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# SEQUENCED REACTIONS WITH SAMARIUM(II) IODIDE

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## I. INTRODUCTION

Maximum efficiency has always been the primary goal of synthetic chemists, making it the driving force for the development of new methods and conceptual advances in synthesis. The focus of methods development has constantly progressed as economic and environmental forces, combined with increased sophistication and sheer intellectual aesthetics, have united to present ever higher goals in the search for "ideal" syntheses.[1]

The overriding concern in any chemical process has always been the yield of a particular transformation, or simply the effectiveness in converting substrates to a single desired product. Inherent in this notion is the concept of selectivity, including the chemoselectivity, regioselectivity, diastereoselectivity, and enantioselectivity of any given chemical reaction.[2] Conceptually more advanced levels of efficiency require a global view of chemical processes. Thus not only the yield of the desired chemical transformation must be considered, but attention must be paid to the overall ease, proficiency, and economy of the reaction with particular emphasis on the critical issues of time, material (solvents, chromatographic supplies, etc.), and eventually the disposal of byproducts.

To this end, diverse concepts have been introduced that must be factored into the overall equation for efficiency. One such notion is the "atom economic" approach to synthesis.[3] This construct dictates that all of the atoms of the substrates and any reagents utilized for any particular reaction should appear in the final products. No byproducts are formed in such reactions, and the overall efficiency is therefore increased because no tedious separations are required and waste disposal is minimized. Examples of atom economic processes include the Diels-Alder reaction, ene reactions, aldol reactions, palladium catalyzed cycloisomerization reactions,[4] and several other metal catalyzed reactions.[3b,5]

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Another level of efficiency is encountered when multiple bonds are formed in a "one-pot process". These sequential reactions (also called domino reactions,[6] cascade reactions,[7] or tandem reactions[8]) hold enormous potential because considerably less time, effort, and material are required in converting simple substrates to more complex target structures than in more traditional multi-pot procedures wherein each individual intermediate must be isolated and subjected to the next set of reaction conditions.

Multicomponent coupling reactions that are able to incorporate all of the previously discussed efficiencies come closest to ideality.[9] At this point in time, processes incorporating as many as seven individual components in a single reaction have been reported with truly spectacular selectivity.

Chemists to date have focused on sequenced processes or multicomponent coupling reactions that proceed under the same fundamental reaction conditions, thereby avoiding the complexities of dealing with various incompatibilities in substrates, reagents, solvents, or reaction conditions. As examples, many multicomponent coupling reactions are thermodynamically controlled condensation reactions occurring under general acid or base catalysis.[9] Similarly, organometallic-catalyzed sequential transformations (e.g., cycloisomerization reactions[4] or cyclization/silylation processes[5c,e]) employ metal complexes with defined reactivities quite specific to particular functional groups and reagents. Within the realm of sequential reactions that occur under a single set of reaction parameters, there is a demand for nucleophiles, electrophiles, diverse catalysts, oxidants, and reductants that are capable of supporting a cascade of reactions leading from starting materials to products.

Obviously, not all reagents or catalysts capable of carrying out a given class of individual reactions (e.g., reductions or reductive coupling reactions), no matter how versatile, will be suitable candidates for utilization in sequential processes. In fact, the selectivities required for each individual step in a cascade of reactions, along with the exquisite timing of events necessary to complete the sequence, combine to create intimidating odds against ultimate success. Among the myriad of reductants available to synthetic chemists, samarium(II) iodide ($SmI_2$) presents itself as the premier reagent for sustaining sequential reactions performed under reducing conditions. First introduced as a synthetic reagent by Kagan and coworkers,[10] it has rapidly become the standard for a variety of individual reductions[11] and reductive coupling reactions.[12] The versatility of the reagent makes it an ideal candidate for sequential processes. Thus, both radical and anionic reactions constituting the core of the most highly utilized synthetic organic reactions (reductive elimination or fragmentation reactions, radical cyclizations, ketyl-olefin coupling reactions, pinacolic coupling reactions, carbonyl addition reactions, aldol reactions, Claisen condensations, Reformatsky-type reactions, conjugate additions, and nucleophilic acyl substitution reactions) are promoted in yields and selectivities usually superior to those using more traditional reductants. Further enhancing the scope of the processes is the fact that the reactivity and/or selectivity of $SmI_2$ can be modified by the addition of catalysts,[13] by solvent effects,[14] by photochemical enhancement,[15] or through other modifications of the reaction conditions.[16] Finally, for appropriately designed substrates, sequential reactions involving diverse intermediates can be carried out in any order.[17] For example, sequential radical reactions have been developed, anionic cascades are feasible, and both radical/anion and anion/radical domino processes have been realised.

This review outlines the considerable progress made to date in adopting individual reactions promoted by $SmI_2$ to sequential synthetic organic reactions. Given the outstanding characteristics of $SmI_2$ as a reductant and reductive coupling agent, the chemistry presented at this juncture undoubtedly represents but a small fraction of the capabilities of this reagent as a promoter of diverse sequential transformations.

## II. SEQUENCES INITIATED BY FRAGMENTATION OR ELIMINATION REACTIONS

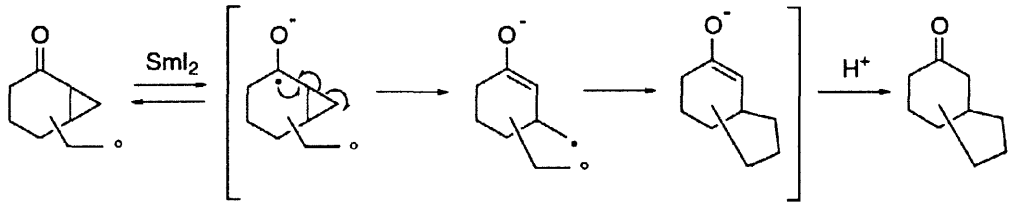
Sequential processes initiated by elimination or fragmentation reactions do not necessarily lead to dramatic increases in molecular complexity because often as many bonds are broken as are created in the process. However, for substrates that can be assembled rapidly, some advantages can derive from a

fragmentation or elimination in the preliminary step of a cascade. Among these are rapid access to unique structures and stereochemical control in subsequent steps of the sequence.

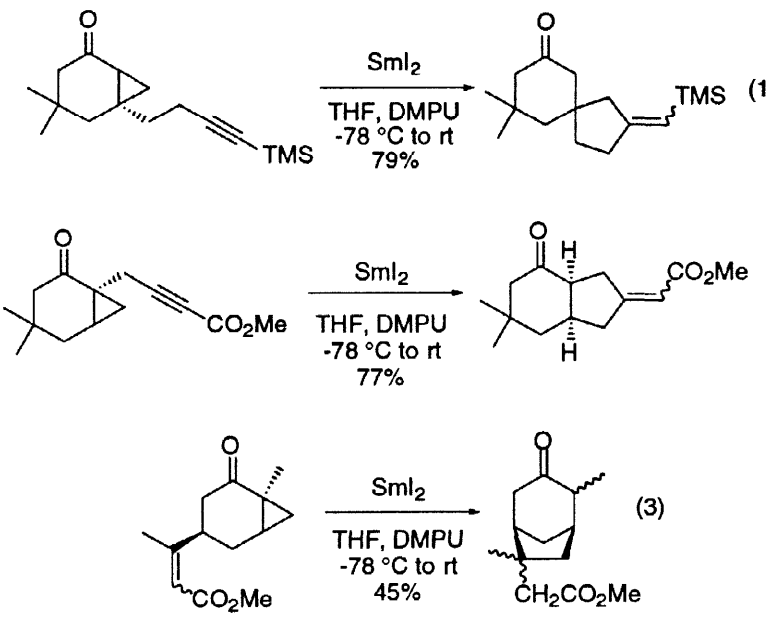
Several $SmI_2$-promoted sequential processes commencing with a fragmentation or elimination process exhibit useful characteristics for small molecule synthesis. Examples detailed below include fragmentation/radical reactions, fragmentation/anionic reactions, fragmentation/ketyl-olefin coupling reactions, and elimination/ketyl-olefin coupling reactions.

Cyclopropanes are readily generated using a variety of reliable methods, and provide substrates in which two stereocenters are set simultaneously. Subsequent fragmentation of the cyclopropyl rings can be induced in a regiocontrolled manner through the intermediacy of cyclopropylcarbinyl radicals. The ring-opened radical thus generated can participate in cyclization reactions with pendant radical acceptors, forming ring-expanded products with control of stereochemistry. This strategy has been utilized quite successfully when cyclopropyl ketones are utilized as substrates for the reaction, the initial radical being derived by electron transfer from $SmI_2$ to the ketone, generating a ketyl (Scheme 1).[18]

Scheme 1

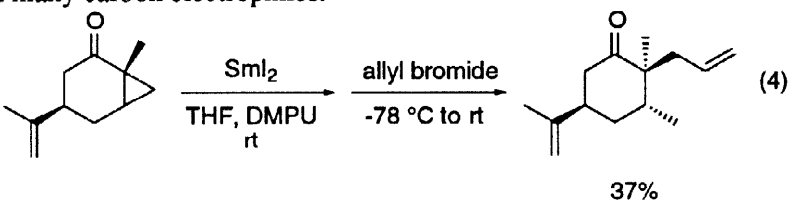



The sequence is best carried out utilizing activated radical acceptors (eqs 1-3). Under the conditions of the reaction, further reduction of the ring-opened radical presumably competes with cyclization,[19] providing an anion incapable of cyclizing. Alkenes and alkynes with low-lying LUMO's exhibit faster radical cyclization rates, and can therefore effectively trap the radical prior to reduction to the organometallic.



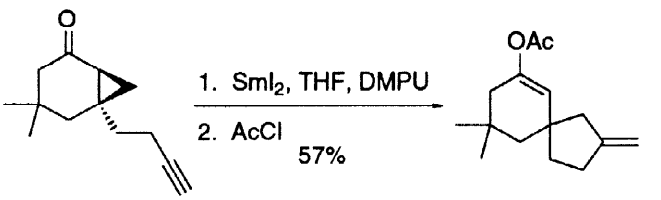

Recognizing that an enolate was generated in this process (Scheme 1), attempts were made to trap this species with external alkyl electrophiles subsequent to the ring-opening event.[18] These efforts proved to

be only modestly successful (eq 4) as samarium enolates appear not to possess sufficient nucleophilicity to react effectively with many carbon electrophiles.[20]




(4)

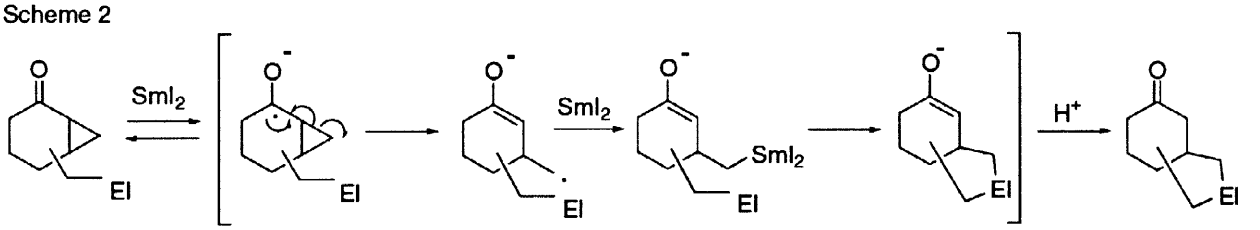
Demonstrating that both the radical and the enolate could be trapped efficiently in select instances, treatment of appropriate substrates with $SmI_2$ followed by a quench with reactive electrophiles led to cyclized, regiodefined enolate derivatives (eq 5).[18]



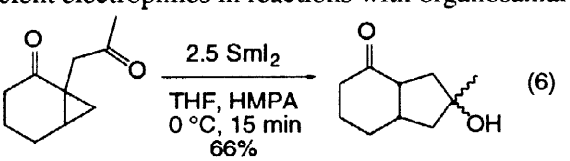

(5)

Generally more successful were sequential reactions wherein the initial radical generated by cyclopropyl ring cleavage was reduced further to an organosamarium species. The latter was then trapped by pendant carbonyl electrophiles (Scheme 2).

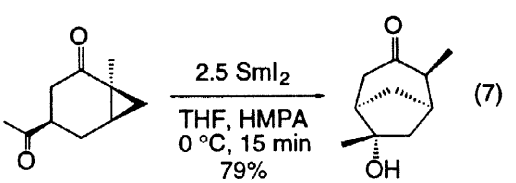
Scheme 2



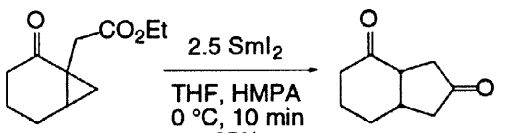

Both ketones and esters were utilized as electrophiles for the reaction (eqs 6-9).[21] Aldehyde electrophiles afforded lower yields of the carbonyl addition product, perhaps because of competitive reduction under the reaction conditions. Epoxide electrophiles were also relatively ineffective electrophiles in analogous reactions. This could be due to Lewis acid promoted rearrangement reactions[22] or to the fact that epoxides are simply inefficient electrophiles in reactions with organosamarium species.



