Samarium(II) Iodide-Induced Reductive Cyclization of Unactivated Olefinic Ketones. Sequential Radical Cyclization/Intermolecular Nucleophilic Addition and Substitution Reactions

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Samarium(II) iodide in the presence of HMPA effectively promotes the intramolecular coupling of unactivated olefinic ketones by a reductive ketyl–olefin radical-cyclization process. The reaction is quite general for the formation of 5- and 6-membered carbocycles and even provides modest yields in less facile cyclization processes as evidenced by the generation of methylcyclooctanol via an 8-endo cyclization. Sequential radical cyclization–intermolecular nucleophilic addition/substitution processes set the SmI_2 reaction apart from its radical-chain, photochemical, and electrochemical counterparts. In addition to delineating the synthetic potential of this reaction, the role played by HMPA in enhancing SmI_2 reactivity has been further refined, and a model correlating the high diastereoselectivity and product distribution in SmI_2-promoted reductive coupling processes with HMPA concentration has been established.

Increased efficiency is a primary goal in selective organic synthesis. Those processes that combine multiple carbon–carbon bond formation with establishment of several stereogenic centers under mild conditions are particularly valued. One protocol exhibiting these characteristics is described below, wherein sequential radical cyclization/intermolecular nucleophilic addition (or substitution) processes are mediated by the agency of samarium(II) iodide. Thus, olefinic ketones are cyclized by a reductive ketyl–olefin coupling process, and the resulting intermediate radical is subsequently reduced to an organosamarium species. The latter is efficiently trapped by a number of diverse electrophiles, providing rapid entry to highly functionalized carbocycles in high yields with excellent stereochemical control. As a result of these studies, considerable light is shed on the role that HMPA plays in SmI_2-promoted reactions.

The application of radical chemistry to organic synthesis has provided organic chemists with an impressive array of tools for effecting molecular transformations.[2] The construction of carbocycles via cyclization of carbon-centered radicals upon unsaturated functional groups has proven to be one of the most synthetically useful subsets of radical chemistry, and radical cyclizations have been incorporated as the key carbon–carbon bond-forming step in recent syntheses of several complex natural products.[3]

The formation of cyclopentanoids via 5-hexenyl radical cyclization is the most common and extensively applied radical annulation reaction. The 5-hexenyl radical is conventionally generated by atom abstraction in a chain process.[4] The synthetic utility of a reaction employing this process is limited, however, because of the loss of functionality at the radical center and at the olefin under normal (Bu_3SnH) reductive cyclization conditions. Partial solutions to this dilemma involve the use of α-heteroatom-substituted radicals,[5] the use of atom-transfer agents,[4,6] utilization of transition-metal complexes to promote these reactions,[7] and trapping of the intermediate-cyclized radical with unsaturated functional groups present in the reaction mixture.[8] The latter protocol is problematic in that it requires a large excess of the trapping agent in return for only modest yields. An additional limitation of chain processes reveals itself in attempts at forming 6-membered and larger rings. The decrease in cyclization rate in 6-exo and larger ring cyclizations results in competitive atom abstraction from the atom donor present or from intramolecular hydrogen atom transfer. Increased yields of noncyclized reduced starting material result.[2b]

Radical cyclizations employing ketyl radical anions and olefins do not have the drawback of limiting functionality as do their alkyl radical chain relatives. Additionally, ketyl formation is possible via chemical,[9] electrochemical,[10] and photochemical processes.[11] Diastereoselectivities are inherently greater in radical anion cyclizations than in their neutral radical counterparts, and protocols in which subsequent reduction of the intermediate cyclized radical to a carbanion followed by reaction with an added electrophile dramatically increases the versatility of the process.[12]

Samarium(II) iodide (SmI_2) has evolved as a unique single electron reducing agent, and its broad application

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in organic synthesis has recently been reviewed.[13] In several cases SmI_2 has proven to be superior to other chemical agents in promoting reductive coupling reactions, including the sequencing of one- and two-electron processes culminating in the formation of an organometallic with nucleophilic potential.[14] Intermolecular and intramolecular ketyl–olefin coupling reactions facilitated by SmI_2 have primarily involved activated carbonyl and/or activated olefinic functionalities.[15] The lower energy π^* orbital of an activated olefin (i.e., an electron-deficient or conjugated olefin) as compared to that of an isolated, unactivated olefin allows more efficient overlap with the ketyl radical anion SOMO and a corresponding increase in addition rate.[16] The increased rate of cyclization brought about by olefin activation is a requirement for many SmI_2-induced radical cyclization reactions.[15a,d,17] Intermolecular coupling of ketones with α,β-unsaturated esters to form butyrolactones has been reported to proceed in fair yield if HMPA is utilized in conjunction with SmI_2.[18] Intramolecular coupling of ketones with enoates proceeds without HMPA in THF heated to reflux, albeit in modest yield.[19] Without HMPA reduction of the carbonyl to a ketyl radical anion is less favorable, and prolonged reaction times at higher temperatures are required.

