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Diverse Methods for Medium Ring Synthesis

GARY A. MOLANDER

Department of Chemistry and Biochemistry, University of Colorado at Boulder, Boulder, Colorado 80309-0215

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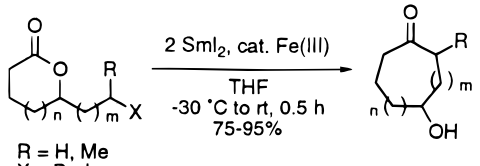
Introduction

Although synthetic approaches to five- and six-membered ring systems are legion, encompassing both cyclization and cycloaddition approaches, seven- and eight-membered ring systems have in some sense remained orphaned. Cyclization strategies to medium-sized rings are often regarded as inappropriate because of entropic factors that impede ring closure.[1] Fortunately, some very imaginative and elegant cycloaddition and annulation approaches have proven useful.[2] Additionally, ring expansion from more readily available carbocycles can provide efficient access to seven- and eight-membered rings.[3]

By coincidence more than through conscious effort, a significant number of synthetic methods developed within our research group over the years have proven valuable for the construction of medium-sized carbocyclic and heterocyclic systems. The approaches fall into three different categories: ring expansion from smaller cyclic units, cyclization methods in which a single bond is created in the key step to construct the medium-sized ring, and annulative approaches in which two acyclic precursors are brought together to generate the cyclic unit with formation of two bonds in a one-pot reaction. This account provides a brief outline of our efforts in medium-sized ring synthesis and provides some sense of the diverse structural motifs that can be accessed by the simple synthetic methods developed.

Ring Expansion

Time and again, samarium(II) iodide (SmI_2) has proven itself to be a unique reagent for a variety of reductive coupling reactions.[4] Among the most fundamental reactions for which this reductant has proven effective is the intramolecular nucleophilic acyl substitution reaction.[5] In appropriately constructed systems, this reaction provides an entry to seven-, eight-, and nine-membered ring hydroxy ketones (eqs 1 and 2). Thus, transannular attack



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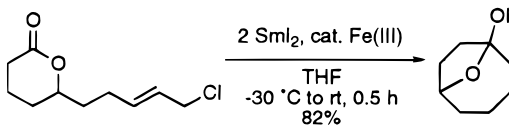

(2)

of an organosamarium species on the lactone generates a tetrahedral intermediate, the collapse of which provides the desired product. This method succeeds in generating medium-sized rings simply because a five- or six-membered transition structure is encountered along the reaction pathway rather than a seven- or eight-membered

Gary A. Molander was born in Cedar Rapids, IA, on Feb 9, 1953. He received his B.S. degree at Iowa State University in 1975, working with Professor Richard C. Larock. He entered the graduate chemistry program at Purdue University in 1975, obtaining his Ph.D. degree in 1979 under the direction of Professor Herbert C. Brown. He joined Professor Barry Trost's group at the University of Wisconsin, Madison, as a National Institutes of Health postdoctoral fellow in 1980, and in 1981 he accepted an appointment at the University of Colorado, Boulder, as an assistant professor of chemistry. He was promoted to Associate Professor in 1988 and Professor of Chemistry in 1990. More than 100 research papers have emanated from Professor Molander's research program. He has received several honors for his work, including an Alfred P. Sloan Foundation Fellowship, the American Cyanamid Academic Award in 1989, and the Arthur C. Cope Scholar Award from the American Chemical Society in 1998. He has been a Visiting Professor at the Université de Paris-Sud, Orsay, France (1989, 1997); Philipps Universität, Marburg, Germany (1989); École Supérieure de Physique et de Chimie Industrielles de Paris (1993); Universidade Federal da Paraíba, Brazil (1998); Universidade Federal de Pernambuco, Brazil (1998); and Universidad Nacional del Litoral, Santa Fe, Argentina (1998).

