Sequencing Reactions with Samarium(II) Iodide

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Contents

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I. Introduction

In pursuit of the "ideal synthesis", the concept of efficiency is not limited simply to high yields but is, in fact, multifaceted.[1] Among many things, the most efficient organic reactions tolerate unprotected functional groups, generate single isomeric products in high yields, and dramatically increase molecular complexity in a single operation. Processes that form multiple carbon−carbon or carbon−heteroatom bonds in a sequence of events without isolation of any intermediates represent a very powerful means to approach this ideality. These one-pot, sequential reactions possess built-in efficiencies that magnify their impact on organic synthesis.

Although conceptually attractive, the complexities involved in the design of sequential reactions can be daunting. To avoid generating complex product mixtures, the yield and selectivity required for each individual reaction in a multistep sequence must be exceedingly high. As a consequence, the difficulties associated with establishing an effective sequential process increase rapidly with the number of individual reactions taking place in the overall process. It is not surprising, then, that only a select group of reagents or specific transformations may be suitable for tandem processes.

One reagent that exhibits exceptional properties for sequential reactions is samarium(II) iodide (SmI_2).[2] This ether-soluble one-electron reducing agent burst onto the scene in the late 1970s and has played an ever-increasing role in organic synthesis since that time. Samarium diiodide promotes a number of important individual reactions found useful in organic synthesis: radical cyclizations, ketyl−olefin coupling reactions, pinacolic coupling reactions, Barbier-type reactions, aldol-type reactions, Reformatsky-type reactions, conjugate additions, and nucleophilic

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acyl substitutions. In these reactions, SmI_2 exhibits remarkable selectivity. Additionally, the reactivity and/or selectivity of SmI_2 can be modified by the addition of catalysts,[2a] by solvent effects,[3] or through other variations of the reaction conditions.[4] The ability to modulate the reactivity of SmI_2 adds to the potential applicability of the reagent in complex sequential processes.

The versatility of SmI_2 is enhanced further in tandem reactions by its ability to promote both one- and two-electron processes. Moreover, if properly designed, these processes can be accomplished in any combination or order. Thus, sequential radical processes, tandem carbanionic reactions, processes initiated by radical reactions and terminated by carbanionic reactions, and transformations initiated by carbanionic reactions followed by radical reactions have all been reported.

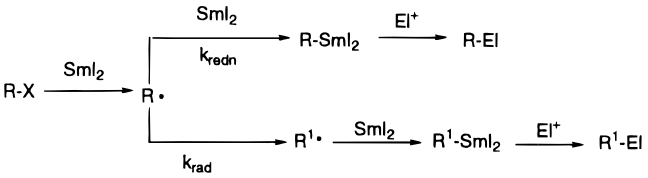
This review is intended to highlight the use of SmI_2 in each of these classes of sequential, or tandem, organic reactions. To this end, the individual carbon−carbon bond-forming reactions promoted by SmI_2 are outlined first, with emphasis placed on the individual characteristics (e.g., experimental conditions, stereoselectivities, and general scope and limitation issues) that become increasingly important in the more complex tandem processes. Although to date not all of these individual reactions have been utilized in sequenced reactions, the potential certainly exists for their implementation in tandem processes. Therefore, for completeness an overview of all such reactions has been provided. A review of sequenced reactions will follow, including only those processes that create multiple carbon−carbon or carbon−heteroatom bonds. Thus, for the purpose of this review, serial processes in which a fragmentation or reductive cleavage precedes a single bond-forming event will not be considered as true sequential processes.[5] The review covers published material through mid-1995.

II. Individual Reactions Promoted by Samarium(II) Iodide

A. Single-Electron Processes

Samarium(II) iodide can be utilized as a reductant to generate radicals from a variety of diverse substrates. Alkyl, aryl, and alkenyl radicals can be produced from halide substrates as well as other precursors. Ketyl radical anions can be generated from aldehydes and ketones. Samarium(II) iodide-promoted radical reactions are often complementary to those carried out with other reductants and frequently offer higher selectivities as well. These features, combined with the reductive reaction conditions, provide opportunities for further functionalization via sequential reactions. The types of radical reactions carried out to date with SmI_2 are outlined below, along with some assessment of their special characteristics and their scope and limitations.

Scheme 1



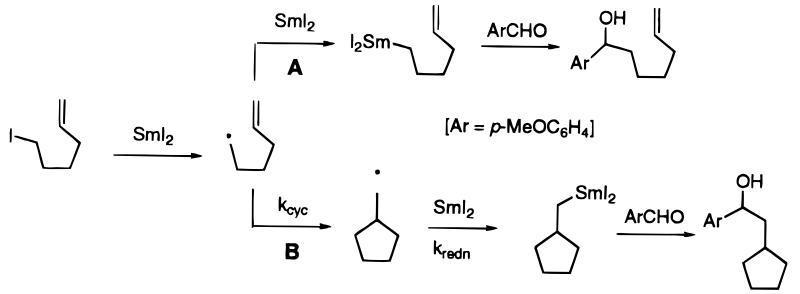
1. Alkyl, Aryl, and Alkenyl Radical Reactions

Samarium(II) iodide is an effective reagent for the initiation of radical reactions via the reduction of organic halides. There are, however, intrinsic limitations in the SmI_2-promoted processes. The reductive reaction conditions required for the generation of the radical also promote reduction of radicals to the corresponding anion (Scheme 1). Thus any desired radical reaction (k_{rad}) must take place significantly faster than reduction of the radical to the corresponding anion (k_{redn}). Several classes of radical cyclization reactions fall into this category, and in suitably designed systems these reactions provide a useful alternative to reactions initiated by tin hydride and silicon hydride. Most importantly, the ability to generate organosamariums via reduction of the resulting radical forms the basis for some of the sequential reactions discussed below. In this regard, the SmI_2-promoted reactions are clearly distinguished from the tin hydride- and silicon hydride-induced processes.

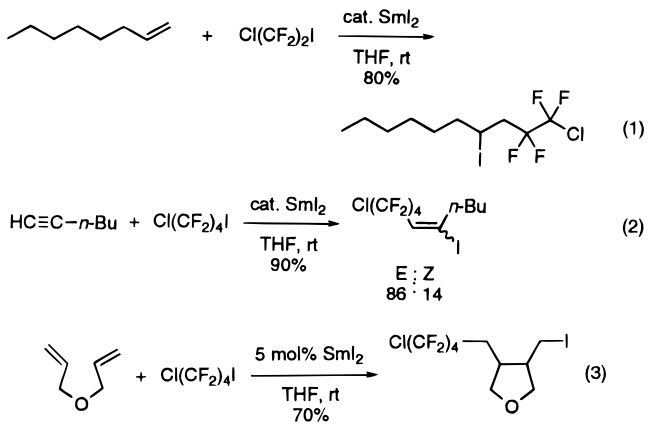
In order to assess which SmI_2-promoted alkyl radical reactions are viable, knowledge of the bimolecular rate constants for reduction of alkyl radicals by SmI_2 is essential. Utilizing a competitive hexenyl radical clock, rate constants for the reduction of a primary radical by SmI_2 in THF/HMPA mixtures have been determined (Scheme 2).[6] Rate constants vary with the HMPA concentration as reflected by the partitioning of the reaction between the two pathways depicted in Scheme 2. In the absence of HMPA, the reduction of 6-iodohex-1-ene was reported to be too slow for these rate experiments. With as little as 2 equiv of HMPA, however, a sufficient reaction rate was achieved to observe partitioning between pathway **A** and pathway **B** in a ratio of 8:92. This translates to a $k_{redn} = 5 \times 10^5\ M^{-1}\ s^{-1}$. The rate of reduction of the radical to the anion increased rapidly with increasing HMPA concentration until about 5−7 equiv of HMPA were added, at which point it reached a value of $7 \times 10^6\ M^{-1}\ s^{-1}$. At this concentration of HMPA, the partitioning of pathway **A** and pathway **B** was 56:44. Similar rate constant analyses have led to the conclusion that tertiary alkyl radicals are reduced to the corresponding anions with a rate constant $\leq 10^4\ M^{-1}\ s^{-1}$. Presumably, the rate constant for reduction of secondary radicals to the anion by SmI_2 lies somewhere in between.

It is apparent that synthetically useful radical processes promoted by SmI_2 can be carried out only if the radical has a sufficient lifetime to undergo the desired radical process. To date, only a single class of intermolecular alkyl radical reactions have satisfied this criterion. Thus, the SmI_2-catalyzed addition of polyhaloalkanes to alkenes and alkynes provides

Scheme 2



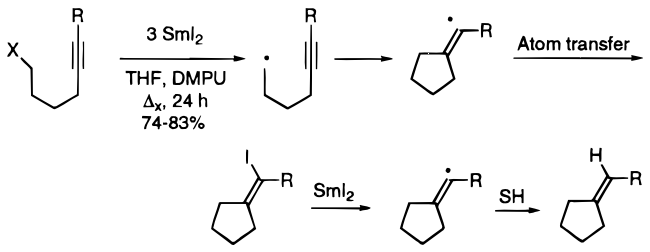
an efficient route to polyhalide-functionalized products (eqs 1−3).[7] This radical chain process provides a useful route to these compounds, which are otherwise generated by photochemical, thermal, electrochemical, or other metal-catalyzed processes.



For the most part, cyclization reactions dominate SmI_2-promoted alkyl radical processes. An obvious advantage of cyclization reactions is that the cyclization is a unimolecular process, whereas reduction of the alkyl radical to the corresponding anion by SmI_2 is a bimolecular reaction. Consequently, low concentrations can be employed to optimize the radical process.

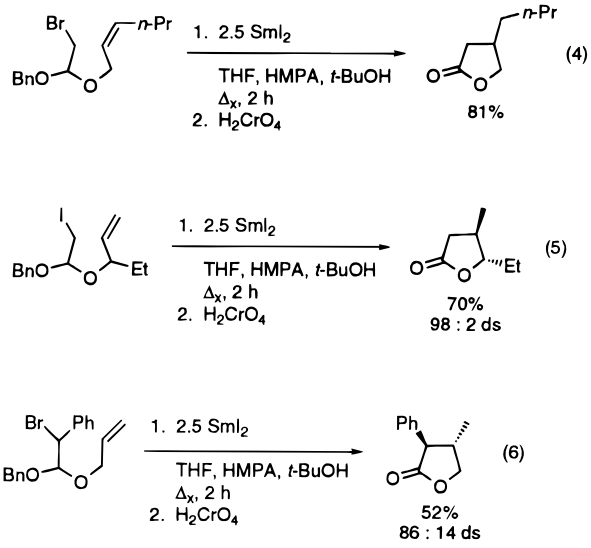
Among the reported cyclization reactions determined to be synthetically useful are cyclizations of 6-halohex-1-ynes.[8] When performed in THF solution in the presence of DMPU, the process is effective for the synthesis of exomethylenecyclopentanes. The SmI_2-promoted reaction probably proceeds by an atom-transfer mechanism (Scheme 3).[9] Thus, reduction of the alkyl halide provides the alkyl radical, which undergoes cyclization to the cyclopentylidene radical. The latter then abstracts an iodine (or bromine) atom from the starting material, generating the alkenyl halide. The alkenyl halide can eventually be reduced back to the cyclopentylidene radical by

Scheme 3



SmI_2, and the resulting alkenyl radical in turn can abstract a hydrogen from the solvent or another hydrogen donor to provide the observed products. It should be noted that unstabilized alkenyl radicals[3a,10] (as well as aryl radicals[3a,10d,11]) abstract hydrogen atoms from donor solvents more rapidly than they are reduced to the corresponding anion by SmI_2. This point becomes of importance in discussions of radical cyclization reactions and the sequential reactions below.

Alkyl radicals possessing an oxygen within the chain cyclize onto alkenes with rates generally an order of magnitude more rapidly (5×10^6 s^{-1}) than their all-carbon analogues. This observation has been used to advantage in a SmI_2-promoted synthesis of lactones that proceeds via an initial radical cyclization (eqs 4−6).[12]



The diastereoselectivity of the reaction is quite high in several cases. The origin of this diastereoselectivity is not entirely clear because the stereochemistry of the starting materials is not defined. However, the stereoselectivity appears to be adequately explained by reaction through the standard chair transition structure, with the allylic stereogenic center anchoring the structure (Figure 1).

α-Heterosubstituted radicals undergo reasonably efficient cyclization reactions onto alkenes as well. For example, appropriately substituted glycosyl phenyl sulfones can serve as precursors to anomeric radicals upon treatment with SmI_2 in THF/HMPA (eq 7).[13] Cyclization affords the observed product as a mixture of diastereomers. It is important to note

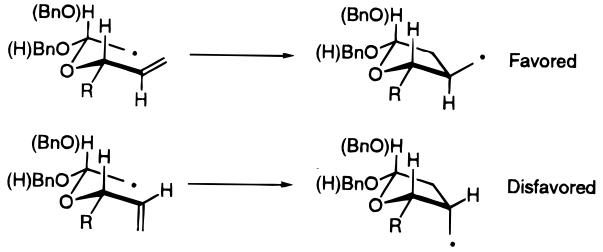
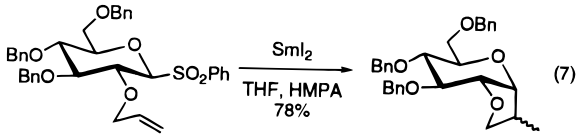


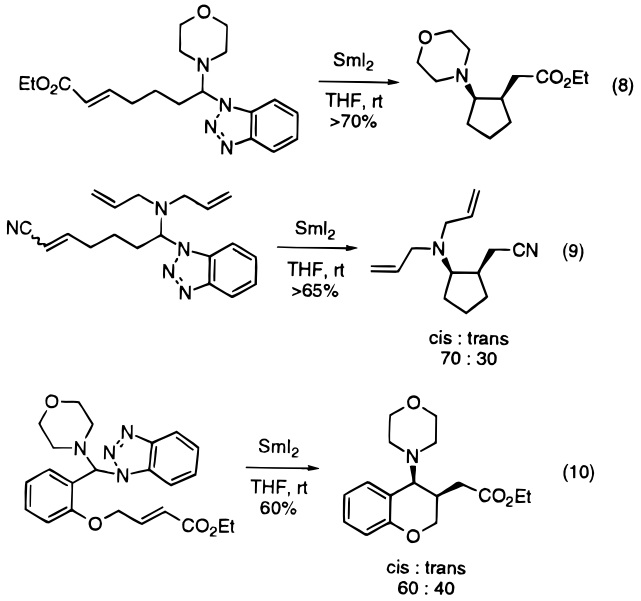
Figure 1.

that cyclization occurred in preference to reduction of the radical to the anion, which would have induced a β-elimination of the allyloxy group.



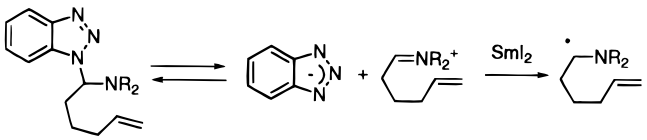
(7)

In a similar fashion, α-amino radicals derived from *N*-[(*N*′,*N*′-dialkylamino)alkenyl]benzotriazoles undergo cyclization to provide the corresponding amino cyclopentanes and amino tetrahydropyrans in modest yields (eqs 8−10).[14] Mixtures of diastereomers are usually obtained in these reactions, with the cis isomers generally predominating.

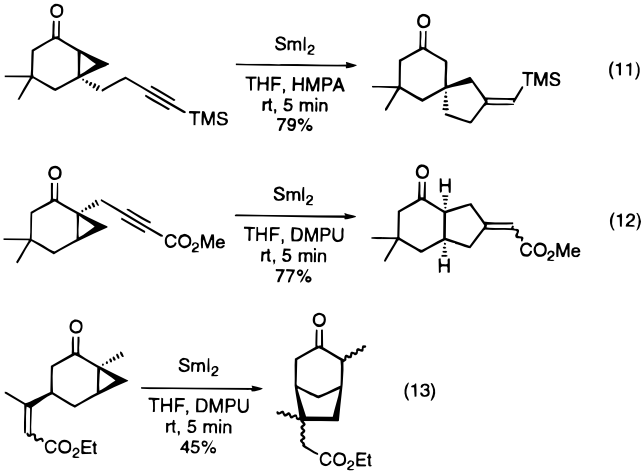


It has been postulated that these reactions proceed by dissociation of the [α-(dialkylamino)alkyl]benzotriazoles into benzotriazole anion and iminium cations. The latter undergo rapid reduction with SmI_2, affording the requisite radical (Scheme 4).

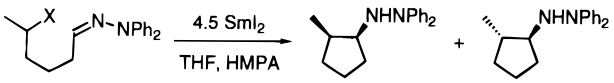
Scheme 4



There are other ways to generate alkyl radicals using SmI_2 aside from the reduction of halides, sulfones, and related functional groups. For example, the reductive cleavage of cyclopropyl ketones provides a unique route to cycloalkylmethyl radicals via a cyclopropylcarbinyl/homoallylic radical rearrangement process.[15] The radical thus generated has been trapped by alkenes and alkynes to provide a concise route to bicyclic ring systems (eqs 11−13).



Although cyclization onto alkenes and alkynes represents the most common mode of reaction for alkyl radicals generated by SmI_2, other functional groups can serve as radical acceptors as well. For example, hydrazones have been found to be exceedingly efficient acceptors for alkyl radicals. Experimentally measured 5-exo cyclization rates of 1.1×10^8 s^{-1} for the *cis*-cyclopentylhydrazines and 4.6×10^7 s^{-1} for the *trans*-cyclopentylhydrazines (both at 80 °C) have been recorded.[16] The 6-exo cyclization rate constant is 9.4×10^5 s^{-1} at 80 °C for both cis and trans hydrazine isomers. Although both tri-*n*-butyltin hydride and SmI_2 have been utilized to effect cyclization of halohydrazones to cyclopentylhydrazines, the latter provides an advantage in that reactions can be performed at a lower temperature, resulting in higher diastereoselectivities. For optimum diastereoselectivity, iodides must be employed as the substrates for the reactions. In this way the reactions can be performed at −78 °C (eq 14). Alkyl bromides do not react with SmI_2 at −78 °C, but do react well at temperatures as low as −42 °C.



X = Br	-42 °C	88% yield	7 : 1 ds
X = I	-78 °C	62% yield	11 : 1 ds

(14)

The sense of diastereoselection in these reactions can be rationalized by reaction of the alkyl radical through a chair transition structure (Figure 2).[16] The structure leading to the trans diastereomer suffers a 1,3-diaxial interaction between the substituent at the radical center and one of the hydrogens on the ring, while this unfavorable interaction is absent in the preferred transition structure.

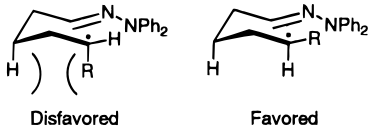
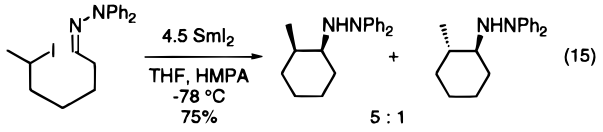
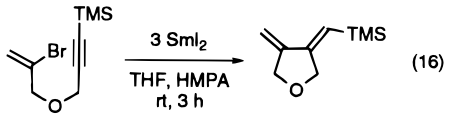


Figure 2.

Although diastereoselectivities observed in the analogous 6-exo cyclization process are somewhat lower, the efficiency of the process is still quite high, and very good yields of the desired aminocyclohexanes can be achieved (eq 15).[16]

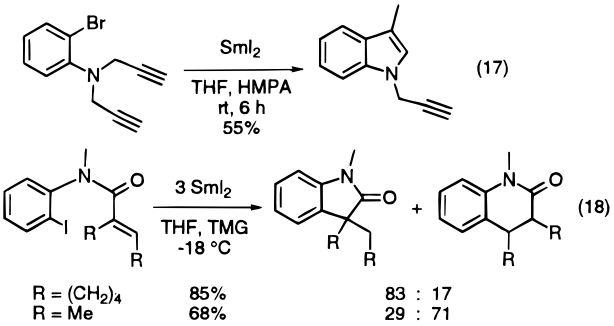


Alkenyl and aryl radicals have the potential to be among the more useful radical intermediates for SmI_2-promoted cyclization reactions because as pointed out above the radicals are not reduced to the corresponding anion at a rate that is competitive with hydrogen atom abstraction from THF. In spite of this, relatively few of these types of reactions have been explored. In limited studies, 5-exo and 6-exo cyclizations of alkenyl radicals derived from bromopropenyl ethers have been examined.[17] Yields were not reported, but it is clear from the data provided that the 5-exo cyclization reactions were selective and reasonably efficient (eq 16), whereas analogous 6-exo cyclization reactions led to low yields of a mixture of products. Although it has been

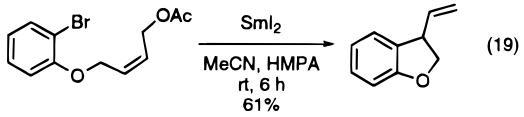


claimed that the high diastereoselectivity in the 5-exo cyclization is a result of rapid hydrogen abstraction from the donor solvent, there is no experimental evidence to support this supposition and with the silyl-substituted alkynes further reduction of the silyl-substituted alkenyl radical to an alkenyl samarium species remains a distinct possibility.

A more thorough examination of the cyclization of aryl radicals onto alkenes and alkynes has been undertaken, resulting in a general approach to the synthesis of benzofurans, naphthofurans, and indoles (eq 17).[3c,10d] Unsaturated amides have been examined as aryl radical acceptors in SmI_2-promoted reactions.[3e] The 5-exo:6-endo cyclization ratio varies somewhat with reaction conditions, but more markedly with substrate (eq 18). The study depicted was undertaken to determine the effect of various additives on reactions promoted by SmI_2. Tetramethylguanidine (TMG) was found to be superior to other additives (e.g., Et_3N, HMPA, DMPU) in its ability to facilitate the aryl radical cyclization.