Cyclization of activated ketones with unactivated olefins has proven to be synthetically useful in forming cyclopentanoids. Molander and Kenny have reported highly diastereoselective SmI_2-induced cyclizations in a series of 2-(3-alkenyl)-β-keto esters and 2-(3-alkenyl)-β-keto amides, providing the corresponding hydroxy cyclopentanecarboxylates.[14a] The electron-withdrawing ester group lowers the energy of the π^* orbital (LUMO) of the ketone, allowing electron transfer from Sm(II) to generate the ketyl radical anion under extremely mild conditions (−78 °C) without the use of HMPA. The ensuing cyclization to form 5-membered rings proved fruitful, but attempts at forming 6-membered rings were unsuccessful because of competing hydrogen atom abstraction from THF.

The SmI_2-promoted intramolecular coupling of unactivated alkenes and alkynes with aldehydes to form 5-membered rings and its application to natural product syntheses has been investigated.[20] However, the reaction with less reactive ketones (acetone E° = <−2.5 V, propanal E° = −2.20 V, benzaldehyde E° = −1.52 V)[21] and formation of 6-membered rings has only recently been published in a single short report.[17] Formation of 5- and 6-membered rings, including oxygen and nitrogen heterocycles, was accomplished via cyclization of the appropriately substituted acetylenic ketones. HMPA was necessary to effect cyclizations, and 6-membered ring formation required activated alkynes in order for the cyclization to proceed.

In studies described herein, the application of SmI_2 toward the synthesis of a series of cyclic alcohols via radical cyclization of unactivated olefinic ketones has been outlined. The concept of coupling one-electron cyclization reactions with two-electron nucleophilic addition and substitution reactions is further delineated. Finally, the crucial role which HMPA plays in SmI_2-promoted reactions is clarified.

Results and Discussion

In order to test the generality of the SmI_2-mediated ketyl–olefin cyclization process a series of acyclic and cyclic olefinic ketones were synthesized and subjected to optimized reaction conditions. Compounds **1a–1h** and **1j** were synthesized via alkylation of the appropriate dimethylhydrazone with the corresponding bromoalkene.[22] Compounds **1k–1m** were prepared by appropriate conjugate addition reactions to the corresponding enone.[23] Dialkylation of ethyl acetoacetate followed by decarboxylation with NaCl in $DMSO/H_2O$[24] afforded compound **1i**. Stereochemistry of the known compounds **2a**,[25] **2b**,[26] **2d**,[5,11] **2e**,[27] **2f**,[11a,b] and **2k**[11a,b] was supported by comparison with published NMR and physical data, and the stereochemical assignment of the major and minor isomers of **2i** was determined by symmetry arguments based upon ^{13}C NMR analysis of the separated diastereomers. The stereochemistry of compound **4f** was determined by known ^1H NMR chemical shift tendencies of similar systems.[5,28] Stereochemistry of the remaining compounds was assigned by analogy.

Optimum reaction conditions for the cyclizations involved slow addition of a solution of the olefinic ketone and 3 equiv of *t*-BuOH in THF (ca. 0.05 M in substrate) to a 0.15 M solution of SmI_2 containing 8 equiv of HMPA at room temperature. Reactions run in the absence of HMPA provided only low yields of the desired products, with simple reduction of the ketone a major side reaction. Interestingly, reactions performed under more concentrated reaction conditions provided dramatically different outcomes. For example, when **1f** (0.2 M in THF) was added to a solution of SmI_2 at −78 °C over a 1-min period, the starting material was consumed in <15 min. Standard workup of the reaction mixture followed by flash chromatography produced a 1:1 stereoisomeric mixture of dimers in 76% yield (eq 1) in addition to a 15% yield of **2f**. The 10-line carbon spectrum for each dimer indicated a single diastereomer was being produced in the initial (cyclization) step of the process. Addition of the same substrate as a 0.05 M solution in THF over 20 min at room temperature resulted in an 89% yield of **2f** and only a trace of the dimer. Rapid reaction of the substrate as a mod-

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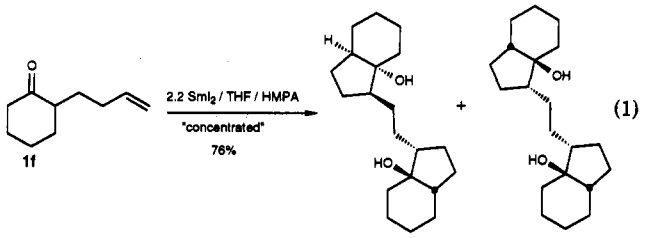

erately concentrated solution evidently creates a local depletion of SmI_2 and simultaneously a high local concentration of intermediate radicals. Subsequent reduction of the radical to an organosamarium species under these conditions is slow compared to diffusion-controlled radical combination. Although the 6-*exo-trig* processes were less prone to this radical dimerization side reaction, all reactions were run under identical conditions.