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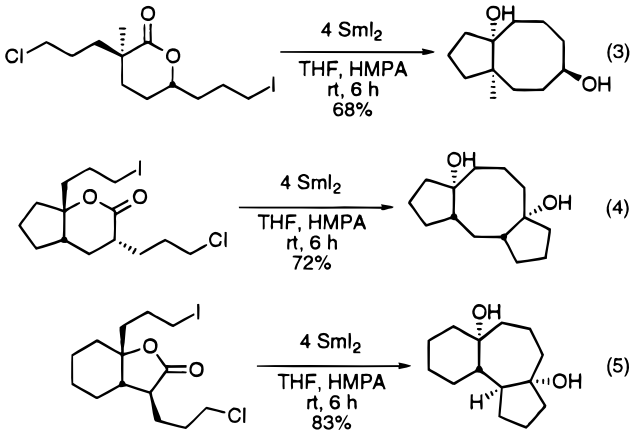
ring that would be encountered in a cyclization reaction. Consequently, the entropic factors that make medium rings difficult to construct are simply avoided.

More efficient are processes wherein two carbon−carbon bonds are formed in a single reaction. For a ring expansion/cyclization protocol with SmI_2 this takes the form of a nucleophilic acyl substitution reaction followed by a nucleophilic carbonyl addition.[6] The initial nucleophilic acyl substitution reaction generates a ketone that takes part in the subsequent carbonyl addition reaction. The selectivity exhibited by SmI_2 permits the initial generation of an organosamarium exclusively from an alkyl iodide. The nucleophilic acyl substitution reaction is followed by reaction of the alkyl chloride with SmI_2 to generate a second organosamarium intermediate that undergoes carbonyl addition with the ketone created in the first reaction (eqs 3−5). The starting materials for these reactions are typically generated in four or five steps, and thus access to reasonably complex bicyclic and tricyclic systems is quite straightforward.

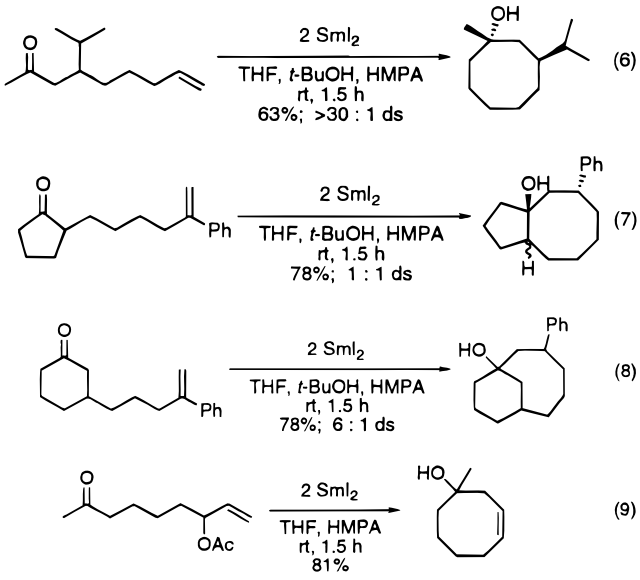


Cyclization Reactions

Normally, simple cyclization routes to medium-membered rings result in low yields of the desired products. Because of entropic factors, the coupling of two reactive termini spaced some distance apart is quite difficult. In seven- and eight-membered rings in particular, developing transannular interactions among the intervening methylene units conspire to make intermolecular coupling much more facile than cyclization.[1] Recently developed olefin metathesis reactions are able to overcome these difficulties and therefore may represent a general approach to the construction of unsaturated medium-sized rings.[7]

In view of the general difficulties in forming medium-membered rings by simple cyclization strategies, it was quite surprising to discover that SmI_2 was capable of promoting a radical cyclization resulting in the synthesis of cyclooctanols.[8] The reaction utilized for this transformation was an intramolecular ketyl−olefin coupling reaction. Although such an approach had been attempted previously under dissolving metal conditions,[9] yields of the cyclooctanols were very low. The advantage of utilizing the milder SmI_2 as a reducing agent for this transformation was postulated to lie in the creation of a more persistent radical anion. It has been suggested that the reduction of ketones with SmI_2 is a reversible process.[10] In the present case, this may provide a pseudo-high-dilution effect, wherein only a small concentration of ketyl is available at any point in time, thus facilitating cyclization over competing intermolecular processes. Upon formation of the ketyl, the HMPA required for these reactions may also shield this reactive intermediate from the proton source in the reaction, providing a species that is more resistant to further reduction by sequential electron transfer/protonation events.