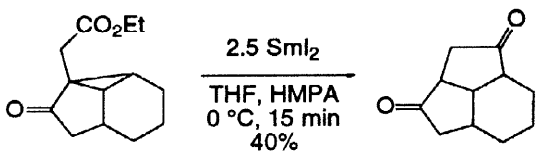

(6)




(7)

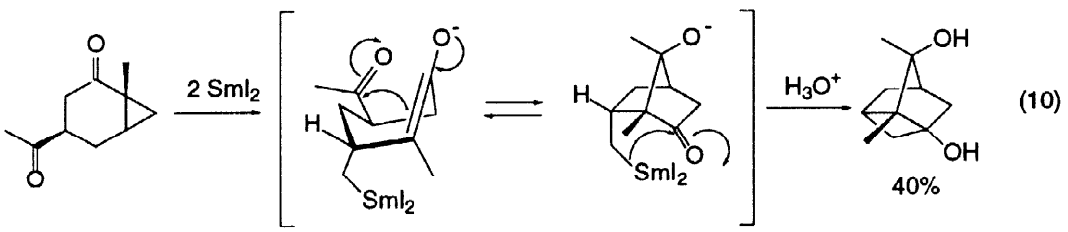



(8)




(9)

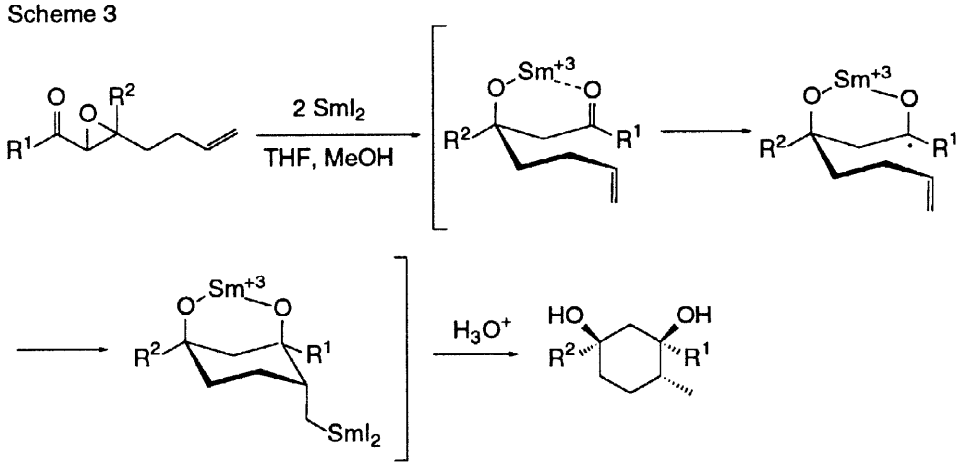
In one substrate, special stereoelectronic features allowed both the enolate and the organosamarium to undergo reaction, generating a tricyclic system in a cascade of anionic cyclizations (eq 10).[21] Thus the enolate generated upon cyclopropyl cleavage underwent an intramolecular aldol reaction with the available ketone. The organosamarium species generated subsequently reacted with the newly-revealed ketone, generating a dialkoxide that was quenched with aqueous acid to provide the observed product.



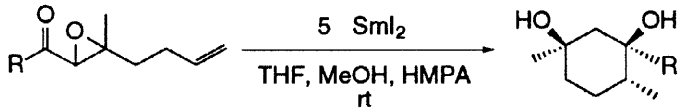

(10)

As with the case of cyclopropyl ketones, epoxy ketones also undergo $SmI_2$-promoted reductive cleavage.[23] In substrates suitably functionalized for reaction via ketyl-olefin cyclization, the alkoxy group resulting from epoxide ring cleavage enforced a rigid template for the subsequent reaction (Scheme 3).[24] Reduction of the ketone to a ketyl initiated cyclization in which stereochemistry at the third stereogenic center was controlled by stereoelectronic effects inherent in ketyl olefin cyclizations.[25]

Scheme 3

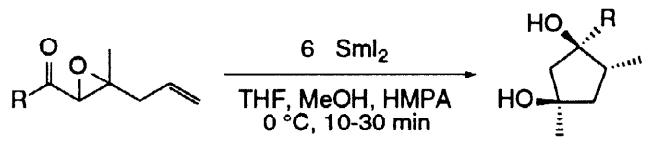



Both five- and six-membered rings were accessible through this process, in generally good yields and high diastereoselectivities (eqs 11-12).[24]




(11)

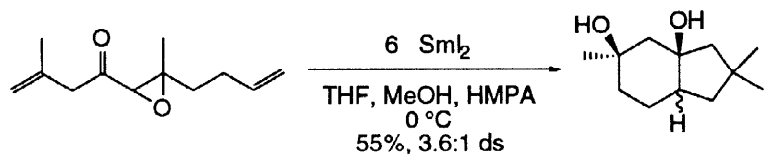
| R | % isoltd yield | diastereoselectivity |
|---|---|---|
| Me | 88 | 12:1 |
| Et | 86 | 10:1 |
| *i*-Pr | 72 | 10:1 |



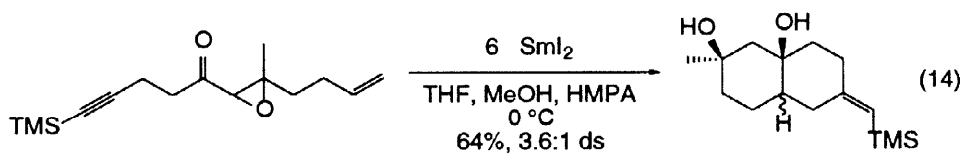

(12)

| R | % isoltd yield | diastereoselectivity |
|---|---|---|
| Me | 61 | >100:1 |
| Et | 65 | 100:1 |
| *i*-Pr | 66 | 50:1 |
| *t*-Bu | 81 | 2:1 |

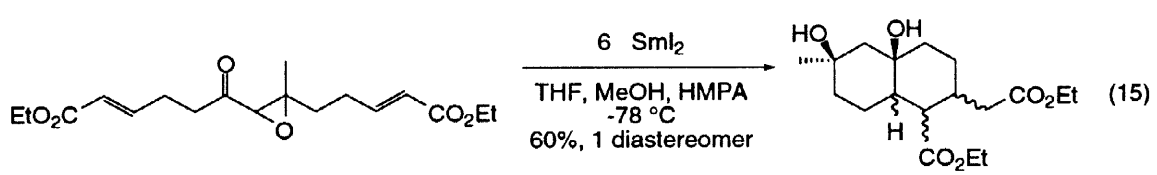
Enhanced efficiencies have been achieved when the initially formed alkyl radical undergoes further cyclization with appropriately positioned alkenes and alkynes.[26] As in the case of the cyclopropyl ketones, activated alkenes and alkynes work most efficiently, providing good yields through the course of the transformations (eqs 13-15). The mechanism by which the product in eq 15 was derived is not known. The final bond formation could derive either from a radical cyclization onto the enoate or an intramolecular Michael addition from an intermediate enolate.




(13)



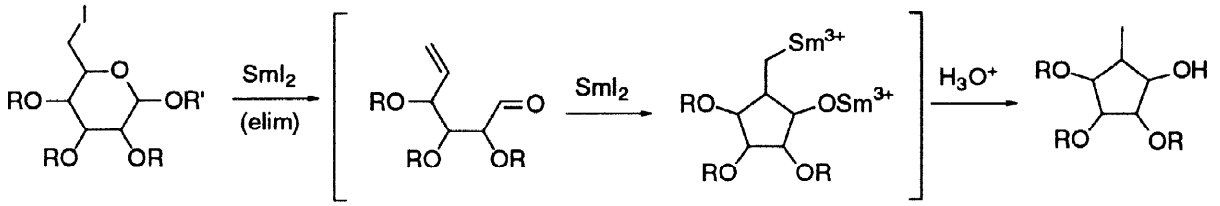

(14)



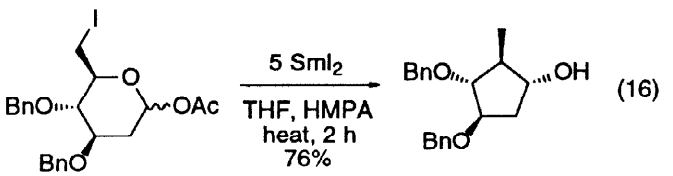

(15)

Elimination reactions from carbohydrate-derived substrates followed by intramolecular ketyl-olefin coupling reactions provide a rapid entry to highly functionalized, stereodefined carbocycles (Scheme 4).[27]

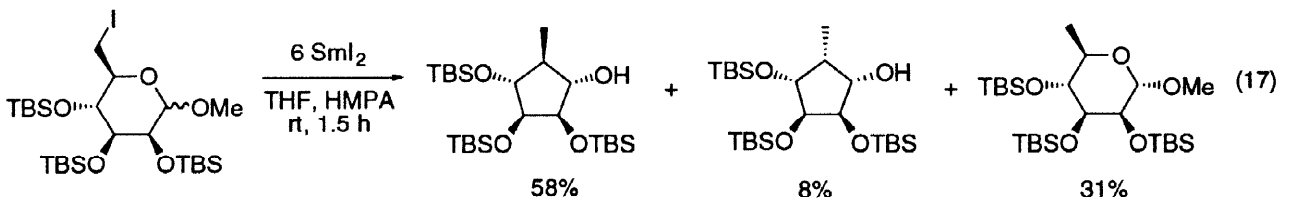
Scheme 4




Generally higher yields were obtained in the sequence when the anomeric substituent was a good leaving group. Diastereoselectivities varied widely depending on the substitution pattern (eqs 16-17).



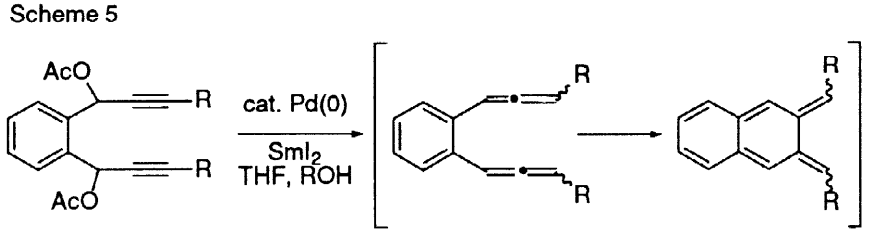

(16)



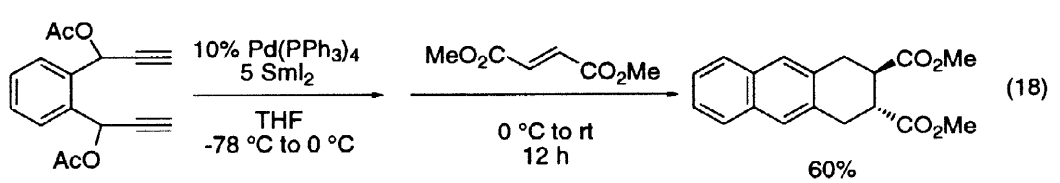

(17)

A novel method for the generation of 2,3-naphthoquinomethanes has been reported as part of a sequential synthesis comprised of reductive elimination/electrocyclization/cycloaddition reactions (Scheme 5).[28] Initially a propargyl/allenyl palladium species was presumably generated, which underwent reductive transmetalation to the corresponding organosamarium complex. Protonation led to the allenes, which were poised for the electrocyclization reaction that generated the 2,3-naphthoquinomethanes.

Scheme 5



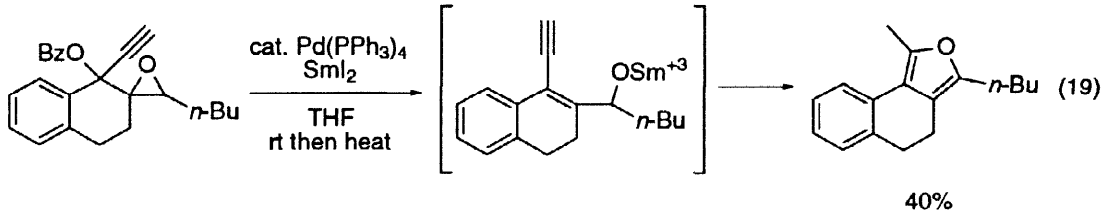

The naphthoquinomethanes thus generated underwent *in situ* Diels-Alder reactions with active dienophiles, generating tricyclic systems in good overall yields (eq 18).




(18)

In a related Pd(0) catalyzed, $SmI_2$-promoted process, 1-(1,2-epoxyalkyl)-2-alkynyl esters were converted directly into substituted furans.[29] The reactions were again initiated by Pd(0) insertion, this time

at a propargyl benzoate, with reductive transmetalation to the organosamarium inducing ring opening of the epoxide, thereby generating intermediate 2-alken-4-yn-1-alkoxides. These underwent palladium catalyzed cyclization and isomerization to afford the desired furans (eq 19).

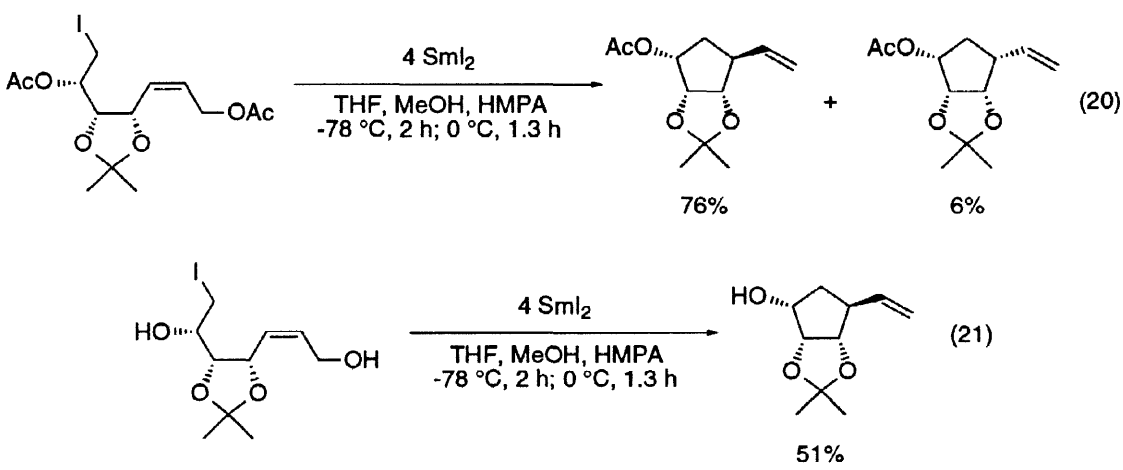



## III. SEQUENCES INITIATED BY RADICAL PROCESSES

A variety of $SmI_2$-promoted sequential reactions initiated by radical cyclizations have been described. The radicals created to commence these cascades have been derived both from halides (to generate alkyl, alkenyl, and aryl radicals) and carbonyl substrates (producing ketyl radical anions). The versatility of $SmI_2$ is thus again nicely demonstrated in this arena.