As indicated in Table I, the 5-*exo*- and 6-*exo-trig* radical cyclization reactions proceed in excellent yield and diastereoselectivity. Incredibly, major byproducts detected in the cyclization of substrates **1c** and **1l** are 3-methyl-9-decen-3-ol and 1-ethyl-3-(3-butenyl)cyclohexanol, respectively, generated as a result of ketyl trapping of ethylene generated in the in situ synthesis of SmI_2. These byproducts were completely absent when reactions were degassed after the generation of SmI_2. The moderate yield of compound **2c**, generated as a result of 8-endo cyclization, provides an excellent indication of the ability to generate even medium-sized carbocycles via this protocol. It is perhaps surprising that 8-membered rings could be generated by this protocol because the unsaturated ketyl intermediate would be expected to exhibit extremely low cyclization rates. The major diastereomers in the exo cyclizations are those with the developing radical center trans to the alkoxy group. This preference has been attributed to several factors, including electrostatic interactions between the negatively charged oxygen and developing methylene radical center,[2a,14a,29] and perhaps other stabilizing interactions between the developing methylene radical and the adjacent alkyl substituent in the transition state.[14a,29a,d] In order to minimize the electrostatic repulsion and promote favorable interactions, a transition state with the largest dihedral angle between the carbonyl (ketyl) and olefinic system is predicted.

Formation of 6-membered rings in excellent yield without byproduct formation resulting from hydrogen atom abstraction and ketone reduction is an obvious advantage of the SmI_2 method over other protocols.[9e,f,10a] Modest stereocontrol over three centers in **2i** and **2j** is interesting and deserves further investigation.

The rapid cyclization of most of the substrates indicates that ketyl formation occurs readily. Cyclization of substrates **1k** and **1l** to form bridged bicyclic products **2k** and **2l** is expected to be slow, however, and provides an indication of the persistence of the intermediate ketyl radical anion. The ability of these intermediates to exist in solution (possibly in equilibrium with the ketone if reduction is reversible) with hydrogen atom donors for extended periods (over 1.5 h for reaction of **1l**) is surprising. The increased diastereoselectivity observed for **2k** as compared to that observed in photochemical cyclization[11] suggests the possibility of either product equilibration or a dramatically different transition-state structure altering the kinetic product ratios by these two different protocols.

Table I. Samarium(II) Iodide-Promoted Cyclization of Olefinic Ketones 1

entry	substrate	product	% isoltd yield (diastereomeric ratio)
1	**1a**, n=1	**2a**	86 (>150:1)
2	**1b**, n=2	**2b**	91 (36:1)
3	**1c**, n=3		52[a]
4	**1d**, n=1, m=1	**2d**	90 (>150:1)
5	**1e**, n=2, m=1	**2e**	92 (93:5:2)
6	**1f**, n=1, m=2	**2f**	89 (>150:1)
7	**1g**, n=2, m=2	**2g**	85 (2:1:1)
8	**1h**, n=0, m=2	**2h**	0
9	**1i**	**2i**	89 (6:1)
10	**1j**	**2j**	86 (4:1)
11	**1k**, n=1	**2k**	88 (17:1)[b]
12	**1l**, n=2	**2l**	66 (17:1)[c]
13	**1m**, n=0	**2m**	0

[a] The major product was 1-methylcyclooctanol as a result of 8-endo cyclization.[29c] In addition, crude NMR and GC/MS indicated a 15% yield of what appeared to be a mixture of 7-exo cyclization isomers which were not isolated. [b] The major diastereomer corresponded to the isomer with the methyl group endo.[10b] [c] Major diastereomer assigned as the endo isomer in analogy to **2k**.

The next objective in our studies was to expand the versatility of the radical cyclization reaction by trapping the intermediate organosamarium species with diverse electrophiles. It is this final step of the two-step, sequential process that sets the SmI_2-promoted process apart from more conventional means of mediating intramolecular ketyl–olefin coupling reactions. The flexibility created by the manifold of conversions the organosamarium intermediate can undergo permits a rapid and efficient increase in molecular complexity in the transformation of simple acyclic substrates to rather elaborate carbocycles. As indicated in Table II, a wide range of electrophiles proved compatible in this process. Highest yields were realized when the electrophile was added to the reaction mixture following cyclization. This procedure is exceptionally convenient because requiring the electrophile to be present with the olefinic ketone starting material would greatly

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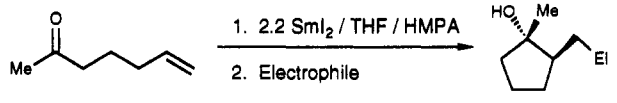
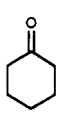
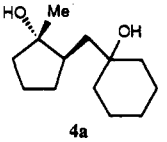
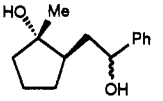
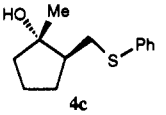
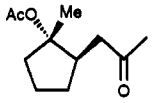
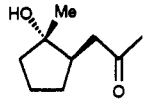
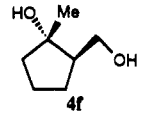
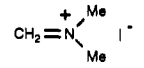
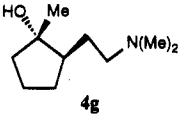
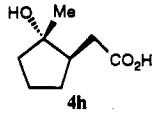
Table II. Sequential Radical Cyclization–Nucleophilic Addition Reactions



