylidene acetal resulted in a 46 % yield of the corresponding product after trapping with PhSeBr. Intermediate **110** was successfully elaborated to both guanacastepenes A (**111**) and E (**112**).



Scheme 27. A cyclobutane fragmentation/ring expansion in the total synthesis of guanacastepenes A (**111**) and E (**112**) (Shipe and Sorensen, 2002).[66]

Bode and Carreira employed a different type of SmI_2-induced fragmentation in their synthesis of epothilones A (**117**) and B (**118**; Scheme 28).[67] They approached what they



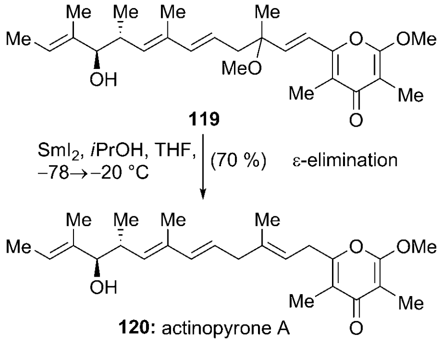
Scheme 28. SmI_2-promoted isoxazole ring cleavage in the total synthesis of epothilones A (**117**) and B (**118**; Bode and Carreira, 2001).[67]

identified as the stereochemically and functionally most challenging portion of the epothilone structure with a [3+2] cycloaddition of a nitrile oxide to fashion isoxazoline **113**. Subsequent SmI_2-induced cleavage of the nitrogen–oxygen bond and boric acid promoted hydrolysis of the imine gave β-hydroxyketone **115** in 76 % yield. This two-step sequence is a useful surrogate for the aldol reaction. Hydroxyketone **115** was elaborated to epothilone A (**117**). Epothilone B (**118**) was synthesized in an analogous manner (**114**→**116**→**118**).

8. Elimination Reactions

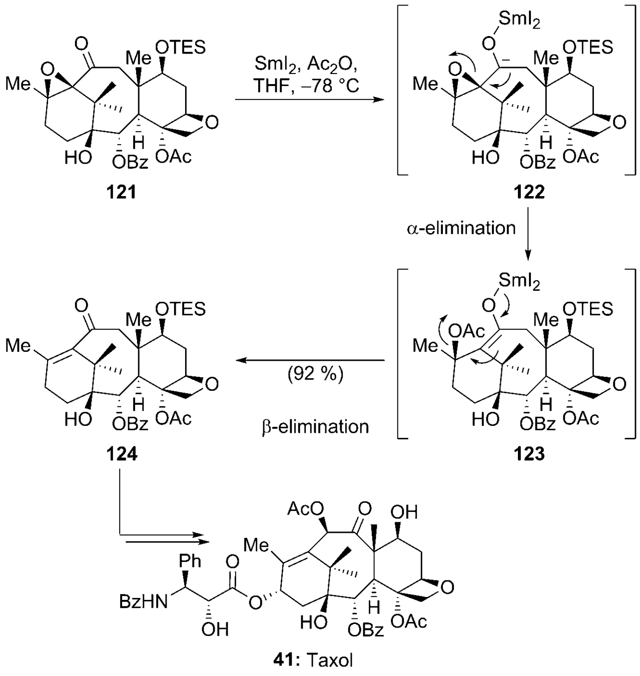
Elimination reactions mediated by SmI_2 are most commonly used in total synthesis to expel substituents vicinal to carbonyl groups (Scheme 2g); indeed, every Reformatsky reaction is such an elimination wherein the intermediate enolate has been diverted for a purpose other than simple quenching. However, SmI_2-induced eliminations may also occur farther away if the carbonyl-containing moiety is part of a conjugated system.[68] Furthermore, SmI_2 has come to light as a means to selectively cleave protecting groups.[69] In many ways, this latter group of eliminations is the same reaction as heterocycle fragmentations, exemplified by the isoxazoline cleavage in the synthesis of epothilone by Bode and Carreira (see Scheme 28).

Tatsuta and co-workers utilized SmI_2 in a reductive deconjugation reaction in the final step of their total synthesis of actinopyrone A (**120**; Scheme 29).[70] This reaction was a technically insightful part of their synthetic route, for the natural substance had been reported to be rather unstable.[71] This instability is likely due to the presence of the olefinic bond just one position away from conjugation with the pyrone system. Therefore, the Tatsuta research group employed a fully conjugated system until the final step, during which elimination of a methoxy group from **119**, induced by SmI_2 in the presence of *i*PrOH, effected ε-elimination to give actinopyrone A (**120**) as an 88:12 mixture of *E* and *Z* isomers. Subsequent chromatographic separation delivered pure actinopyrone A (**120**) in a satisfying 70 % yield. To the best of our knowledge, this is the first example of a SmI_2-mediated ε-elimination that is not driven by ring strain (for example, epoxide opening).



Scheme 29. Synthesis of actinopyrone A (**120**) through an ε-elimination of a methoxy group (Tatsuta and co-workers, 2006).[70]

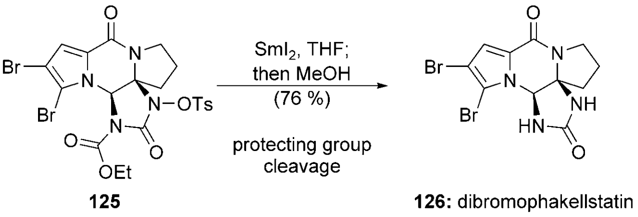
In their total synthesis of Taxol (**41**), Danishefsky and co-workers used SmI_2 to reductively eliminate an α,β-epoxyketone and generate the corresponding enone.[72] Thus, treatment of epoxide **121** with SmI_2 and Ac_2O at −78 °C presumably effected two successive single-electron reductions of the ketone to form carbanion **122** (Scheme 30). Fragmen-



Scheme 30. Epoxide elimination in the total synthesis of Taxol (**41**; Danishefsky and co-workers, 1995).[72]

tation of the neighboring epoxide ring afforded, after acetylation, β-acetoxy system **123**. This unstable species underwent a second elimination reaction under the same conditions to deliver enone **124** in 92% yield. The latter compound was successfully elaborated to synthetic Taxol (**41**).

The action of SmI_2 promoted the simultaneous cleavage of two nitrogen protecting groups in the total synthesis of dibromophakellstatin (**126**; Scheme 31) by Lindel and co-workers.[73] Alkaline hydrolysis of their protected compound **125** (NaOEt) did not afford the desired product, but, rather, resulted in cleavage of the cyclic urea system and displacement of the tosylamine moiety by an ethoxide group. In contrast, the use of 2.5 equivalents of SmI_2 led to rapid and clean (95% yield) deprotection of the tosylamine group. With 5 equivalents of SmI_2, slow cleavage of the carbamate also proceeded, thus providing dibromophakellstatin (**126**) in 76% overall yield. The use of even more SmI_2 (7.5 equiv) resulted in selective debromination at the C2 position of the pyrrole ring of dibromophakellstatin.