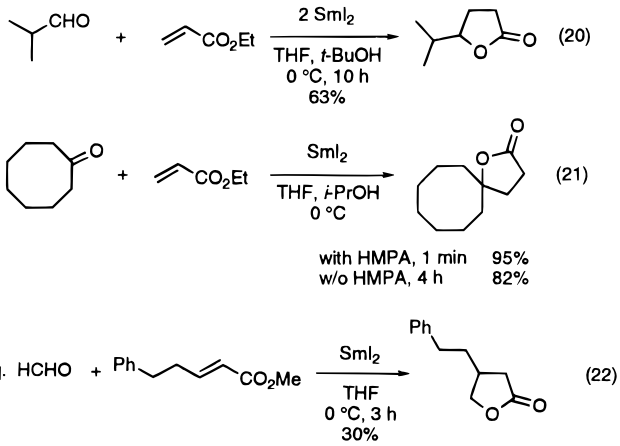
Finally, a radical addition/elimination sequence can be utilized to create a new carbon−carbon bond and retain olefin functionality in the final product. Thus, the use of allylic acetates as the radical acceptors results in β-elimination of the acetate following radical cyclization and reduction of the resulting radical to the anion (eq 19).[10d]



2. Ketyl Radical Anion Reactions

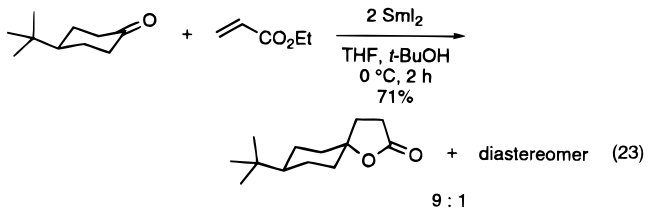
To date, the ketyl−olefin coupling reaction and related processes represent the most widely studied radical reactions promoted by SmI_2. A variety of partners have been utilized in investigations of this reaction, and both intermolecular and intramolecular versions of the reaction have been explored. Stereochemical features of the reaction have been investigated as well, and the reaction thus serves as a highly useful means to couple aldehydes and ketones to alkenes and alkynes.

The intermolecular version of the ketyl coupling reaction is restricted to substrates that are good acceptors for nucleophilic radicals. For example, α,β-unsaturated esters are among the best partners for the reaction.[18] In this case, lactones are the observed products of the reaction (eqs 20−22). A proton source



is apparently essential for the reaction, and HMPA effectively promotes the reaction in the sense that reaction times can be reduced dramatically in the presence of this agent. It is notable that aqueous formaldehyde can be utilized as a substrate for the reaction, although only modest yields of coupled products were observed. It is also interesting that in one example Cp_2ZrCl_2 was an effective additive for the reaction. Although it was postulated that the latter served as a Lewis acid promoter, this rationale should be viewed with some skepticism.

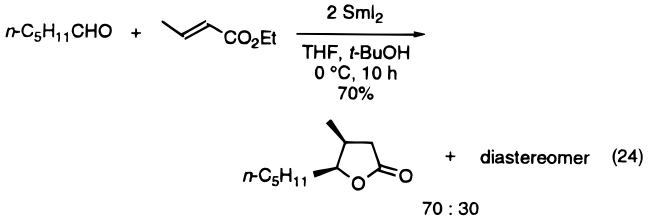
Studies of the stereochemistry of these reactions have revealed some interesting features. For example, the product observed in the coupling of 4-*tert*-butylcyclohexanone with ethyl acrylate results from approach of the unsaturated ester from the axial orientation (eq 23).[18b] This is in contrast to SmI_2-promoted allylation,[2a] alkylation,[19] and iodomethylation[20] reactions of 4-*tert*-butylcyclohexanone, where



(23)

equatorial attack predominates. The sense of asymmetric induction can perhaps be attributed to the preferred configuration of the ketyl intermediate, which has been proposed to exist with orbital extension in the axial direction on the basis of both experimental and theoretical studies.[21]

There are considerable discrepancies associated with reported diastereoselectivities in reactions of crotonates with aldehydes, even though the reactions appear to have been performed under very similar reaction conditions. In one report, the diastereoselectivity in the reaction was 70:30 in favor of the cis isomer (eq 24),[18b] whereas another group has reported >99:1 diastereoselection for the cis isomer in a related system (eq 25).[18c,d] The diastereoselectivity appears to be independent of the unsaturated ester isomer used,[18d] but unfortunately the nature and magnitude of diastereoselection remains ambiguous.



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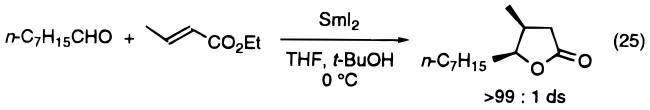

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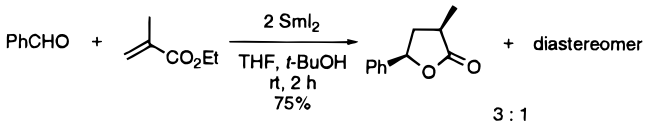
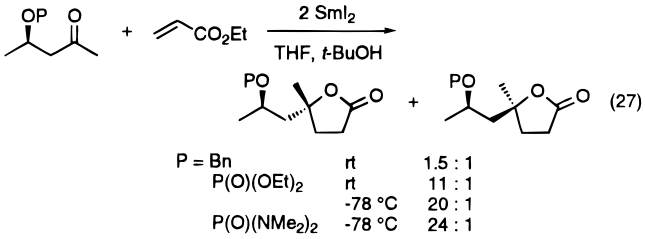
Reported diastereoselectivities in the coupling of methacrylates with carbonyl substrates varies between 1:1 and 6:1 (eq 26),[18] and in some cases the sense of asymmetric induction has not been confirmed.[18c] α,β-Disubstituted enoates appear to react well with ketones, although mixtures of diastereomers result. However, no coupled products were obtained in reactions of such highly hindered unsaturated esters with aldehydes.[18c]



(26)

Considerable evidence suggests that facial selectivity in attack of radicophiles on ketyls may be governed by the relative stabilities of the ketyls themselves, and that, although significantly pyramidalized, low inversion barriers exist between the two limiting configurations.[21] Consequently, efforts to restrict the conformation of ketyls and thereby provide a bias for one configuration over another provides a means for acyclic stereocontrol in reactions of ketyl intermediates. This postulate has been tested using the Lewis acidic Sm(III) counterion as a template to provide chelation control of the conformation and configuration of the ketyl complex. Interestingly, in a study of 1,3-relative asymmetric induction the highest diastereoselectivities were not achieved through a six-membered ring chelate as might be anticipated (eq 27, P = Bn), but rather through an eight-membered ring assembly [P = P(O)(NMe$_2$)$_2$].[18d]



(27)

Although at first this appears unusual, eight-membered ring Sm(III) chelates have been postulated as stereochemical control elements in other instances, most notably in intramolecular Reformatsky-type reactions[22] and in intramolecular redox reactions.[23] In the present case, the observed sense of asymmetric induction has been rationalized as proceeding through an eight-membered ring chelate in which both methyl groups are oriented pseudoequatorially, with attack of the unsaturated ester occurring from the pseudoaxial direction (Figure 3).

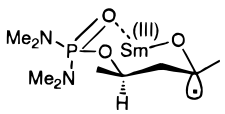
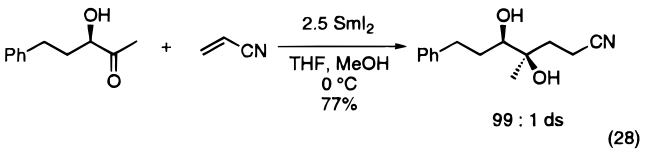


Figure 3.

With free hydroxyl groups as the chelating substituent, high levels of 1,2-asymmetric induction have been achieved through a five-membered ring chelate (eqs 28−30).[24] As might be expected on the basis of



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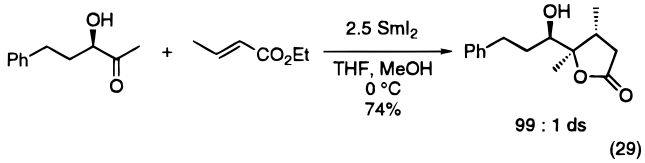

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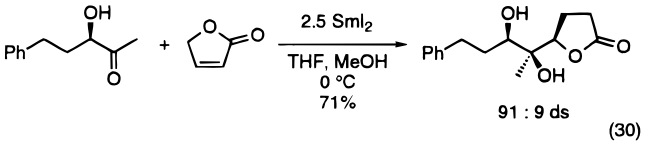
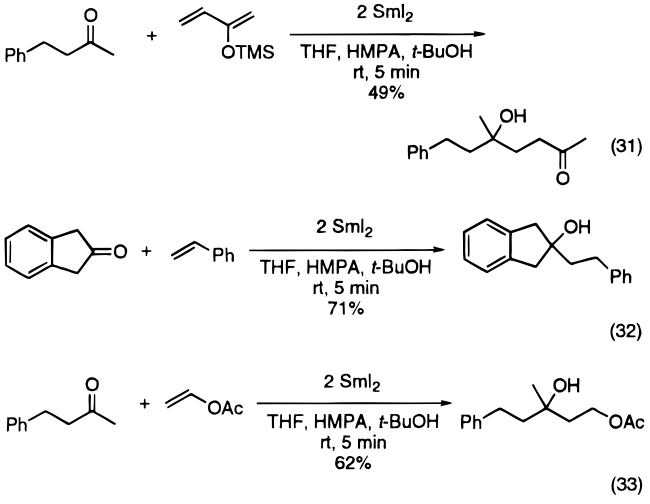


(30)

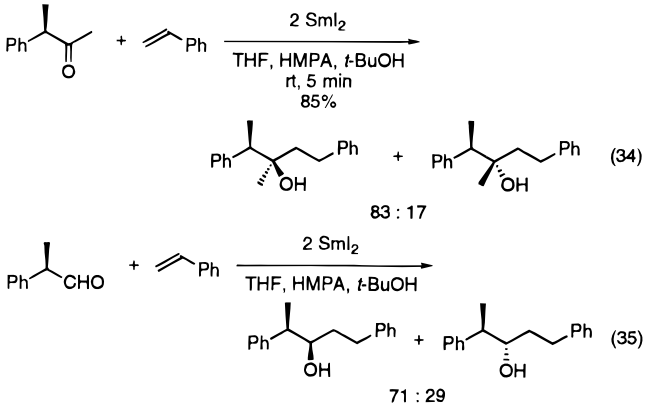
chelation control, the use of HMPA as an additive to these reaction mixtures results in lower diastereoselectivities. In contrast to previously reported coupling reactions of this type involving β-substituted enoates (eq 25),[18d] these reactions appear to be stereospecific. Thus in the present transformation there is strict fidelity in the conversion of *E* and *Z* substrates to the stereoisomeric products (eqs 29 and

30). Furthermore, the sense of relative asymmetric induction in these cases would appear to be diametric to those reported in related studies.[18d] The source of these discrepancies remains to be determined.

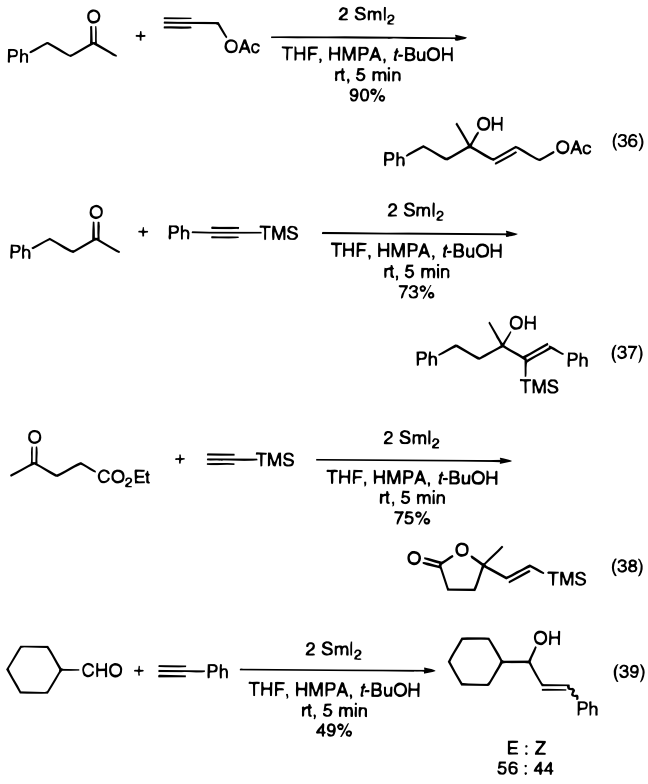
In addition to conjugated esters and nitriles, other conjugated alkenes (e.g., styrene and 1,3-dimethylbutadiene) as well as alkenylsilanes, vinyl acetates, and allylic acetates serve as efficient ketyl acceptors in the SmI_2-promoted intermolecular coupling reactions (eqs 31−33).[25] Not all of these are highly selective, however, and competing reactions often result in the formation of several different products. For example, the allylic radical generated by addition of the ketyl to 2,3-butadiene results in the formation of mixtures of olefinic isomers in the coupled products, and coupling to allylic acetates is complicated by β-elimination of the acetate upon conversion of the initial radical generated to the anion.



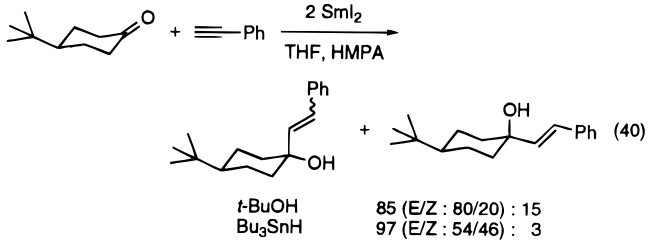
In an isolated study, relative asymmetric induction in the addition of an α-chiral ketone and aldehyde to styrene was examined (eqs 34 and 35).[18d,26] Reasonably high induction was observed, and the sense of asymmetric induction observed led to the conclusion that the relative stabilities of the ketyl configurations were responsible for the diastereoselection.[21]



In addition to stabilized alkenes, alkynes can also serve as suitable acceptors for ketyls in intermolecular coupling reactions (eqs 36−39).[26] In these reactions, carbon−carbon bond formation occurred at the terminus of terminal alkynes used in the study, and internal alkynes always reacted at their more electropositive end. Some type of activating group appears necessary in these processes, as 1-octyne provided only a 21% yield of the desired product.



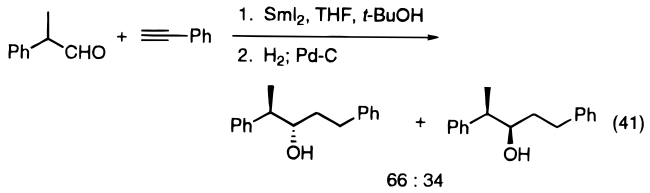
The diastereoselectivity observed in the reaction of 4-*tert*-butylcyclohexanone with phenylacetylene is dependent on the hydrogen atom (or proton) source utilized in the reaction (eq 40).[26] Tri-*n*-butyltin



hydride provides higher diastereoselectivity as an additive than does *tert*-butyl alcohol. Axial attack of the radicophile predominates using both additives. In this sense, the reactions are comparable to cyclohexanone ketyl additions to unsaturated esters (eq 23).[18b] The increased diastereoselection observed in reactions where Bu_3SnH is used has been ascribed to its enhanced hydrogen donor ability, that in turn provides a greater proportion of the kinetic product of the reaction.

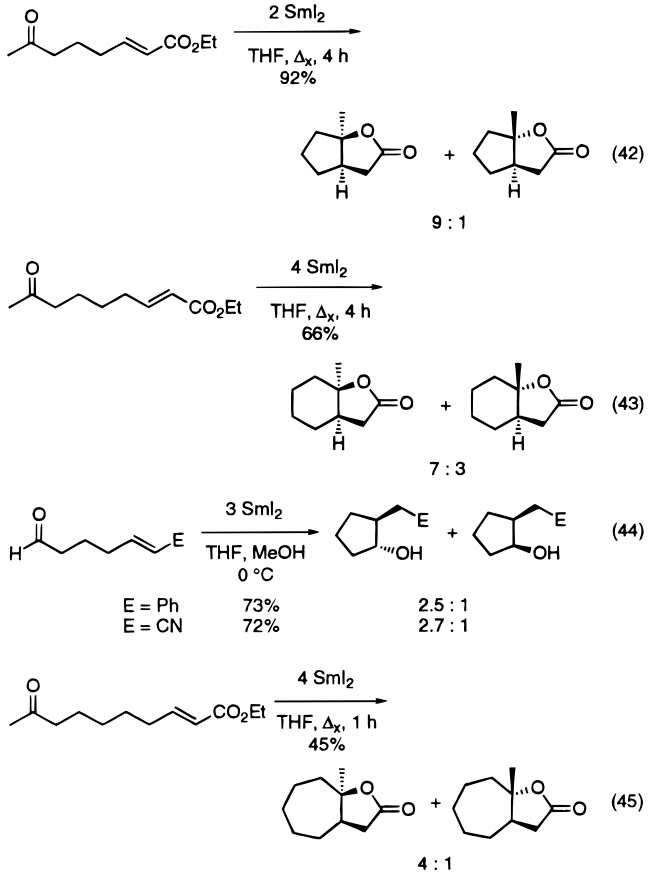
Surprisingly, reaction of 2-phenylpropanal with phenylacetylene generates a mixture of diastereomeric products in which the predominant diastereomer is the reverse of that observed in the coupling of the same aldehyde with styrene (compare eqs 35 and 41).[26] Although it has been suggested that this reflects a thermodynamic preference in a reversible

process, there is no experimental evidence offered to support this postulate.



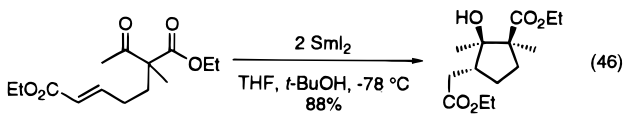
(41)

Intramolecular ketyl olefin coupling reactions promoted by SmI_2 are quite efficient, and as expected, a wider range of acceptors is tolerated than in the intermolecular version of this reaction. Electron-deficient alkenes have been extensively studied as partners for the reaction, and a number of structurally diverse examples have been reported. Five- and six-membered ring syntheses have been accomplished with such substrates (eqs 42−44), and even seven-membered rings have been generated in modest yields (eq 45).[18b,27] Diastereoselectivities were modest in these unrestricted systems.



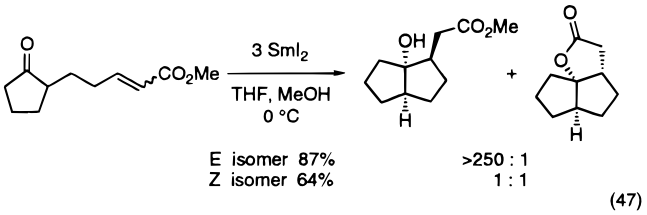
(42) (43) (44) (45)

Chelation can be utilized to control the relative stereochemistry about the developing hydroxyl and carboxylate stereocenters in ketyl olefin cyclizations of β-dicarbonyl substrates.[10b] In such reactions, the Sm(III) Lewis acid generated during the reductive coupling process can be utilized as a template for stereochemical control, providing a facial bias in the attack of the ketyl on the unsaturated ester (eq 46).



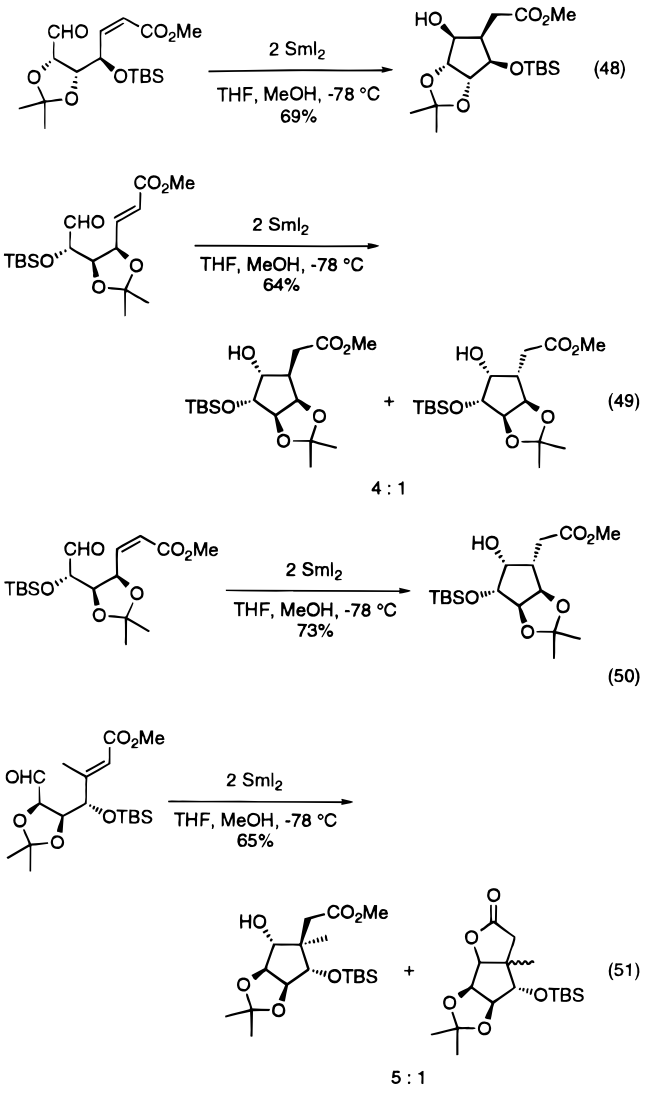
(46)

Conformationally restricted bicyclic substrates generally provide higher diastereoselectivities and higher yields than analogous acyclic precursors.[27b] Olefin geometry plays a critical role in controlling the diastereoselectivity in cyclizations leading to fused bicyclic systems. Whereas *E* olefinic isomers provide high diastereoselectivities in the cyclization reactions, the corresponding *Z* isomers lead to 1:1 mixtures of stereoisomeric products (eq 47). A combination of steric effects and electronic effects have been postulated to account for the dramatic differences observed.