1a 4

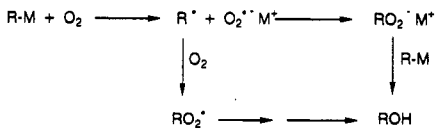
entry	electrophile	product	% isoltd yield (diastereomeric ratio)[a]
1		 4a	80
2	PhCHO	 4b	83 (3:1)[b]
3	$(PhS)_2$	 4c	77
4	Ac_2O	 4d	85[c]
5	Ac_2O	 4e	74[d]
6	O_2	 4f	69 (15:1)
7		 4g	73
8	CO_2	 4h	65

[a] A single diastereomer as determined by fused silica capillary GC and NMR analyses, unless stated otherwise. [b] Presumably, a mixture of epimers at the benzylic carbon. [c] The reaction was run with 5 equiv of acetic anhydride at room temperature for 6 h. [d] The reaction was run with 2 equiv of acetic anhydride at 0 °C for 15 min. In addition, a 12% yield of 4d was isolated.

diminish the number of compatible reaction partners.

In nearly all cases, the sequential process led to a single diastereomeric product as determined by fused silica capillary GC analysis and/or NMR spectroscopy. One exception was compound **4b**, which was isolated as a 3:1 mixture of diastereomers, ostensibly as a result of unselective carbonyl addition of the organosamarium intermediate to the prochiral benzaldehyde electrophile. A second exception occurred in the generation of **4f** by oxidation of the intermediate organosamarium with O_2. This procedure resulted in the isolation of a 15:1 mixture of diastereomers. The major diastereomer is believed to be the expected trans isomer as supported by the upfield shift of the methyl carbon in the ^{13}C NMR (owing to steric compression).[5,28] The minor isomer in this case may arise from reversible ring closure/opening under the oxidative conditions of the reaction. The mechanism of alkyl organometallic addition to molecular oxygen is considered to proceed through an alkyl radical intermediate as outlined in Scheme I.[30]

Scheme I



In the present case, the possibility of equilibration of the intermediate organosamarium prior to addition to the electrophile is a conceivable pathway.[31] However, we found no change in diastereoselectivity of **2a** formation whether a proton source was added in situ with **1a** during cyclization or if the proton source was added up to 1 h following cyclization. These results led us to believe that the initial cyclization of the unsaturated ketyls to the intermediate cyclopentyl carbinyl radical intermediate is reversible, but under *reductive* conditions this radical is rapidly converted to an organosamarium species by SmI_2 prior to isomerization. Only under the *oxidizing* conditions of entry 6 was any isomeric cyclized product detectable. Swartz, Kariv-Miller, and Harrold have previously observed the cyclization of **1a** under reductive electrochemical conditions.[32] In their system a dependence of cis and trans isomer ratios on reduction potential of the active reducing species as well as other factors was noted. Consequently, they too have concluded that the ketyl–olefin cyclization step is a reversible process.

As mentioned above, HMPA was required to promote efficient ketyl–olefin cyclization in the desired manner. Although HMPA has a profound effect on the reactivity of SmI_2 in a variety of diverse processes, the precise role of HMPA in facilitating these transformations has always been controversial. We have carried out several experiments designed to elucidate some of the factors involved in the effective role this additive plays in ketyl–olefin reductive coupling processes.

The use of HMPA in SmI_2 reactions was first reported by Inanaga.[18a] Reports subsequent to this initial account have outlined the use of this additive to reduce functional groups with relatively negative reduction potentials (e.g., chloroalkanes[33] and α-oxygenated esters[34]). In effect, HMPA increases the reducing ability of SmI_2 solutions.[35] The precise reason for this could be deaggregation of SmI_2 (the solution structure of SmI_2 is unknown) or a result of

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(35) Solvated electrons are undoubtedly not involved. The negative electrode potential (−3.1 V vs SCE) required to generate solvated electrons in HMPA makes this possibility virtually impossible. Furthermore, while Na in THF/HMPA reacts very rapidly with alcohols and isolated olefins, solutions of SmI_2 in THF/HMPA are stable for >48 h with these substrates. (a) Normant, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1046. (b) Fraendel, G.; Ellis, S. H.; Dixs, D. T. *J. Am. Chem. Soc.* **1965**, *87*, 1046. (c) van Andel, P. M. J.; Wonders, A. H.; Barendrecht, E. *J. Electroanal. Chem.* **1991**, *301*, 87. (d) Alpatova, N. M.; Krishtalik, L. I.; Pleskov, Y. U. *Top. Curr. Chem.* **1987**, *138*, 149.

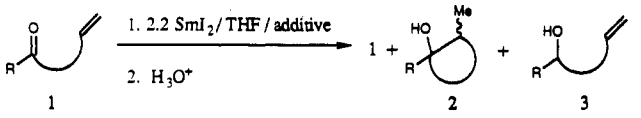
f-orbital perturbation owing to ligand field effects in the presence of the strong donor ligand HMPA, raising the energy of the HOMO (electron-donating orbital) and thereby increasing the Sm(II)/Sm(III) cell emf.[36] A combination of these two effects might also be considered. Reports in the literature reveal that the reduction potentials of several lanthanides are strongly dependent on associated ligand(s).[37] As an example, Massaux and Duyckaerts[37d] observed a negative shift of 0.86 V in the reduction potential of Eu(III) upon addition of 5% DMSO by volume as cosolvent in propylene carbonate. Similar effects were observed for the reduction potentials of Sm(III) and Yb(III).