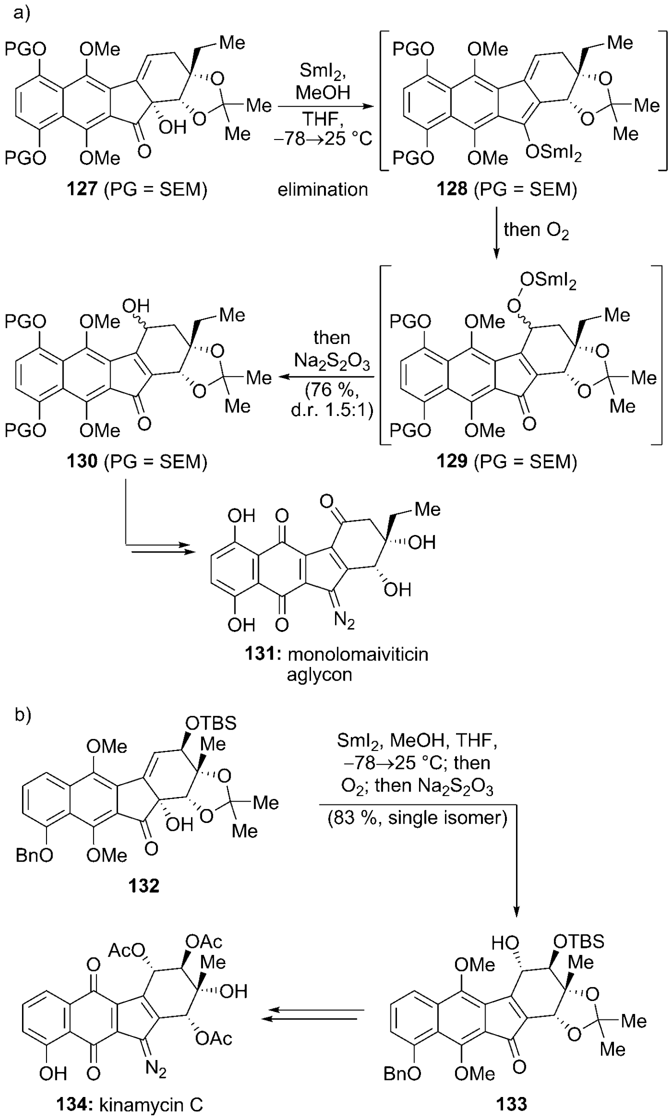


Scheme 31. Synthesis of dibromophakellstatin (**126**) through SmI_2-mediated double deprotection (Lindel and co-workers, 2005).[73]

9. Cascade Reactions

Many of the most impressive examples of the use of SmI_2 in total synthesis are those in which an entire sequence of reactions is promoted in cascade fashion.[6] These elegant cascade reactions can create significant molecular complexity by forming rings and/or creating multiple stereogenic centers. In this section, a selection of SmI_2-promoted cascade reactions in total synthesis will be discussed to further highlight the power of this reagent in terms of efficiency and selectivity. To be sure, even more impressive applications will be conceived and executed in the future.

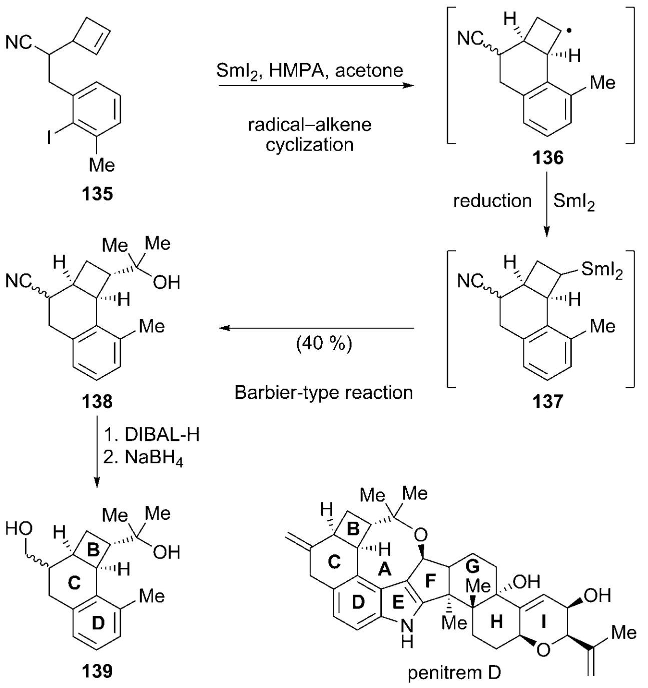
In a recent synthesis of the lomaiviticin aglycon monomeric unit **131** (Scheme 32a),[74] Nicolaou et al. developed an unusual SmI_2-promoted isomerization. Treatment of α-hydroxyketone **127** with SmI_2 in the presence of MeOH gave access to conjugated Sm^{III} enolate **128**, which was then treated with O_2 gas to generate hydroperoxide species **129**. Quenching with $Na_2S_2O_3$ then furnished the regioisomeric hydroxyketone **130** in 76% yield as an inconsequential 1.5:1 mixture of diastereomers. Hydroxyketone **130** was successfully transformed into the lomaiviticin aglycon monomeric unit **131**.



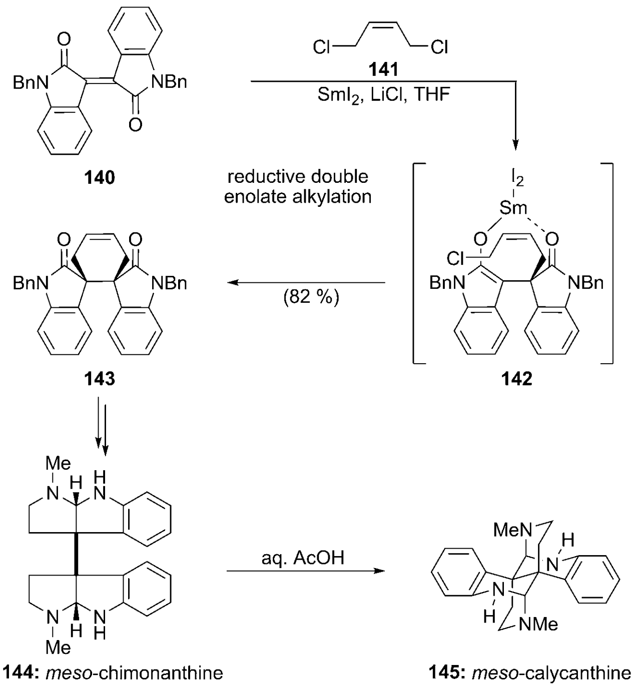
Scheme 32. a) A SmI_2-mediated isomerization in the synthesis of monolomaiviticin aglycon (**131**) and b) application in the total synthesis of kinamycin C (**134**; Nicolaou et al., 2009).[74,75]

This protocol was also applied by Nicolaou et al. to improve the synthesis of kinamycin C (**134**; Scheme 32b).[74,75] Thus, exposure of α-hydroxyketone **132** to the newly defined reaction conditions (SmI_2, MeOH; then O_2; then $Na_2S_2O_3$) gave the desired isomeric product **133** as a single stereoisomer in 83% yield. This constitutes a marked improvement over the previously reported four-step procedure, which generated the requisite alcohol **133** in 55% overall yield from α-hydroxyketone **132**.