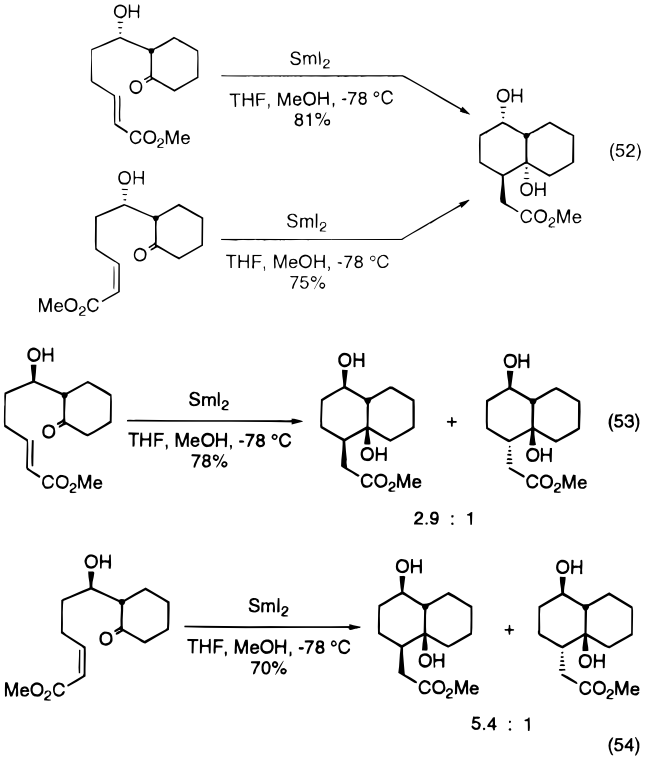
(47)

A dependence on olefin geometry is also observed in highly functionalized systems derived from carbohydrates (eqs 48−51). For these types of conformationally restricted substrates with polar functional groups, relative asymmetric induction in the cyclization event is often high.



(48) (49) (50) (51)

The powerful influence of appropriately positioned hydroxyl groups in facilitating intermolecular ketyl olefin coupling reactions and controlling stereochemistry has been alluded to previously (cf. eqs 28−30). The significant influence of free hydroxyl groups on intramolecular coupling reactions has been examined with equal success.[28] Even in the absence of promoters such as HMPA, these reactions proceed smoothly at low temperatures, providing high yields of the desired products with excellent diastereoselectivity in some cases (eqs 52−54). In fact, the addition of



HMPA decreased the diastereoselection in the reaction, and protection of the hydroxy group as a *tert*-butyldimethylsilyl ether resulted in the complete recovery of starting material. Both of these observations can be viewed as evidence of the important role that the free hydroxyl group plays in enhancing the reactivity of the substrate and in controlling the stereochemistry through chelation.

The diastereoselectivities of the reactions depicted in eqs 52−54 have been rationalized on the basis of both steric and electronic effects in chelated transition structures (Figure 4). For the reactions depicted in eq 52, the controlling factor is postulated to be an electronic effect. Mutual repulsion of partial negative charges on the nucleophilic ketyl oxygen and the developing methylene radical center[29] favors transition structure **A** over that of **B**. In the conversions outlined in eqs 53 and 54, steric effects dominate. Nonbonded repulsions between the methoxycarbonyl group and the cyclohexanone ring outweigh the electrostatic interaction, thereby favoring transition structure **C** over that of **D**.

In addition to linearly fused bicyclic systems, bridgehead bicyclic systems have also been synthesized using SmI_2-promoted ketyl−olefin coupling reactions.[30] Unsaturated esters were determined to

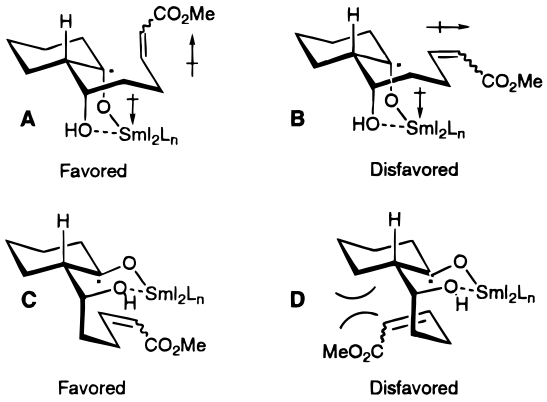
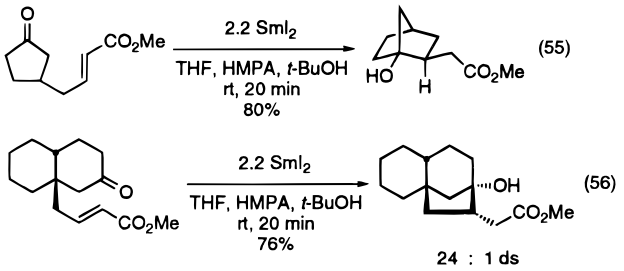
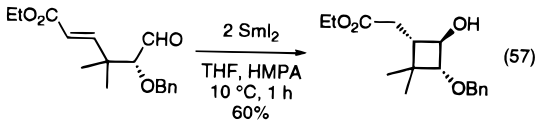


Figure 4.

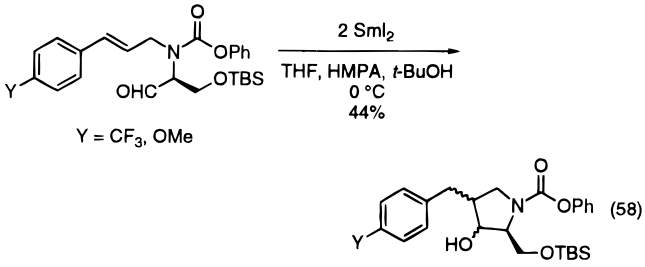
be better ketyl acceptors than unsaturated ketones, and in the limited study diastereoselectivities for the reactions were quite high (eqs 55 and 56).



Five- and six-membered ring syntheses are the most common and perhaps the highest yielding processes for ketyl−olefin coupling, but a cyclobutanol synthesis based upon the same transformation has also been reported (eq 57).[31] Although only a single example appears in the initial disclosure, the 4-exo-trig cyclization holds promise as a general route for the selective synthesis of highly functionalized cyclobutanols and related derivatives.

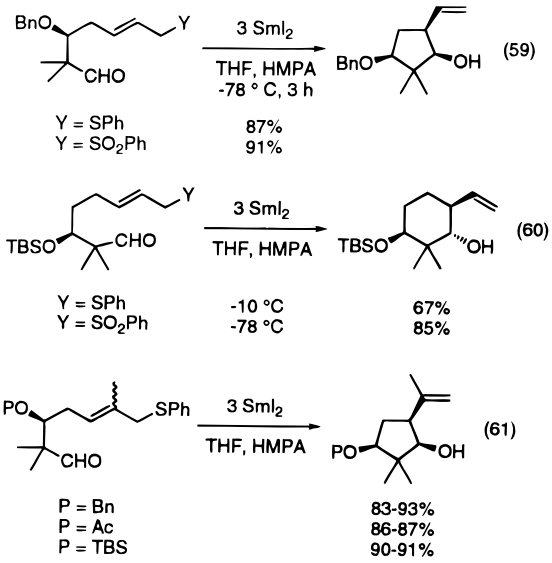


Although most efforts in SmI_2-promoted ketyl olefin cyclization reactions have been directed toward the synthesis of carbocycles, activated alkenes have been employed for the formation of nitrogen heterocycles as well.[32] Only two successful examples have been reported. In these, yields were modest and mixtures of diastereomers were isolated as well (eq 58).



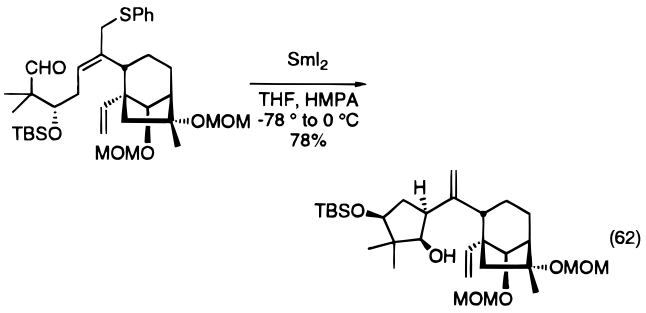
Radical addition/elimination reactions using allyl sulfides as ketyl acceptors have been explored in

conjunction with a synthesis of (−)-grayanotoxin III (eqs 59−61).[33] Both five- and six-membered rings can

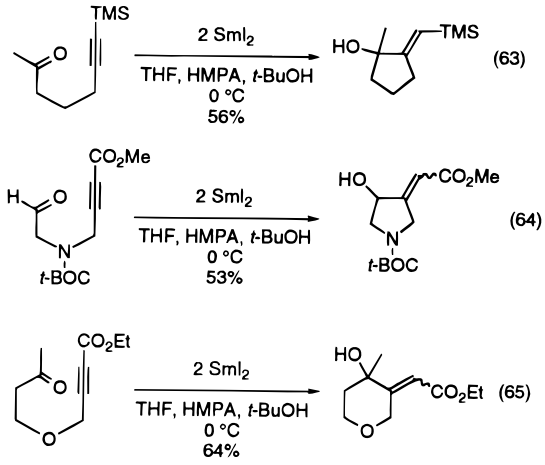


be accessed in this manner. The observed diastereoselectivities are quite high, although the reactions are not stereospecific with regard to olefin geometry. Allyl sulfones provide the same products as the analogous allyl sulfides, often in higher yields and under milder reaction conditions. Although the same type of radical addition/elimination mechanism has been proposed for the allyl sulfones, an alternative mechanism is possible. In analogous intermolecular reactions, allyl sulfones react with aldehydes and ketones by what has been postulated to be a Barbier-type coupling reaction.[34] This is supported by the regioselectivities in these reactions, which are not consistent with a conversion involving strictly a ketyl addition/elimination. With regard to the intramolecular reactions, it would be incredibly coincidental if both sulfides and sulfones reacted by two completely different mechanisms yet arrived at the same isomeric products. Nevertheless, caution is due in assessing the mechanism involved in reactions of the allyl sulfones with aldehydes and ketones.

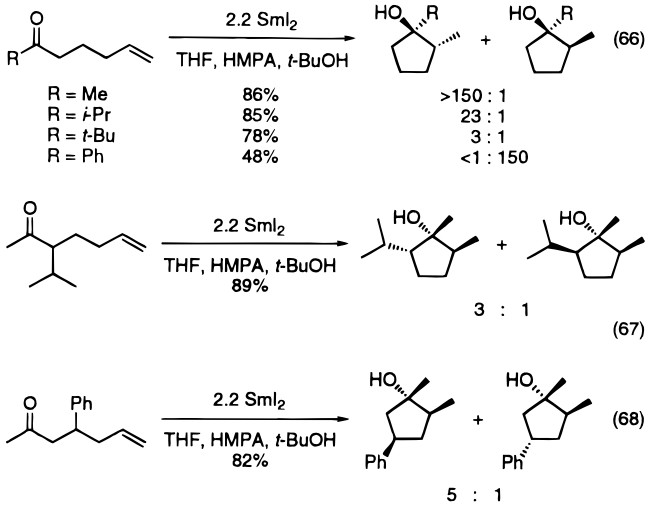
Upon completion of the model studies, the addition/elimination reaction of an aldehyde ketyl with an allyl sulfide was employed as one of three key SmI_2-promoted steps in the synthesis of (−)-grayanotoxin III (eq 62).[35] The reaction proceeded with excellent stereochemical control in line with the preliminary studies presented above.



In addition to activated alkenes, activated alkynes can also serve as acceptors in cyclization reactions. Carbocycles, nitrogen heterocycles, and oxygen heterocycles are all accessible by this strategy, and both five- and six-membered rings can be synthesized (eqs 63−65).[36] Stereochemical control about the alkene generated in the reaction is variable, and in general ketone ketyl precursors provide higher yields in the cyclizations than their aldehyde counterparts.



The persistence of ketyl radical anions under the reductive reaction conditions created by SmI_2 permits their use in cyclization reactions with nonstabilized alkenes, alkynes, and other functional groups. In this regard the ketyl reactions are distinguished from their alkyl radical counterparts. The general class of 5-exo-trig cyclizations using acyclic substrates to generate carbocycles represents the simplest conceivable transformation. Within this class yields are high, but diastereoselectivities vary with the substituent on the ketone (eq 66).[37] The relative asymmetric induction engendered by substituents α or β to the carbonyl are modest (eqs 67 and 68).



Virtually all of the stereochemical trends in this series can be rationalized on the basis of a chairlike transition structure (Figure 5).[37] In the favored

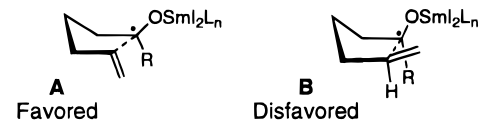


Figure 5.

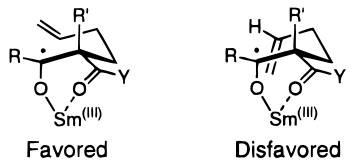
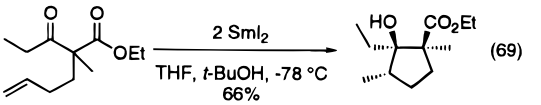
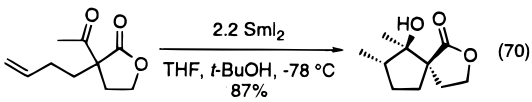


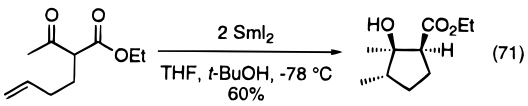
Figure 6.

transition structure, the ketone substituent (R) is nearly eclipsed with the developing methylene radical center (**A**). The anti relationship of the π-system and the ketyl oxygen is likely stereoelectronic in nature as noted previously.[29] As the steric bulk of the alkyl substituent increases, the less favored transition structure (**B**) becomes increasingly important as steric interactions between R and the methylene unit increase. Substituents located α and β to the carbonyl assume pseudoequatorial orientations in the transition structures, and thereby control relative asymmetric induction.

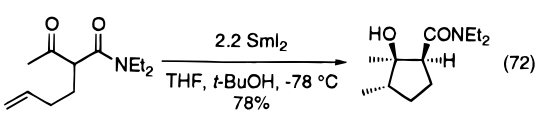
Chelation control can be employed to control diastereoselectivity in β-keto ester and β-keto amide substrates.[10b] The fundamental features of diastereoselection are the same in these cyclization reactions as in previously described radical cyclizations promoted by SmI_2, with chelation of the β-dicarbonyl center imposed upon the other stereoelectronic effects in the transition structure (Figure 6). It is interesting to note that HMPA is not required for these reactions, and yet they can still be carried out under exceedingly mild conditions. This is undoubtedly because the β-dicarbonyl unit provides a chelating center for the samarium species involved in the reaction, and the electron-withdrawing nature of the carboalkoxy unit lowers the LUMO of the ketone carbonyl, making it easier to form the ketyl. Both effects work in concert to make the conversion from ketone to ketyl kinetically and thermodynamically more favorable. The scope of the reaction is quite broad. For example, non-enolizable (eqs 69 and 70) and enolizable β-keto esters (eq 71) participate in the reactions. Yields vary from 50 to 75% but diastereo-





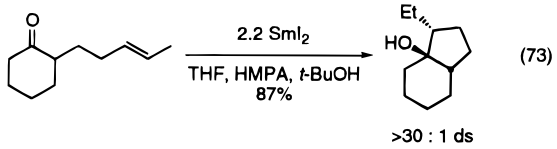


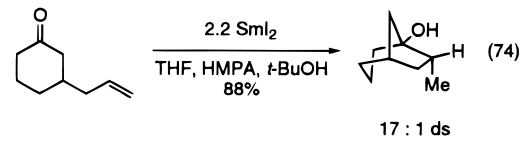
selectivities are uniformly high. β-Keto amides can also be used in the reaction, although yields vary dramatically with the substituent on the ketone carbonyl (eq 72). More hindered groups lower the

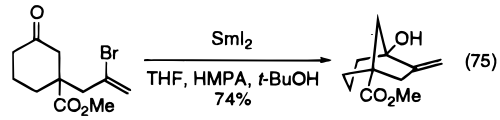


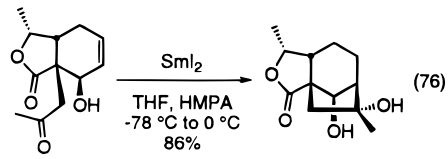
yields quite drastically. Although HMPA and other cosolvents have not been employed in these cyclizations, one or more of these additives could improve the yields of these cyclizations.

High diastereoselectivities are generally observed in 5-exo-trig bicyclization reactions promoted by SmI_2. Both linearly fused bicyclics (eq 73)[37] and bridged bicyclic systems have been generated by this process (eq 74),[38] and one example has been reported wherein a radical addition/elimination process has been achieved (eq 75).[39] As further evidence of its utility in organic synthesis, the ketyl 5-exo-trig bicyclization reaction was utilized as a key step in the synthesis of (−)-grayanotoxin III (eq 76).[35] The diastereoselectivity observed in this reaction has been ascribed to chelation control, with the Sm(III) ion generated upon single electron transfer to the ketone complexing with the C-14 hydroxy group in a seven-membered ring chelate.



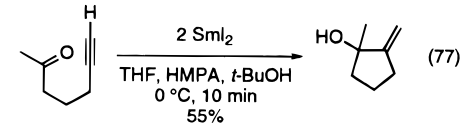






Alkynes have also been utilized as radical acceptors in 5-exo-dig cyclizations involving ketyl radicals. Both nonchelation[36] and chelation-controlled[10b] processes have been reported (eqs 77 and 78). Yields are modest in both series for unactivated alkynes, and it is a general observation that activation with trialkylsilyl groups or stronger electron-withdrawing groups are required for optimum yields. Ketone ketyl precursors appear to provide higher yields in general than their aldehyde counterparts,[36] although an aldehyde ketyl/alkyne coupling has been used with success in the synthesis of isocarbacyclin (eq 79).[40] In this particular cyclization, SmI_2 was found to be superior to several other reducing agents for the conversion.

A limited study on the coupling of allenes has also been reported.[41] In these reactions, 5-exo-trig cyclizations predominate, and reasonably high diastereo-



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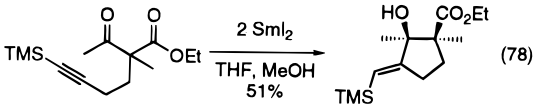

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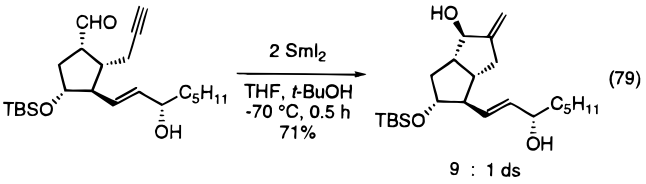
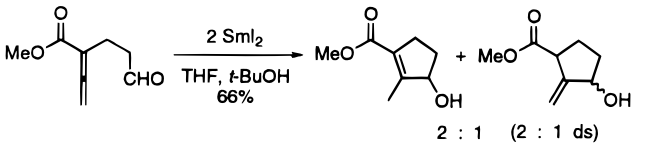


(79)

selectivities can be achieved as well (eqs 80 and 81).



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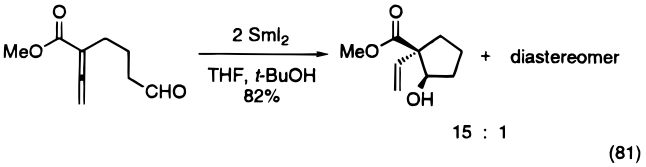
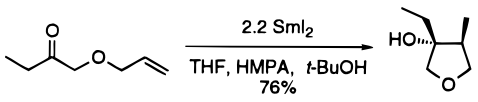


(81)

The sense of diastereoselection in the latter example was postulated to be the result of complexation through a nine-membered Sm(III) chelate (Figure 7).

Five-membered ring oxygen heterocycles and nitrogen heterocycles can be accessed by 5-exo-trig cyclizations of ketyls onto unstabilized alkenes. High yields and diastereoselection were achieved in the single tetrahydrofuran synthesis reported (eq 82),[37] whereas generally low yields and low diastereoselectivities were observed in the generation of pyrrolidines by an analogous cyclization on alkenes and alkynes (eqs 83 and 84).[32,42] Competitive reductive elimination of



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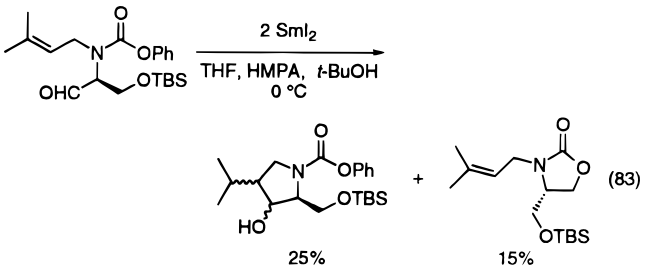

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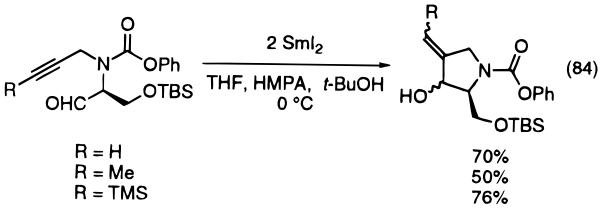

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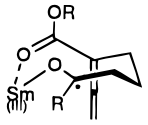
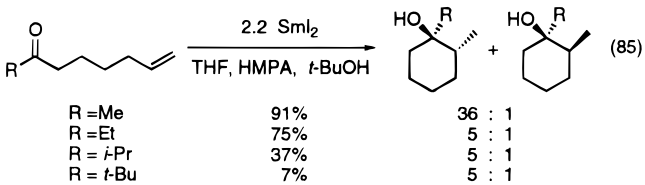


Figure 7.

the α-heterosubstituent from the ketyl radical anion may account for the low yields in these cyclizations.

Fewer studies of 6-exo cyclization reactions promoted by SmI_2 have been reported, in part because the general inclination is for yields and diastereoselectivities in this series to be lower than for those of the corresponding 5-exo cyclizations. Simple reduction of the ketone to the corresponding alcohol, hydrogen atom-transfer processes, and 7-endo cyclization comprise significant byproducts in some cases.[37] Nevertheless, in general the same trends follow for 6-exo cyclization of acyclic substrates as were observed in 5-exo cyclizations (eqs 85−87).[37] As steric hindrance about the carbonyl increases, the yield of the desired cyclization products decreases and more byproduct formation is observed. Furthermore, relative asymmetric induction in α- and β-substituted carbonyl substrates is modest (eqs 88 and 89). Interestingly, significant chelation control is achieved with hydroxy groups placed β to the carbonyl (eq 90). As a result, this substituent reverses the sense of asymmetric induction observed with alkyl substituents at the β position.