Whatever the reasons, the SmI_2-promoted ketyl−olefin cyclization is surprisingly successful for a wide variety of substitution patterns and leads to good to excellent yields of cyclooctanols (eqs 6−9). Interestingly, the 8-endo



process is highly preferred over the available 7-exo process. This is presumably a stereoelectronic phenomenon, reflecting the proper trajectory required to achieve optimal orbital overlap between the ketyl and the alkene. Although more reactive alkyl radicals also favor the 8-endo mode of cyclization, in this case the ratio is only 2:1.[11] As might be expected, substituents on the alkene that increase the radical SOMO−alkene LUMO interactions in the transition state leading to product provide enhanced cyclization rates and higher yields of products. Aryl groups are particularly effective in this regard (eqs 7 and 8), although even allylic acetoxy groups have a noticeable effect (eq 9). In the latter, the acetoxy group is removed during the course of the reaction by a β-elimination process from an organosamarium intermediate generated by reduction of the cyclized radical generated upon the intramolecular coupling event. In fact, this elimination process is itself beneficial in that it obviates the need to employ a proton source in situ to quench the final organosamarium intermediate. As mentioned previously, proton sources facilitate the reduction of the ketyl intermediates to alcohols, thereby preventing cyclization. Acyclic alcohols are the major byproduct formed in low-yielding cyclizations.

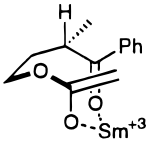
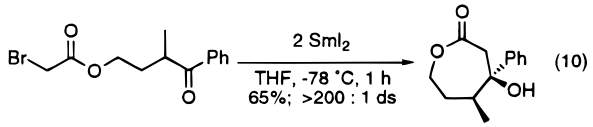


FIGURE 1. Chelated intermediate in SmI_2-promoted Reformatsky cyclization

Seven-membered ring lactones can also be generated by SmI_2 chemistry, this time employing an intramolecular Reformatsky-type reaction.[12] The special characteristics of SmI_2 chemistry have been postulated to play a critical role in the success of these reactions as well, albeit in a different manner than in the radical cyclizations described earlier. In these nucleophilic reactions the Sm^{3+} ion generated upon electron transfer to the α-halo ester serves as a template to organize the carbonyl addition of the ester enolate via a chelated intermediate (Figure 1). In addition to facilitating the cyclization (i.e., providing high yields), the Sm^{3+} ion serves as a stereochemical control element in these processes as well (eqs 10−12). Remarkably, in this process tertiary benzylic alcohols situated β to a carbonyl can be generated without suffering elimination under the essentially neutral reaction conditions (eq 10).



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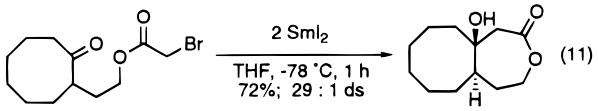

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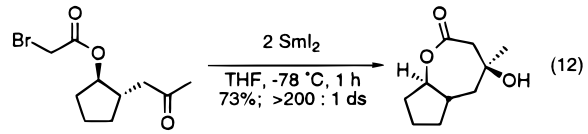
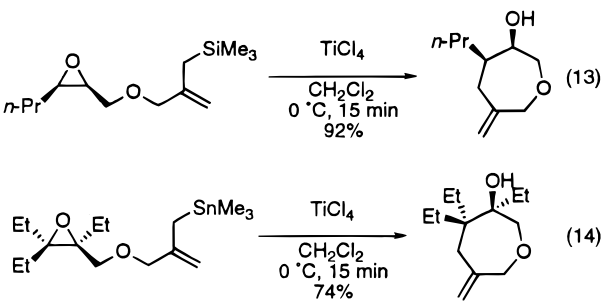


(12)