An unusual radical/ionic crossover reaction[5] was executed by Curran and co-workers in their synthesis of penitrem D model compound **139** (Scheme 33).[76] This cascade sequence commenced with generation of an aryl radical from iodide **135**, which proceeded to attack the tethered cyclobutene system to form cyclobutyl radical **136**. This transformation could be induced by nBu$_3$SnH or SmI_2 with comparable efficiency, but the ability of SmI_2 to subsequently



Scheme 33. Synthesis of the BCD ring system (**139**) of penitrem D through a radical–alkene cyclization/Barbier-type reaction cascade (Curran and co-workers, 2004).[76]

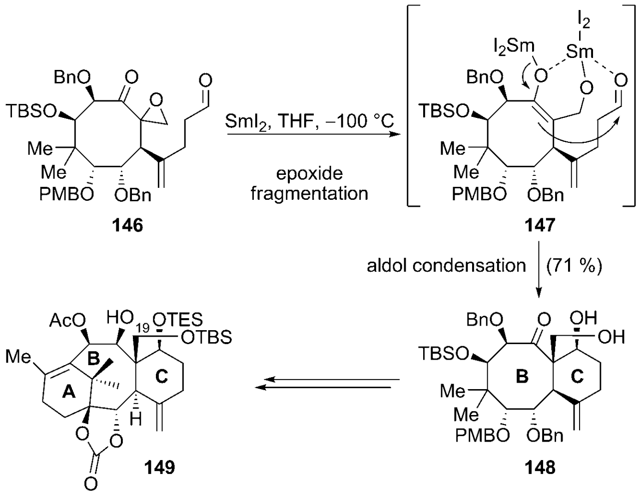


Scheme 34. A reductive double enolate alkylation in the total synthesis of *meso*-chimonanthine (**144**) and *meso*-calycanthine (**145**; Link and Overman, 1996).[77]

lead to an ionic reaction allowed an impressive propagation of the cascade. Thus, further reduction of secondary radical **136** afforded organosamarium species **137**, which underwent a Barbier-type reaction with acetone to give tertiary alcohol **138** in 40% overall yield for the cascade sequence. The latter compound was obtained as a 1:1 mixture of nitrile stereoisomers, reflecting the diastereomeric mixture of starting cyclobutene **135**. Quenching of radical intermediate **136** prior to the Barbier reaction represented a major side reaction, and the corresponding compound was also isolated in 40% yield. Although the yield of desired product **138** was moderate, this example, nonetheless, highlights the potential for powerful cascade reactions that utilize the ability of SmI$_2$ to access both radical and polar reactions. Reduction of nitrile **138** (1. DIBAL-H; 2. NaBH$_4$) gave primary alcohol **139**, the structure and stereochemistry of which was verified by X-ray crystallographic analysis to be that corresponding to the BCD system of penitrem D.

The total synthesis of *meso*-chimonanthine (**144**; Scheme 34) and *meso*-calycanthine (**145**, Scheme 34) by Link and Overman employed a novel enolate alkylation cascade to generate a spirocyclic cyclohexene system.[77] Initially, the reaction of isoindigo **140** with dichloride **141** in the presence of SmI$_2$ with or without HMPA did not yield any of the desired cyclohexene system **143**, forming instead only the corresponding dihydroisoindigo. Double alkylation of the latter compound with dichloride **141**, promoted by *n*BuLi or KHMDS, gave access to the desired product **143** contaminated with an isomeric cyclobutane system resulting from S$_N$2′ ring closure. Remarkably, however, it was discovered that the use of LiCl as an additive enabled a clean reductive double alkylation of **140** to deliver in a single operation cyclohexene **143** in 82% yield with nearly complete stereocontrol (d.r. >20:1). This reaction is thought to proceed through the intermediacy of an initially formed samarium dienolate, monoalkylation of which gives **142**. An intramolecular alkylation then provides the observed product **143**, with the samarium ion of the Sm^{III} enolate serving to chelate the lactam oxygen atom and thus induce formation of the *meso* isomer (see **142**). The role of LiCl is not clear, but its profound impact on the reaction pathway cannot be explained by a simple salt effect, since the addition of KCl does not induce the same results. Possible explanations for the role of LiCl include aggregation resulting from addition of the halide salt, a change in the coordination sphere of the samarium metal, or transmetalation from samarium to lithium.[49] Cyclohexene **143** was converted into *meso*-chimonanthine (**144**), which was then transformed upon exposure to aqueous acetic acid into *meso*-calycanthine (**145**) by following the published procedure.[78]

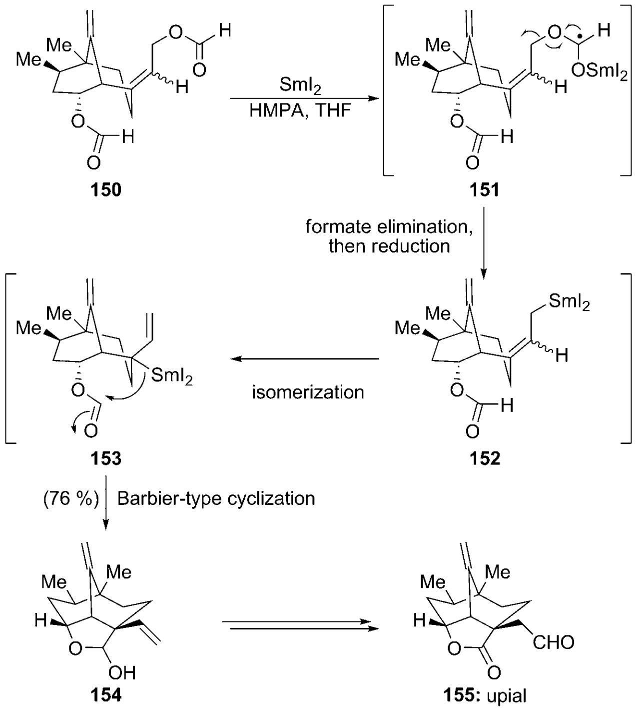
Having previously employed SmI$_2$ to generate the eight-membered B ring of Taxol (see Scheme 10), Mukaiyama and co-workers again turned to this reagent in their synthesis of 19-hydroxy taxoid **149** (Scheme 35), a compound which they hoped would enable the development of analogues with superior water solubility.[79] The desired sequence of events involved initial formation of Sm^{III} enolate **147** through fragmentation of the epoxide ring of **146** followed by an intramolecular aldol cyclization to generate diol **148**. Although many different additives were investigated, it was discovered that optimal conditions, which gave diol **148** in 71% yield, involved the use of SmI$_2$ at −100 °C in the absence



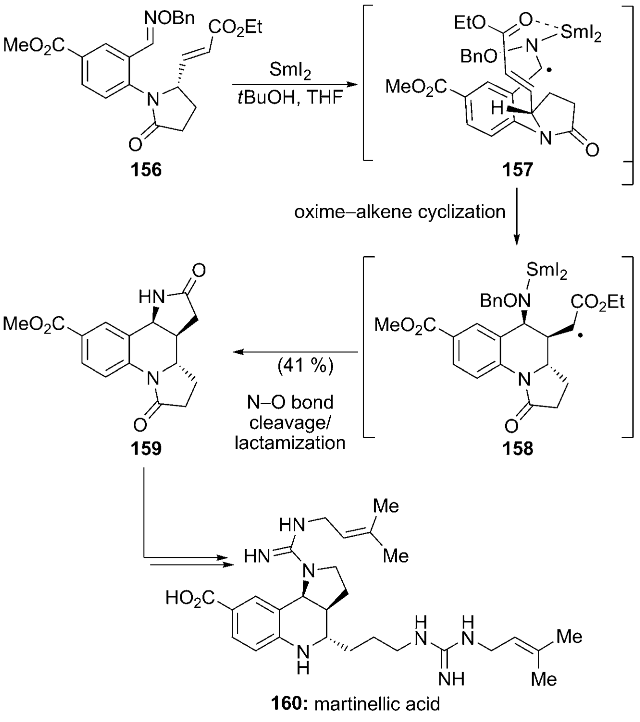
Scheme 35. Synthesis of the C ring of a 19-hydroxy taxoid (**149**) through an epoxide fragmentation/aldol cyclization cascade (Mukaiyama and co-workers, 2004, 2005).[79]

of additives. Two diastereomers were also isolated: one epimeric at the newly formed quaternary center (10% yield), and one with the opposite sense of stereochemistry at both of the newly formed stereogenic centers (15% yield). Interestingly, the final possible diastereomer, namely one epimeric at the secondary alcohol, was not observed under any conditions. Increasing the temperature of the reaction led to a decrease in the yield of the desired BC ring system **148**, with no increase in the formation of the stereoisomeric products. The use of additives such as H_2O, MeOH, *i*PrOH, and HMPA at −78 °C resulted in a reduced yield of diol **148** and a higher yield of an epimeric product. Diol **148** was advanced to TBS-protected 19-hydroxy taxoid **149**.