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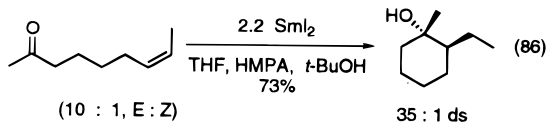

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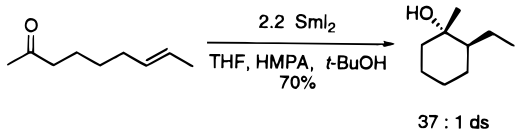

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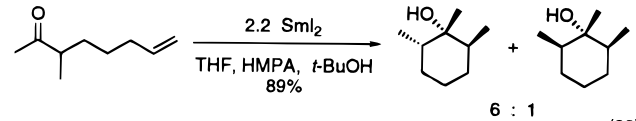

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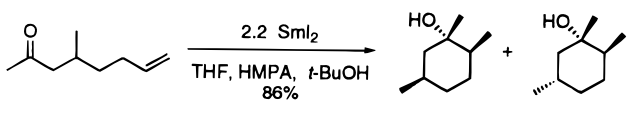

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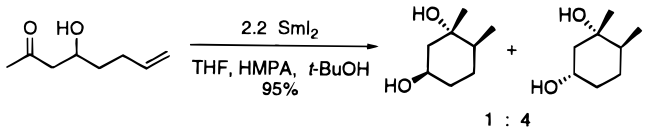

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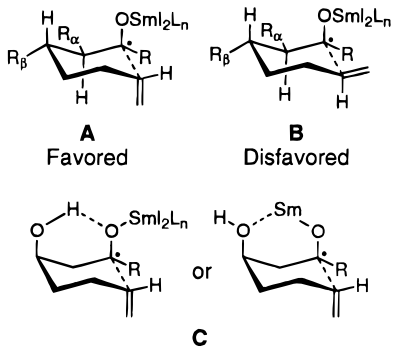
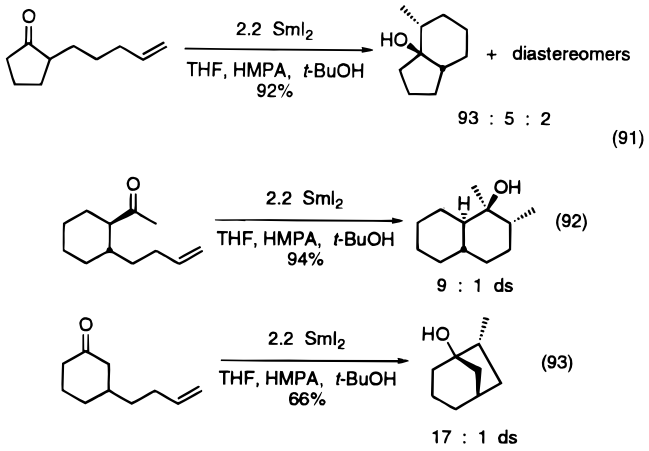


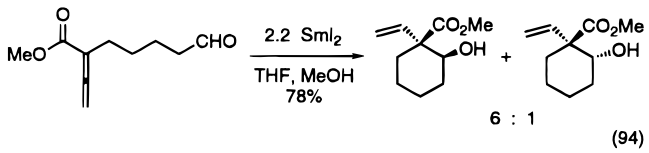
Figure 8.

Rationalization for the observed diastereoselectivities is again based upon transformations through chairlike transition structures (Figure 8). Stereoelectronic effects in the transition state of unsubstituted substrates provide slightly more stabilization of structure **A** than that of **B**.[29] Alkyl substituents α and β to the carbonyl in monosubstituted substrates anchor these transition structures by establishing themselves in pseudoequatorial orientations, leading to the major isomers observed. The hydroxy substituent can provide chelation control through transition structure **C** in which it is pseudoaxially oriented, thus reversing the diastereoselection observed with β-alkyl substituted derivatives.

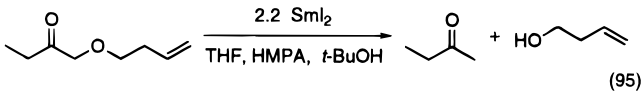
Bicyclizations proceeding in the 6-exo mode can be effected by the intramolecular ketyl olefin coupling process promoted by SmI_2 (eqs 91−93).[37,38] In nearly all cases for which there is a direct comparison, the SmI_2-induced reactions provide higher yields and stereoselectivities than reactions carried out using other methods.



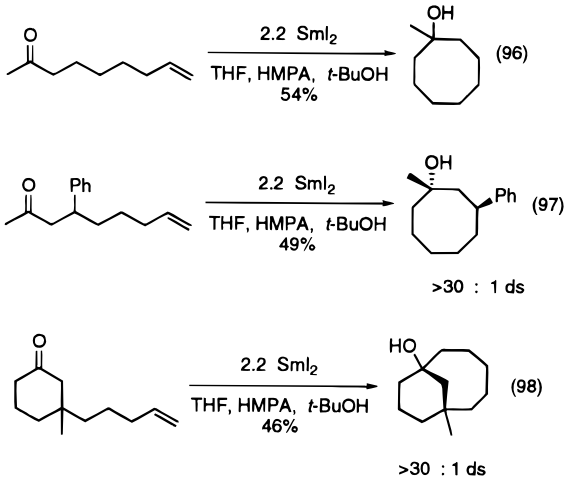
Allenes can also be utilized to synthesize functionalized cyclohexanols. In the single example reported, methanol was required as a cosolvent with THF. Under these conditions conjugate reduction of the enoate substrate was inhibited, and a high yield of the desired product was achieved with reasonable diastereoselectivity (eq 94).[41]



The synthesis of six-membered ring heterocycles by a SmI_2-promoted ketyl olefin coupling reaction appears limited. Cyclization of the ketyl is slow enough that competitive reductive elimination of the heterosubstituent occurs when it is attached to the α carbon (eq 95).[37] Consequently, the 6-exo cyclizations will only be successful when the heteroatom cannot be reductively eliminated.

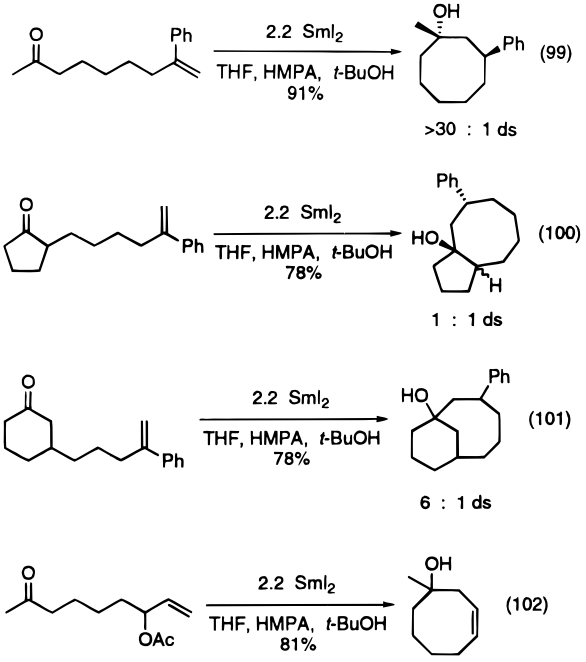


In a most surprising discovery, it has been determined that SmI_2 promotes the synthesis of cyclooctanols through an 8-endo cyclization process.[43] Yields are generally modest for unactivated alkenes (eq 96), and substitution about the carbonyl lowers the yield considerably. The byproducts are exclusively the reduced ketones, isolated in yields of about 30%. No products derived from 7-exo cyclization have been observed. Diastereoselectivities are generally low, but in suitably substituted systems can be quite high (eqs 97 and 98). In view of the failure of dissolving

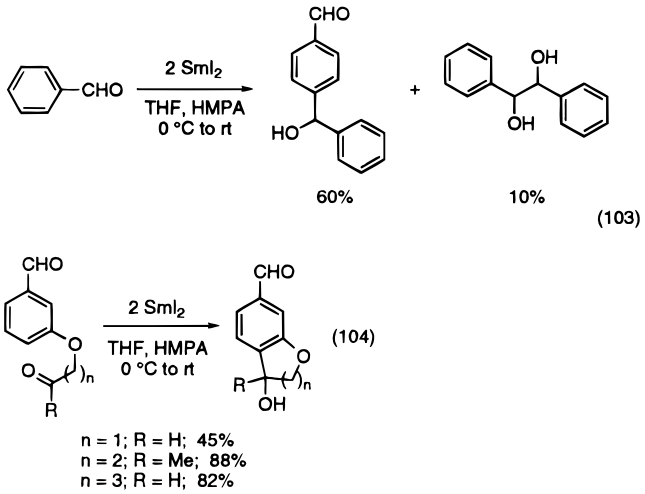


metal reductions to accomplish analogous cyclizations,[44] the SmI_2 results are intriguing. The success of this protocol may be due to the reversible nature of the SmI_2 reduction of ketone carbonyls.[45] Thus, at any given time there may be only a small equilibrium concentration of the ketyl available for coupling, resulting in a pseudo high dilution effect. In these entropically challenged systems, this pseudo dilution effect would minimize byproduct formation and promote the desired cyclization. The presence of HMPA may also inhibit nonproductive reactions by shielding the ketyl, once formed, from solvent and other species in solution.[43]

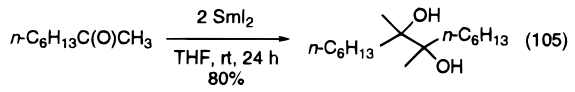
As might be anticipated, activated alkenes permit the 8-endo cyclization to proceed in much higher yields. Aryl-substituted alkenes are particularly effective, although cyclization is enhanced in substrates with activating substituents at the allylic position as well (eqs 99−102).[43] In the case of the allylic acetate, reduction of the cyclooctyl radical produced upon cyclization results in a β-elimination of the acetoxy substituent, generating a cyclooctene.



The effectiveness of SmI_2-promoted ketyl coupling reactions to aromatic systems appears to be highly substrate dependent and dramatically affected by reaction conditions as well.[46] For example, treatment of benzaldehyde with SmI_2 in THF provides a virtually quantitative yield of the corresponding pinacol (hydrobenzoin). In the presence of HMPA, however, the reaction is diverted to provide aryl-coupled product as the major isomer formed (eq 103).[46a] Generally more successful are intramolecular versions of this reaction, wherein high yields of cyclized material can be isolated (eq 104).[46a] Even in these intramolecular reactions, however, activation of the aromatic systems appears necessary. Thus 5-phenyl-2-pentanone provides only a trace of the desired cyclized material.[46b]

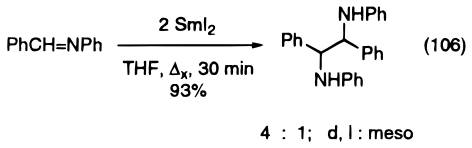


Pinacolic coupling and related processes represent another broad class of reactions undergone by ketyl radical anions. Treatment of aldehydes or ketones with SmI_2 in the presence of a proton source such as methanol results in selective reduction to corresponding alcohols, and formation of pinacols is negligible. However, in the absence of a proton source, both aldehydes and ketones are cleanly coupled in the presence of SmI_2 to generate pinacols (eq 105).[47]

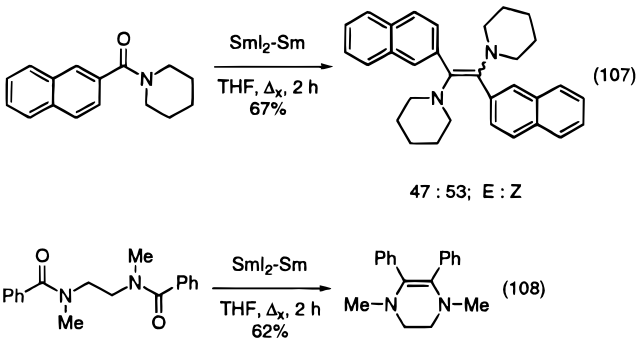


Yields are excellent in nearly every case, and the method thus competes effectively with other established procedures for this process. Unfortunately, roughly equimolar ratios of threo and erythro isomers are generated in these reactions. Aromatic aldehydes and aromatic ketones couple within a few seconds at room temperature in THF. Aliphatic aldehydes require a few hours under these conditions, and a day is needed for complete reaction of aliphatic ketones. Amines, nitriles, and nitro groups are tolerated under these conditions. Surprisingly, carboxylic acids can also be incorporated into substrates with little attenuation in yields of pinacolic products. It is not clear why competitive reduction to alcohols is not observed in this instance, because a proton source is obviously provided by the acid under the reaction conditions.

Related to the pinacolic coupling reaction is the dimerization of aldimines that can be effectively promoted by SmI_2 (eq 106).[48] Both alkyl and aryl aldimines can be coupled, but neither is highly diastereoselective. Under similar conditions, ketimines are quantitatively reduced to the corresponding secondary amines.

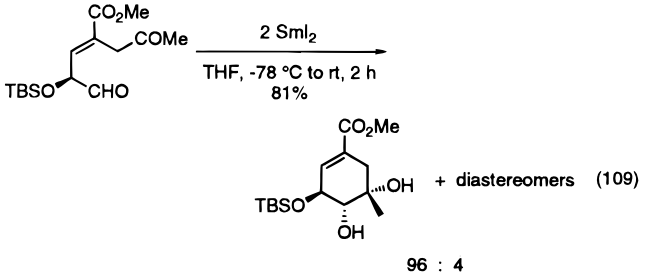


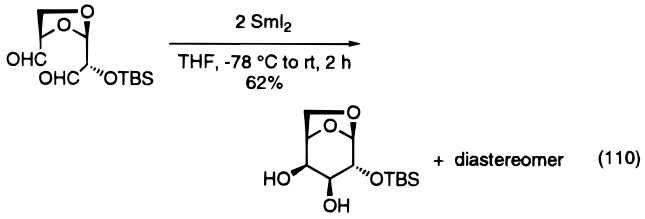
An unprecedented coupling of amides utilizing SmI_2/Sm(0) has been reported that results in the formation of vicinal diaminoalkenes.[4a] Both intermolecular (eq 107) and intramolecular versions (eq 108) of the reaction have been studied. Yields are modest in both types of reactions, with aryl amides providing higher yields that the corresponding aliphatic amides. Limited mechanistic studies suggest that the reaction may proceed via intermediate α-amino carbenes.

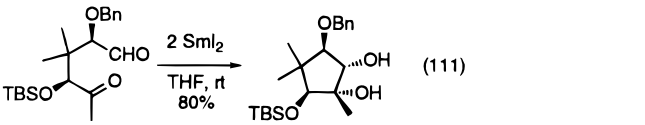


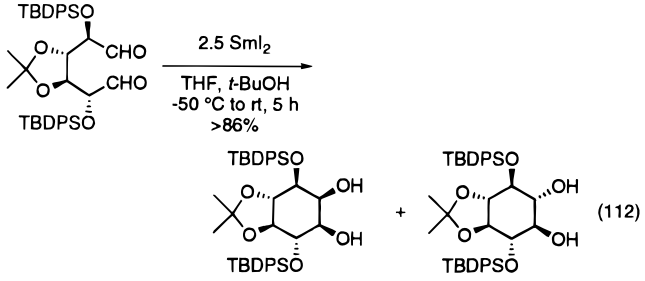
Considerable stereochemical control is achieved in intramolecular pinacolization reactions promoted by SmI_2. Cyclization of a variety of 1,5- and 1,6-dialdehydes have demonstrated near exclusive formation of the cis diols.[49] Heterosubstituents α to the

carbonyls do not interfere with the coupling process, indicating that reductive dimerization is much more rapid than reductive cleavage[2e] of these substituents. Furthermore, polar substituents α to the carbonyls end up anti to the diol stereocenters in the final product, providing a stereocontrol element as well (eqs 109−112).

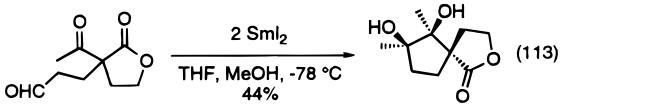


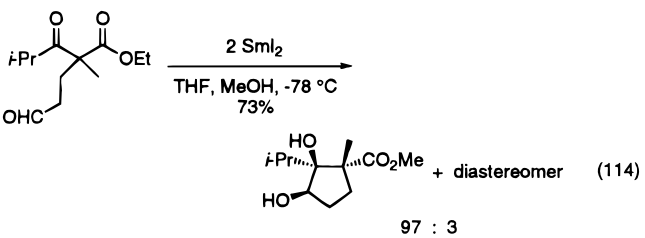




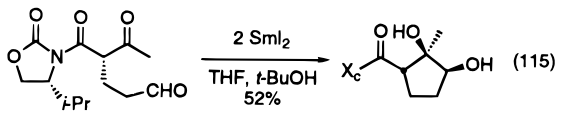


Chelation control can be utilized to achieve excellent yields and control of stereochemistry over three contiguous stereocenters in intramolecular pinacolic coupling reactions promoted by SmI_2 (eqs 113 and 114).[10b,50]

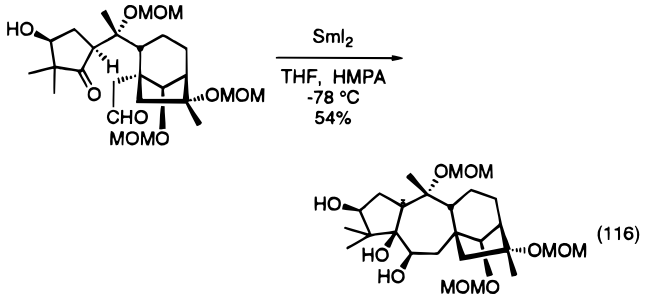




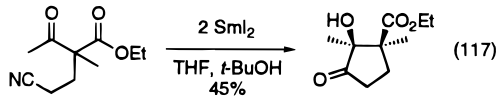
Both five- and six-membered rings can be generated by this process, but substantially lower yields and diastereoselectivities are observed for the latter. Yields obtained for β-keto amide substrates are also somewhat lower than those observed in the β-keto ester series. However, a chiral, nonracemic oxazolidinone has been employed with success, permitting entry to highly functionalized, enantiomerically pure dihydroxycyclopentanecarboxylate derivatives (eq 115).



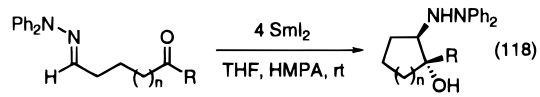
A stereocontrolled, intramolecular pinacolic coupling reaction has been utilized as the final key step in the total synthesis of (−)-grayanotoxin III (eq 116).[35]



Other processes related to pinacolic coupling reactions can be promoted by SmI_2. One such example is a ketone−nitrile reductive coupling process. This process permits construction of highly functionalized carbocycles with substantial control of stereochemistry,[10b,50] although yields are somewhat diminished because of the reluctance of nitriles to undergo the ketyl radical anion addition reaction (eq 117).



Finally, the cyclization of carbonylhydrazines can be carried out with SmI_2, providing an excellent route to 2-aminocyclopentanols (eq 118).[16] Curiously, higher diastereoselectivity is observed in these cyclizations when the reactions were performed at ambient temperatures than when they were cooled. In all cases, the trans isomer was favored to the extent of >15:1.



n	R	% yield
1	H	62
1	Me	63
2	H	58
2	Me	62

B. Two-Electron Processes

In addition to the single-electron processes outlined above, SmI_2 is also capable of mediating a variety of formal two-electron processes as well. In most respects, the chemistry associated with SmI_2-pro-

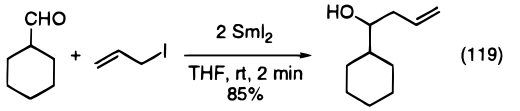
moted reactions is highly complementary to more traditional organolithium, organomagnesium, and organozinc chemistry. Furthermore, the two-electron processes play a major role in the sequential conversions described below because the combination of one- and two-electron chemistry sets SmI_2 apart from virtually every other reductive coupling agent currently available.

1. Barbier- and Grignard-Type Reactions

Both samarium Barbier and samarium Grignard protocols have been reported. The usefulness of the samarium Grignard procedure is minimal.[19] These reactions appear limited in scope to primary and secondary alkyl halides, and even in these restricted cases the reactions are capricious. It is thus economically and synthetically more prudent to utilize organomagnesiums or organolithiums when carbonyl additions with discrete organometallics are required.

The samarium Barbier reaction, on the other hand, succeeds in cases where organolithium or organomagnesium chemistry fails. Additionally, SmI_2 permits the use of an expanded set of substrates that cannot be used with these more traditional reagents. The SmI_2-Barbier protocol has thus found an important and useful niche in organic synthesis.

Intermolecular samarium Barbier reactions are more limited in scope than their intramolecular counterparts. Nevertheless, the intermolecular versions are synthetically useful for a variety of combinations of organic halides and carbonyl substrates. Allylic, propargylic, and benzylic halides (chlorides, bromides, and iodides) are highly reactive substrates in samarium Barbier reactions, reacting within minutes at ambient temperatures in THF solution (eqs 119 and 120).[2a,c,51] Both aldehydes and ketones can



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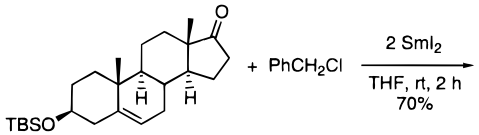
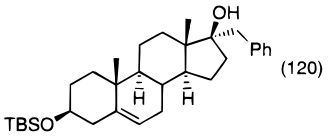




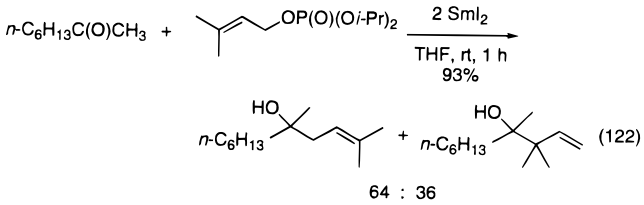
(120)

serve as partners for the reactions, and even in cases where the ketone is highly hindered acceptable yields of the coupled products can be obtained.[2c] Unsymmetrical allylic halides yield mixtures of regioisomers and stereoisomers in the reactions, and propargylic halides provide both propargyl alcohols and allenic products. The lack of selectivity exhibited in these reactions limits their usefulness for synthesis.