Factors other than reduction potential also play a role in the efficacy of HMPA as an additive in SmI_2-promoted reactions. In the present study, ketyl radical anions appear to have greater persistence when generated in the presence of HMPA than without this additive. Crystal structures of HMPA–lanthanoid complexes have been determined, and in all cases the HMPA molecules are coordinated via their oxygen atoms. For example, Hou and co-workers reacted $YbCl_3$ with excess HMPA in THF, producing $YbCl_3(HMPA)_3$ in quantitative yield.[38] They determined that the HMPA molecules occupy the two axial positions and an equatorial position in the distorted octahedron. Studies by Donoghue and co-workers revealed that the maximum number of HMPA ligands able to bind to Ln(III) perchlorates was 6.[39] In all cases (Ln = La – Lu), treatment of $LnCl_3$ with 3 equiv of $AgClO_4$ followed by excess HMPA resulted in the isolation of crystals which corresponded to $[Ln(HMPA)_6](ClO_4)_3$. These results are in contrast to DMSO and *N,N*-dimethylacetamide complexes, in which the number of ligands decreased with decreasing ionic radius of the lanthanides.[40] Although these results do not explicitly prove the structure of the Sm(II) or Sm(III) complexes with HMPA, it is unlikely that these complexes contain more than six HMPA ligands.

Our preliminary results on the SmI_2-induced intramolecular cyclization of unactivated olefinic ketones with a THF/HMPA solvent system indicated a dependence of product distribution on HMPA concentration, prompting a more detailed investigation into the correlation between HMPA concentration and product ratios. Experiments were designed in which three substrates of markedly different cyclization rates were subjected to a series of five reaction conditions. The absolute rate constants for the three substrates **1d**, **1b**, and **1k** are not known; however, their relative rates are **1d** (5-*exo-trig*) > **1b** (6-*exo-trig*) > **1k**.[41]

As indicated in Table III, all three substrates cyclized readily in the presence of 8 equiv of HMPA (condition A). The 88% yield of **2k** and 17:1 (endo:exo) diastereoselectivity is in sharp contrast to the 75% yield and 1.5:1

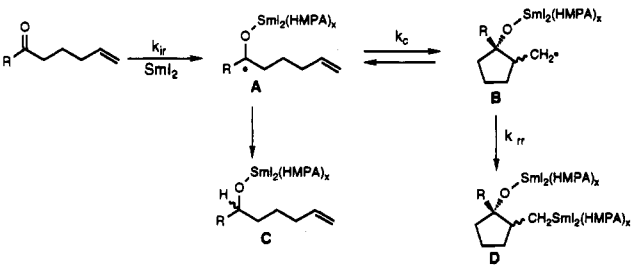
Table III. Effect of HMPA and DMPU on Product Distribution



substrate	condns	product (%)	rctn time	% de of 2	combined isoltd yield (%)
1d	A	**2d** (100)	<15 min	>99	90
	B	**2d** (100)	<15 min	>99	89
	C	**2d** (98), **3d** (2)	2 h	96	91
	D	**1d** (33), **2d** (62), **3d** (5)	36 h	92	95
	E	**1d** (36), **2d** (62), **3d** (2)	36 h	94	92
1b	A	**2b** (100)	<15 min	94	91
	B	**2b** (99), **3b** (1)	<15 min	88	91
	C	**2b** (30), **3b** (70)	4 h	89	90
	D	**1b** (39), **2b** (6), **3b** (55)	36 h	88	95
	E	**1b** (41), **2b** (43), **3b** (16)	36 h	94	86
1m	A	**2m** (100)	30 min	88	88
	B	**2m** (87), **3m** (13)	30 min	64	93
	C	**2m** (29), **3m** (71)	5 h	14	89
	D	**2m** (4), **3m** (96)	48 h	0	95
	E	**1m** (22), **2m** (68), **3m** (10)	36 h	8	91

[a] Conditions: (A) 8 equiv of HMPA; (B) 4 equiv of HMPA; (C) 2 equiv of HMPA; (D) no additive; (E) 8 equiv of DMPU.