Another medium ring heterocyclic synthesis that relied on a metal chelate effect was developed in our laboratory.[13] In this case, a $TiCl_4$-catalyzed, intramolecular reaction of allylsilanes and allylstannanes with epoxides led to the construction of stereodefined oxepanes (eqs 13 and 14). Like the intramolecular Reformatsky-type reaction described above, this process, too, was driven by chelation effects. It took advantage of the ability of the Lewis acid catalyst to chelate the epoxide oxygen and the alkyl ether oxygen. This had the effect of polarizing the distal carbon−oxygen bond of the epoxide preferentially, inducing a 7-endo cyclization of the allylic nucleophile (Figure 2). Regioselectivity was complete, as the chelated intermediate was unable to achieve the requisite collinear relationship between the incoming nucleophile and the polarized epoxide carbon−oxygen bond for 6-exo cyclization. In this manner, the stabilization of incipient positive charge by chelation overrides the normal entropic and stereoelectronic elements that are important in non-Lewis acid-promoted reactions.[14] In addition to being completely regioselective for formation of the oxepanes, the conversions were also completely diastereoselective. Unfortunately, this process could not be extended to the construction of eight-membered oxygen heterocycles.



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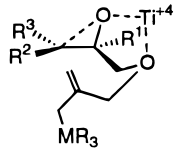


FIGURE 2. Chelated intermediate for $TiCl_4$-promoted allylmetallic cyclization

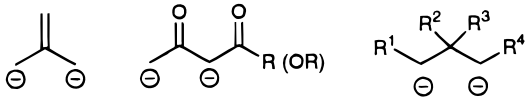


FIGURE 3. Dianionic synthetic equivalents developed for medium ring synthesis

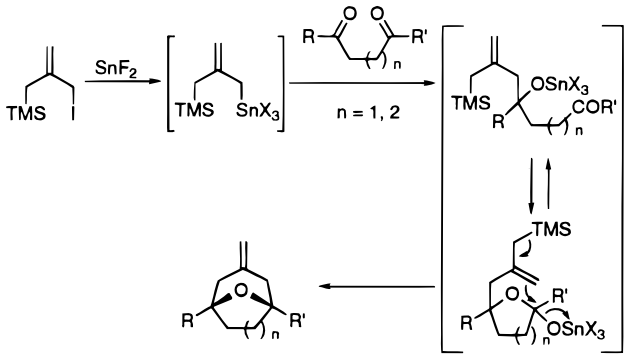
Annulation Reactions

The condensation of two acyclic units through creation of two bonds in a single process is by far the most efficient means of creating cyclic molecules. Mechanistically such conversions may take place in either a concerted manner (like the Diels−Alder cycloaddition reactions) or in a sequential mode that is characteristic of many [3 + 2] annulations for five-membered ring synthesis. From a synthetic point of view, either process is sufficient so long as regiochemistry and stereochemistry can be controlled.

For all of the reasons outlined in the discussion of cyclization reactions, [$m + n$] annulation reactions leading to seven- and eight-membered rings are highly challenging. Although some metal catalyzed processes are particularly effective in the construction of medium-sized rings in tethered systems,[2] certainly no method developed to date possesses the generality of the Diels−Alder reaction that is utilized for the synthesis of the analogous six-membered rings.

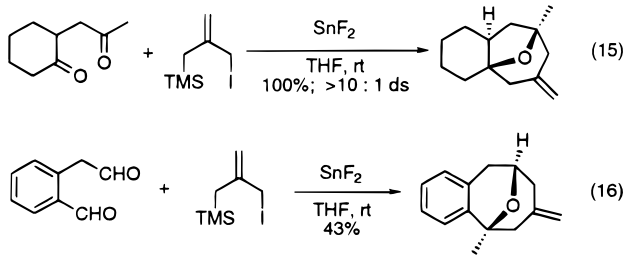
The annulative approaches to medium-sized rings we created were unconventional ones. We sought to develop dinucleophilic synthons that would react with simple, readily available dielectrophiles to generate the desired carbocycles in a sequential process (Figure 3). At first glance, such a strategy appears fraught with potentially lethal pitfalls. For unsymmetrical dinucleophiles, chemoselectivity must be achieved in the first (intermolecular) reaction with an unsymmetrical dielectrophile. If the dielectrophile is chiral, excellent diastereoselectivity in the initial addition would be necessary. If both dielectrophilic