Unlike magnesium Barbier reactions, substrates other than allylic halides can serve as precursors for the SmI_2-promoted version of the coupling reactions. For example, allyl sulfones react with aldehydes and ketones in the presence of SmI_2 (eq 121).[34] These reactions require HMPA as an additive, and several hours are needed for the reactions to proceed to completion. As in the case of the allylic halides, mixtures of regioisomers result when unsymmetrical allylic sulfones are used.

(121)

Allylic phosphates have also been utilized as precursors for Barbier-type coupling processes (eq 122).[52] However, this protocol is more limited in scope because aldehydes and easily reduced ketones (e.g., acetophenone and benzophenone) undergo competitive pinacol formation. The generation of regio- and stereoisomeric homoallylic alcohols from unsymmetrical precursors again detracts from the value of the method.



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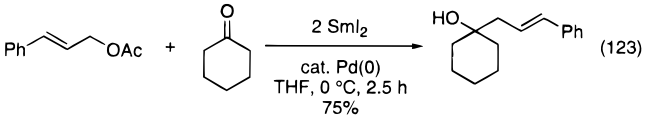
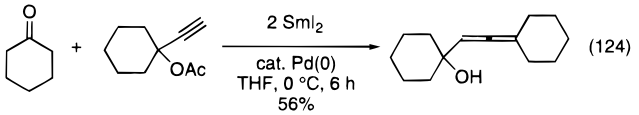
A fourth protocol for the Barbier-type coupling of allylic and propargylic systems involves the Pd(0)-catalyzed coupling of allylic acetates and propargylic acetates. The mechanism of this process presumably involves the inital generation of allylpalladiums, followed by reductive transmetalation to provide the corresponding allylsamariums. The latter undergo the carbonyl addition reaction (eq 123).[53] In most cases, carbon−carbon bond formation occurs at the least-substituted terminus of the allylic unit, providing higher regioselectivities than the other SmI_2-promoted processes. A wide range of aldehydes and ketones can be utilized in the reaction, although aromatic and α,β-unsaturated substrates cannot be used owing to competitive pinacolic coupling reactions.



(123)

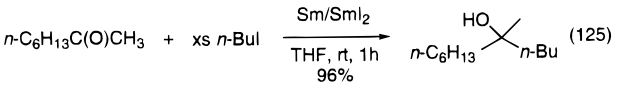
In a similar vein, propargyl acetates undergo the Pd(0)-catalyzed coupling with ketones.[54] This reaction, too, has its limitations. Aldehydes can only be utilized with highly reactive propargylic acetates because of competitive pinacolic coupling. Primary propargylic acetates produce mixtures of allenic and homopropargylic alcohols, whereas most secondary and all tertiary propargylic carboxylates provide exclusively the allenic alcohols (eq 124).



(124)

Reaction conditions for intermolecular Barbier reactions involving alkyl halides promoted by SmI_2

are very much dependent on the presence or absence of additives and catalysts. For example, primary organic iodides and even organic tosylates undergo Barbier-type coupling with ketone substrates, but require heating for 8−12 h in boiling THF. The tosylates presumably react by an initial Finkelstein-type reaction which converts them to the corresponding iodides. The iodides are subsequently involved in the coupling process. Alkyl bromides are less reactive, and alkyl chlorides are virtually inert.[2a] The presence of excess samarium metal appears to enhance the reactivity of the reducing media, allowing similar reactions to proceed at room temperature within 1−2 h (eq 125).[4b] Milder reaction conditions can also be achieved by adding catalytic quantities of Fe(III) salts to the reactions. In this case, too, reaction is complete within hours at room temperature.

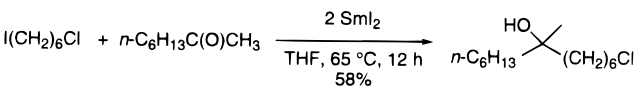


(125)

The highest reactivity can be achieved by utilizing HMPA as a cosolvent with THF for the Barbier reaction. In THF/HMPA, both *n*-BuBr and *sec*-BuBr are cleanly coupled to 2-octanone within 1 min at room temperature, providing greater than 90% yields of the desired tertiary alcohols.[3a] The full scope of the role that HMPA plays in these reactions is not known, but certainly it increases the reducing ability of SmI_2 and serves to deaggregate the reagent as well.[38,55]

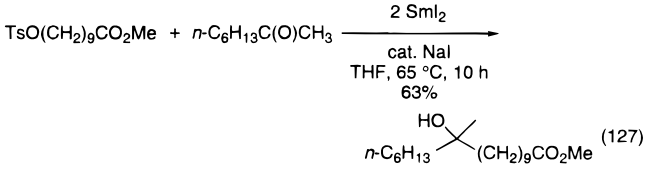
As with many of the previously discussed intermolecular Barbier reactions, the coupling reactions of alkyl halides are confined to ketone carbonyl substrates. The use of aldehydes in these reactions leads to a mixture of products resulting from a Meerwein−Ponndorf redox process initiated by reaction of secondary samarium alkoxide intermediates with the aldehyde.[51,56]

Selective transformations of polyfunctional substrates can be accomplished by taking advantage of the unique discrimination afforded by SmI_2. Because of the difference in reduction potentials between primary organic iodides and those of organic chlorides, selective alkylation of ketones can be accomplished by utilizing appropriately functionalized dihalides (eq 126) or chloro-substituted sulfonate esters.[2a] Alkenyl halides and, presumably, aryl halides also remain intact under reaction conditions wherein alkyl iodides can be coupled.

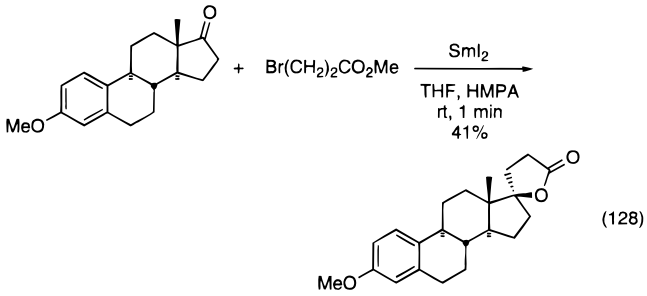


(126)

Nitriles and esters are less reactive under normal SmI_2-promoted reaction conditions than ketones. Consequently, it is possible to perform a Barbier-type coupling reaction in the presence of these functional groups and isolate the desired product in reasonable overall yield (eq 127).[2a] This tolerance of esters also makes it possible to perform Barbier-type reactions using 3-bromopropanoates, 4-bromobutanoates, or 5-bromopentanoates. Yields appear quite variable in these instances, perhaps because of competitive intramolecular nucleophilic acyl substitution (eq 128).[57]

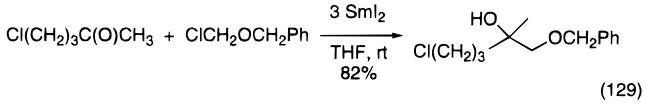


(127)

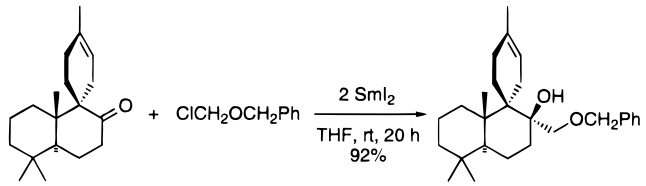


(128)

Numerous α-heterosubstituted nucleophiles or their equivalents can be generated and reacted with aldehydes and ketones under SmI_2-mediated conditions. For example, a hydroxymethylation process has been developed on the basis of the SmI_2-mediated Barbier-type reaction.[58] Treatment of aldehydes or ketones with benzyl chloromethyl ether in the presence of SmI_2 provides alkoxymethylated products. Subsequent reductive cleavage of the benzyl ether affords hydroxymethylated products (eq 129). The procedure is particularly useful for ketones with a high propensity for enolization. In this regard the method proved useful in a key step in the synthesis of (±)-desoxystemodinone (eq 130).[59]



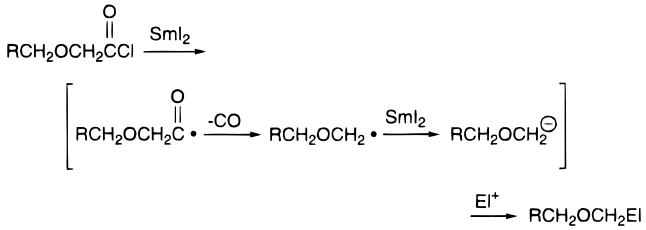
(129)



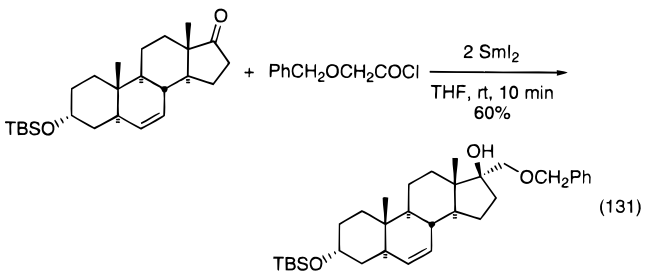
(130)

A second protocol for alkoxyalkylation involves the decarbonylation of α-alkoxy acid chlorides in the presence of ketones (Scheme 5).[60] By a direct comparison of methods, this procedure does not appear as efficient as the more direct alkoxyalkylation described above. Nevertheless, high yields are generally obtained and in those instances where the α-alkoxy acid chlorides are readily available this

Scheme 5

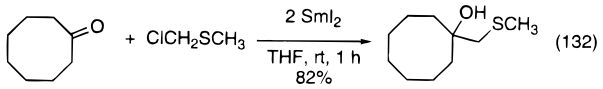


appears to provide a viable alternative route to the carbonyl addition products (eq 131).



(131)

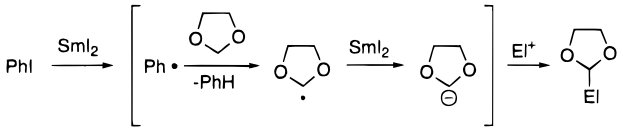
Analogous to the alkoxyalkylation reaction is a method for the synthesis of β-hydroxy thioethers employing the SmI_2-promoted Barbier-type reaction of chloromethyl sulfides with aldehydes and ketones.[61] Reactions of enolizable aldehydes are modest, but nonenolizable aldehydes and ketones appear to provide excellent yields of the desired products (eq 132).



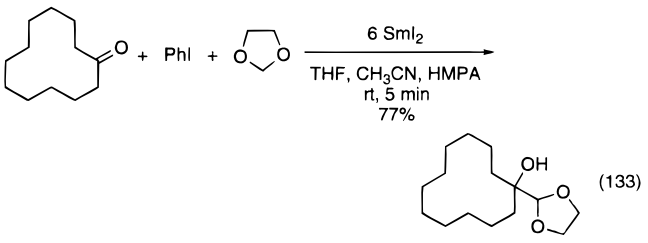
(132)

The development of a method for the masked formylation of aldehydes and ketones also involves an indirect generation of the requisite nucleophilic species (Scheme 6).[62] The method takes advantage

Scheme 6



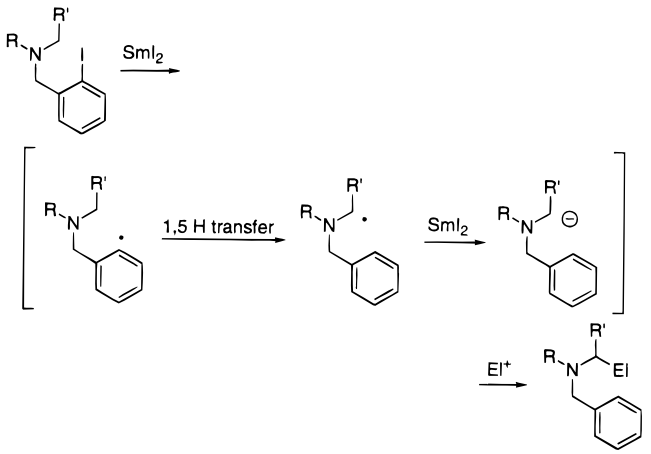
of the capability of SmI_2 to reduce iodobenzene to the aryl radical, and the fact that further reduction of this radical to the anion is slow compared to hydrogen abstraction from a good hydrogen donor.[3a] Consequently, the aryl radical thus generated rapidly abstracts a hydrogen atom from dioxolane, which is then reduced to the anion by a second equivalent of SmI_2. Carbonyl addition to aldehydes and ketones ensues, providing the desired formylation products (eq 133). For all practical purposes the reaction is limited to dioxolane itself, because the hydrogen donor must be used as a solvent in the reaction in order to achieve reasonable yields.



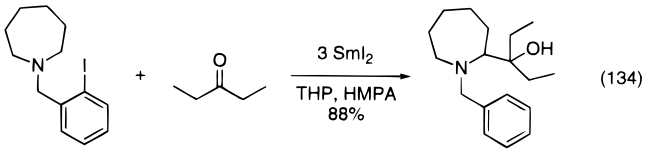
(133)

Aminoalkylation of carbonyl substrates has also been accomplished by two unique and very different methods. In the first, tertiary amines possessing a pendent *o*-iodobenzyl group on nitrogen undergo reduction and 1,5-hydrogen atom transfer to generate an α-amino radical. This radical was subsequently

Scheme 7



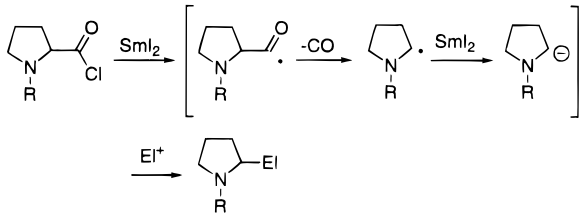
reduced to an organosamarium species, which can be trapped by carbonyl electrophiles (Scheme 7).[63] In this manner, a variety of tertiary amines have been alkylated α to the nitrogen in excellent overall yields (eq 134).



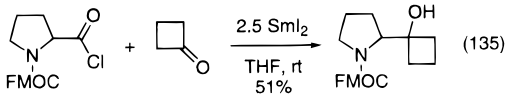
(134)

The protocol in the second reported α-alkylation of amines involves an initial reduction of protected amino acid chlorides with subsequent decarbonylation. The radical produced can again be reduced to the corresponding organometallic, with subsequent carbonyl addition completing the sequence (Scheme 8).[64] Moderate yields are generally observed in these

Scheme 8



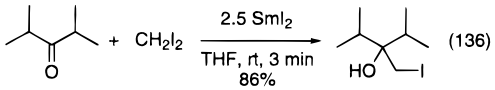
reactions (eq 135). The lower yields have been ascribed to hydrogen (or proton) abstraction competing with carbonyl addition as well as pinacolization of the carbonyl substrate. The method is currently restricted to proline derivatives, which represents a further limitation of the method.

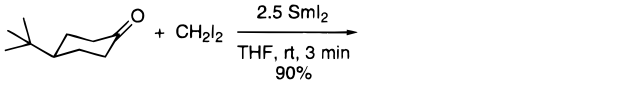


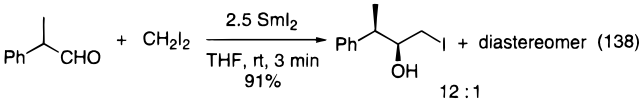
(135)

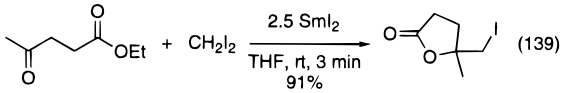
Samarium(II) iodide can be utilized as the reducing agent to bring about the iodomethylation of a diverse range of aldehydes and ketones.[20] For example, highly hindered ketones react well, providing excellent yields of iodohydrin (eq 136). High diastereoselectivity is achieved in reactions with both cyclic and acyclic carbonyls (eqs 137 and 138), and the

method is tolerant of other functional groups such as esters (eq 139).

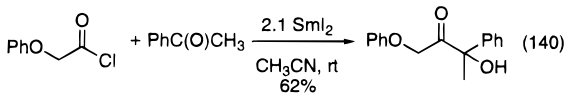


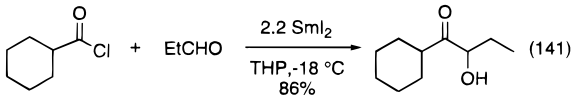




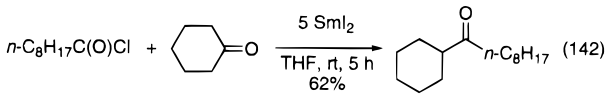


Samarium acyl anions can be generated by the reaction of SmI_2 with carboxylic acid chlorides. The acyl anions created in this manner react with aldehydes and ketones, leading to the synthesis of α-ketols.[3b,d,65] Reactions are best performed in acetonitrile or tetrahydropyran in order to prevent Lewis acid-promoted ring opening of tetrahydrofuran by the acid chloride. Utilizing these solvents affords excellent yields of the desired α-hydroxy ketones (eqs 140 and 141).

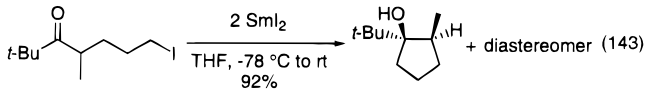


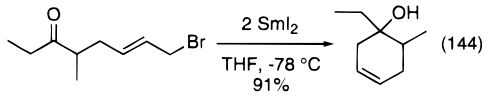


Acyl anion coupling with carbonyl substrates with subsequent reduction of the α-alkoxy ketone can be accomplished when an excess of SmI_2 is utilized for the initial Barbier process.[66] Under the conditions of the reaction, an α-hydroxy ketone is generated first, and this is then reduced by SmI_2 to an α-keto radical. The latter abstracts a hydrogen from THF to complete the process (eq 142). No deuterium is incorporated when these reactions are quenched with D_2O, indicating that enolates are not involved.

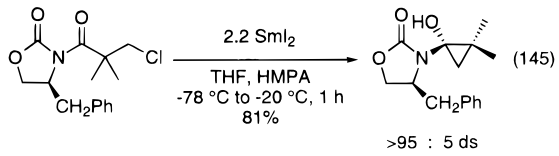


Since its first description in the early 1900s[67] until the 1980s, the promise of Barbier-type cyclization reactions for the construction of five- and six-membered rings remained largely unfulfilled. Thus, treatment of appropriate haloalkyl ketones with alkali and alkaline earth metals or organolithium reagents typically failed to bring about the desired reductive coupling reactions in reasonable yields. Samarium(II) iodide provided a general solution to this important, long-standing problem. In intramolecular Barbier-type reactions, SmI_2 is by far the most general reductive coupling agent in terms of utility and scope of application. Isolated cyclopentanols can be synthesized diastereoselectively when δ-iodoalkyl ketones are treated with SmI_2 in THF at −78 °C and allowed to warm to room temperature (eq 143).[68] The cyclization is not inhibited by steric encumbrance about the carbonyl, and the procedure thus provides a useful approach to the synthesis of hindered cyclopentanols. Cyclohexanols can be accessed by the cyclization of allylic halide substrates (eq 144).[69]

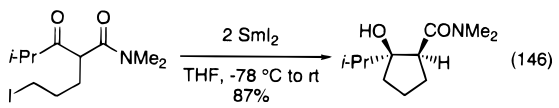




The Sm(III) ion generated after electron transfer in Barbier-type processes can be utilized as an effective Lewis acid template to control stereochemistry via chelation in suitably functionalized substrates. For example, the samarium Barbier reaction of nonracemic β-chloro-substituted amides derived from oxazolidinones provides high yields of the corresponding cyclopropanols, often with high diastereoselectivity (eq 145).[70]

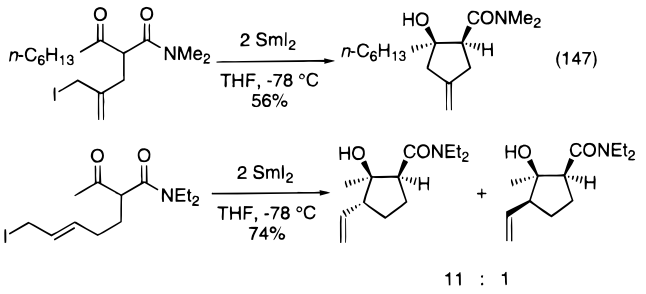


Rigid, chelated intermediates have also been proposed in the cyclization of iodoalkyl-substituted β-keto amides (eq 146).[69] The Sm(III) ion generated in the reaction again serves to control stereochemistry in the cyclization process. Samarium(II) iodide-promoted cyclization reactions of β-keto amides proceed under kinetic control; there is no evidence to suggest that equilibration takes place under the reaction conditions, and a single diastereomer is generated in each example. Six-membered rings can also be constructed by this process, although yields are somewhat lower. Approximately 30% of the reaction mixture consists of byproducts derived from simple reduction of the ketone to an alcohol in these cases.

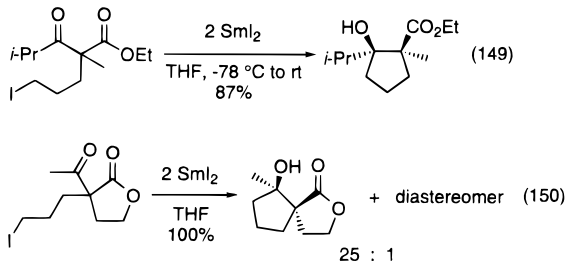


Allylic halide precursors also react with excellent stereochemical control through chelation. In these instances, both five- and six-membered rings comprising several different substitution patterns can be accessed (eqs 147 and 148).[69] While yields and diastereoselectivities are quite high in five-membered

ring synthesis, six-membered rings are generated in lower yields and with attenuated selectivity.