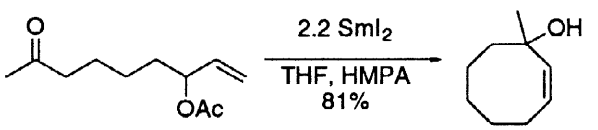
Radical addition reactions that terminate in an elimination process comprise perhaps the simplest example of a sequenced radical process. For these reactions the cyclized radical initially formed subsequently undergoes reduction to an organosamarium species, inducing the β-elimination process. As noted previously, the elimination does not necessarily increase molecular complexity, but can be utilized to retain functionality in the final product and to convey stereochemical information in the process.

Numerous leaving groups have been utilized in the elimination component of the sequence. In studies of alkyl radicals derived from carbohydrate precursors, both acetates and hydroxyl groups have been utilized (eqs 20-21).[30] Interesting to note is that no β-elimination occurs at the initial reaction center - the cyclization is clearly a radical process. In the case of allylic alcohol acceptors, the generation of a Lewis acidic $Sm^{+3}$ species undoubtedly facilitates departure of the normally reluctant hydroxyl leaving group. The overall process results in an efficient, enantiocontrolled synthesis of highly functionalized cyclopentane derivatives.



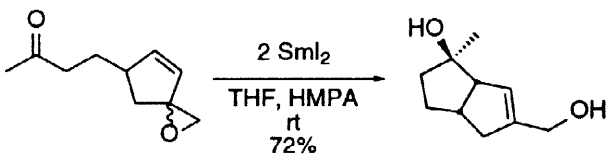

A good leaving group has been employed for a two-fold purpose in an unusual cyclooctenol synthesis employing a $SmI_2$-promoted cyclization/elimination sequence.[31] Initial studies in cyclooctanol syntheses demonstrated the feasibility of an 8-endo ketyl-olefin cyclization with unactivated alkenes. Yields in these initial studies were modest. That the process occurred at all could be ascribed to the persistence of the ketyl

radical anions generated under the reaction conditions. Thus, ketyl radical anions are postulated to form reversibly in the presence of $SmI_2$.[32] Additionally, these radical anions do not undergo further reduction. Furthermore, ketyls are not particularly prone to quenching by hydrogen atom abstraction from the solvent, disproportionation, or other means.[33] Consequently, the lifetime of these species is significantly enhanced as compared with less highly stabilized radicals. The combination of these features, apparently unique to the $SmI_2$-promoted process,[34] provides a pseudo-dilution effect for the generation of the ketyls and an adequate lifetime for the slow cyclization to take place. To improve the yields, it was rationalized that electron-withdrawing groups on the alkene or at the allylic position would enhance the cyclization rate of the reaction by lowering the LUMO of the alkene radical acceptor. This turned out to be the case. By choosing a group that also served as a leaving group after the cyclization event, functionality was also retained in the newly formed ring (eq 22).

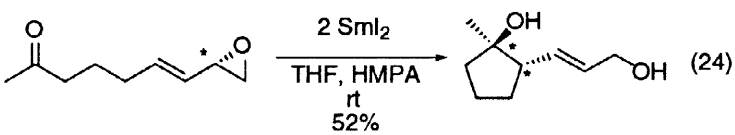


(22)

Epoxides have also served as effective "leaving groups" in radical cyclization/fragmentation processes. In this case, ketyl radical anions were again utilized as the radical precursors (eqs 23-25).[35] The use of allylic epoxides as radical acceptors retained not only the double bond, but also an alcohol for further functionalization. Enantioselective syntheses were achieved by utilizing readily available, enantiomerically pure epoxide substrates for the reactions. Interestingly, the reactions were completely diastereoselective with regard to stereocenters created at the olefin (compare eqs 24 and 25). Unfortunately, the method appears to be limited to 5-exo cyclizations.



(23)



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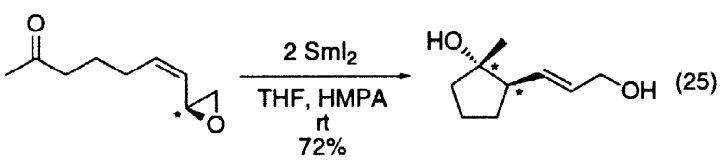
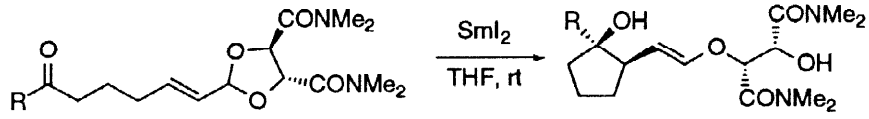


(25)

An extraordinary example of 1,5-asymmetric induction has been demonstrated in the ketyl-olefin cyclization/fragmentation of chiral, nonracemic unsaturated acetals (eq 26).[36] The enol ethers resulting from the ketyl-olefin cyclization/elimination sequence were hydrolyzed to the corresponding aldehydes, with concomitant recovery of the chiral auxiliary.




(26)

| R | % isoltd yield | diastereoselectivity |
|---|---|---|
| Me | 81 | 97:3 |
| Et | 83 | 97:3 |
| *t*-Bu | 74 | 93:7 |
| H | 50 | 96:4 |

The observed results have been explained by the ability of acetals derived from *N,N*-dimethyl tartramides to chelate the $Sm^{3+}$ generated after electron transfer, enforcing a rigid transition structure for cyclization (Figure 1). This chelate was able to overcome the stereoelectronic bias of ketyl-olefin coupling reactions to generate products wherein the hydroxyl group and the newly created substituent on the cyclopentanol ring normally appear trans to one another.[25]

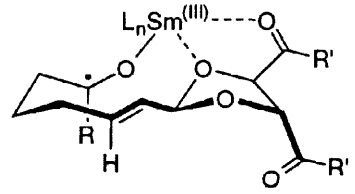
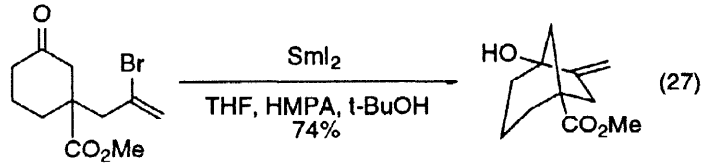


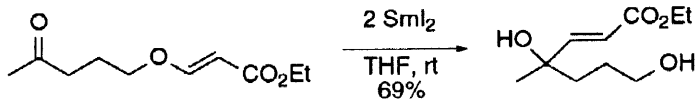

**Figure 1**. Transition structure for the conversion of unsaturated acetals to substituted cyclopentanols.

The reaction of ketyls with 2-bromoalkenes in an exo coupling mode leads to an addition/elimination sequence resulting in the creation of exomethylene groups on the newly formed ring (eq 27).[37] The overall process is equivalent to the addition of ketyls to terminal alkynes.

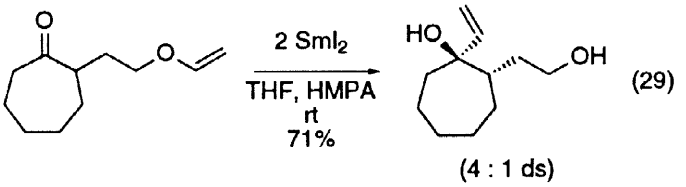



(27)

This chemistry has been expanded to enol ether ketyl acceptors, where the overall transformation has resulted in a unique way to carry out an alkenyl addition to ketones (eqs 28-29).[38] In these examples, the ketyl-olefin cyclization led to an enolate or organosamarium species with a leaving group positioned β to the negative charge. Spontaneous β–elimination subsequently led to the observed products. In effect, the protecting group of an aldol or homoaldol substrate became the "nucleophile" in a net carbonyl addition process.

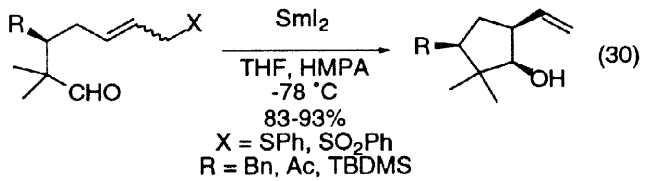



(28)



(29)

Sulfur-based leaving groups have also been employed in ketyl-olefin coupling/elimination sequences. Sulfides and sulfones perform equally well in these reactions (eqs 30-31)[39] although it is feasible that they react via different mechanisms. Thus the ease with which sulfones are reduced by $SmI_2$[11] makes it possible that these transformations proceed by an allylmetallic route. Certainly the products in both cases are identical to those that would be obtained by the intramolecular addition of an allylmetallic to an aldehyde. The current method employing sulfides and sulfones may have advantages over more traditional allylmetallic routes (employing allylic halide substrates under reductive coupling conditions) in terms of stereochemical control. Additionally, the sulfur-based substrates may be more readily available, and exhibit enhanced stability over allylic halide precursors.



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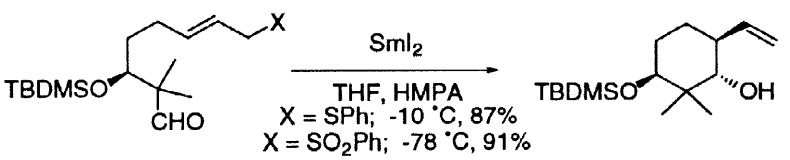
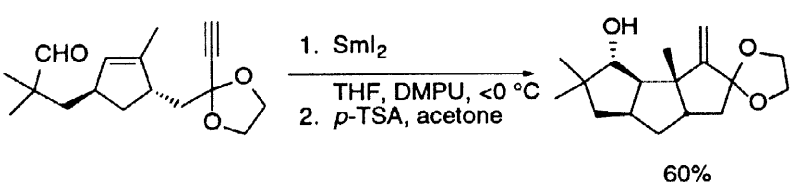


(31)

Somewhat surprisingly, only a single radical/radical sequential process promoted by $SmI_2$ has been reported.[40] This reaction was performed within the context of a total synthesis of (±)-hypnophilin, and involved a ketyl-olefin cyclization followed by cyclization of the resulting radical onto a pendant alkyne (eq 32). The tertiary radical formed after the initial cyclization exhibited reasonable persistence under the reaction conditions, allowing further cyclization onto the alkyne. The exomethylenyl radical generated in the final step presumably abstracted a hydrogen atom prior to reduction by $SmI_2$ (only 1.3 equivalents of $SmI_2$ were necessary), thus completing the sequence.

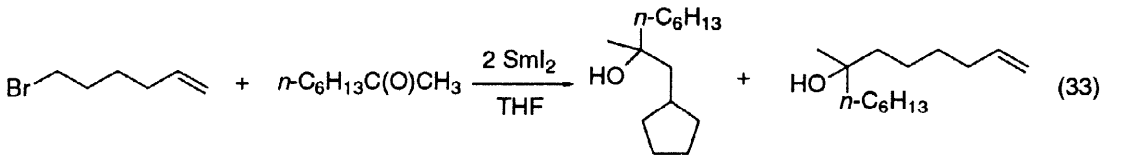


(32)

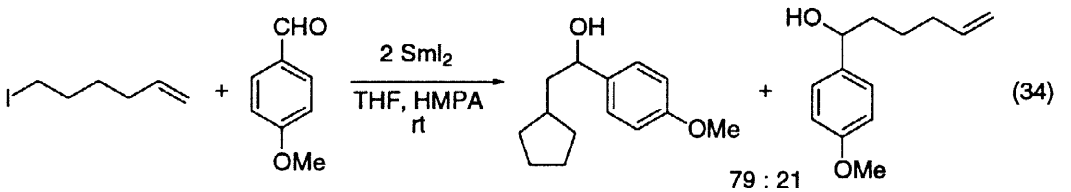
60%

Much more common are sequential radical cyclization/nucleophilic addition or -substitution reactions. In these processes the radical generated upon cyclization is reduced under the reaction conditions to generate an organosamarium species. The latter have been trapped intramolecularly by a pendant electrophile. Alternatively, electrophiles can be added to the reaction mixture to quench the resulting anion. Both alkyl and ketyl radicals have been employed as intermediates in the first step of these reactions.