Scheme 1



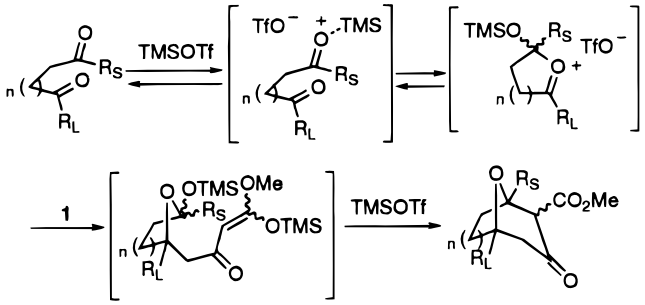
sites were prochiral (for example aldehydes or ketones), relative asymmetric induction between the first bond-forming event and the second would have to be controlled. Finally, as depicted, the strategy does not address the critical problem of having to create a medium-membered ring by what would ostensibly be a simple cyclization reaction. As it transpires, the last issue was addressed by strategies that generated a reactive intermediate along the reaction pathway. These intermediates provided structural constraints that permitted the medium-sized rings to be formed through what was formally five- and six-membered ring transition structures rather than less favorable seven- and eight-membered ones.

Our initial studies in the development of a trimethylenemethane dianion equivalent illustrate the point (Scheme 1). In the initial step of the reaction, stannous fluoride reacts with 3-iodo-2-[(trimethylsilyl)methyl]propene to generate an allylstannane. Addition of this organometallic to the dicarbonyl substrate generates an adduct that rapidly forms a five- or six-membered ring metalated hemiacetal. Spontaneous cyclizaton of the allylsilane on this activated species generates the desired bicyclic system. As anticipated, both seven- and eight-membered ring systems could be accessed by this method, and diastereoselectivities in the process were generally quite high (eqs 15 and 16).[15]

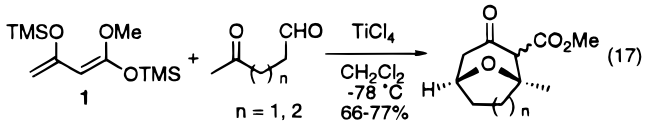


Utilization of a symmetrical dianion equivalent prevents some of the problems that would be created in reactions of unsymmetrical dielectrophiles. The drawback is that the products of these reactions become pseudo-symmetrical. Desymmetrization about the exomethylene group for the purpose of synthesizing specific target structures then poses a significant challenge. To address this issue, we developed bis(trimethylsilyl) enol ethers as synthetic equivalents of β-dicarbonyl dianions. The discrete reactivity of the two nucleophilic centers of the bis-

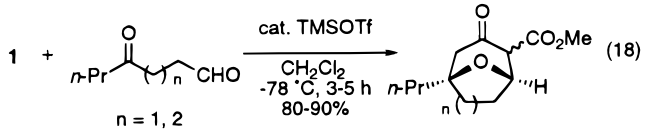
Scheme 2



(trimethylsilyl) enol ethers was well-documented, and we envisioned that the differential reactivity between these sites could be translated into high regioselectivity if the annulation process was applied to keto aldehyde dielectrophiles. Initial studies employing $TiCl_4$ as a Lewis acid promoter for the reactions bore out this prediction.[16] Unsymmetrical seven- and eight-membered ring systems could be created with excellent regioselectivities (eq 17).