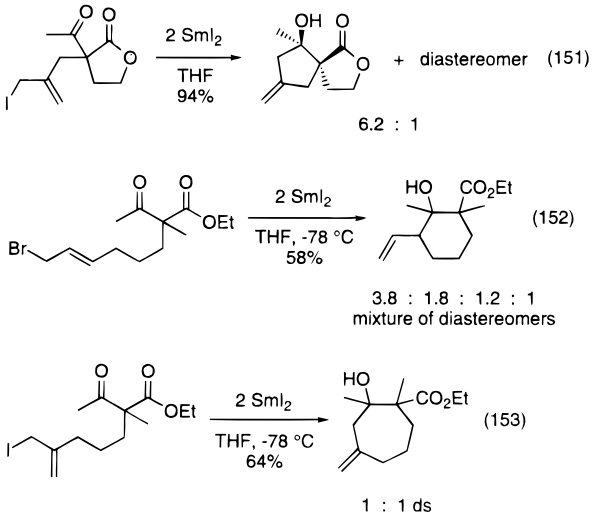


Appropriately substituted β-keto esters have been explored as substrates for intramolecular Barbier cyclization. Although the approach is highly successful for the synthesis of hydroxycyclopentanecarboxylates (eqs 149 and 150), six-membered rings are inaccessible utilizing this procedure.[69] In contrast to

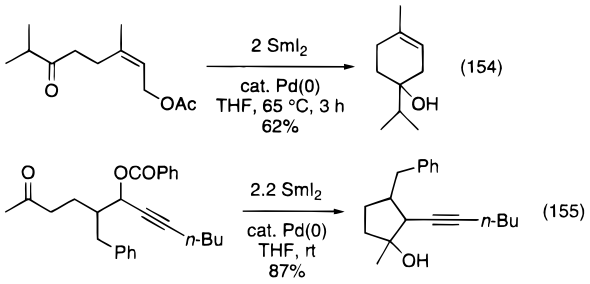


β-keto amide substrates, the corresponding reactions involving β-keto esters are under thermodynamic control. The observed diastereoselectivity is the result of a retroaldol−aldol process which serves to equilibrate the initially formed samarium aldolates. In spite of this, diastereoselectivity is quite good in most cases. However, it is highly dependent on substituent and solvent effects. In particular, the use of coordinating solvents or additives (such as tetraglyme, 18-crown-6, or *N,N*-dimethylacetoacetamide) which serve to strip the Sm(III) ion away from the chelating center diminishes the diastereoselectivity observed in these reactions.

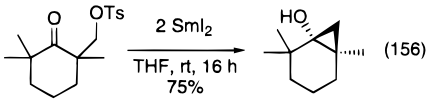
Allylic halide substrates in the β-keto ester series cyclize very efficiently, and convenient routes to five-, six-, and even seven-membered rings are feasible, although diastereoselectivities are variable (eqs 151−153).[69]



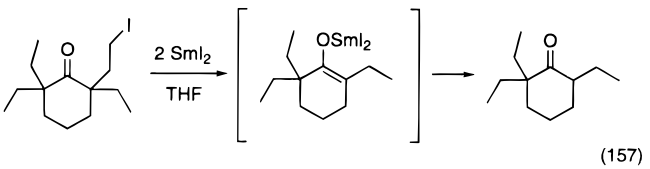
A unique protocol for the construction of cycloalkanols via a SmI_2-promoted Barbier-type process involves the Pd(0)-catalyzed cyclization of allylic (eq 154)[53] and propargylic acetates or benzoates (eq 155).[5e] These reactions are postulated to proceed via the intermediate allyl- or allenylpalladium species, with reductive transmetalation by SmI_2 leading to the corresponding organosamariums which take part in the carbonyl addition. Diastereoselectivities in these reactions are not high, and aldehydes are not suitable electrophiles for these reactions.



Among the more valuable applications of the SmI_2 reductive coupling technology is the synthesis of bicyclic alcohols using the Barbier protocol. Three-, five-, and six-membered rings have all been synthesized by this procedure. The construction of cyclopropanols involves treatment of an α-tosyloxymethyl cyclohexanone with SmI_2 (eq 156).[71] It should be noted that this reductive coupling takes place with a very hindered, neopentyl-type tosylate. This invokes considerable question as to the mechanism of this cyclization, because the tosylate would not appear to be subject to displacement by iodide under the mild conditions of the reaction.

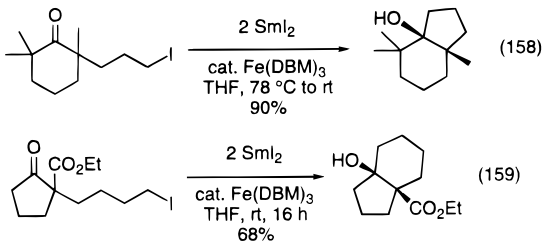


Syntheses of cyclobutanols by this protocol have not yet been thoroughly explored. In the single reported attempt to generate a cyclobutanol, the desired cyclization did not occur. Rather, a reductive elimination took place, generating a samarium enolate (eq 157).[71] Because of the special nature of this highly hindered substrate, it would not seem appropriate to extrapolate this reactivity pattern to all related cyclizations.

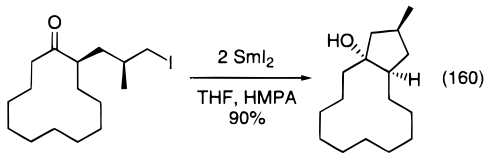


Because of their ubiquity, five- and six-membered rings are the most important targets for synthesis via an intramolecular Barbier process.[72] Development of the samarium Barbier approach to six-membered rings in fused bicyclic systems is particularly significant, because there exists no reliable and convenient alternative method for this simple annulation process. Reactions proceed with considerable diastereoselectivity when cyclopentanone substrates

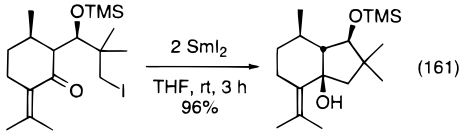
are utilized, or when substituents are placed α to the carbonyl in other cycloalkanones (eqs 158 and 159).



The SmI_2-mediated intramolecular Barbier procedure has been applied to diverse systems, and in virtually every case has proven to be superior to other protocols. Suginome and Yamada have applied the technique to syntheses of exaltone and (±)-muscone (eq 160).[73] Yields employing the SmI_2 protocol in the cyclization were much better than those utilizing Mg/$HgCl_2$ or *n*-butyllithium as the reductants.

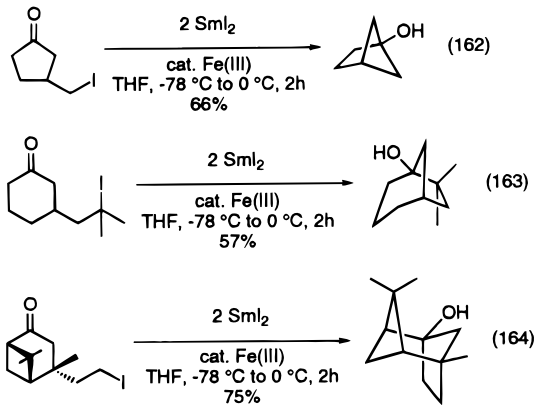


Very little work has been reported on the Barbier-type cyclization reactions utilizing α,β-unsaturated enones. A priori one might assume that these substrates would be a problem. The lower reduction potential of the conjugated system could lead to competitive reaction manifolds. In the limited studies reported, however, cyclizations occur with high efficiency, providing the desired allylic alcohols in excellent yields and with high diastereoselectivity (eq 161).[74]

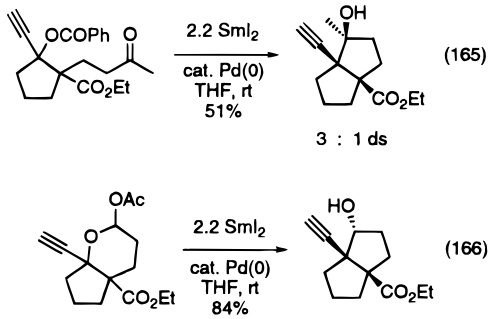


The SmI_2-mediated intramolecular Barbier synthesis can be applied to the synthesis of bridged bicyclic alcohols as well as the fused bicyclic systems described above.[75] The generality of this procedure is demonstrated by the diversity and complexity of substrates undergoing cyclization. For example, highly strained bicyclo[2.1.1]hexan-1-ols are generated in acceptable yield (eq 162). Ketones possessing primary, secondary, and even tertiary and neopentyl iodides can all be utilized as precursors for the reaction (eq 163), and highly hindered ketones provide excellent yields of cyclized products (eq 164). Neither magnesium metal nor organolithiums can be utilized to promote these cyclizations. Consequently, SmI_2 exhibits a unique reactivity pattern that is difficult if not impossible to duplicate using these and other reductive coupling agents.

The Pd(0)-catalyzed cyclization reaction of propargylic acetates can be utilized for the construction of bicyclic systems.[5e] Both internal and terminal alkynes can be employed in the reaction, and dense functionality can be incorporated into the ring systems with

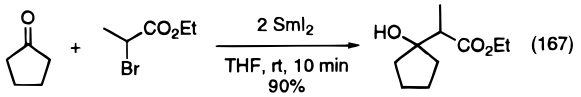


good stereochemical control in some instances (eq 165). Aldehydes are not suitable substrates for the process. However, substrates engineered to incorporate a masked aldehyde release concentrations of aldehyde equal to the catalyst concentration during the course of the reaction (eq 166). The aldehydes thus generated in situ can be trapped by the organosamarium nucleophile and thereby avoid significant competitive reduction by the SmI_2.



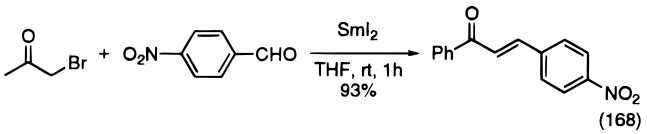
2. Aldol- and Reformatsky-Type Reactions

Samarium(II) iodide-mediated Reformatsky-type coupling reactions can be carried out between α-halo esters and ketone electrophiles (eq 167).[2a,76] Al-



though a systematic survey has not been conducted, this reaction appears to provide a useful alternative to normal Zn-promoted Reformatsky reactions. The latter often perform well only when an activated form of Zn is utilized, and thus the homogeneous conditions afforded by SmI_2 may provide some advantages. The samarium version of the Reformatsky reaction is particularly useful in reactions with highly hindered ketone substrates.[2c]

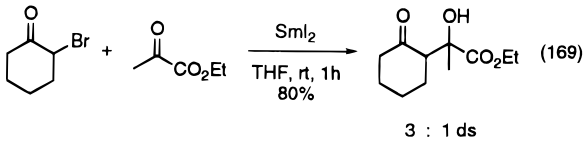
In a similar fashion, aldol-type reactions have been described in which α-halo ketones can be coupled to aldehydes (eq 168).[77] Only 1 equiv of SmI_2 is



required for these reactions. Presumably, iodide also

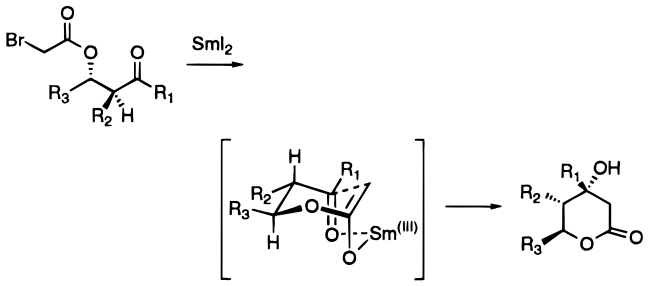
serves as a reductant in the process, facilitating the generation of the samarium enolate. Optimum reaction conditions require that the α-halo ketone, aldehyde, and SmI_2 be mixed together at once. Pregeneration of the enolate with subsequent addition of the aldehyde provides little of the desired products.

Aldol-type reactions with α-keto carboxylates have been carried out, providing an entry to α-hydroxy-γ-keto carboxylates (eq 169).[78] In these condensations, dehydration has been prevented. However, in reactions capable of generating diastereomers, low selectivity is observed.

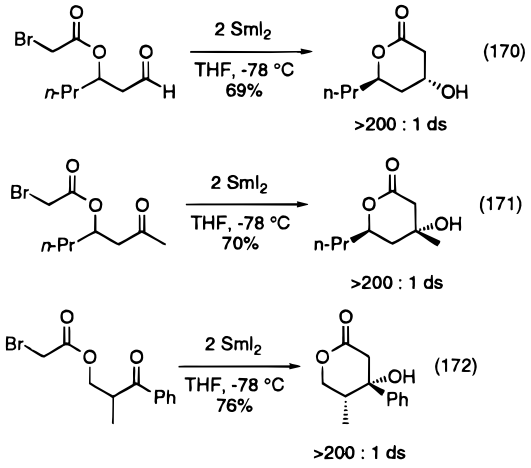


As in the Barbier reactions described above, intramolecular versions of the Reformatsky-type reactions have seen further development and applications than their intermolecular counterparts. Reactions of SmI_2 with β-bromoacetoxy carbonyl substrates are proposed to generate a Sm(III) ester enolate, with cyclization taking place through a rigid cyclic transition structure enforced by chelation (Scheme 9).[22]

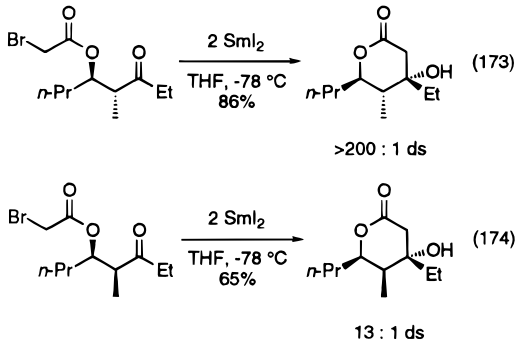
Scheme 9



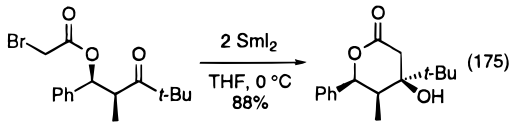
Virtually all of the observed trends in diastereoselectivity can be explained on the basis of this eight-membered ring samarium chelate. For example, reductive cyclizations of β-bromoacetoxy aldehydes (eq 170) and β-bromoacetoxy ketones (eq 171) promoted by SmI_2 afford β-hydroxy δ-valerolactones with very high levels of 1,3-asymmetric induction.[22,79] High 1,2-asymmetric induction is achieved only in substrates possessing a relatively large group on the ketone (eq 172).



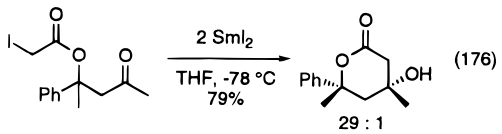
In contrast to other reported methods of 1,3-asymmetric induction, the SmI_2-mediated intramolecular Reformatsky procedure permits strict control of stereochemistry even in diastereomeric pairs of substrates bearing α substituents (eqs 173 and 174).[22] Diastereoselectivity is somewhat lower for syn diastereomeric substrates, where one substituent must be pseudoaxially disposed in the proposed transition structure leading to product. However, 1,3-asymmetric induction is still predominant, overwhelming the directing effect of the stereocenter α to the carbonyl.



Diastereoselectivity further erodes in syn diastereomeric substrates as substituents become more and more highly hindered, to the point where the sense of asymmetric induction is opposite to that predicted by the simple six-membered transition structure above (eq 175).[22] For such substrates, reactions presumably transpire through alternative boat transition structures.

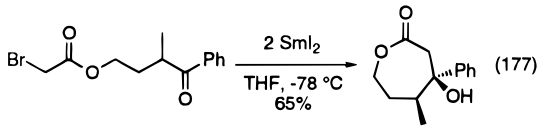


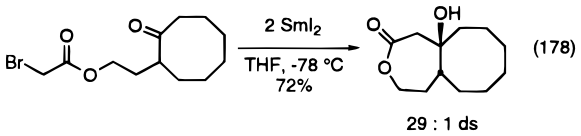
Perhaps most impressive is the degree of 1,3-asymmetric induction that can be derived from a tertiary stereocenter (eq 176).[22] Consideration of the chelated six-membered transition structure implies that the phenyl group in this example occupies the pseudoaxial orientation. This orientation is expected on the basis of conformational analyses of 1-methyl-1-phenylcyclohexane derivatives.

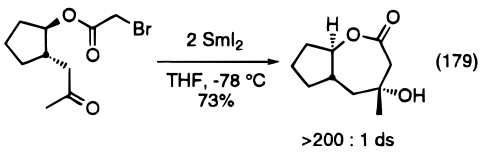


High levels of 1,2-asymmetric induction are also achieved in intramolecular Reformatsky-type reactions forming seven-membered lactones (eqs 177 and 178).[22] Although 1,3-asymmetric induction can be high in entropically restricted systems (eq 179), it is generally low (about 3:1) and 1,4-asymmetric induction is virtually nonexistent.

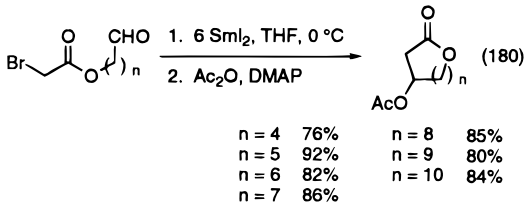
The SmI_2-promoted intramolecular Barbier procedure has been adapted to permit construction of medium- and large-ring molecules.[80] Both α-halo esters and α-halo ketones have been utilized as

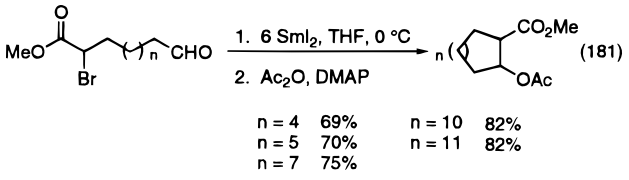


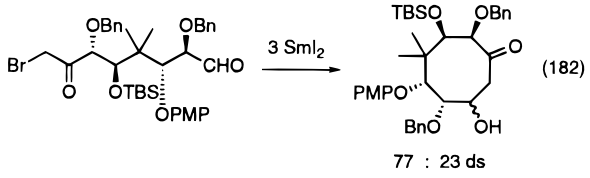


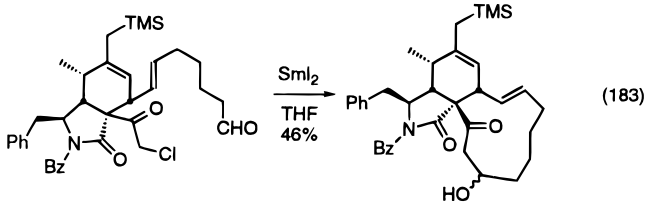


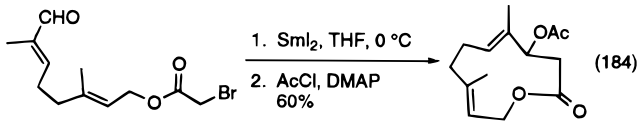
substrates for the reaction, and eight- through 14-membered ring compounds can be synthesized in this fashion in reasonable yields (eqs 180−184). Diastereoselectivities in these SmI_2-mediated cyclizations are quite variable.



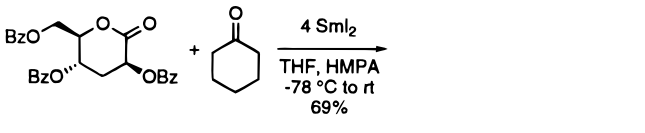


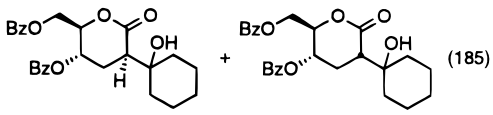


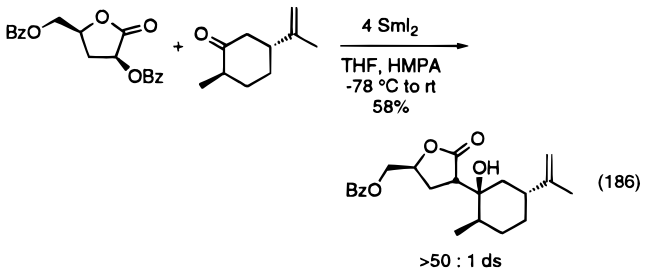




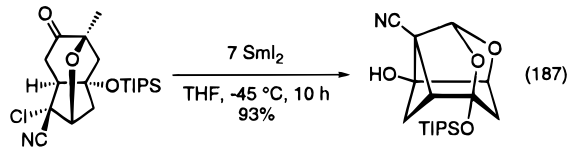
An interesting variant of the Reformatsky-type coupling reaction relies on the ability of SmI_2 to reductively cleave α-alkoxy ketones, generating samarium enolates. The latter can be protonated to permit isolation of the unsubstituted ketones,[81] but also reacted with ketones to provide the coupled products (eqs 185 and 186).[5a−c]





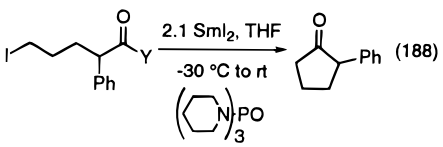


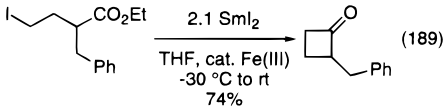
Finally, a novel analog of the aldol and Reformatsky reaction has been employed as a key step in the synthesis of (±)-paeoniflorigenin and (±)-paeoniflorin (eq 187).[82]



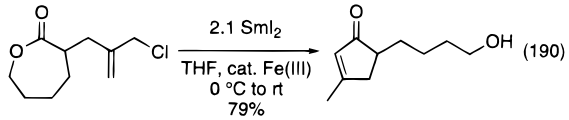
3. Nucleophilic Acyl Substitution Reactions

Esters and amides are normally unreactive toward organic halides in intermolecular reactions promoted by SmI_2. However, highly selective intramolecular nucleophilic acyl substitutions are accomplished under mild conditions when appropriately substituted carboxylic acid derivatives are treated with SmI_2 (eq 188).[83] The method is amenable to the synthesis of four-, five-, and six-membered rings (eq 189), and primary alkyl, secondary alkyl, and allylic halides all participate in the reaction. In the case of allylic halides, isomerization of the double bond occurs under the reaction conditions, leading to the isolation of conjugated ketones (eq 190). The reaction has been utilized to gain entry to spirocyclic systems with control of stereochemistry about remote stereocenters (eq 191) and as a means to carry out ring expansions (eq 192). Reactions are run under mild conditions and are apparently near neutral. Consequently, little or no epimerization of stereocenters α to the ketone carbonyl is observed (eq 193).