One of the features that limits the use of alkyl radicals in sequential processes is that these radical intermediates poised for cyclization can undergo competitive reduction to the corresponding organosamarium species. The rate constant for reduction of a primary radical by $SmI_2$ in THF has been estimated to be between 5 x $10^5$ $M^{-1}$ $s^{-1}$ and 7 x $10^6$ $M^{-1}$ $s^{-1}$, depending on HMPA concentration.[19] For radicals derived from substrates like 6-bromohex-1-ene ($k_{cyc}$ = $10^5$ $s^{-1}$), mixtures of cyclic and acyclic products were observed under normal conditions for $SmI_2$-promoted reactions (eq 33).[41] Even under optimized, extremely dilute conditions ([$SmI_2$] = 0.021 M) unwanted reduction to the acyclic organosamarium species cannot be avoided, and mixtures of products were observed (eq 34).[19]

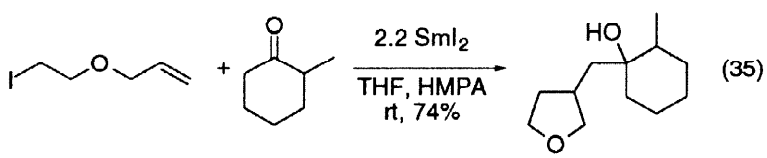



(33)



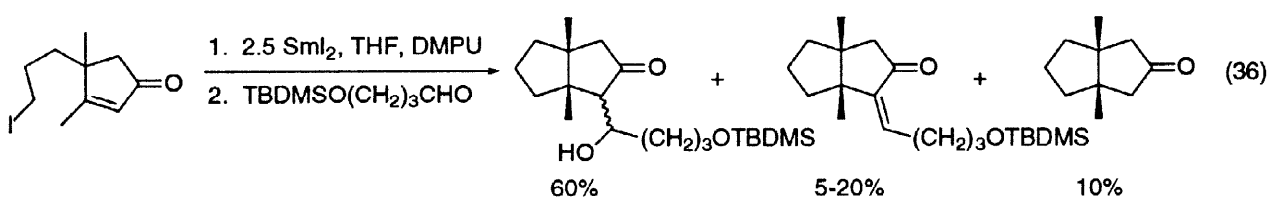

(34)

Alkyl radical intermediates with higher rates of cyclization undergo the desired sequence of events more successfully. Among primary alkyl radicals, those with heteroatoms along the chain cyclize at enhanced rates ($k_{cyc}$ = $10^6$ $s^{-1}$), and provide more successful cyclization/addition sequences (eq 35).[42]

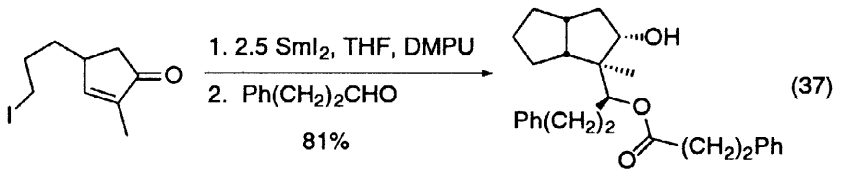



(35)

Unsaturated ketone radical acceptors also enhance cyclization rates, and the resulting enolates have been trapped with aldehyde electrophiles.[32] The process is unfortunately not particularly general, and in reported cases mixtures of products were generated. For example, aldol products, enones, and protonated material were observed (eq 36), as well as products resulting from intramolecular Tischenko redox processes (eq 37).

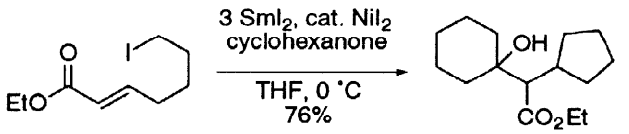



(36)

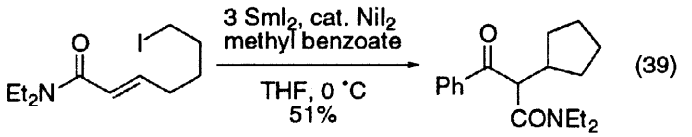



(37)

More selective were radical conjugate addition/enolate trapping reactions involving unsaturated amide and -ester substrates.[38] The enolates generated in these cases undergo subsequent aldol reactions (eq 38), Claisen condensations (eq 39), and intramolecular Michael reactions (eq 40) in reasonable (unoptimized) overall yields.




(38)

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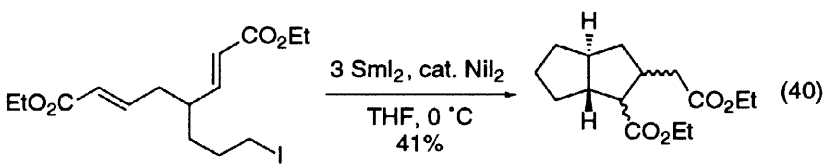
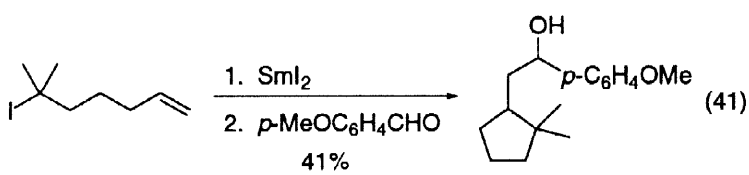



(40)

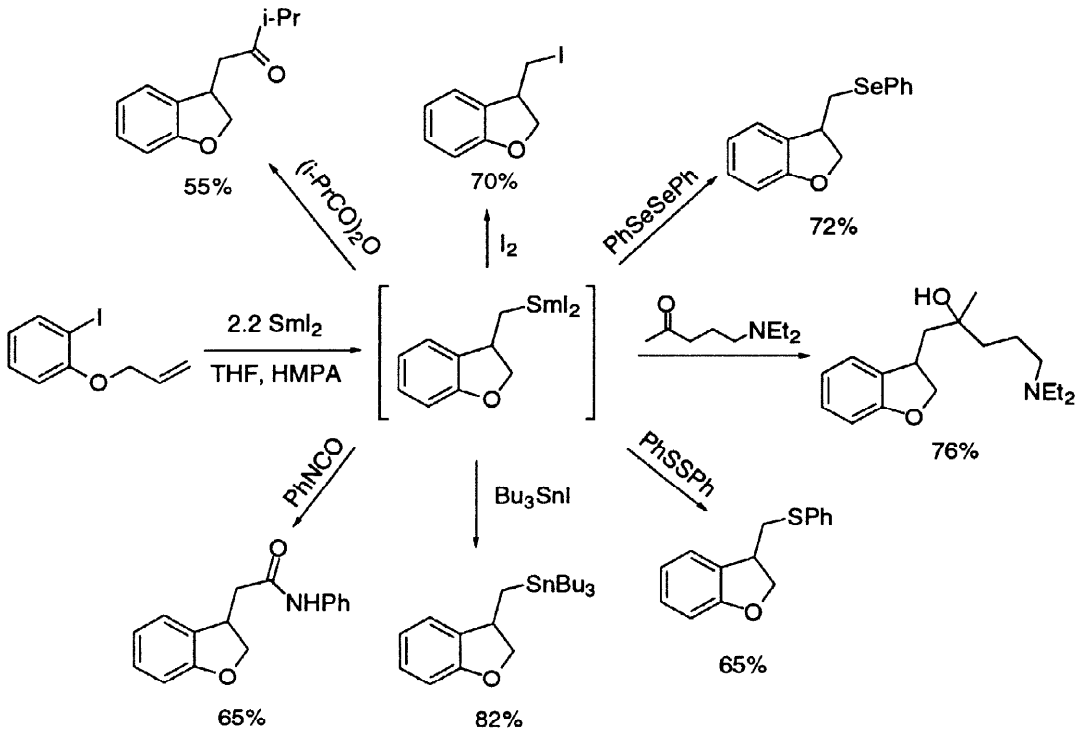
Another strategy to improve radical cyclization/nucleophilic sequences with $SmI_2$ employed substrates leading to intermediates with more persistent radicals; i.e., those that are less rapidly reduced to the corresponding organometallic under the reaction conditions. Tertiary halides constitute one such class of substrates. Unfortunately, the rate of cyclization of the corresponding tertiary radicals is also depressed, and thus sequential processes are only modestly successful (eq 41).[43]




(41)

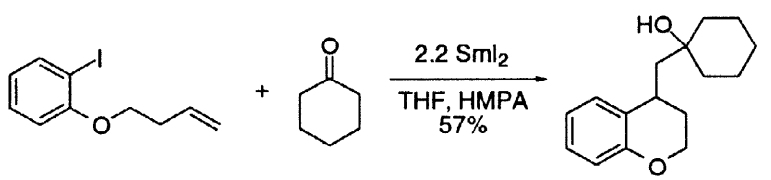
One of the more successful classes of substrates for sequential radical cyclization/nucleophilic sequences with $SmI_2$ are aryl halides (Scheme 6).[42,44]

Scheme 6

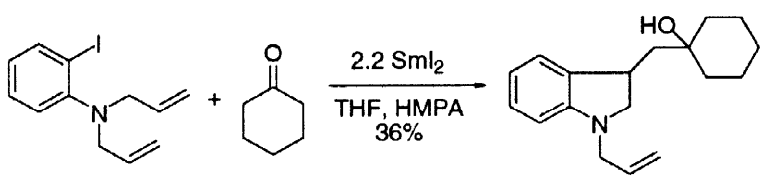



Aryl radicals are reasonably resistent to reduction by $SmI_2$,[45] providing them with an adequate lifetime for cyclization. Furthermore, aryl radicals cyclize in a 5-exo mode with measured rate constants of up to $4 \times 10^9$ $s^{-1}$.[44b] The combination of these two factors provides for a reasonably general cyclization process. There are, however, some limitations in the overall process. For example, only primary and secondary radicals generated in the cyclization process can be reduced to organosamariums. Furthermore, the lack of nucleophilicity of the resulting organosamarium species limits the cascade process to some degree. Thus allylic halides, benzylic halides, epoxides, ethyl bromoacetate, acetonitrile, and other alkylating agents fail to undergo reaction in acceptable yields.[42] Carboxylic acid chlorides, TMSCl, and TsCl also fail to react, presumably because they facilitate the ring opening of THF under the reaction conditions.[42] In spite of these limitations, a number of electrophiles have been trapped by the organosamarium intermediate, leading to a versatile process for the elaboration of dihydrobenzofurans.

Six-membered ring cyclizations work reasonably effectively for the formation of oxygen heterocycles (eq 42), as does the cyclization of unsaturated amines to afford the corresponding nitrogen heterocyclic system (eq 43).[42]

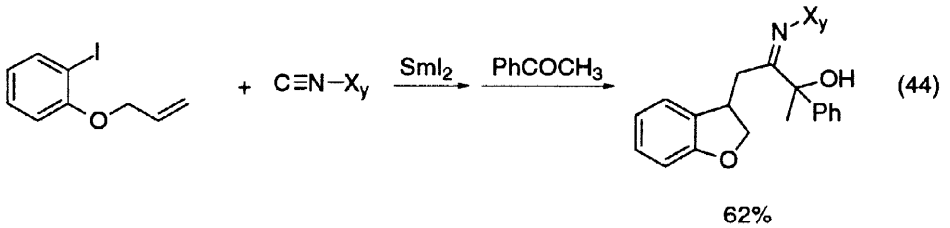



(42)

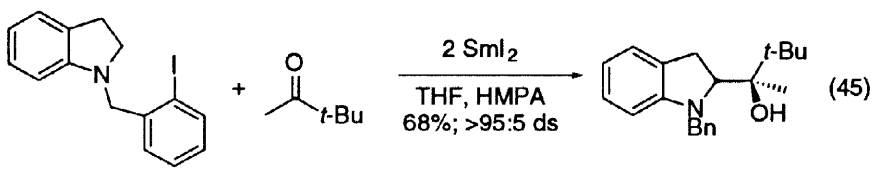


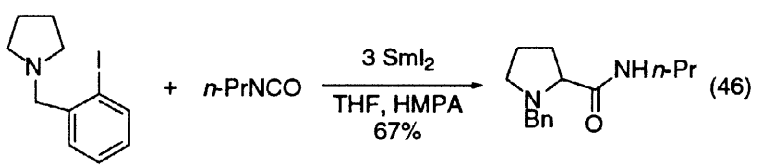

(43)

Three component coupling reactions have been realized utilizing an aryl radical cyclization as the first step of a radical/anion/anion process (eq 44).[44a] The cyclized radical was subsequently reduced to the corresponding anion, which reacted with xylyl isocyanide to generate an iminoylsamarium species. This acyl anion equivalent was treated with acetophenone, generating the observed carbonyl addition product in excellent overall yield. In the overall transformation, the xylyl isocyanide has reacted as an acyl cation/acyl anion equivalent, stitching together a nucleophile and an electrophile surrounding the imine.

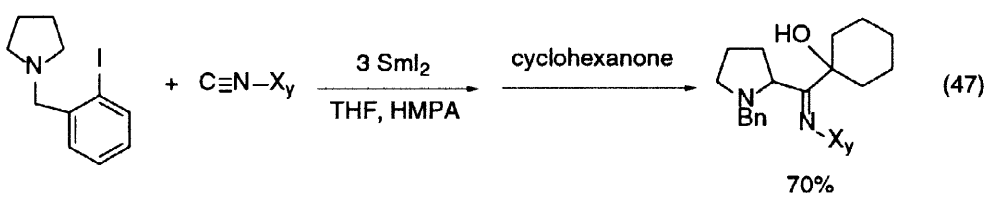



Atom transfer reactions have been utilized to generate organosamariums at the α position of amines.[46] In *o*-iodobenzyl substituted amines, reduction of the aryl halide to the corresponding aryl radical induces transfer of a hydrogen from the α position of the amine to the aromatic ring. Reduction of the resulting α amino radical to the anion and subsequent coupling with carbonyl electrophiles generates the desired products (eqs 45-46).



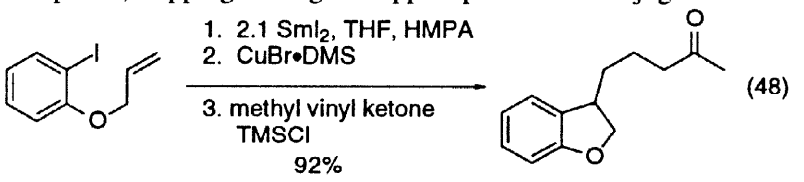




Three component coupling chemistry has been carried out using the same protocol. An atom transfer process generated the initial α-amino radical.[46a] Reduction to the anion and entrapment with xylyl isocyanide generated an intermediate acyl anion equivalent, which underwent carbonyl addition to afford the observed product (eq 47).