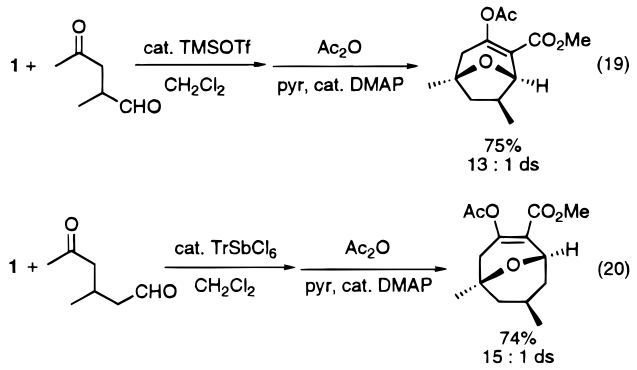


Although in general the $TiCl_4$ reactions worked quite well, there were some experimental problems in their implementation. The reactions were not catalytic in $TiCl_4$, and the use of a stoichiometric amount of this corrosive material created problems both in its handling for large scale reactions and in workup procedures. Consequently, an extensive screening was carried out in an attempt to optimize the Lewis acid promoter for these reactions. During the course of this survey, trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triphenylcarbenium hexachloroantimonate(V) ($TrSbCl_6$) showed surprising results that not only provided a solution to the problems encountered with $TiCl_4$ but also led to a novel concept for regio- and stereochemical control in these Lewis acid promoted carbonyl addition reactions of bifunctional substrates (Scheme 2).[17] Thus activation of the less hindered carbonyl by these Lewis acids induced intramolecular participation by the remaining, more hindered carbonyl to form an electrophilic oxonium ion. Nucleophilic attack of the terminal carbon of the dinucleophilic synthon at this electrophilic center followed by cyclization generated the observed product. This unique mechanism provided products that were regiochemically complementary to the $TiCl_4$-promoted reactions (eq 18). Furthermore,

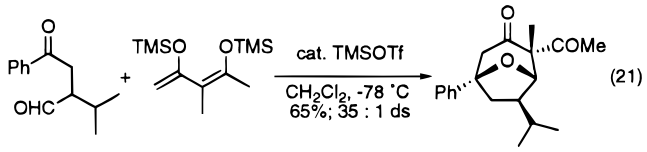


diastereoselectivity in these reactions was enhanced as a result of the cyclic nature of the oxonium intermediate. Even with existing stereogenic centers remote from the carbonyl electrophile, high relative asymmetric induction

in the annulation could be achieved (eqs 19 and 20).



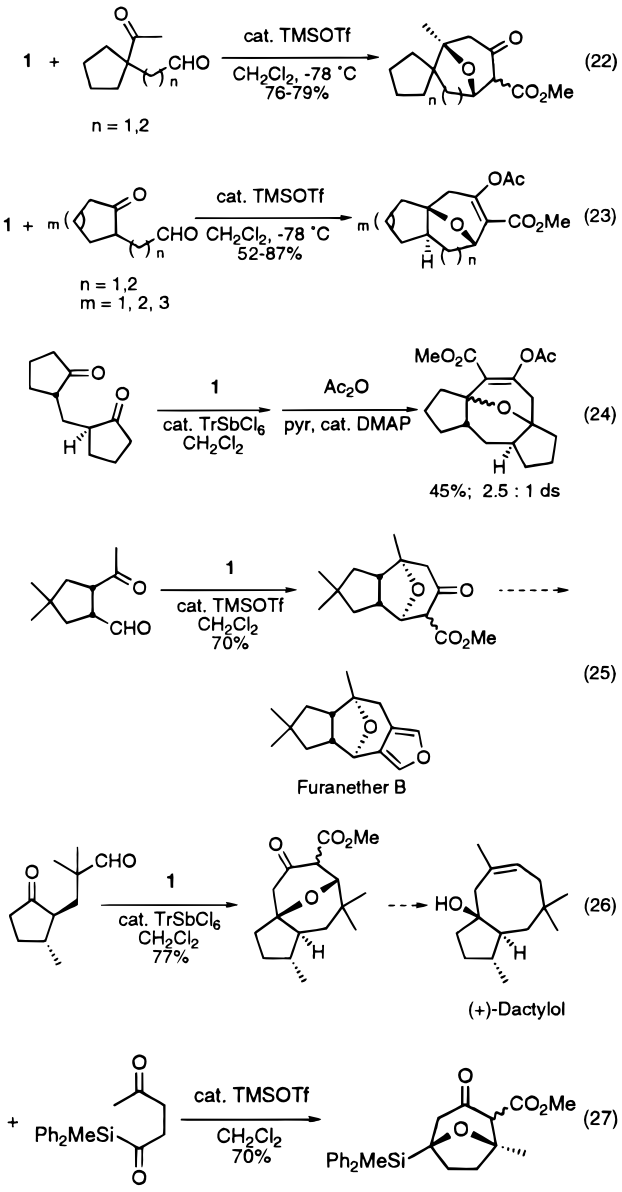
Prochiral dinucleophilic synthons could also be employed with similarly effective results. The example provided in eq 21 demonstrates the ability to create quaternary centers with very high stereochemical control, as well as the capability of utilizing β-diketone dianionic synthons for the reactions.