(189)



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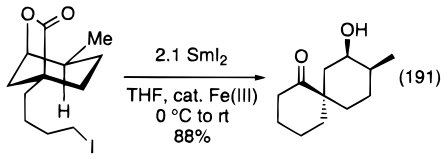
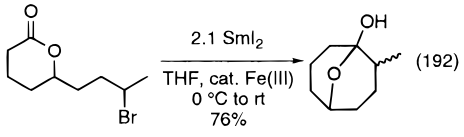
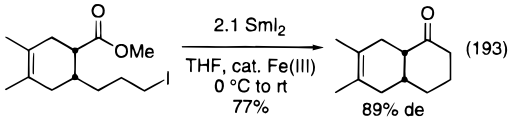


(191)

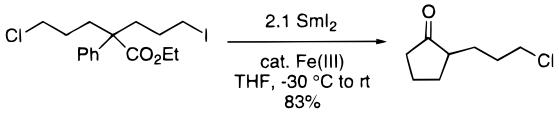


(192)



(193)

The nucleophilic acyl substitution reaction forms the basis for several of the more significant sequencing processes to be discussed. Thus a single reaction in appropriately functionalized molecules provides products poised for further reaction in sequential processes. For example, the dihalo carboxylate depicted in eq 194 provides a ketone that is a substrate for an intramolecular Barbier-type reaction, and the unsaturated halo ester in eq 195 affords a cyclopentanone which is suitably functionalized for ketyl olefin cyclization.



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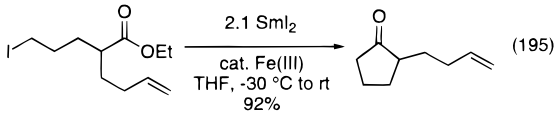
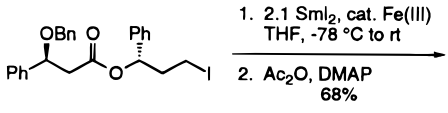


(195)

A modified version of this reaction has been employed to synthesize stereodefined acyclic ketones in which the stereocenters are remote from one another.[84] Thus treatment of 3-iodopropyl carboxylates with SmI_2 leads to a facile intramolecular nucleophilic acyl substitution with the generation of the corresponding acyclic ketones (eqs 196−198). Competitive reductive elimination inhibits formation of the desired product when oxygen or nitrogen is situated α to the carbonyl. However, all other substitution patterns examined led to reasonable yields and high diastereoselectivities or enantioselectivities.

By contrast, the homologous 4-iodobutyl carboxylates undergo an initial nucleophilic acyl substitution reaction followed by an intramolecular Meerwein-Ponndorf-Verley redox reaction (Scheme 10).[23b] The latter reaction is reversible and stereospecific. The



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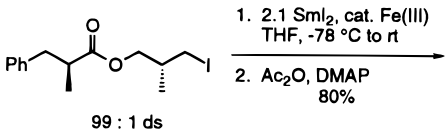

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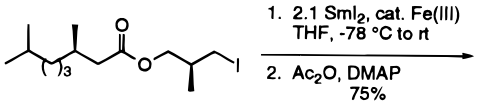
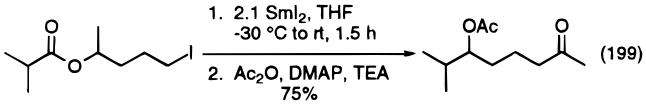


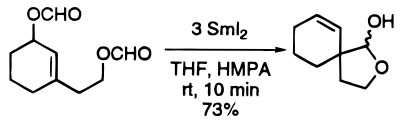
(198)

equilibrium is apparently driven by steric interactions between the oxidosamarium(III) moiety and the alkyl group on the adjacent carbon (structure **C** vs **D**). In favorable cases (where R_L is sterically bulky), the reaction can be driven to provide a single product (eq 199).



(199)

Reactions of 1-[2-(formyloxy)ethyl]-3-formylcycloalkenes with SmI_2 initially proceed by a reductive cleavage of the allyl formate to produce an allylsamarium species. The allylsamarium thus generated undergoes an intramolecular nucleophilic acyl substitution reaction on the remaining formate, leading to the synthesis of cyclic hemiacetals (eq 200).[85] The reaction has been employed as a key step in the synthesis of upial (eq 201).[86]



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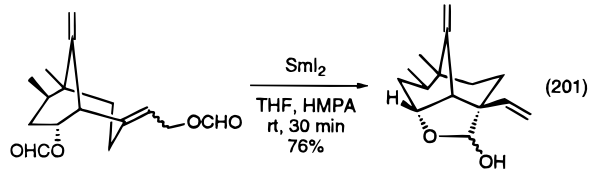
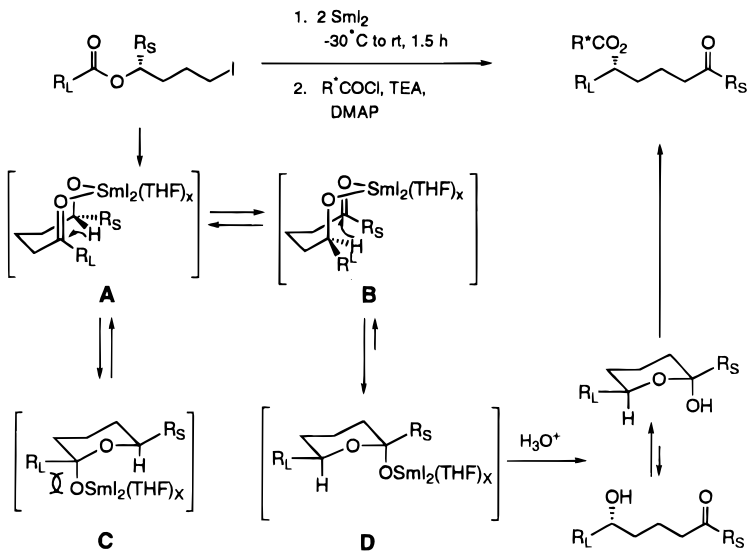


(201)

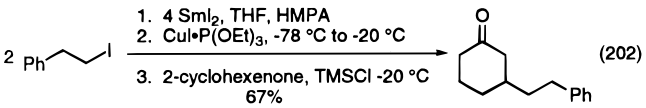
4. Conjugate Addition Reactions

Although organosamariums generated by the reaction of SmI_2 with alkyl halides normally undergo 1,2-addition in reactions of conjugated ketones, the addition of a copper(I) complex facilitates the 1,4-addition process.[87] In particular, the use of a CuI·$(OEt)_3$ complex promotes the conjugate addition reaction of a variety of primary and secondary alkyl

Scheme 10

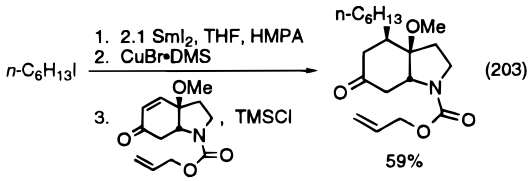


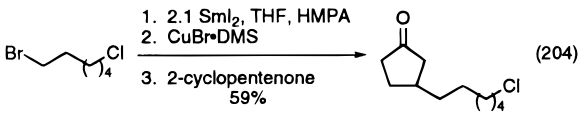
halides with assorted enones (eq 202).[87a] Yields are



modest to good in the examples provided. The yields are based upon the enone, however, and thus only readily available organic halides appear suitable as precursors for the reaction. Because the synthesis of organosamariums is often capricious and apparently not general,[19] this represents a further limitation of the method.

The copper-catalyzed conjugate addition of organosamariums to α,β-unsaturated ketones and nitriles can be accelerated by TMSCl, and this protocol represents an improved method for the synthesis of the desired conjugate addition products.[87b] The method is tolerant of some functional groups (eqs 203 and 204), but still appears limited in terms of the organosamariums that can be utilized.



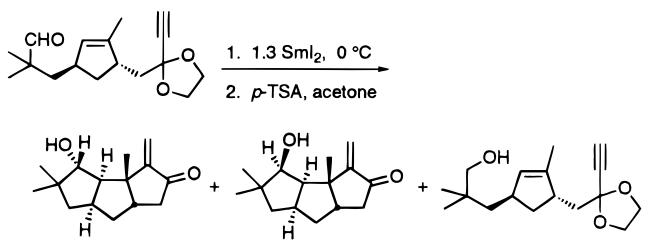


III. Sequential Reactions Promoted by Samarium(II) Iodide

The emerging utility of SmI_2 as a useful synthetic reagent resides not only in its ability to promote individual reactions in a singularly selective manner, but also in its capacity to promote sequential reactions in an equally efficient way. Most importantly, SmI_2 can be utilized to sequence both one- and two-electron processes in any combination or order, depending upon the substrates' design. Thus serial radical reactions, radical reactions followed by anionic reactions, anionic reactions succeeded by radical reactions, and tandem anionic reactions are all feasible. The full extent of the power of these methods has yet to be fully explored, but the progress that has been documented along these lines is outlined below.

A. Sequential Radical Processes

In view of the success of tin hydrides and silicon hydrides to promote sequential radical reactions, it is perhaps not surprising that only a single example of a SmI_2-mediated sequential radical reaction has been reported.[88] This tandem bicyclization was employed as the key step in the synthesis of (±)-hypnophilin and the formal total synthesis of (±)-coriolin (eq 205). Less than 2 equiv of SmI_2 were necessary for the cyclization, indicating that the process is initiated by single-electron reduction of the aldehyde to the ketyl, with subsequent cyclization of this ketyl onto the cyclopentene double bond. The resulting tertiary radical is reasonably persistent under the reductive reaction conditions, permitting cyclization onto the tethered alkyne. The cyclopentylidene radical thus generated abstracts a hydrogen atom prior to reduction by SmI_2, thus terminating the sequence.

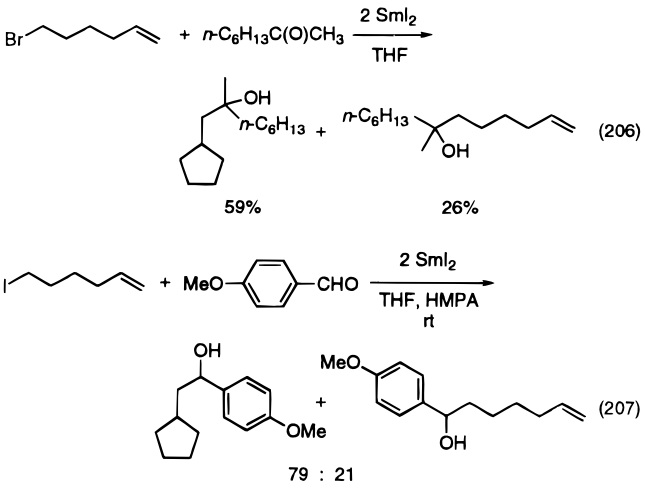


Certainly many other sequential radical processes are viable using SmI_2. The only limitation is that

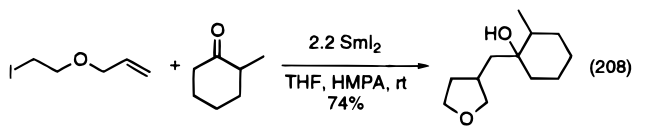
any radical intermediates generated under the reaction conditions must undergo cyclization (or other desired radical reactions) faster than they can be reduced to the corresponding anion. Although tin hydrides and silicon hydrides have traditionally dominated this area, there are certainly sequences that would benefit from further development of SmI_2-induced chemistry, particularly in reactions initiated by ketyl cyclizations.

B. Radical/Anionic Sequences

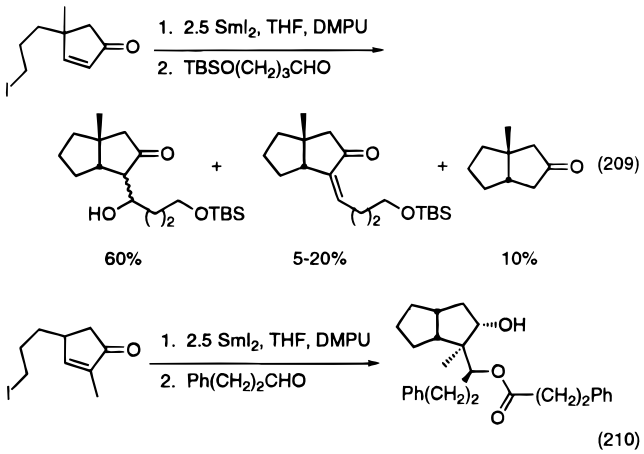
To date, the most thoroughly studied sequences promoted by SmI_2 have been those in which a radical process is followed by an anionic reaction. The first of these reactions was detailed in 1981, and served to point out not only the promise of SmI_2-sequenced reactions, but their limitations as well. Thus 6-bromohex-1-ene, upon treatment with SmI_2 in the presence of 2-octanone, provided a 59% yield of the radical/anion sequenced product along with 26% of the simple Barbier-coupled product (eq 206).[76] In this reaction, reduction of the initially formed 5-hexenyl radical competes with cyclization of the radical onto the alkene, resulting in the observed mixture of products. Under more dilute reaction conditions ($[SmI_2] = 0.021$ M) the ratio of products can be modestly affected in favor of the cyclization process, but the comparatively slow cyclization of the 5-hexenyl radical with respect to its reduction still leads to mixtures of cyclized and normal Barbier products (eq 207).[6]



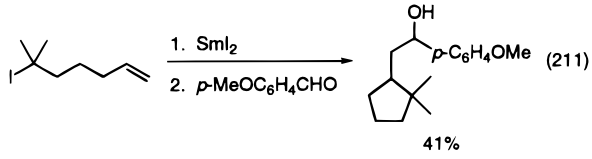
Radical intermediates that undergo more rapid cyclization allow significant improvements to be made in the tandem process. Among primary alkyl radicals, those incorporating an oxygen heteroatom along the chain cyclize quite rapidly ($k_{cyc} = 10^6$ s^{-1}). These cyclizations thus occur at rates which exceed the rate of reduction of the radical to the anion by SmI_2, and thus the sequential radical/anion process is viable (eq 208).[10c,12]



Unsaturated ketones also facilitate the cyclization of alkyl radicals derived from halides. In this case the resulting anion generated upon further reduction is an enolate, which in principle can be trapped by a variety of electrophiles. Although the essence of this process has been carried out with aldehydes serving as the enolate electrophile,[89] caution is warranted as to the detailed mechanism of the process. In particular, whether the initial electron acceptor is the halide or the enone is highly debatable. Yields are variable in these sequential reactions. Dehydrated byproducts, protonated ketone (eq 209), and products resulting from intramolecular Tischenko redox processes (eq 210) contaminate the reaction mixture.

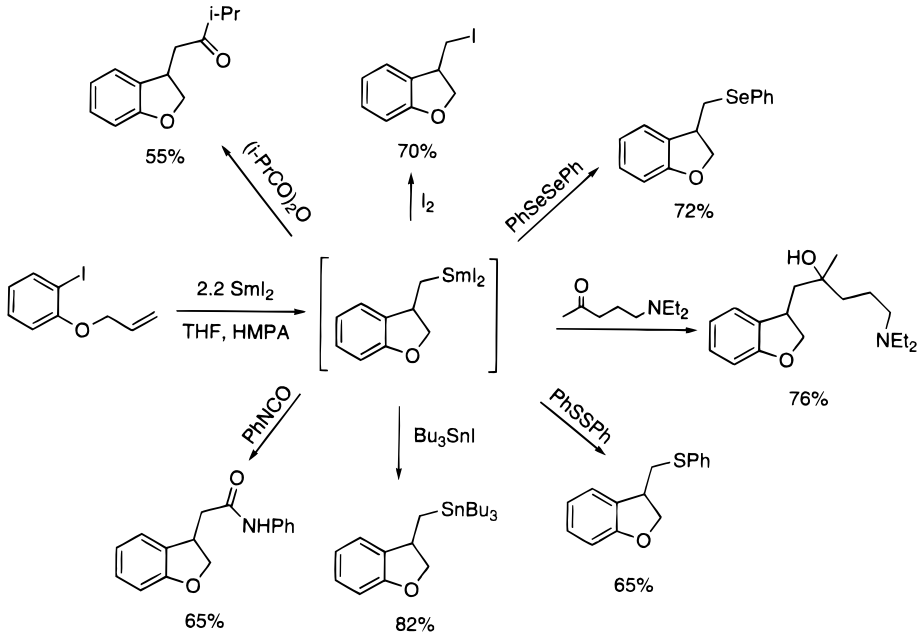


A second strategy for improving sequential reactions under reductive conditions involves the use of more persistent radicals, i.e., those that are reduced more slowly to the corresponding anions. Tertiary alkyl radicals are among those that might be classified in this category. Unfortunately, cyclization rates for tertiary radicals may also be slowed, and preliminary results in sequential cyclization/trapping studies have showed only modest success (eq 211).[45]

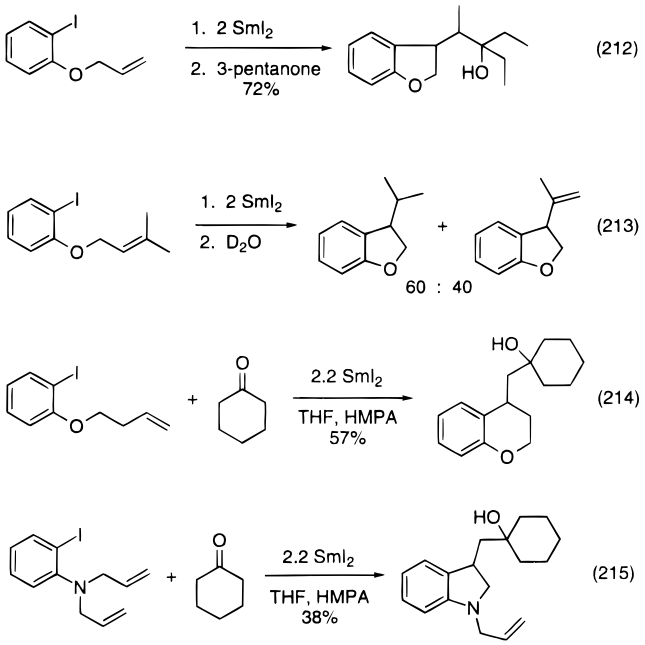


Aryl radicals have received a great deal of attention in tandem radical/anion sequences.[10c,19,90] As outlined previously, these radicals are quite persistent, resisting further reduction to the corresponding aryl samarium. Furthermore, aryl radicals cyclize with rates of up to 4×10^9 s^{-1} in a 5-exo trig process, thereby permitting radical cyclization and subsequent nucleophilic trapping of a variety of aldehydes, ketones, and other reactive electrophiles (Scheme 11). The nucleophilicity of the organosamarium species is limited, however, and thus a variety of electrophiles fail to undergo reaction in acceptable yields. These include allylic halides, benzylic halides, epoxides, ethyl bromoacetate and other alkylating agents, carboxylic acid halides, TMSCl, TsCl, and acrylonitrile.[19] The types of radical intermediates

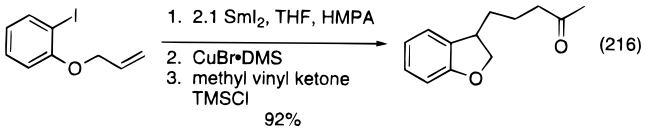
Scheme 11



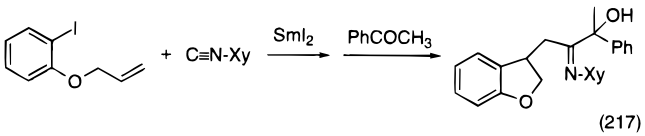
that can be converted to organosamariums after the initial cyclization event are also limited. Only primary and secondary alkyl radicals can be reduced in the second step to organosamariums, which are subsequently trapped by electrophiles (eq 212).[19] Tertiary radicals undergo preferential disproportionation and hydrogen abstraction (eq 213).[19] The analogous 6-exo cyclization process can be incorporated into a sequential process (eq 214), as can the 5-exo process leading to the synthesis of nitrogen heterocycles (eq 215).[10c]



The range of electrophiles utilized in the sequential process can be expanded by transmetalation of the intermediate organosamarium species to organocopper reagents.[87] In this manner α,β-unsaturated ketones can be utilized as the electrophiles, permitting termination of the radical/anion sequence in a conjugate addition reaction (eq 216).

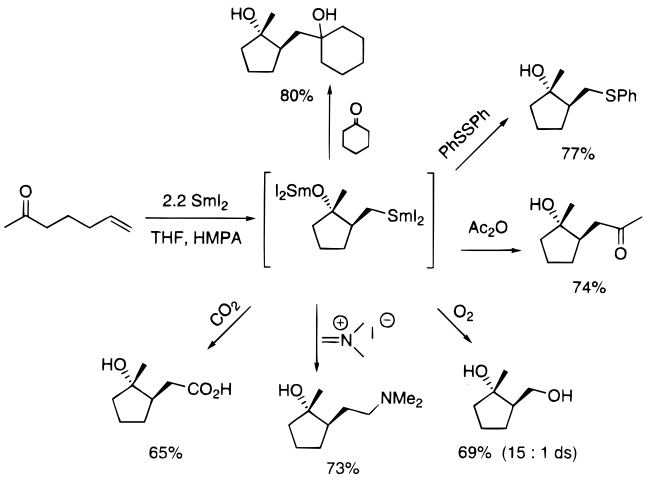


A radical/anionic/anionic sequence has been described on the basis of initial cyclization of an aryl radical (eq 217).[19] In this set of reactions, radical cyclization provides the cyclized organosamarium. Reaction of this anion with xylyl isocyanide affords an iminoylsamarium reagent, which was subsequently trapped with acetophenone. The overall yield of 62% represents very high conversions for each of the three individual carbon−carbon bond-forming reactions involved in the overall sequence.