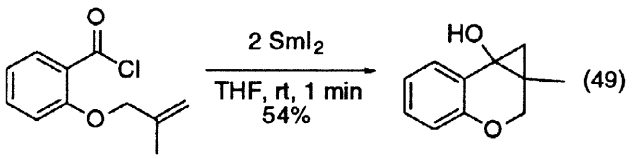

It has been pointed out that the organosamarium species generated in sequential processes react with a somewhat limited pallette of electrophiles. Extension of the range of electrophiles that can be utilized in $SmI_2$-promoted sequential reactions has been achieved by transmetalation reactions to the corresponding

organocopper intermediates (eq 48).[47] Utilizing this strategy, α,β-unsaturated ketones have been employed as the terminating electrophiles, trapping the organocopper species in a conjugate addition reaction.




(48)

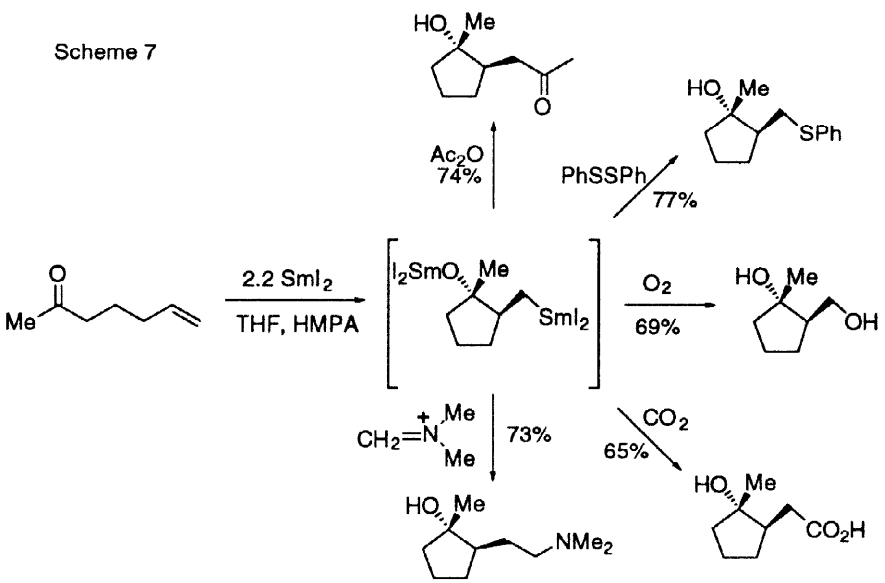
Acyl radicals have been generated by the reaction of $SmI_2$ with carboxylic acid chlorides.[14b,d,48] When 2-allyloxybenzoyl chlorides were the subject of this reaction, the intermediate acyl radical was trapped by the alkene, providing a cyclized radical. Subsequent reduction by a second equivalent of $SmI_2$ generated the corresponding organosamarium species, which underwent intramolecular carbonyl addition, generating a cyclopropanol (eq 49).[49]



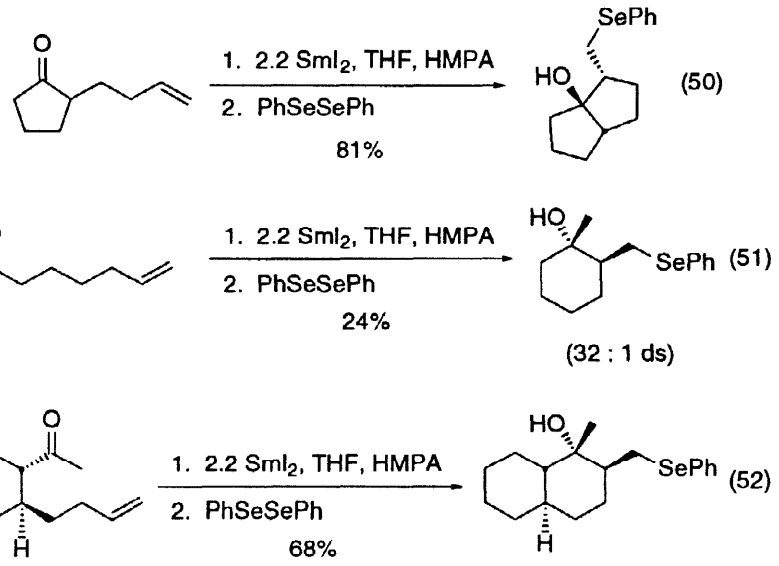

(49)

Radical/anionic cascades initiated by ketyl cyclization have proven to be among the more successful $SmI_2$-promoted sequential reactions (Scheme 7).[13b] As pointed out previously, there are several inherent advantages in the use of ketyl radicals to initiate radical sequences, all of which lead to more persistent radicals that are provided adequate time to cyclize without significant byproduct formation. Stereoelectronic effects in the cyclization reaction itself lead to high diastereoselectivities of the observed products.[25] Finally, the organosamariums generated after subsequent reduction of the cyclized radical react with a variety of external electrophiles or intramolecularly with pendant electrophiles.

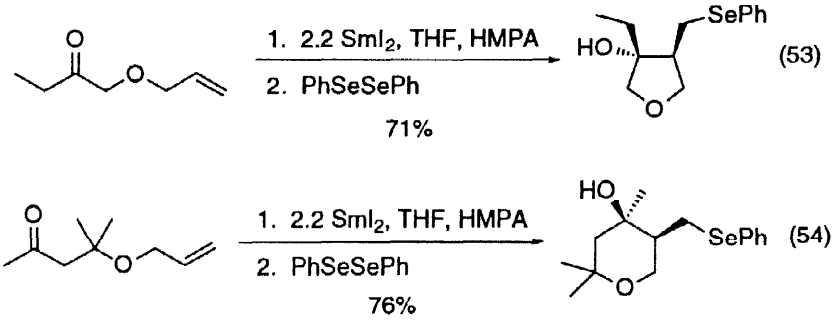
Scheme 7



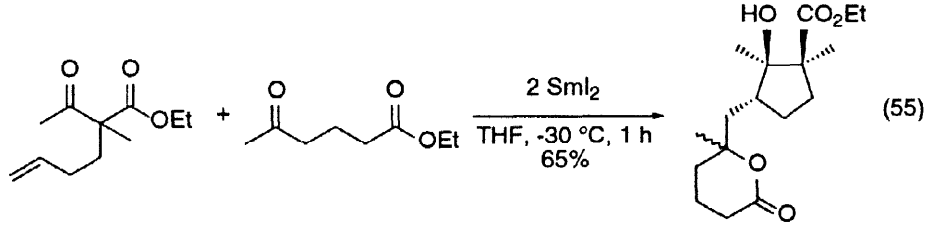

Five-membered ring cyclizations are the most efficacious (eq 50), but six-membered rings can also be generated provided the 6-exo cyclization rates are sufficiently rapid (eqs 51-52).[25]

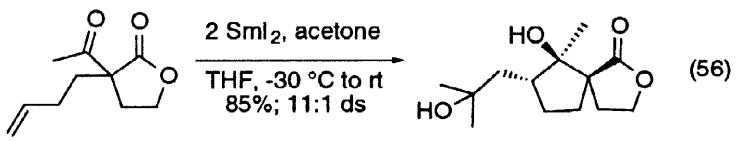



Cyclization rates also play a role in the synthesis of oxygen heterocycles. Heterosubstituents α to the carbonyl are subject to rapid reductive cleavage via the same ketyl radical anion intermediate that is involved in the cyclization reactions.[23] Although 5-exo cyclization reactions are rapid enough to compete very effectively with the reductive coupling process (eq 53), 6-exo cyclizations provide mixtures of cyclization products and reductive cleavage products. Substrates for 6-exo cyclization with the heteroatom β to the carbonyl cannot participate in the reductive cleavage process, and thus in these instances high yields of cyclized products have been realized (eq 54).




Utilizing the Lewis acidic character of the $Sm^{+3}$ species generated upon electron transfer, chelation controlled radical cyclization/nucleophilic addition reactions have been achieved in which up to three contiguous stereocenters are generated (eqs 55-58).[50] The hydroxyl center and the carboxylate center are controlled by chelation, while the third stereocenter is directed by stereoelectronic effects inherent in ketyl-olefin coupling reactions.[25] As illustrated, both β-keto esters and β-keto amides have been utilized in the reactions. A variety of substitution patterns about these systems led to diverse structural motifs in the final products.



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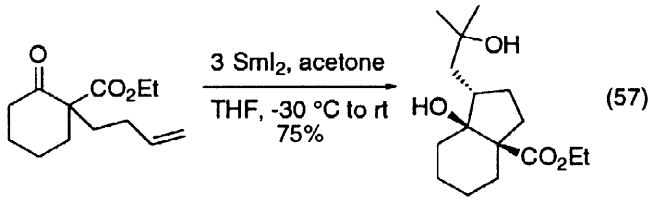


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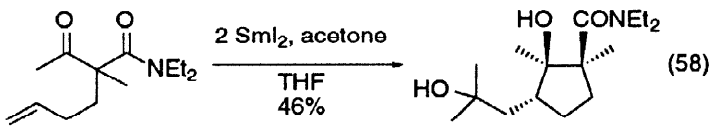
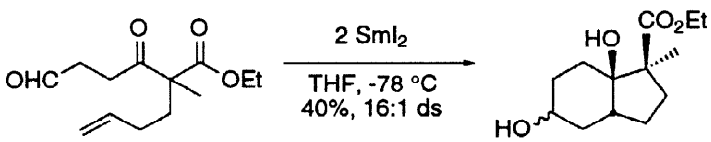


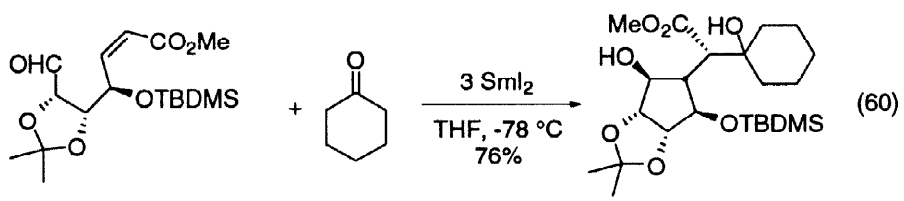

(58)

Although only a single example has been reported, wholly intramolecular versions of this sequential process also appear feasible (eq 59).[51]




(59)

Cascade reactions employing activated alkenes in the ketyl-olefin coupling reaction have been demonstrated. The enolate intermediates generated under these reaction conditions partake in aldol-type condensation reactions in the second step of the sequential reactions (eqs 60-61).[52]

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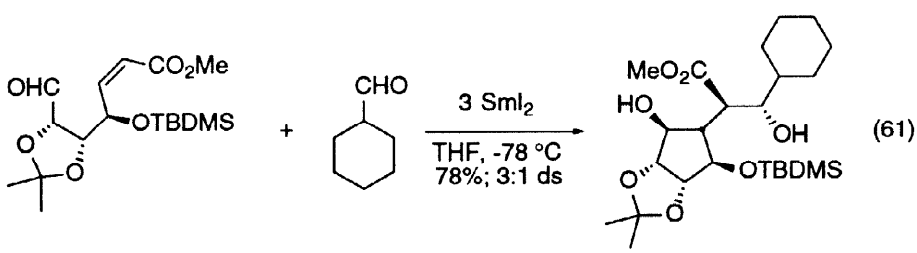
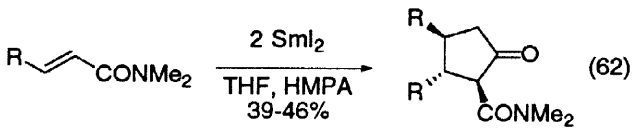



(61)

A unique sequential radical/anion process results in the rapid construction of stereodefined cyclopentanone carboxamides.[53] Thus, treatment of α,β-unsaturated amides with $SmI_2$ results in a β,β-homocoupling, presumably via conjugate radical addition of a reduced enamide with an unreduced partner. Further reduction with a second equivalent of $SmI_2$ generates an enolate, which undergoes a Dieckmann

condensation to afford the observed products (eq 62). Through further transformations these products were converted to potentially useful $C_2$-symmetric chiral ligands.



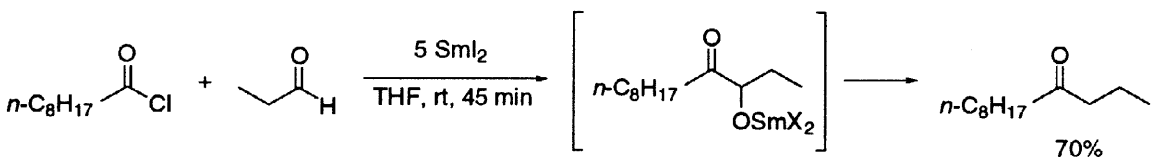

(62)

R = Me, Ph, *o*-BnOC$_6$H$_4$

## IV. SEQUENCES INITIATED BY ANIONIC PROCESSES

Unlike some reagents that are only capable of initiating radical cascades, $SmI_2$ has demonstrated a tremendous potential to sustain domino processes that begin with anionic reactions as well. This versatility is one of the hallmarks of $SmI_2$ chemistry, making it an unparalleled reagent for conducting sequential reactions under reductive coupling conditions.