In their total synthesis of upial (**155**; Scheme 36),[80] Yamada and co-workers utilized an elimination and Barbier cyclization reaction sequence to construct the complex tricyclic core of the molecule. Originally developed for the synthesis of spirocyclic γ-butyrolactones,[81] the versatility and adaptability of this cascade sequence was demonstrated in this application. Thus, treatment of diformate **150** with SmI_2 in the presence of HMPA produced hemiacetal **154** in a pleasing 76% yield. The proposed mechanism for this reaction commences with the selective formation of a ketyl radical at the allylic formate to give intermediate **151**. Elimination of formate then yields a primary allylic radical, which is further reduced by SmI_2 to afford organosamarium species **152**. This compound is geometrically incapable of reacting through an intramolecular Barbier-type cyclization, and thus it isomerizes to tertiary organosamarium intermediate **153**, cyclization of which delivers hemiacetal **154**. The ionic nature of the cyclization is supported by deuterium labeling studies performed during the development of the original cascade. A short sequence of manipulations converted hemiacetal **154** into upial (**155**).



Scheme 36. An elimination/Barbier cyclization cascade in the total synthesis of upial (**155**; Yamada and co-workers, 1993).[80]



Scheme 37. A SmI_2-promoted cyclization cascade in the total synthesis of martinellic acid (**160**; Naito and co-workers, 2008).[82]

In the total synthesis of martinellic acid (**160**; Scheme 37),[82] Naito and co-workers used a radical addition–cyclization–elimination (RACE) reaction which could be promoted by $n\mathrm{Bu}_3\mathrm{SnH}$ or SmI_2 to establish the dihydropyrroloquinoline core of the natural product. Having previously developed the methodology for the RACE reaction between oxime ethers and α,β-unsaturated esters,[83] they

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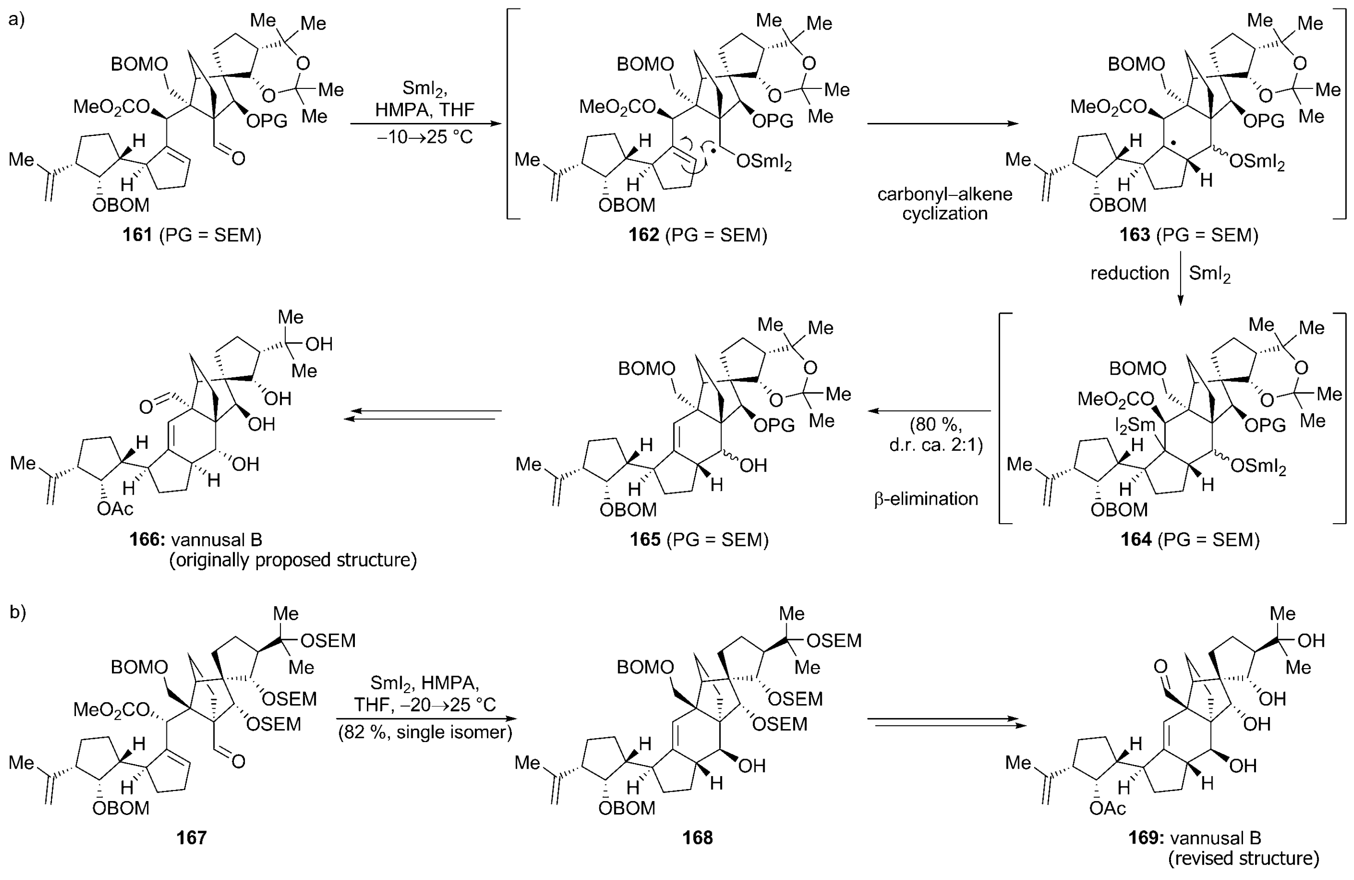
treated precursor **156** with nBu$_3$SnH and AIBN in refluxing benzene to produce desired product **159** in 29% yield, along with five related products in 26% combined yield. While the desired product could be purified through careful chromatographic separation from the other substances, the use of SmI_2 was investigated to determine whether the yield and selectivity of this cascade sequence could be further improved. Gratifyingly, treatment of precursor **156** with SmI_2 in the presence of tBuOH produced markedly improved results, with the desired product **159** now isolated in 41% yield and with only one other diastereomer obtained (10% yield). Chelation of a Sm^{III} ion between the ester and the nitrogen atom of the initially formed α-aza radical species (see **157**) was proposed to account for the significantly enhanced diastereoselectivity of the SmI_2-mediated variant of the reaction. This apparently enforced the desired *cis* orientation of the two functional groups during the oxime–alkene cyclization to generate **158**, which underwent subsequent reductive cleavage of the nitrogen–oxygen bond and spontaneous lactamization to deliver the observed product **159**. This compound was then converted into martinellic acid (**160**) in a straightforward manner.