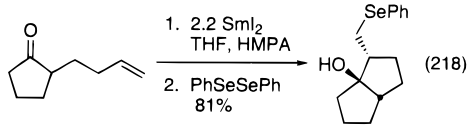


A diverse range of sequential radical/anionic sequences initiated by ketyl cyclizations have been described. The persistence of ketyl radicals under reductive reaction conditions permits greater flexibility with regard to the initial radical than alkyl radicals and even aryl radicals, and greater inherent stereoselectivity is generally observed in these reactions as well. The diversity of reagents that can be utilized to trap the organosamarium species generated after radical cyclization has been delineated in reactions using 6-hepten-2-one (Scheme 12).[38] Aldehydes, ketones, anhydrides, oxygen, carbon dioxide, and Eschenmoser's salt, among others, all provide high yields of the desired products, with stereochemistry firmly established in the cyclization event. The

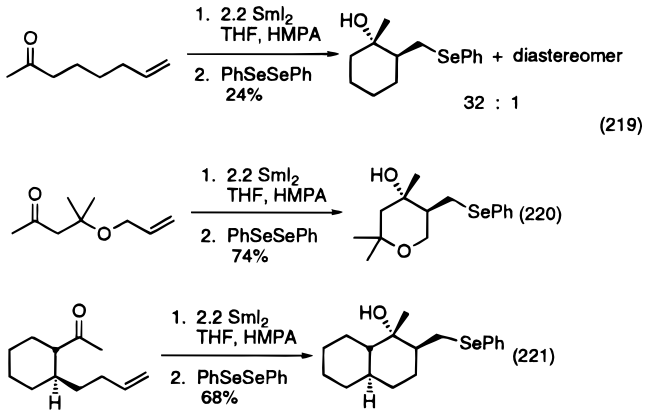
Scheme 12



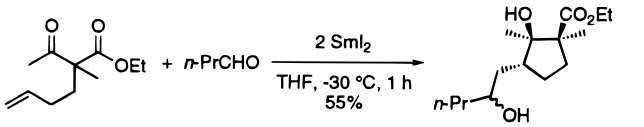
process can be utilized for the creation of functionalized bicyclic systems as well (eq 218).

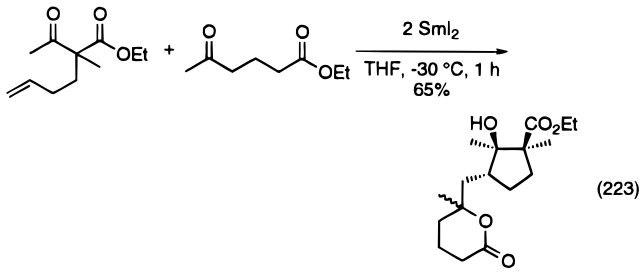


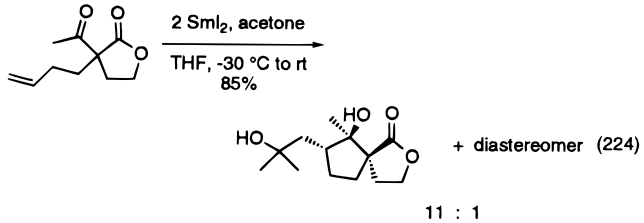
In limited cases (where cyclization is sufficiently rapid), the analogous 6-exo radical cyclization process can be utilized to initiate the sequential process (eq 219).[37] Successful examples include those in which oxygen heterocycles are incorporated within the chain undergoing cyclization (eq 220), and entropically favored cyclizations resulting in the generation of bicyclic systems (eq 221).

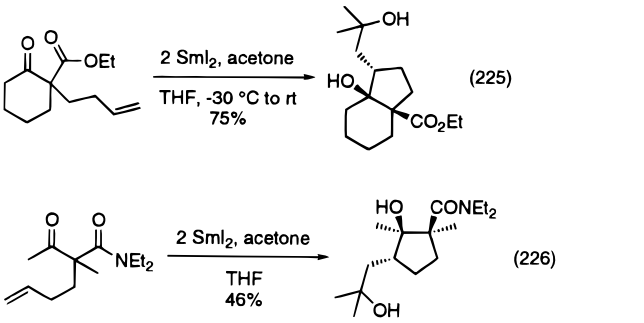


Sequential processes utilizing β-keto ester and β-keto amide substrates permit chelation-controlled reactions terminating in a carbonyl addition reaction.[91] Reactions reported have been performed with the β-dicarbonyl substrate, aldehyde or ketone electrophile, and SmI_2 all present at the same time. Efforts to trap the organosamarium species generated subsequent to the cyclization event have been unsuccessful, presumably because of a facile retroaldol reaction which destroys the initially formed complex. In spite of this limitation, the overall transformation can be utilized to synthesize a variety of complex target structures from relatively simple acyclic substrates (eqs 222−226).

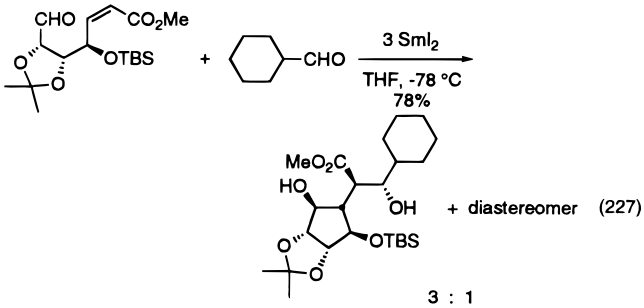






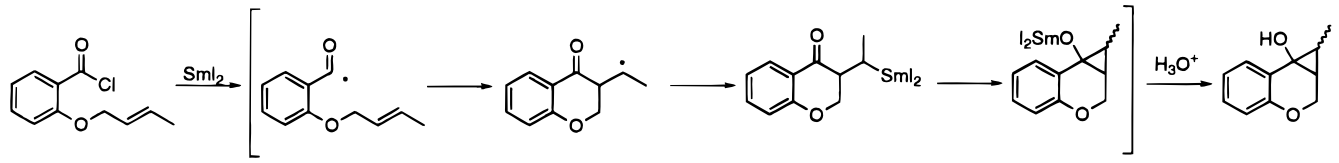


Samarium(II) iodide-promoted ketyl cyclizations onto unsaturated esters results in the formation of samarium ester enolates. The enolates formed in this manner can undergo aldol-type reactions with aldehydes, and the two-step process thus constitutes another unique means by which sequential reactions can be accomplished (eq 227).[92]

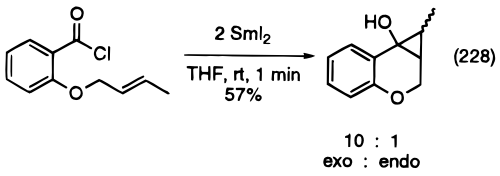


A sequential process initiated by an acyl radical cyclization and terminated by an intramolecular Barbier reaction has been described.[93] Thus when 2-allyloxybenzoyl chlorides are treated with SmI_2, the

Scheme 13



resulting product is a cyclopropanol (eq 228). Al-

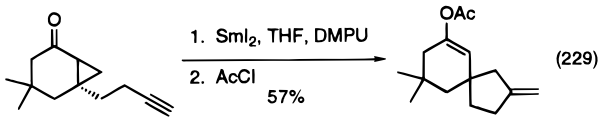


(228)

10 : 1
exo : endo

though other mechanisms are feasible, perhaps the most likely mechanism involves generation of an acyl radical which undergoes intramolecular addition to the double bond, thereby forming a new radical (Scheme 13). This radical can then be reduced by a second equivalent of SmI_2, generating an anion. The organosamarium(III) intermediate thus generated reacts with the ketone, forming the observed cyclopropanol.

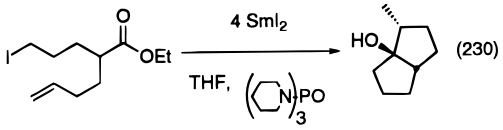
A sequenced reaction of sorts results from the radical ring opening of cyclopropyl ketones mediated by SmI_2.[15] The resulting homoallylic radicals can undergo cyclization with pendent unsaturated side chains, while the enolate can be trapped by various electrophiles. Although in principle a variety of enolate reactions are feasible, in practice only enol acetates have been generated by this process (eq 229).



(229)

C. Anionic/Radical Sequences

The versatility of SmI_2 in its role as a sequencing reagent can be appreciated by a demonstration of its ability to promote both radical reactions followed by anionic reactions and anionic reactions succeeded by radical reactions. The latter class of sequential reactions are represented by ketyl olefin cyclization reactions which are preceded by nucleophilic acyl substitutions. Thus, the intramolecular nucleophilic acyl substitution reaction generates a ketone which is poised for further radical reaction by its ketyl. This reactivity pattern has been exploited in a number of sequential bicyclization processes (eq 230).[83,94] The reaction sequence appears highly general in its application, permitting the synthesis of a wide range of bicyclic systems. In fact, both heterocycles and carbocycles can be created in the one-pot process. Thus, in spite of the facility by which heterosubstituents α to ketones and esters can be reductively cleaved,[2e,81] α-heterosubstituted esters provide a starting point for the construction of heterocycles (eq 231). Both five- and six-membered rings can be assembled (eq 232), and a variety of substitution patterns and functional groups can be tolerated as well (eqs 233 and 234). Finally, both linearly fused (eq 235) and angularly fused tricyclic systems (eq 236) can be accessed quite efficiently from readily available starting materials.



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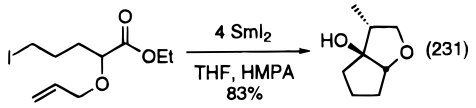

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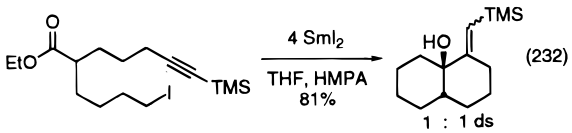
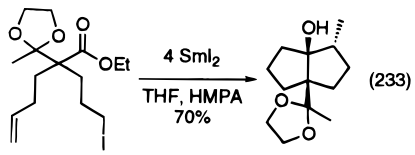
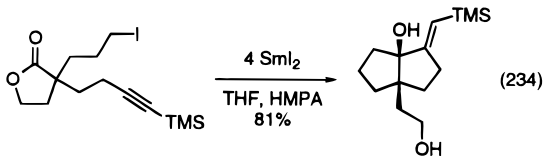


(232)

1 : 1 ds



(233)



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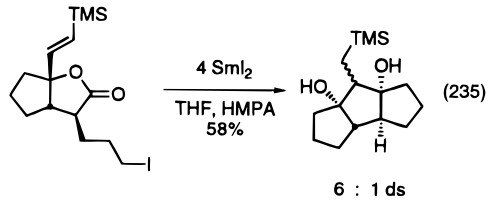

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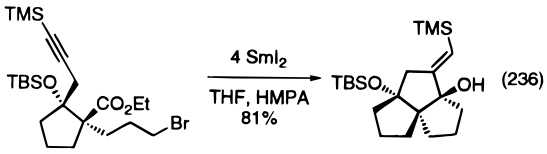
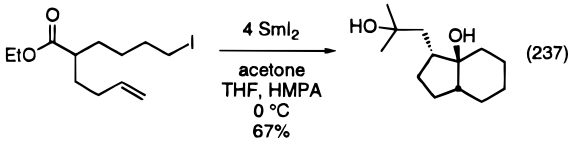


(236)

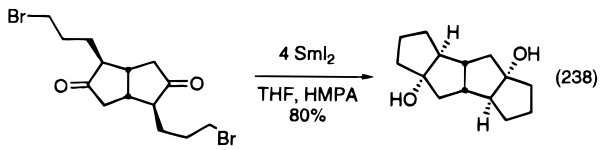
This chemistry can be taken one step further. After radical cyclization in the second step of the sequence, reduction of the resulting radical generates a new organosamarium. This can be trapped by electrophiles, completing a sequential anionic/radical/anionic sequence (eq 237). Although further development of the reaction conditions may permit extension of this chemistry to other electrophiles in the terminating step, only ketones have been explored to date.

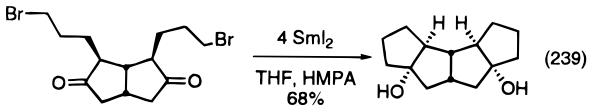


(237)

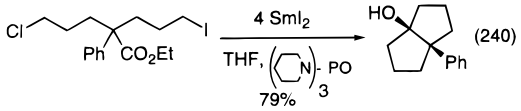
D. Sequential Anionic Processes

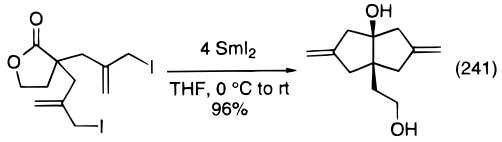
Just as a variety of sequential radical/radical reactions have proven feasible, so have tandem anionic/anionic sequences shown demonstrable effectiveness in synthetic organic sequences promoted by SmI_2. The most straightforward of these reactions is one in which two intramolecular Barbier-type reactions occur in one pot. This strategy has been utilized quite effectively as a key step in the synthesis of polyquinenes (eqs 238 and 239).[95]

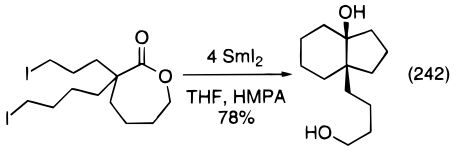


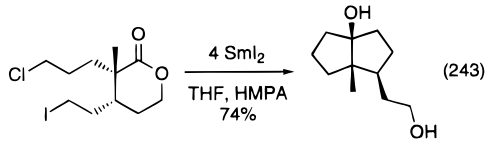


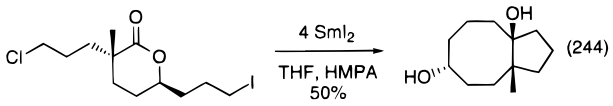
Another versatile dianionic process for the synthesis of bicyclic and tricyclic systems involves a sequence of nucleophilic acyl substitution followed by a samarium Barbier reaction (eq 240).[83,96] This approach to bicyclic systems has been determined to be generally applicable for transformations involving nucleophilic acyl substitution or carbonyl addition through five- or six-membered transition structures. Allylic halides as well as alkyl halides perform well in the reaction (eq 241), and substitution patterns can be altered to provide a structurally diverse array of products (eqs 242−244). The latter example is notable for the selective reaction of the alkyl iodide in preference to the alkyl chloride. This selectivity is required for the success of the overall transformation. Additionally, it represents a strategy for ring expansion that is of use in the construction of seven- and eight-membered rings.



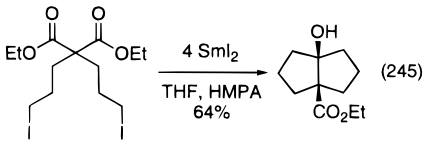


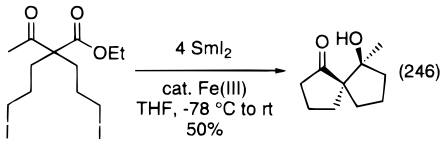




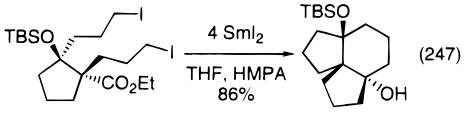


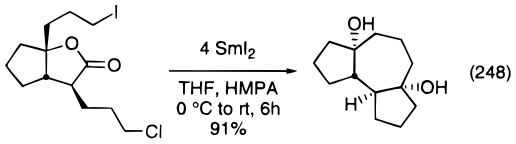
Substrates can be designed to allow a nucleophilic acyl substitution to precede a Barbier-type reaction (eq 245), or alternatively permit an intramolecular carbonyl addition to be followed by a nucleophilic acyl substitution (eq 246).[96] Structurally quite different products result from these diverse reaction pathways, and both transformations are highly stereoselective through chelation control.





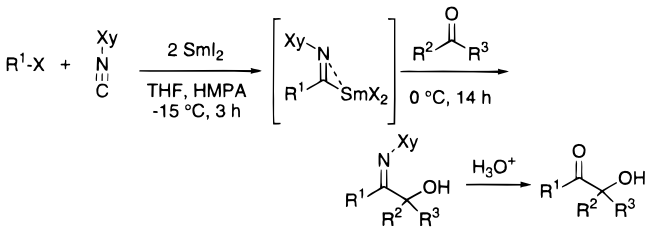
Tricyclic systems can also be prepared in a highly stereoselective manner from readily available starting materials (eqs 247 and 248).[96] Both angularly fused and linearly fused motifs are accessible, again depending on the substitution patterns of the starting materials.



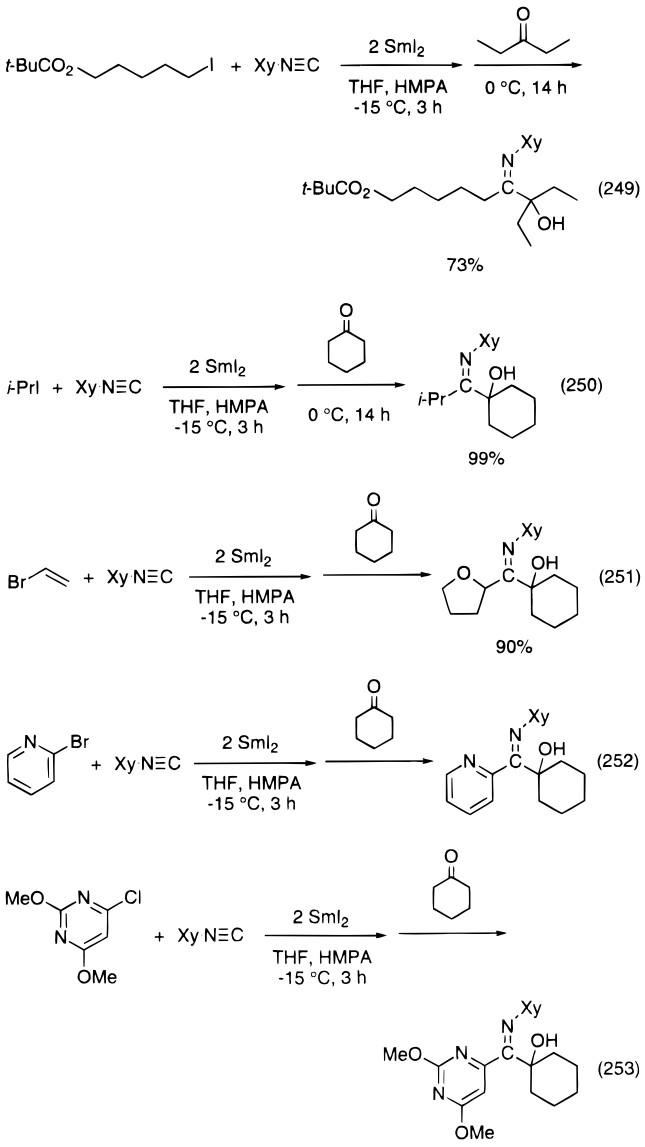


A SmI_2-mediated three-component coupling of organic halides, 2,6-xylyl isocyanide, and aldehydes or ketones provides a unique approach to α-hydroxy ketones.[97] The reaction proceeds by initial coupling of the organic halide with the isocyanide (Scheme 14). Subsequent reaction of the resulting (α-iminoalkyl)-samarium(III) with the carbonyl substrate and hydrolysis completes the overall transformation.[19,45,97] Both primary and secondary alkyl halides take part in the reaction (eqs 249 and 250).[97] Benzylic halides also can be utilized, but yields are modest. Tertiary alkyl halides can be induced to add to the isonitrile, but subsequent addition to the carbonyl does not take place and the intermediate aldehyde imine is isolated. Alkenyl halides and aryl halides typically do not add to the isocyanide, but rather the radicals generated from these substrates abstract a hydrogen atom from THF, generating a THF moiety that takes

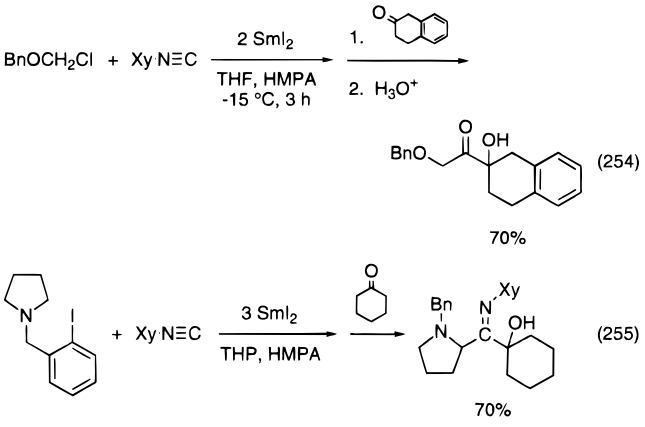
Scheme 14



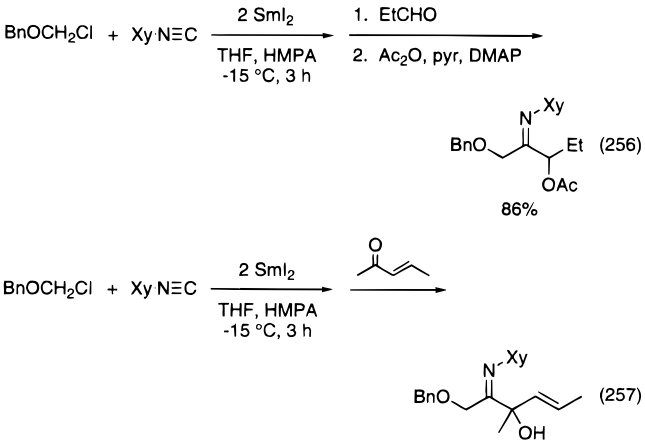
part in the initial addition (eq 251).[97] There are, however, exceptions to this reactivity pattern (eqs 252 and 253).[97]



α-Heterosubstituted halides react in a highly efficient manner (eq 254),[97] and the atom-transfer method for metalation of amines can be utilized to effect the three-component coupling with α-aminosamariums as well (eq 255).[63]



With regard to the carbonyl substrates utilized in the final coupling, both aldehydes and ketones can be utilized (eq 256), and even readily enolizable ketones such as β-tetralone undergo effective addition (eq 254).[97] α,β-Unsaturated ketones undergo exclusive 1,2-addition in the terminal step of the two-step process (eq 257).



IV. Conclusions

Although tremendous progress has been made in the application of SmI_2 to selective organic synthesis during the past decade, it is clear that many new areas remain to be explored. In addition to scores of individual reactions that undoubtedly have not been discovered, the promise afforded by SmI_2 to sequence reactions provides limitless possibilities for the conversion of simple substrates to complex products through one-pot, multistep sequences.

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VI. References

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