Scheme II



(endo:exo) diastereoselectivity observed for the same product under photoreductive cyclization conditions.[11b] In progressively decreasing the amount of HMPA from 8 equiv to no additive, the amount of **3** generated by hydrogen atom abstraction from solvent increased and the stereoselectivity of **2** decreased. Addition of greater than 8 equiv of HMPA had no additional effect on diastereoselectivity, nor did it alter the ratio of products upon cyclization of **1c**. Addition of 8 equiv of DMPU (condition E) resulted in a purple heterogeneous mixture. Reaction rates under these conditions were similar to those of condition D; however, the amount of **3** produced was lower and stereoselectivities were slightly higher. These results are consistent with those of others,[9b,42] who observed that complexing additives such as tetraglyme and HMPA were found to decrease unwanted dimerization and solvent hydrogen atom abstraction reactions. Our attempts at using other complexing agents such as DME and pyridine met with little or no success. These results indicate that the addition of HMPA decreases the effective rate of hydrogen abstraction (**A** to **C**) relative to that of cyclization (**A** to **B**, Scheme II). In the case of **1k**, the slowest cyclizing substrate, complete reversal of product distribution

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(37) (a) Iwase, A.; Araki, Y.; Takahashi, R. *Electrochim. Acta* **1990**, *35*, 1713. (b) Gilbert, B.; Demarteau, V.; Duyckaerts, G. *J. Electroanal. Chem.* **1978**, *89*, 123. (c) Nugent, J. L.; Baybarz, R. D.; Burnett, J. L. *J. Phys. Chem.* **1973**, *77*, 1528. (d) Massaux, J.; Duyckaerts, G. *Bull. Soc. Chim. Belg.* **1975**, *84*, 6.

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(40) (a) Krishnamurthy, V. N.; Soudararajan, S. *J. Inorg. Nucl. Chem.* **1967**, *29*, 517. (b) Moeller, T.; Vincenti, G. *J. Inorg. Nucl. Chem.* **1965**, *27*, 1477.

(41) Cyclization of the 7-octen-2-yl radical and 6-hexen-2-yl radical occur with respective k's = 5.7×10^9 and 1.1×10^5 s^{-1}. Under identical conditions substrates **1d** and **1b** cyclized in <15 min while **1l** required ca. 30 min, ref 29c.

(42) Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* **1984**, *25*, 3225.

was observed in the absence of HMPA when compared to results obtained when 8 equiv of HMPA were present in the reaction mixture.

In reference to our observations, the decrease in the rate of hydrogen abstraction (A to C) relative to cyclization (A to B) with increasing HMPA concentration could be attributed to two factors. In the absence of HMPA, THF complexes with Sm(II) and is present when the samarium ion coordinates to the carbonyl prior to reduction (assuming an inner sphere process). The THF is then readily available as a hydrogen atom donor in the conversion of A to C, and as the rate of cyclization decreases for different substrates, the amount of byproduct C becomes more pronounced. As HMPA is added to the reaction mixture it preferentially complexes with the Sm(II) and displaces THF from the Sm(II) coordination sphere. In this fashion HMPA effectively shields the reacting carbonyl center from hydrogen atom donors, creating a more persistent radical.[43] In this process the relative rate of hydrogen abstraction (A to C) decreases with respect to the intramolecular cyclization rate (A to B). The bulkier HMPA ligands are also postulated to destabilize the transition state leading to the minor diastereomeric carbocycle in which the developing radical center is nearly eclipsed with the ketyl oxygen. This may explain the observed increased diastereoselectivity with increased additive concentration, as well as the increased diastereoselectivity in SmI_2-promoted processes with HMPA added as compared to electrochemical and photochemical processes of the same substrates also under kinetic control.[11,32]

A second conceivable analysis would involve considering the reversibility of the cyclization (conversion of A to B) and the increase in the rate of radical reduction (B to D) with added HMPA. In this scenario, as HMPA is added to the reaction mixture the resulting increase in alkyl radical reduction with respect to cyclization would decrease the concentration of cyclized intermediate B and minimize any equilibration of diastereomers through intermediate A. A previous study in our laboratory involving the 5-exo cyclization of stabilized ketyl intermediates,[14] which are presumably more prone to thermodynamic equilibration,[44] in fact provided no evidence of equilibration under SmI_2-mediated reduction conditions. Excellent diastereoselectivities of the expected kinetic product were obtained in all cases. These results imply that the rate of alkyl radical reduction is rapid even in the absence of HMPA. Therefore, the expected increase in the second reduction step which can be attributed to added HMPA should not affect product distributions or diastereoselectivities. This leads us to postulate that the congested Sm(II)–HMPA reducing species is solely responsible for the observed products and diastereoselectivities.

Conclusions

Samarium(II) iodide in the presence of HMPA has been shown to effect a series of ketyl–olefin cyclization reactions. The increased reducing ability of these solutions has been attributed to ligand field effects brought about by the strong donor ligand HMPA. In addition to increasing the reducing strength of the resulting solutions, enhanced diastereoselectivities were observed owing to an added steric component in the cyclization transition states. The unique ability of SmI_2 to promote reactions by way of two-electron sequencing, resulting in an organosamarium species with broad nucleophilic potential, has been reiterated. The potential of effecting reactions not exhibited by SmI_2 in THF by the use of strong donor ligands other than HMPA has been further established.

Experimental Section

Reagents. Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under argon. Hexamethylphosphoric triamide (HMPA, Aldrich) was heated at reflux over BaO at reduced pressure and then distilled from Na at 1 mmHg and stored under Ar. Samarium metal was purchased form Rhône-Poulenc Inc., Phoenix, AZ, and was weighed and stored under an inert atmosphere. CH_2I_2 was purchased from Fluka Chemicals and was distilled prior to use. Standard benchtop techniques were employed for handling air-sensitive reagents and all reactions were carried out under Ar.