A SmI_2-mediated cascade sequence involving a ketyl–olefin cyclization followed by a carbonate elimination was employed by Nicolaou et al. to forge a key cyclohexene ring in their synthesis of the originally assigned structure of vannusal B (**166**; Scheme 38a).[84] This ring was formed through the reaction of aldehyde **161** with SmI_2 in the presence of HMPA, and provided the observed product **165** in 80% yield as an approximately 2:1 mixture of secondary alcohol epimers. As this sequence generated the undesired stereochemistry at the ring fusion, the secondary alcohol was subsequently subjected to elimination to correct this problem. Thus, the mixture of epimeric products was inconsequential. The proposed mechanism of this reaction involves formation of a ketyl radical to give **162**, which then reacts in a ketyl–olefin cyclization to produce tertiary radical **163**. Further reduction gives transient organosamarium species **164**, which undergoes elimination of the neighboring methyl carbonate group to deliver the observed product **165**. Interestingly, the presence of the SEM protecting group on the hydroxy group neighboring the aldehyde appears to be important for the efficiency of this process. The use of an acetonide protecting group produces the desired product in significantly lower yield, with the major product resulting from fragmentation of the bicyclo[2.2.1]heptane system followed by elimination of the carbonate. Correction of the ring-fusion stereochemistry and completion of the synthesis provided a substance that possessed the assigned structure of vannusal B (**166**), but did not match the authentic natural material.

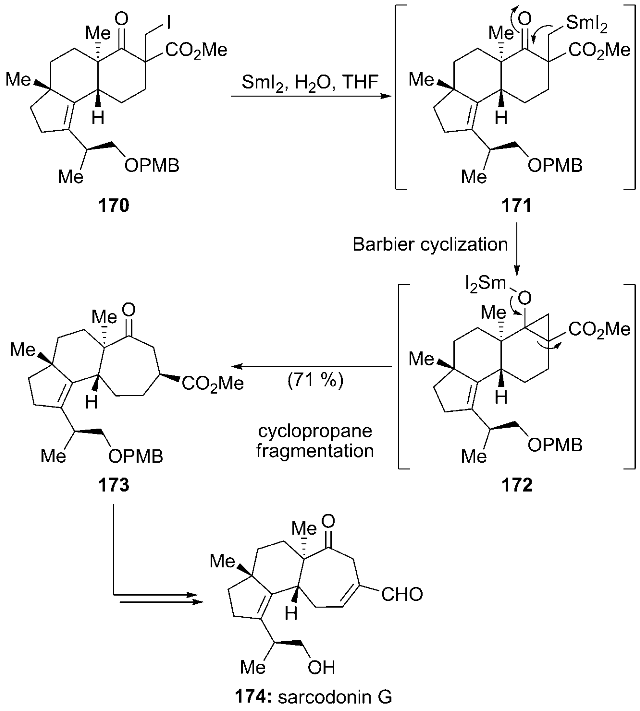
The true identity of vannusal B was recently determined by Nicolaou et al. through total synthesis.[85] In their synthesis



Scheme 38. SmI_2-mediated ring closure in the total synthesis of the a) originally proposed (**166**) and b) corrected (**169**) structures of vannusal B (Nicolaou et al., 2008, 2009).[84,85]

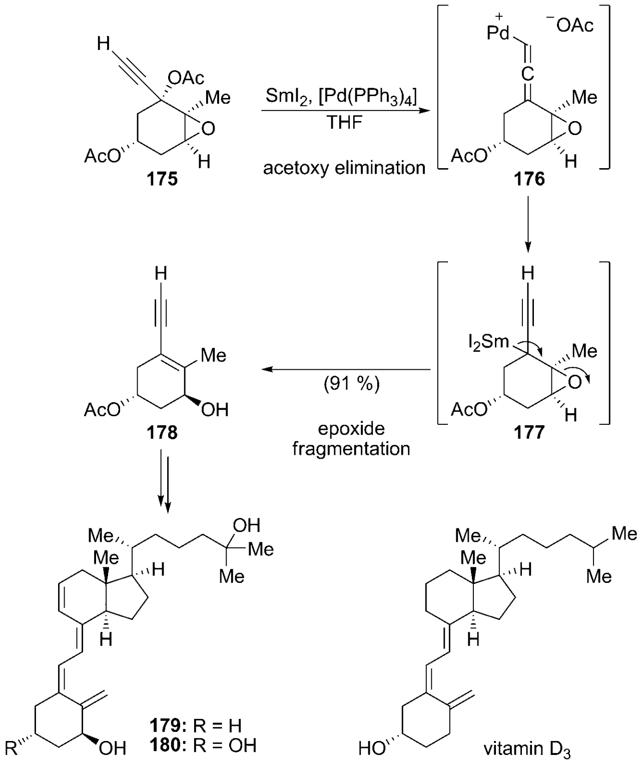
of the corrected structure of vannusal B (**169**; Scheme 38b), the SmI_2-mediated ring closure from aldehyde **167** was even more efficient since it led directly to the desired stereoisomer of cyclization product **168** in 82% yield with complete stereocontrol. Importantly, since no inversions of stereocenters were required, only a few manipulations were needed to complete the synthesis of the corrected structure of vannusal B (**169**).

Piers et al. used SmI_2 to perform a ring expansion and construct the seven-membered ring of sarcodonin G (**174**; Scheme 39).[86] Previous studies indicate that the ring expansion most likely occurs through a Barbier–cyclopropane fragmentation reaction pathway.[87] Initial reduction of the carbon–iodine bond of **170** produces a primary radical, which can be subsequently reduced to give organosamarium intermediate **171**. Barbier cyclization of the organosamarium species onto the nearby ketone generates cyclopropane **172**. It has also been proposed that this intermediate may arise from radical coupling between a ketyl radical generated at the ketone and one generated from the primary iodide.[88] In either case, fragmentation of **172** then delivers cycloheptanone **173**, which was isolated in 71% yield. Interestingly, the mixture of epimeric starting materials **170** was inconsequential, and the product was obtained as a single stereoisomer. A straightforward sequence of manipulations on cycloheptanone **173** gave sarcodonin G (**174**). This was the first application of this useful ring-expansion cascade sequence in a total synthesis. Nakada and co-workers later employed the same methodology successfully in their total syntheses of cyathane diterpenoids allocyathin B_2[89] and erinacine B.[90]



Scheme 39. SmI_2-mediated ring expansion in the total synthesis of sarcodonin G (**174**; Piers et al., 2000).[86]

An unusual cascade reaction incorporating both palladium catalysis and SmI_2-mediated reduction was featured in a total synthesis of two 9,11-dehydrovitamin D_3 analogues (**179** and **180**; Scheme 40) reported by Aurrecoechea and co-workers.[91] Reaction of diacetate **175** with SmI_2 in the presence of 2.3 mol% $[Pd(PPh_3)_4]$ produced the desired product **178** in 91% overall yield. The first step in this cascade reaction, an acetoxy elimination developed by Inanaga and co-workers,[92] was proposed to proceed through formation of allenylpalladium intermediate **176** by oxidative addition of the Pd^0 catalyst to propargylic acetate **175**. SmI_2 can then reductively regenerate the Pd^0 catalyst and form an allenic organosamarium intermediate, which presumably is in equilibrium with the isomeric propargyl organosamarium species **177**. Epoxide opening, possibly assisted by another molecule of SmI_2 serving as a Lewis acid, can then proceed to provide allylic alcohol **178**. This compound was a useful building block in the synthesis of 9,11-dehydrovitamin D_3 analogues **179** and **180**. Prior to this publication, organosamarium species generated from organopalladium intermediates had not been demonstrated to undergo similar elimination or fragmentation reactions; in previous studies, only protonation of the resulting organosamarium species had been observed.[92] This unique cascade serves as an elegant example of how SmI_2 can be combined with other reagents to promote novel and advantageous reactions.