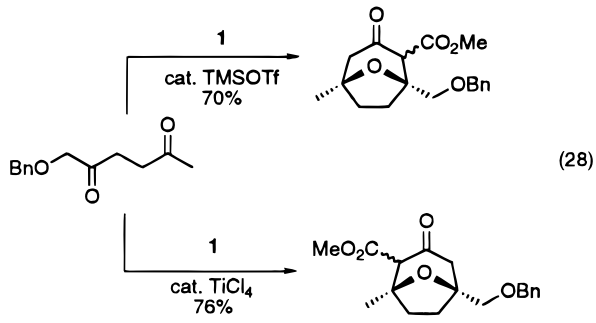


These [3 + 4] and [3 + 5] annulations were extended to the stereocontrolled synthesis of tricyclic ethers.[18] A variety of substitution patterns and structural motifs could be assembled in these processes (eqs 22−24). The annulative strategy was used as the key step in syntheses of two natural products: furanether B (eq 25)[19] and (+)-dactylol (eq 26).[20]

Several embellishments to the synthetic method were subsequently added. Two of these dealt with issues of regioselectivity. As described, the regioselectivity of the TMSOTf-catalyzed reaction was complementary to that of the $TiCl_4$-promoted process. A means was sought to reverse the annulation regioselectivity of keto aldehydes using the more convenient TMSOTf. This was accomplished by employing acylsilanes as synthetic equivalents of aldehydes (eq 27).[21] The larger trialkylsilyl groups directed the Lewis acid to the less hindered ketone for initial complexation, and neighboring group participation of the ketone followed by the annulation process as normal led to bicyclic ethers. Desilylation of protected versions of these products with fluoride ion resulted in annulation products regioisomeric to those of keto aldehydes.

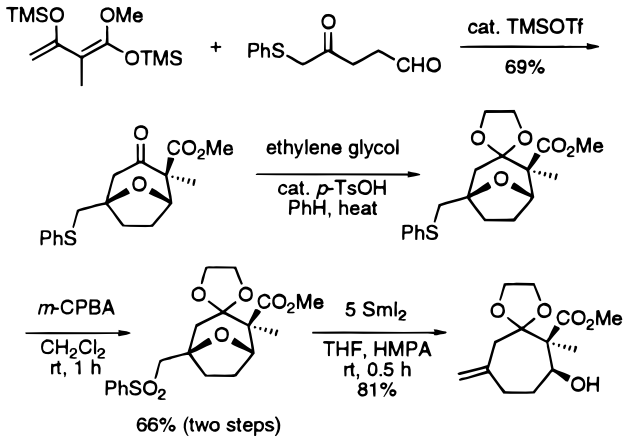
The regioselectivities in the annulation processes described to this point relied exclusively upon steric effects that influenced initial complexation of the Lewis acid with the dicarbonyl dielectrophile. Somewhat surprisingly, benzyloxy substituents were shown to affect regioselectivities dramatically in the annulation reactions by what must be an electronic and/or chelating effect.[22] Although the precise nature of this influence remains an enigma, the net result is that another means to control regioselectivity was achieved by a combination of substituent effects and Lewis acids (eq 28).