6-Hepten-2-one (1a). ^1H NMR (300 MHz, $CDCl_3$): δ 5.75–5.61 (m, 1 H), 4.97–4.87 (m, 2 H), 2.36 (t, J = 7.3 Hz, 2 H), 2.05 (s, 3 H), 2.01–1.94 (m, 2 H), 1.62–1.50 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.79, 137.83, 115.07, 42.62, 32.84, 29.75, 22.58.

7-Octen-2-one (1b). ^1H NMR (300 MHz, $CDCl_3$): δ 5.81–5.64 (m, 1 H), 4.98–4.83 (m, 2 H), 2.96 (t, J = 7.3 Hz, 2 H), 2.11 (s, 3 H), 2.08–1.94 (m, 2 H), 1.52–1.41 (m, 2 H), 1.36–1.28 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.07, 138.43, 114.61, 43.47, 33.40, 29.76, 28.26, 23.16.

8-Nonen-2-one (1c). ^1H NMR (300 MHz, $CDCl_3$): δ 5.80–5.71 (m, 1 H), 4.98–4.87 (m, 2 H), 2.39 (t, J = 7.3 Hz, 2 H), 2.10 (s, 3 H), 2.04–1.97 (m, 2 H), 1.59–1.50 (m, 2 H), 1.38–1.22 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.34, 138.84, 114.38, 43.64, 33.49, 29.81, 28.56, 28.53, 23.56.

2-(3-Butenyl)cyclopentan-1-one (1d). ^1H NMR (300 MHz, $CDCl_3$): δ 5.82–5.68 (m, 1 H), 5.05–4.90 (m, 2 H), 2.35–1.31 (m, 11 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.51, 138.07, 115.07, 48.42, 38.11, 31.56, 29.49, 28.77, 20.65.

2-(4-Pentenyl)cyclopentan-1-one (1e). ^1H NMR (300 MHz, $CDCl_3$): δ 5.84–5.70 (m, 1 H), 5.01–4.89 (m, 2 H), 2.37–1.18 (m, 13 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.56, 138.53, 114.64, 49.01, 38.10, 33.67, 29.52, 29.14, 26.82, 20.68.

2-(3-Butenyl)cyclohexan-1-one (1f). ^1H NMR (300 MHz, $CDCl_3$): δ 5.82–5.69 (m, 1 H), 5.01–4.91 (m, 2 H), 2.35–1.21 (m, 13 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.35, 138.54, 114.72, 49.80, 42.04, 33.82, 31.16, 28.40, 27.99, 24.88.

2-(4-Pentenyl)cyclohexan-1-one (1g). ^1H NMR (300 MHz, $CDCl_3$): δ 5.81–5.69 (m, 1 H), 4.97–4.84 (m, 2 H), 2.38–1.10 (m, 15 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.35, 138.67, 114.38, 50.53, 41.88, 33.77, 33.76, 28.81, 27.91, 26.36, 24.73.

3-Methyl-7-octen-2-one (1i). ^1H NMR (300 MHz, $CDCl_3$): δ 5.77–5.68 (m, 1 H), 4.98–4.87 (m, 2 H), 2.47–2.44 (m, 1 H), 2.08 (s, 3 H), 2.00–1.96 (m, 2 H), 1.60–1.27 (m, 4 H), 1.03 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.86, 138.38, 114.74, 46.96, 33.63, 32.17, 27.95, 26.35, 16.08.

4-Methyl-7-octen-2-one (1j). ^1H NMR (300 MHz, $CDCl_3$): δ 5.80–5.71 (m, 1 H), 5.00–4.88 (m, 2 H), 2.38 (dd, J = 15.9, 5.9 Hz, 1 H), 2.20 (dd, J = 15.9, 8.1 Hz, 1 H), 2.09 (s, 3 H), 2.05–1.94 (m, 3 H), 1.40–1.16 (m, 2 H), 0.86 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.04, 138.61, 114.49, 51.05, 35.88, 31.12, 30.35, 28.65, 19.54.

3-(2-Propenyl)cyclohexan-1-one (1k). ^1H NMR (200 MHz, $CDCl_3$): δ 5.63–5.55 (m, 1 H), 4.93–4.86 (m, 2 H), 2.30–1.20 (m, 11 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.21, 135.41, 116.45, 47.43, 41.10, 40.51, 38.46, 30.56, 24.85.

3-(3-Butenyl)cyclohexan-1-one (1l). ^1H NMR (300 MHz, $CDCl_3$): δ 5.81–5.62 (m, 1 H), 5.04–4.83 (m, 2 H), 2.44–1.23 (m, 13 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.87, 138.25, 114.75, 47.95, 41.40, 38.31, 35.58, 31.08, 30.73, 25.12.

General Procedure for Preparation of SmI_2/THF/HMPA. Samarium metal (0.30 g, 2.0 mmol) was added under a flow of Ar to an oven-dried round-bottomed flask containing a magnetic stirring bar and septum inlet. The flask and samarium were gently flame dried and cooled under Ar. To the samarium was added 13 mL of THF followed by CH_2I_2 (0.482 g, 1.8 mmol), and the mixture was allowed to stir at room temperature for 1.5 h. HMPA (2.51 mL, 14.5 mmol) was added, and the resulting purple solution was allowed to stir 10 min before addition of the olefinic ketone.