Scheme 40. A palladium- and samarium-mediated cascade sequence in the synthesis of vitamin D_3 analogues **179** and **180** (Aurrecoechea and co-workers, 1989).[91]

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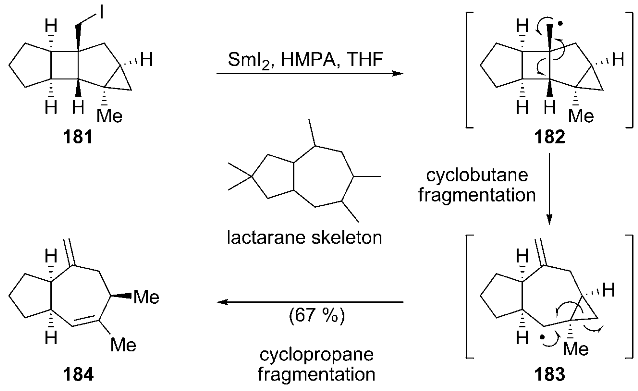
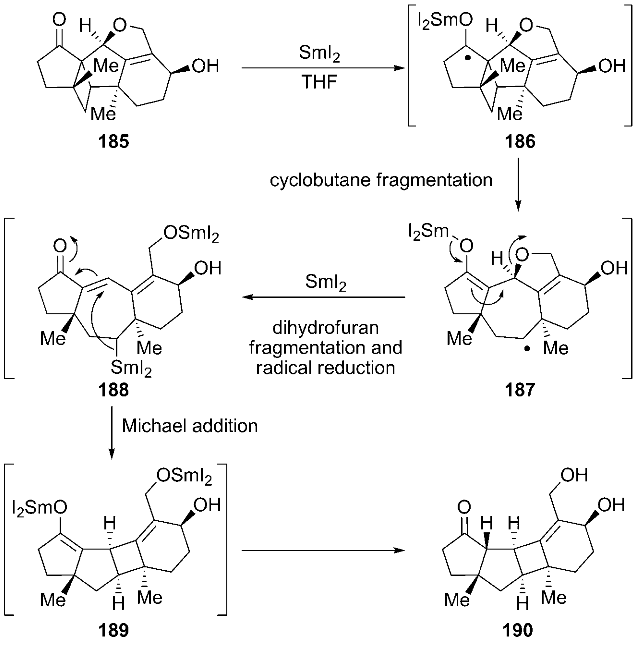
A cyclobutane/cyclopropane fragmentation sequence was developed by Lange and Corelli for the synthesis of sesquiterpene lactarane system **184** (Scheme 41).[93] Thus, the target compound was formed from tetracyclic iodide **181** in 67% yield. The mechanism through which this transformation is proposed to occur commences with an initial reduction of the carbon–iodine bond by SmI_2 in the presence of HMPA to produce primary radical **182**. Fragmentation of the strained cyclobutane system of **182** then produces cycloheptyl radical **183**, which is poised to fragment the nearby cyclopropane system and form a primary radical. Further reduction to an organosamarium species and quenching of the anion then yields the desired product **184**. Attempts to produce a [6.3.0]bicycloundecane system (namely, the eight-membered ring analogue) by the same method were unsuccessful, only resulting in deiodination. However, a related cascade sequence suitable for the formation of [6.3.0]bicycloundecane systems had previously been disclosed by Lange and Gottardo.[94]



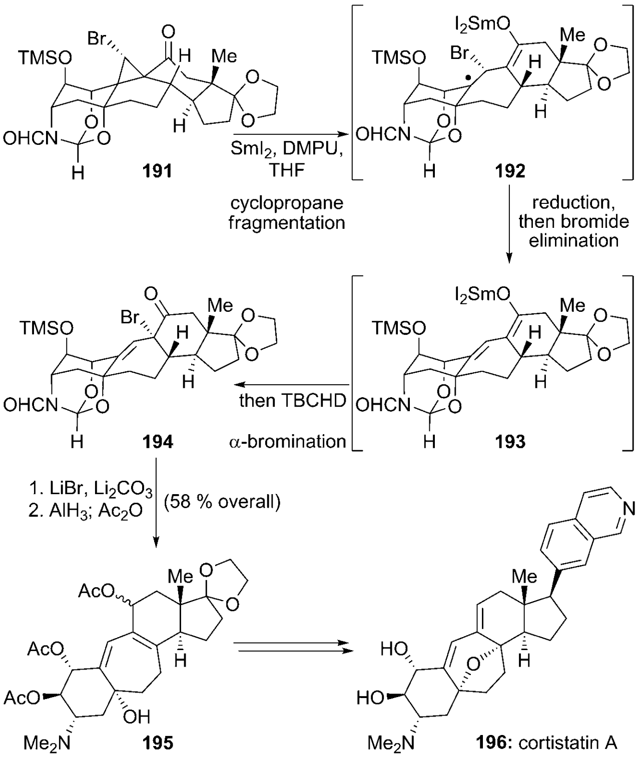
Scheme 41. Synthesis of lactarane system **184** through a cyclobutane/cyclopropane fragmentation cascade (Lange and Corelli, 2007).[93]

A remarkable cascade sequence mediated by SmI_2 was encountered by Shipe and Sorensen during their model studies toward guanacastepenes A and E (**111** and **112**; see Scheme 27).[66] Thus, reaction of SmI_2 with pentacycle **185** produced the unexpected compound **190** as the only isolable product (Scheme 42). The proposed mechanism of this reaction entails formation of ketyl radical **186** followed by cyclobutane fragmentation as desired to produce cycloheptyl radical **187**. Rupture of the dihydrofuran ring adjacent to the Sm^{III} enolate and reduction of the radical then yielded diorganosamarium species **188**, protonation of which would have rendered the desired product. Instead, an unexpected transannular conjugate addition onto the enone moiety occurred to produce the cyclobutane-containing ring system **189**, which upon protonation gave the isolated product **190**. This sequence of events suggested that intermediate **188** exists only transiently and, therefore, would not be useful in practice. However, this realization led to the application of the cyclobutane fragmentation in the completion of the total synthesis of guanacastepenes A and E (**111** and **112**; see Scheme 27).