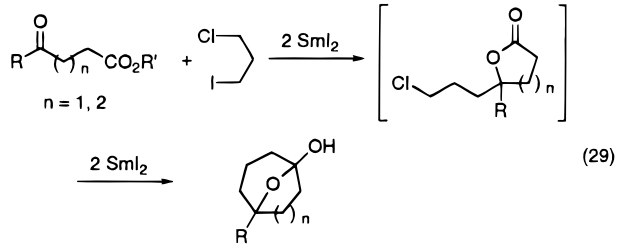
The bis(trimethylsilyl) enol ether annulations described thus far all resulted in the formation of bicyclic ethers. To unveil the medium-sized carbocycle, a reaction scheme was developed that provided rapid entry to highly functionalized systems in relatively few reliable steps (Scheme 3). Thus, annulation utilizing a phenylthio-substituted dicarbonyl substrate allowed a reductive cleavage to

Scheme 3



release the carbocyclic ring. The phenylthio groups could be present anywhere along the dicarbonyl chain, leading to both endocyclic alkenes and exoalkylidenes. This diversity, along with variations in the annulation process itself as delineated above, provides a highly versatile entry to substantially functionalized seven- and eight-membered rings.

We have most recently returned to SmI_2 chemistry for the development of two other annulative approaches to medium-sized carbocycles. In the first, the reaction of α,ω-dihaloalkanes with keto esters in the presence of SmI_2 provides a route to seven-, eight-, and nine-membered hydroxy ketones (eq 29).[23] This protocol again takes



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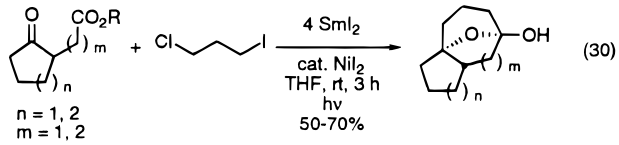
advantage of the ability of SmI_2 to reduce iodides in preference to chlorides. Somewhat surprisingly, cyclopropanes are not observed in the reactions of 1,3-dihalopropanes with the reductant, and consequently the resulting organosamariums are generated cleanly. Chemoselectivity is achieved in the reaction of these organometallics with the ketone of the dielectrophilic substrate. The alkoxide formed in the carbonyl addition forms a lactone with the ester, providing a template for the ring expansion to occur. Subsequent oxidative metalation of the chloride with SmI_2 followed by intramolecular nucleophilic acyl substitution on the lactone creates the observed products.

The process is reasonably general for a wide range of substitution patterns in both the dihalide and the keto ester (eqs 30 and 31). The ready availability of the starting materials makes this protocol a versatile one for medium-ring synthesis.

Finally, a related scheme involving an initial ketyl–olefin coupling/ring expansion sequence has been developed.[24] The initial ketyl-olefin coupling reaction of a haloalkyl-substituted ketone with various acrylate esters



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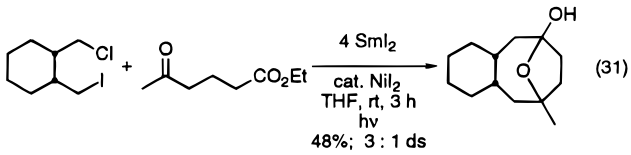
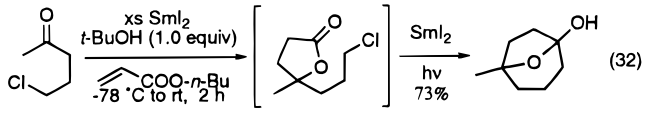


(31)

generates a lactone intermediate that undergoes intramolecular nucleophilic acyl substitution, generating the desired medium ring hydroxy ketones (eq 32). The reaction has been generalized, and thus again a variety of ring systems and substitution patterns can be accessed utilizing this simple procedure (eq 33).



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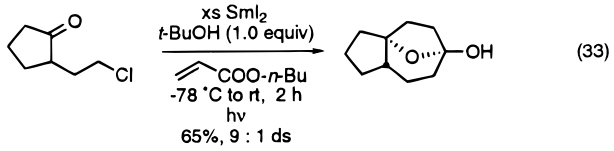

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Conclusions

There remains no single synthetic approach to medium ring compounds comparable to that of the Diels–Alder reaction for the synthesis of six-membered systems. What is apparent, however, is that many strategies are emerging that, considered together, permit access to a variety of useful structural motifs and substitution patterns of interest to the synthetic community. Future methods will undoubtedly emerge that address more comprehensive annulative approaches to medium rings, including the increasingly significant issue of enantioselective access to these important systems.

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