Among the simplest sequences initiated by an anionic process are those in which a coupling reaction is succeeded by an elimination or fragmentation reaction. One example demonstrating this concept involves the addition of acyl anions to carbonyl substrates. The acyloin intermediates were reductively cleaved in situ to provide a one-pot synthesis of the corresponding carbonyl compounds (eqs 63-64).[54]

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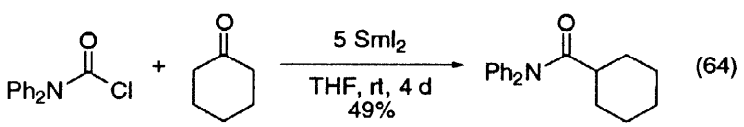
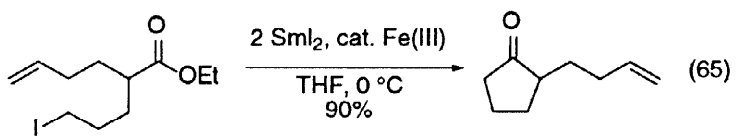
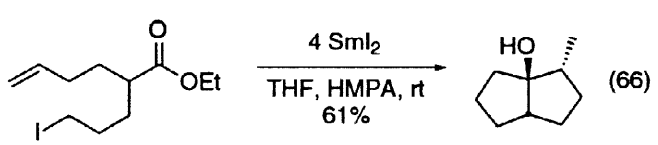



(64)

A two-step, one-pot sequence that has proven extraordinarily general is one that involves an initial intramolecular nucleophilic acyl substitution followed by a ketyl-olefin cyclization process. In initial studies, unsaturated iodoalkyl esters were found to undergo efficient nucleophilic acyl substitution, providing the corresponding unsaturated esters (eq 65).[55] These intermediates are themselves substrates for $SmI_2$-promoted cyclization via the ketyl radical, and in fact with an excess of $SmI_2$ the cascade process was carried out quite efficiently (eq 66).



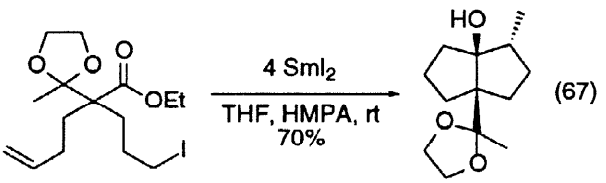

(65)



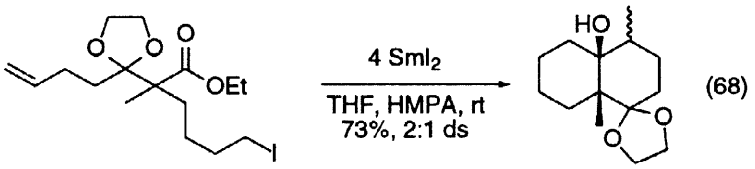

(66)

The reaction has been generalized, providing a highly comprehensive approach to stereodefined polycyclic systems.[56] Both five- and six-membered ring systems have been accessed by the method (eqs 67-

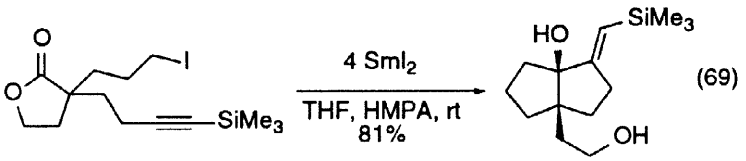
68). Butyrolactones are able to serve as the initial electrophile for the reaction, and activated alkynes have been employed as effective acceptors in the radical cyclization reaction (eq 69). Different structural motifs have been accessed by simply changing the substitution pattern of the readily available precursors. For example, both linear triquinanes (eq 70) and angular triquinanes (eq 71) have been generated in modest to excellent yields.



(67)



(68)



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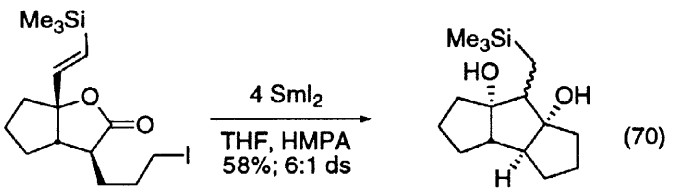
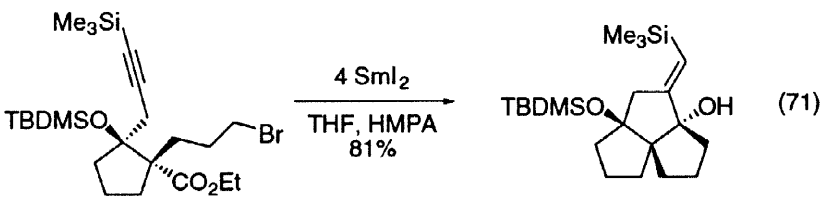
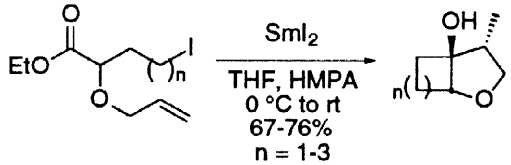


(70)

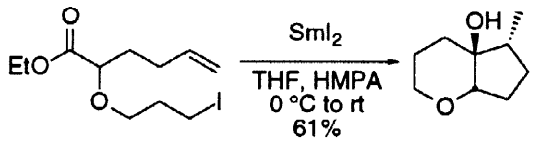


(71)

Somewhat surprisingly, oxygen heterocycles have been prepared by the same general method.[57] Thus, in spite of the tendency for α-heterosubstituted esters and -ketones to undergo rapid reductive cleavage under the same reaction conditions,[55] these α-heterosubstituents survive both the nucleophilic acyl substitution reaction and the subsequent ketyl-olefin coupling reaction to afford good yields of the desired products. As with some of the previously described processes, this sequential process is quite versatile, providing entry to a variety of structurally diverse oxygen heterocycles. Four-, five- and six-membered carbocyclic as well as heterocyclic rings can be formed in the initial nucleophilic acyl substitution reaction, while the second phase is limited to five- and six-membered ring construction (eqs 72-73).

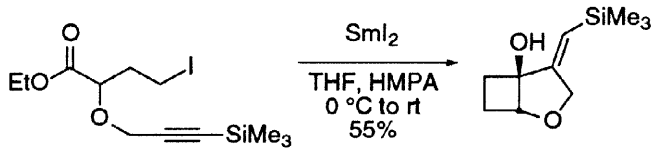



(72)




(73)

Activated alkynes have been utilized as radical acceptors for the ultimate ketyl cyclization (eq 74). 2-Bromoalkenes can be employed as terminal alkyne equivalents in the same type of radical addition/elimination sequence described previously (eq 75).

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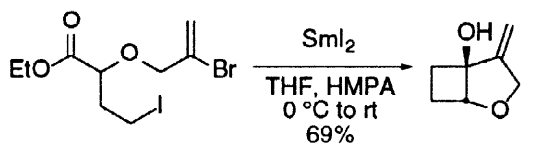
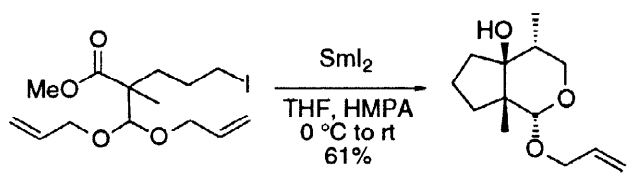



(75)

Acetals derived from allyl alcohol or propargyl alcohols are excellent substrates for the two-step process, providing stereodefined bicyclic products (eqs 76-77).

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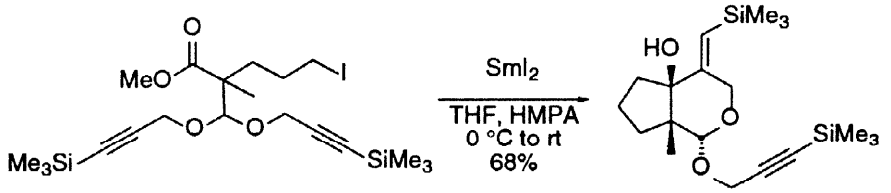
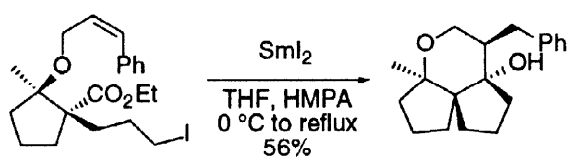
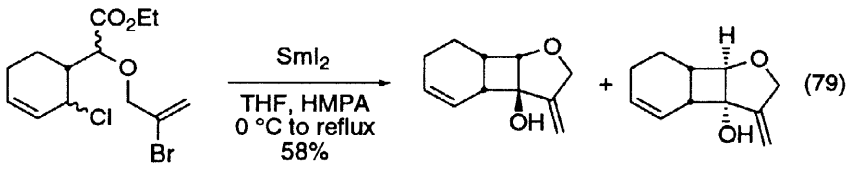



(77)

Elaborate tricyclic systems have been synthesized from readily available starting materials, providing some indication of the diversity of structural arrangements possible with this protocol (eqs 78-79).

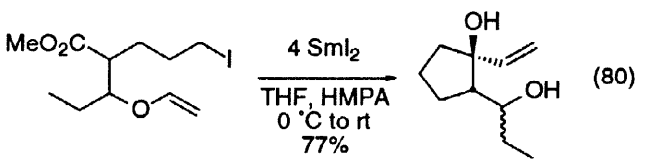



(78)



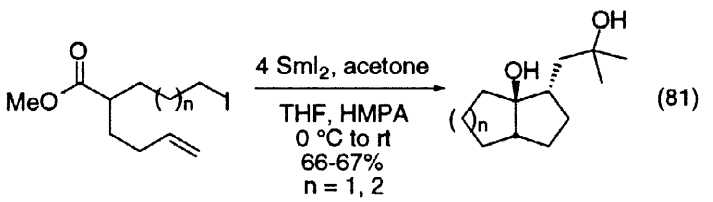
(79)

In addition to the anion/radical/elimination reaction described above for the synthesis of heterocycles (eq 75), enol ethers derived from ester aldols have been found to participate in an analogous three-step, one-pot process (eq 80).[38] After the initial nucleophilic acyl substitution reaction, the ketyl-enol ether coupling/elimination reaction induces net alkenyl transfer to the ketone. Although at this time the reaction has been performed only on a single substrate that was composed of a mixture of diastereomers, it appears likely that the process will prove to be highly general and stereoselective.



(80)

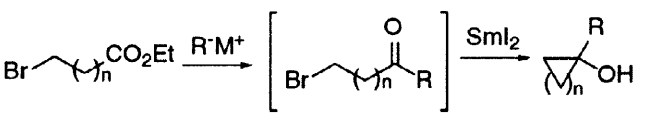
A limited number of anion/radical/anion cascades have been described.[56] In these processes, the initial nucleophilic acyl substitution/ketyl-olefin cyclization reactions led to a radical that was ultimately reduced to an organosamarium species. This nucleophile was trapped by external electrophiles such as ketones, providing products wherein three carbon-carbon bonds were created in a one-pot process. Although further development may permit other electrophiles to participate in the reaction, to date only ketones have been employed (eq 81).



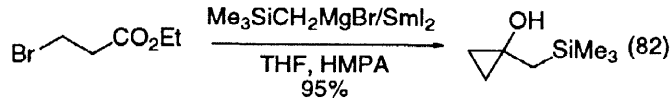
(81)

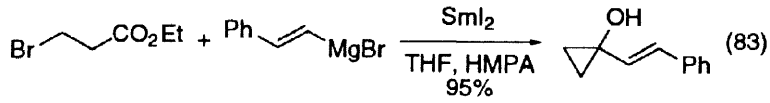
A number of highly successful processes in which an initial anionic reaction is followed by a second anionic transformation have been described. One interesting example of this involved Grignard reagents or other organometallics in combination with $SmI_2$ for the synthesis of cycloalkanols from haloesters.[58] The proposed mechanism of the reaction involves an initial addition of the chosen organometallic to the ester, providing the corresponding ketone in a nucleophilic substitution reaction (Scheme 8). A Barbier cyclization reaction of the resultant halo ketone affords the observed products.

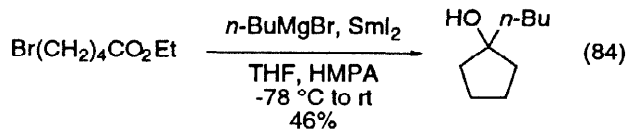
Scheme 8



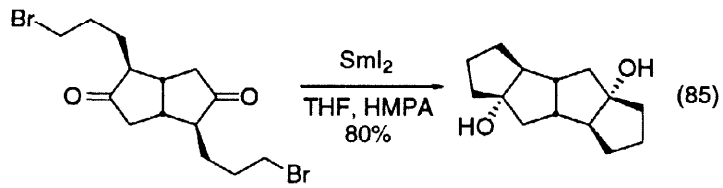

Simple three-, five-, and six-membered rings were generated in the process, although the procedure was most efficient for the synthesis of cyclopropanols (eqs 82-84). Attempts to synthesize cyclobutanols resulted in mixtures consisting primarily of tetrahydrofurans. The latter were created as a result of intermediate alkoxide cyclization onto the halide.

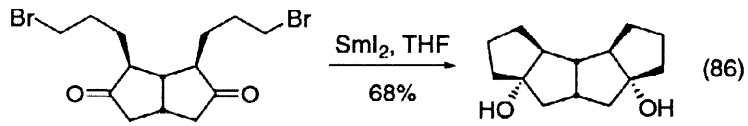


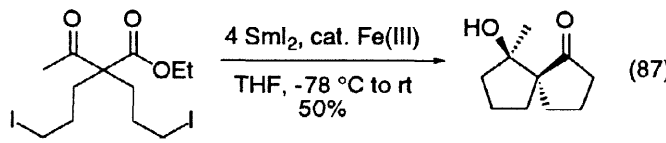




Procedures in which $SmI_2$ has been employed to carry out two intramolecular Barbier reactions have been utilized for the synthesis of polycyclic precursors to polyquinenes (eqs 85-86).[59] This provided a demonstration of a reaction wherein two pronucleophiles (the halides) were able to react separately with two different electrophiles embedded within the same substrate.