Scheme 42. An unexpected cascade sequence during a guanacastepene model study (Shipe and Sorensen, 2006).[66]

In their synthesis of the unusual steroid cortistatin A (**196**; Scheme 43), Baran and co-workers discovered a novel fragmentation/elimination/bromination cascade sequence mediated by SmI_2.[95] Thus, treatment of bromoketone **191**

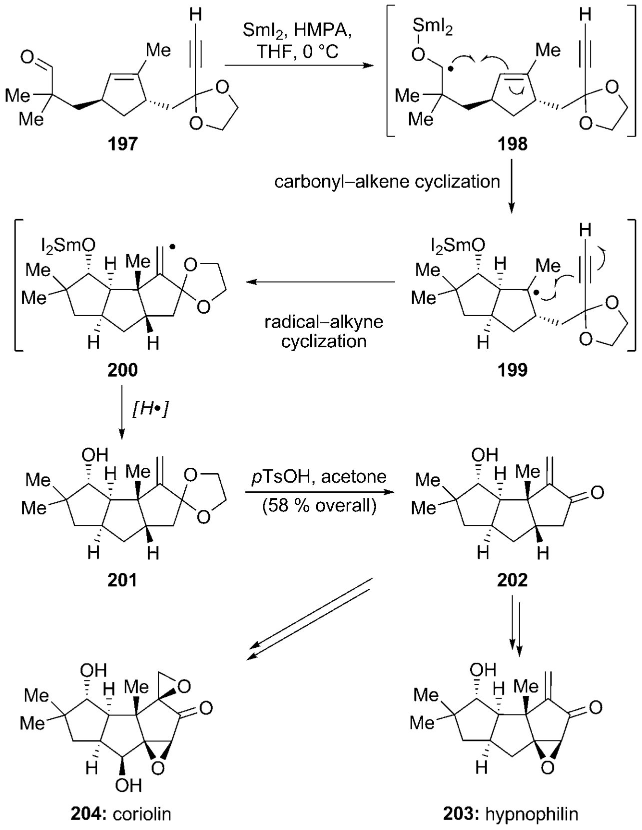


Scheme 43. A SmI_2-promoted fragmentation/elimination/bromination cascade in the total synthesis of cortistatin A (**196**; Baran and co-workers, 2008).[95]

with SmI_2 in the presence of the additive DMPU followed a few minutes later by addition of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD)[96] afforded α-bromoketone **194**. Although TBCHD is not a common brominating agent, it was found after a comprehensive search that its use gave superior yields and diastereoselectivities than did traditional reagents such as NBS. The reaction likely proceeded through initial formation of a ketyl radical followed by cyclopropane fragmentation to generate tertiary radical **192**. The latter can undergo another single-electron reduction and bromide elimination to give extended enolate **193**. Alternatively, a direct SmI_2-mediated reductive bromide cleavage might also have generated **193**. Finally, bromination at the α position delivered the desired product **194**.

Subsequent elimination of bromide (LiBr, Li_2CO_3), AlH_3-promoted reduction, and acetylation (Ac_2O) gave advanced intermediate **195** in an impressive 58 % overall yield from bromoketone **191**. Pentacycle **195** was then elaborated in a short reaction sequence to cortistatin A (**196**).

Curran and co-workers completed a total synthesis of hypnophilin (**203**) and a formal synthesis of coriolin (**204**; Scheme 44) through the use of a SmI_2-mediated radical cascade reaction.[97] In a model system, $n\mathrm{Bu_3SnH}$/AIBN was found to be superior to other reagents, including SmI_2 in the presence of HMPA. These conditions, however, required an additional manipulation in the preparation of the precursor, namely the formation of a mixed phenylthio(trimethylsilyl)oxy acetal. Frustratingly, aldehyde **197** was not amenable to conversion into hemithioacetals or hemiselenoacetals, and, therefore, was not suitable for the cyclization conditions defined in the model study. Remarkably, whereas SmI_2 and HMPA was an inferior reagent combination for the model cyclization, it promoted the successful cyclization of aldehyde **197** to give the desired product **201** in high yield and diastereoselectivity. Acidic cleavage of the ketal produced tricyclic system **202** in 58 % overall yield for the two-step sequence. This cascade reaction proceeds through initial formation of ketyl radical **198** from aldehyde **197**. A carbonyl–alkene cyclization generates the *cis*-fused ring of tertiary radical **199**, which can then undergo a radical–alkyne cyclization. As only 1.3 equivalents of SmI_2 were required, the resulting vinyl radical **200** is proposed to abstract a hydrogen radical from the solvent (THF) rather than undergo further reduction. This supposition is also supported by the absence of deuterium incorporation upon quenching with D_2O. HMPA was found to be an essential additive in this reaction, as only an 11 % yield of the desired product was obtained without this cosolvent. Furthermore, substituting HMPA with the less-bulky DMPU resulted in lower stereocontrol. Tricyclic compound **202** was successfully converted into both hypnophilin (**203**) and coriolin (**204**).



Scheme 44. A SmI_2-promoted radical cascade in the total synthesis of hypnophilin (**203**) and formal synthesis of coriolin (**204**; Curran and co-workers, 1988).[97]

Another radical cascade fashioned two rings in the synthesis of paeonilactone B (**210**; Scheme 45 a) by Kilburn and co-workers.[98] Thus, treatment of methylenecyclopropyl ketone **205** with SmI_2 in the presence of HMPA and *t*BuOH provided the desired fused bicyclic system **209** in 63 % overall yield as a 10:1 mixture of tertiary alcohol epimers. Initial formation of a ketyl radical (**206**) followed by 5-*exo-trig* cyclization produced primary radical **207**, which readily underwent fragmentation of the cyclopropane ring to afford cyclohexyl radical **208**. A 5-*exo-dig* cyclization and subsequent reductive quenching of the resulting vinyl radical delivered the observed product **209**. HMPA was an essential additive for this process—in its absence, the yield dropped to 20 % and the diastereomeric ratio of the product was 1.3:1 in favor of **212**. The use of DMPU was also ineffective—although the resulting yield was acceptable (40 %), the undesired product epimer **212** predominated (d.r. 1.5:1). Tertiary alcohol **209** was elaborated in a short reaction sequence to paeonilactone B (**210**).

Interestingly, treatment of the epimeric methylenecyclopropyl ketone **211** (Scheme 45 b) under the same reaction conditions provided the epimeric product **212** in 79 % yield as a > 30:1 mixture of diastereomers. The stereochemical course of these reactions can be rationalized by a transition state in the carbonyl–alkene cyclization that places the bulky HMPA-bound alkoxysamarium species in a pseudoequatorial position. The use of the sterically less demanding additive DMPU in place of HMPA erodes the stereoselectivity of the reaction. A few years later, Kilburn and co-workers detailed the use of this cascade reaction on an allylic ether substrate, which they employed in their total synthesis of 6-*epi*-paeonilactone A[99] and construction of the eudesmane sesquiterpenoid skeleton.[100]

An unusual and impressive catalytic, oxidative SmI_2-mediated cascade was reported by Corey and Wang in their

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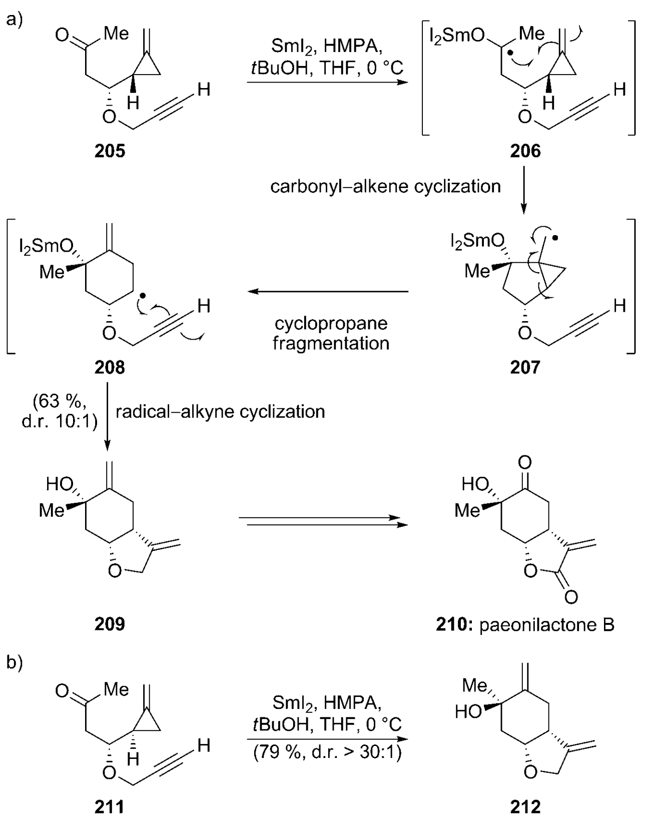
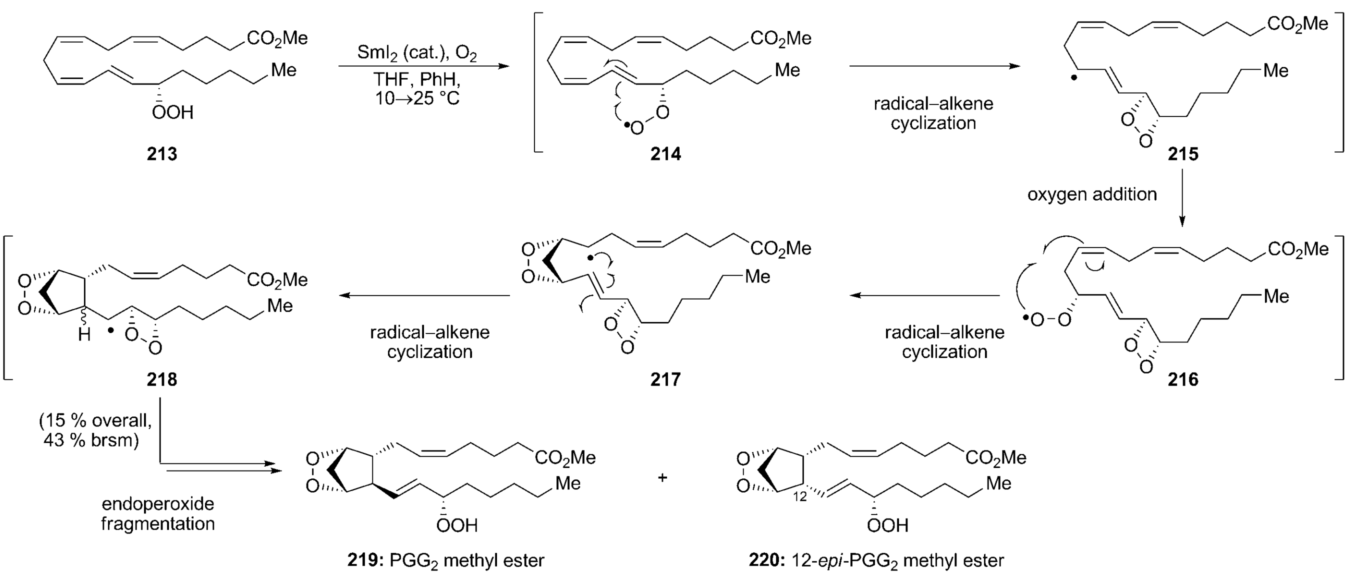


Scheme 45. a) A SmI_2-mediated cascade in the synthesis of paeonilactone B (**210**) and b) clarification of the source of stereoinduction (Kilburn and co-workers, 1998).[98]

bioinspired (and potentially biomimetic) synthesis of prostaglandin endoperoxides PGG_2 methyl ester (**219**) and 12-*epi*-PGG_2 methyl ester (**220**; Scheme 46).[101] Thus, a THF/benzene solution of hydroperoxide **213** containing an excess of O_2 was treated with a catalytic amount of SmI_2 that had been premixed with O_2. This provided 12-*epi*-PGG_2 methyl ester (**220**) and PGG_2 methyl ester (**219**) in 15 % overall yield (43 % brsm) as a 3:1 mixture (**220**/**219**) of chromatographically separable products. Although SmI_2 is generally known as a single-electron reducing agent used in stoichiometric quantities—and, indeed, has served such a purpose in all the other examples within this Review—in this example, the SmI_2 catalyzed an exquisitely controlled addition of O_2 in a cascade sequence that installed two rings, including an unusual endoperoxide system. Premixing SmI_2 with O_2 effected immediate decolorization to form what was presumed to be $I_2SmOOSmI_2$. This species is proposed to initially abstract a hydrogen radical from the hydroperoxide of **213** (possibly through the intermediacy of $I_2SmO^\bullet$), thereby giving access to hydroperoxide radical **214**. A 4-*exo-trig* radical–alkene cyclization gave access to allylic radical **215**, which combined with one equivalent of O_2 to afford hydroperoxide radical **216**. A 5-*exo-trig* cyclization generated secondary radical **217**, which underwent a second 5-*exo-trig* cyclization to form intermediate **218**. Fragmentation of the strained four-membered endoperoxide ring and abstraction of $H^\bullet$ from another molecule of **213** completed the formation of PGG_2 methyl ester (**219**) and 12-*epi*-PGG_2 methyl ester (**220**), and allowed propagation of the chain reaction. In light of the significant increase in molecular complexity, the yield of this transformation is most impressive.

10. Summary and Outlook

In the three decades since the first explorations of the synthetic utility of samarium diiodide (SmI_2), its importance in organic synthesis has grown significantly. It is noteworthy that three separate total syntheses of Taxol (**41**; see Schemes 10, 25, and 30) employed SmI_2 for unrelated trans-



Scheme 46. Synthesis of PGG_2 methyl ester (**219**) and 12-*epi*-PGG_2 methyl ester (**220**) through a SmI_2-catalyzed oxidative cascade (Corey and Wang, 1994).[101]

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formations. Access to this multitude of reaction types is what makes SmI_2 chemistry both so rich in possibilies and, at times, so difficult to control. However, as demonstrated by the examples in this Review, careful fine-tuning of substrate structure and reaction conditions—including solvents, cosolvents, additives, and temperature—can yield controlled and highly useful transformations with high efficiency and stereoselectivity. In particular, cascade sequences involving SmI_2 offer virtually limitless possibilities, with access not only to both radical and ionic reactions but also opportunities for catalytic and oxidative modes of action. To be sure, many more impressive and useful applications of this reagent in chemical synthesis will be invented and discovered in the future.

Abbreviations

Ac	acetyl
AIBN	2,2′-azobis(2-methylpropionitrile)
Bn	benzyl
BOM	benzyloxymethyl
brsm	based on recovered starting material
Bz	benzoyl
Cbz	benzyloxycarbonyl
DIBAL-H	diisobutylaluminum hydride
DMA	dimethylacetamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
Fmoc	fluorenylmethyloxycarbonyl
HFIP	hexafluoroisopropanol
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
KHMDS	potassium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
MOM	methoxymethyl
MS	molecular sieves
NBS	*N*-bromosuccinimide
PGG_2	prostaglandin G_2
PMB	*para*-methoxybenzyl
PMP	*para*-methoxylphenyl
py	pyridine
RACE	radical addition-cyclization-elimination
SEM	[2-(trimethylsilyl)ethoxy]methyl
SOMO	singly occupied molecular orbital
TBAF	tetra-*n*-butylammonium fluoride
TBCHD	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
Val	valine

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