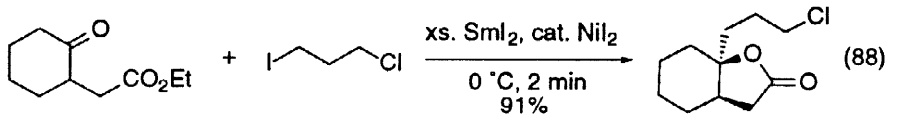



Bis(haloalkyl)-substituted β-keto esters represent another class of multifunctional substrates in which two carbon-carbon bond-forming events have been realized. In these substrates, a Barbier reaction occurred selectively, affording an intermediate alkoxy ester. Chelation of the two carbonyls with the $Sm^{+2}$ in this initial process insured the formation of a single diastereomeric alkoxide. Subsequent nucleophilic acyl substitution onto the ester provided the observed spirocyclic hydroxy ketone (eq 87).[60]

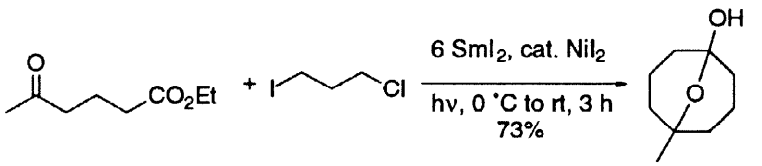



In another type of reaction in which a dinucleophilic species interacts with dielectrophiles, keto esters were reacted with dihaloalkanes in the presence of $SmI_2$ to generate seven-, eight-, and nine-membered rings.[61] Under the nickel-catalyzed reaction conditions employed,[13a] there was high selectivity for reaction of the $SmI_2$ with the alkyl iodide in preference to the alkyl chloride. Also of interest in this first stage of the reaction is the fact that little if any cyclopropane is formed from the dihalide, a reaction commonly observed in the reaction of many reductants with 1,3-dihalides.[62] Selective Barbier reaction with the ketone provided the alkoxide, which spontaneously cyclized to form a lactone. Using slightly more than two equivalents of $SmI_2$, these lactones were isolated in excellent yields (eq 88).



(88)

In the one-pot sequential process (eqs 89-91), an excess of $SmI_2$ was employed along with the nickel catalyst, and in addition the reaction was photolyzed[15] to induce the nucleophilic acyl substitution reaction of the chloride on the lactone. The latter process would be only difficulty carried out in the absence of light. Allylic halides are of course much more reactive than alkyl halides under these conditions, and thus no photolysis was required for bisallyl halide systems (eq 92).



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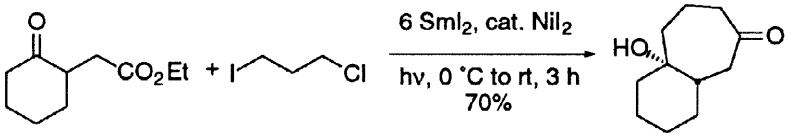
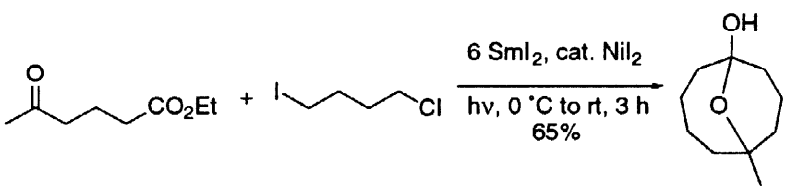
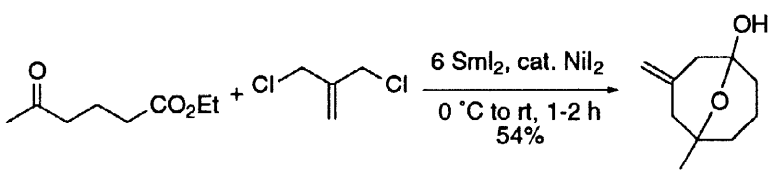


(90)

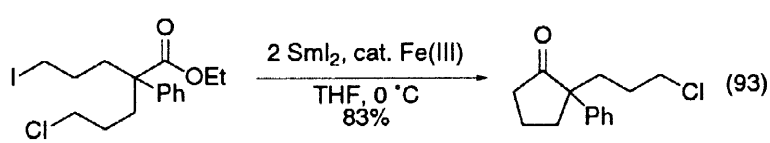


(91)



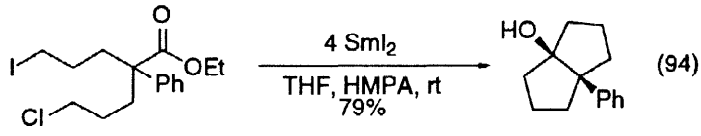
(92)

Sequential reactions have also been developed wherein a substrate possesses two dinucleophilic synthons and a single electrophilic center. In these systems, the initial electrophile (an ester) was converted in the first step of a two step process to a second electrophile (a ketone), capable of reaction with the second pronucleophile. Dihalides were again utilized as precursors in these reactions, and high selectivity was achieved in systems where iodides and chlorides were competing for two equivalents of $SmI_2$ (eq 93).[55]

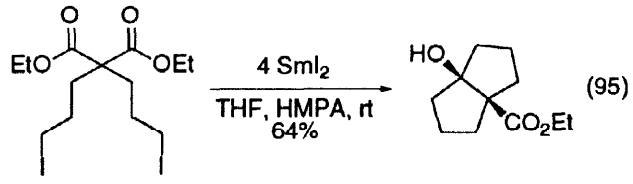


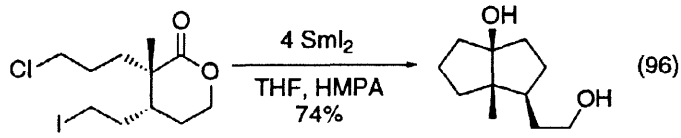
(93)

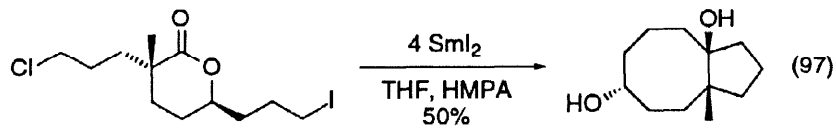
The sequential process took place smoothly under similar conditions with four equivalents of $SmI_2$, a carbonyl addition reaction following the nucleophilic acyl substitution reaction to complete the process (eq 94).[55]

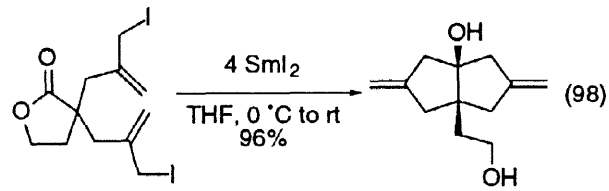


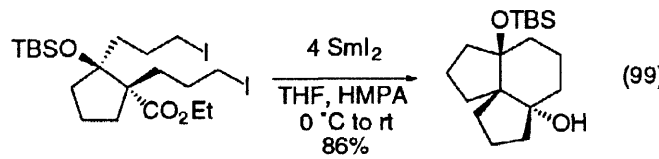

Diverse ring systems have been generated utilizing this fundamental protocol.[50] For example, in symmetrical β-diesters nucleophilic acyl substitution occurred at one of the centers, generating a ketone. This newly created electrophile subsequently reacted in preference to the remaining ester (eq 95). Lactones have been utilized as substrates for the reaction. Depending on the substitution reaction, small (eq 96) or medium-ring products (eq 97) were generated. Allylic halides reacted effectively for the synthesis of bicyclics containing exomethylene substituents (eq 98). Both angularly fused (eq 99) and linearly fused tricyclic systems (eq 100) were also accessible from readily available starting materials.

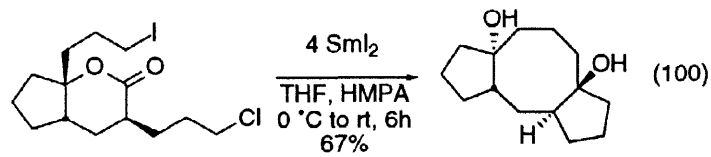


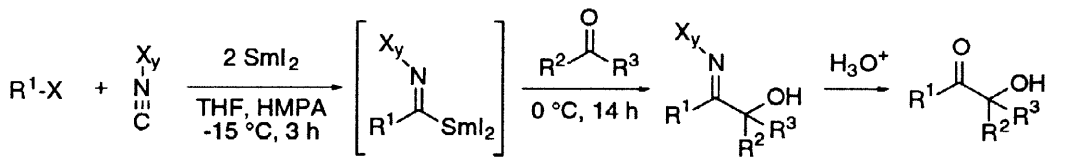



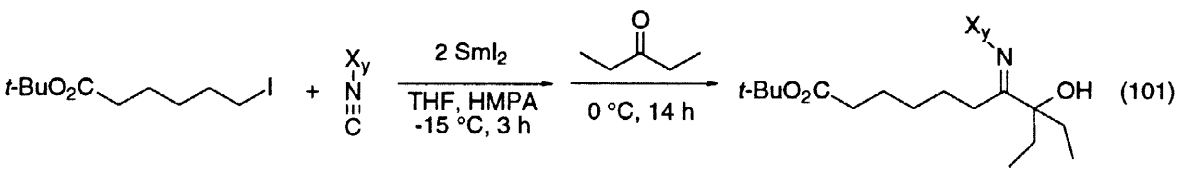

α–Hydroxy ketones comprising a variety of substitution patterns were generated through a $SmI_2$-promoted three-component coupling reaction.[63] Organic halides, xylyl isocyanides, and aldehydes or

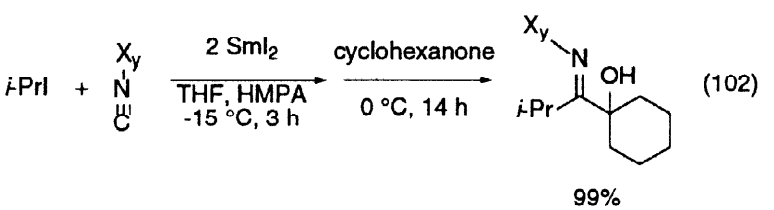
ketones constitute the three substrates for the reaction, which proceeds by initial reaction of the halide with the isocyanide, generating an α-iminoalkyl samarium(III) species (Scheme 9). Reaction of this acyl anion equivalent with the carbonyl substrate followed by hydrolysis of the resulting α-hydroxy imine completes the sequence.

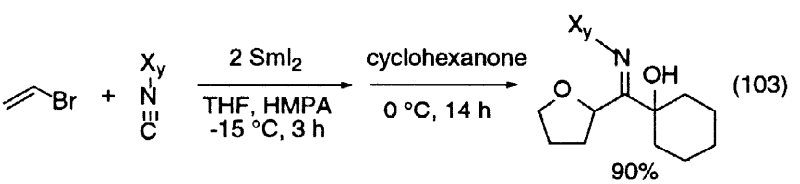
Scheme 9

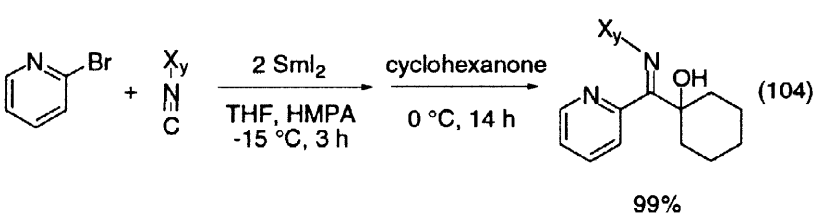



The scope of this protocol has been examined, and the overall process appears to be extraordinarily general. Primary alkyl halides (eq 101) as well as secondary halides (eq 102) participate in the reaction. Benzylic halides can be utilized, but yields are modest. Tertiary alkyl halides readily add to the nitrile, perhaps by a radical addition mechanism, but the subsequent carbonyl addition is inefficient and the intermediate imine is isolated. Alkenyl halides and aryl halides are only difficultly reduced to the corresponding organometallics,[45] and the intermediate radical readily abstracts a hydrogen from solvents like THF. In the present case, the anion resulting from this hydrogen abstraction and subsequent reduction undergoes addition to the isocyanide and further coupling to the carbonyl electrophile (eq 103). Thus, although there are some exceptions (eq 104), alkenyl and aryl halides are not suitable precursors for the reaction.

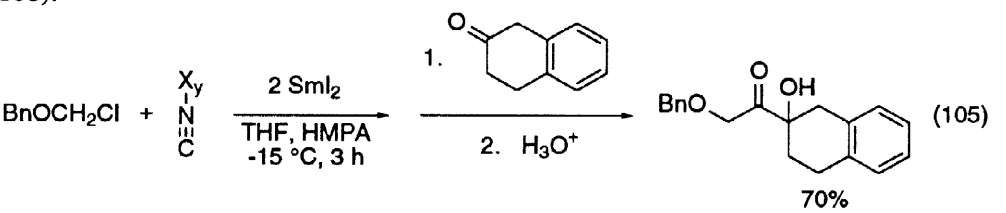


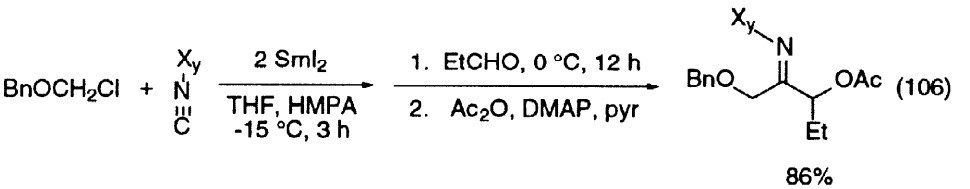



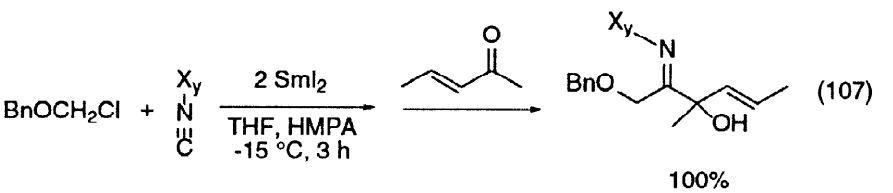



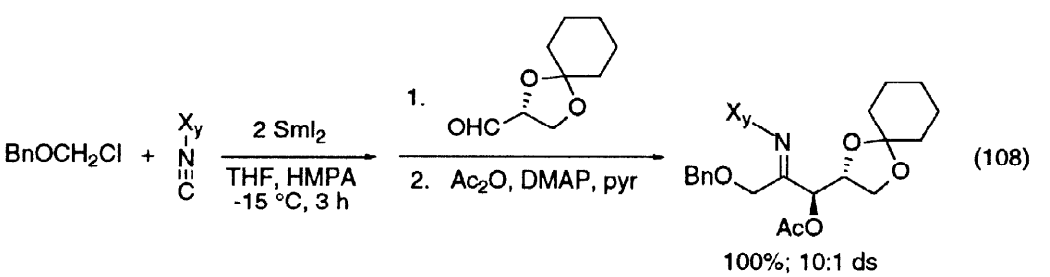



Chloromethyl benzyl ether is an efficient halide precursor in analogous reactions, and it has been utilized as an α-hydroxymethyl anion equivalent in the three-component coupling reactions.[64] Both ketones (eq 105) and aldehydes (eq 106) were suitable substrates for the final coupling. α,β-Unsaturated ketones provided exclusively the product of 1,2-addition (eq 107). Reasonably high diastereoselectivity has been observed in a reaction with a chiral, nonracemic aldehyde substrate, resulting in an efficient synthesis of ketoses (eq 108).

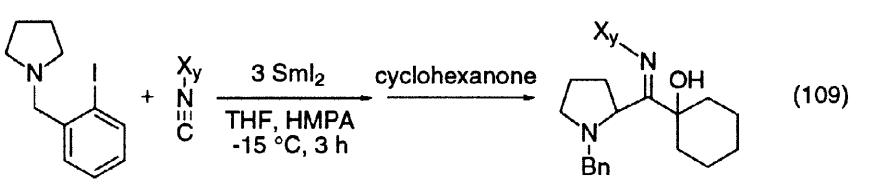


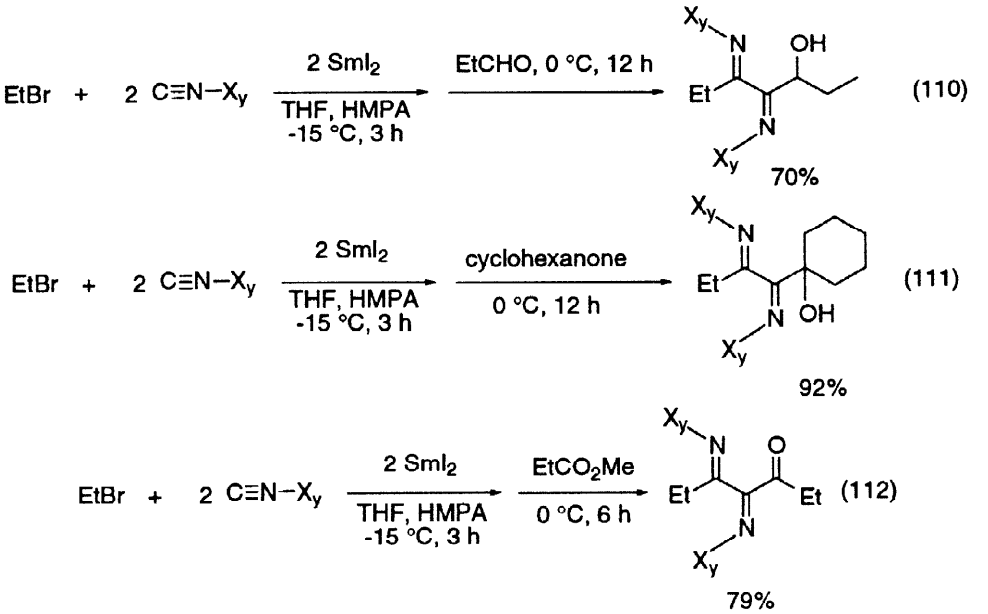




In addition to the α-hydroxymethyl anion equivalent, α-amino carbanion equivalents have been employed in the three-component coupling cascades.[46] The atom-transfer method for metalation of amines was employed in this case, resulting in an efficient coupling route to the desired α-hydroxy imines (eq 109).

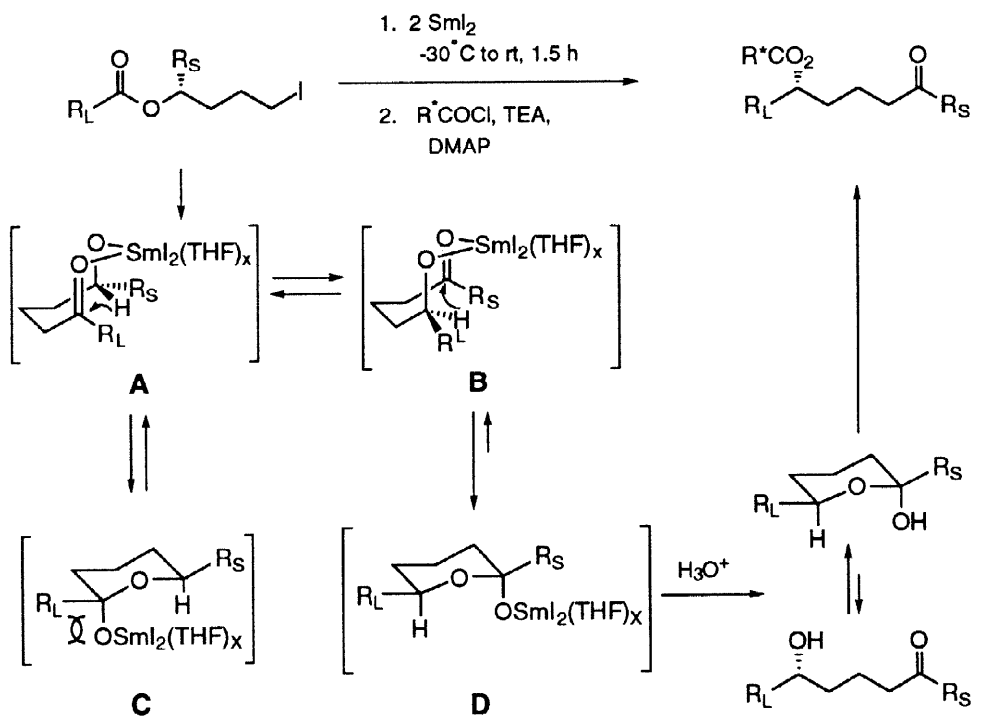


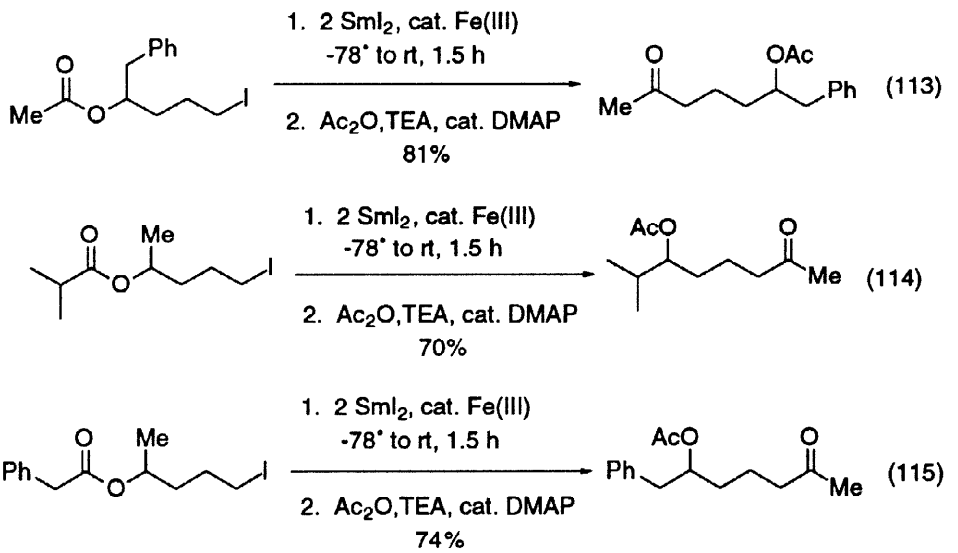

The xylyl isocyanide chemistry has even been extended to four component coupling reactions.[65] In this protocol, an alkyl halide, two equivalents of the xylyl isocyanide, and a carbonyl substrate participated in the overall sequence. Aldehydes (eq 110), ketones (eq 111), and esters (eq 112) have all been utilized as the final electrophilic component of the reactions.




A rather unusual anionic/anionic sequence has been discovered that involves an intramolecular nucleophilic acyl substitution reaction followed by an intramolecular Meerwein-Ponndorf-Verley redox reaction (Scheme 10).[66] The redox reaction has been demonstrated to be reversible and stereospecific. The equilibrium is driven by steric interactions between the oxidosamarium(III) species and the alkyl group on the adjacent carbon (**C** versus **D**). In cases where $R_L$ is sterically small, the product appears to result from a simple nucleophilic acyl substitution reaction (eq 113). However, when $R_L$ is the more sterically bulky substituent, it becomes apparent that an equilibrium is involved, and in favorable cases a single product resulting from the sequential process can be isolated (eqs 114-115).

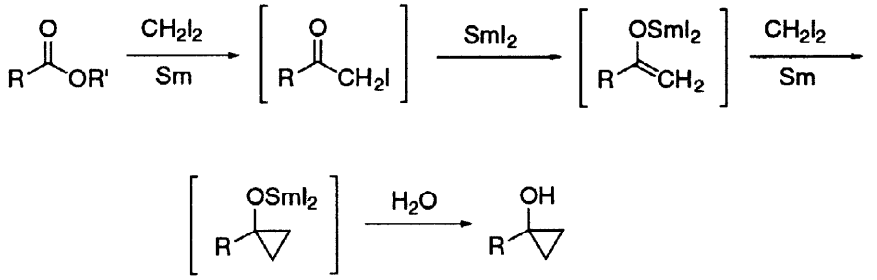
Scheme 10



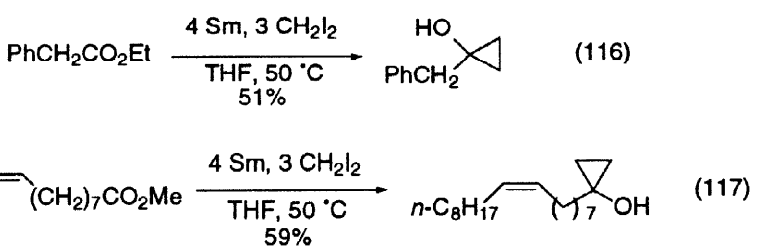


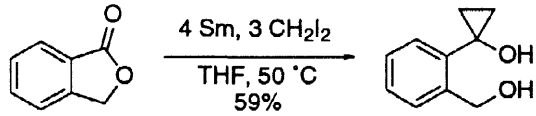

Finally, a complicated series of reactions has been employed to directly convert carboxylic acid esters to cyclopropanols (Scheme 11).[67] Esters react with diiodomethane and $SmI_2$ (generated in situ) to undergo a nucleophilic acyl substitution reaction forming the corresponding iodomethyl ketones. Reduction of this α-heterosubstituted ketone with further equivalents of $SmI_2$ generates an enolate that undergoes cyclopropanation with the carbenoid created by the reaction of samarium metal with diiodomethane.

Scheme 11




The yields achieved in the transformation of the substrates examined are impressive, particularly in view of the complex nature of the overall conversions. Both simple esters (eqs 116 and 117) as well as lactones (eq 118) afford good yields of the desired cyclopropanols.






(118)

## V. CONCLUSION

Among the diverse reducing agents that might be capable of sustaining cascade reactions, $SmI_2$ stands alone in terms of its selectivity, efficiency, and ease of use. In terms of the types of global efficiencies outlined in the introduction of this review, in its various uses the reagent has satisfied all but one - atom economy. Even here, some progress has been made in carrying out $SmI_2$ reactions in a catalytic manner,[68] and it is not inconceivable that a means might be developed (e.g., electrochemical regeneration of the reductant) that could one day satisfy this criterion as well.

Nonetheless, even if $SmI_2$-promoted processes remain forever stoichiometric, one can safely argue that the increases in molecular complexity produced by this homogeneous reductant make it a reagent without peer in the realm of reductive cascade reactions.

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## Biographical sketch

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Christina Harris received her B.S. degree in 1992 from Oklahoma State University, Stillwater and her Ph.D. degree in 1997 under the direction of Professor Gary A. Molander at the University of Colorado, Boulder. She is the recipient of the Marion L. Sharrah Fellowship in Chemistry (1996), a University of Colorado Graduate School Fellowship (1992-95), the Skinner Scholarship in Chemistry (1990-92), the Women in Energy Scholarship (1991-92), the Anne Clark McHale Scholarship (1991-92), and the CRC Press Freshman Chemistry Award (1989). Christina is also a member of the Phi Kappa Phi Honor Society.