General Procedure for Cyclization of Olefinic Ketones 1. To the above SmI_2 solution was added the olefinic ketone (0.72 mmol) and t-BuOH (0.160 g, 2.16 mmol) in 14 mL of THF over

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(44) Julia, M.; Maumy, M.; Mion, L. *Bull. Soc. Chim. Fr.* **1967**, 2641.

a 15-min period. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O and brine and then dried over $MgSO_4$, and the solvent was removed under reduced pressure. Final purification involved filtering through a short column of Florisil to remove residual HMPA and Kugelrohr distillation or flash chromatography. In each case below the starting olefinic ketone is given, followed by the product yields.

(1*R,2*R**)-Dimethylcyclopentan-1-ol (2a).** 6-Hepten-2-one (**1a**, 0.116 g, 1.04 mmol), yield 0.102 g (86%), bp 60 °C (25 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 1.96–1.48 (m, 6 H), 1.82 (br s, 1 H), 1.20–1.12 (m, 1 H), 1.09 (s, 3 H), 0.82 (d, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.90, 44.67, 40.06, 31.73, 22.71, 20.45, 15.40. IR (CCl_4): 3419, 2940, 2856 cm^{-1}. HRMS calcd for $C_7H_{14}O$: 114.1045, found 114.1051. LRMS (EI) m/e: 114 (3), 85 (20), 71 (100), 58 (40).

(1*R,2*R**)-1,2-Dimethylcyclohexan-1-ol (2b).** 7-Octen-2-one (**1b**, 0.140 g, 1.11 mmol), yield 0.129 g (91%) as a 36:1 mixture of diastereomers, bp 90 °C (25 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 1.70–1.15 (m, 9 H), 1.48 (s, 1 H), 1.04 (s, 3 H), 0.87 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 73.00, 42.23, 41.32. 31.99, 25.25, 24.06, 20.72, 15.26. IR (CCl_4): 3407, 2916, 2874 cm^{-1}. LRMS (EI) m/e: 128 (18), 85 (43), 71 (100), 58 (34). Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.82; H, 12.66.

1-Methylcyclooctan-1-ol. 8-Nonen-2-one (**1c**, 0.137 g, 0.980 mmol), yield 0.072 g (52%). In addition, 0.039 g (28%) of **3c** was isolated, bp 70 °C (20 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 1.79–1.36 (m, 14 H), 1.32 (br s, 1 H), 1.16 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 73.36, 38.01, 29.81, 28.18, 24.75, 22.54. IR (CCl_4): 3412, 2919 cm^{-1}. HRMS calcd for $C_9H_{18}O$: 142.1358, found 142.1351. LRMS (EI) m/e: 142 (1), 127 (20), 71 (100).

(1*R,2*S**,5*R**)-2-Methylbicyclo[3.3.0]octan-1-ol (2d).** 2-(3-Butenyl)cyclopentan-1-one (**1d**, 0.141 g, 1.02 mmol, yield 0.124 g (90%), mp 57–58 °C, bp 60 °C, (0.1 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 2.08–1.98 (m 2 H), 1.95–1.36 (m, 8 H), 1.23–0.96 (m, 3 H), 0.92 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 92.80, 51.48, 45.42, 36.03, 34.94, 32.41, 29.86, 25.73, 13.25. IR (CCl_4): 3407, 2940, 2856 cm^{-1}. HRMS calcd for $C_9H_{16}O$: 140.1201, found 140.1184. LRMS (EI) m/e: 140 (9), 111 (29), 97 (94), 84 (100).

(1*R,2*S**,6*S**)-2-Methylbicyclo[4.3.0]nonan-1-ol (2e).** 2-(4-Pentenyl)cyclopentan-1-one (**1e**, 0.152 g, 1.00 mmol), yield 0.142 g (92%) as a 93:5:2 mixture of diastereomers, mp 55–58 °C, bp 75 °C (0.1 mmHg). ^1H NMR (300 MHz, $CDCl_3$) δ 2.12–1.98 (m, 1 H), 1.78–0.96 (m, 14 H), 0.91 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 85.19, 48.33, 40.29, 32.47, 31.61, 29.48, 29.06, 25.41, 19.66, 16.28. IR (CCl_4): 3430, 2916, 2856 cm^{-1}. LRMS (EI) m/e: 154 (16), 125 (23), 112 (57), 97 (100), 84 (50). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.23; H, 11.68.

(1*R,6*R**,9*S**)-9-Methylbicyclo[4.3.0]nonan-1-ol (2f).** 2-(3-Butenyl)cyclohexan-1-one (**1f**, 0.158 g, 1.04 mmol), yield 0.142 g (89%), bp 75 °C (0.1 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 1.89–1.12 (m, 15 H), 0.83 (d, J = 6.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.12, 45.31, 44.61, 28.10, 27.50, 24.05, 23.37, 21.04, 20.27, 12.56. IR (CCl_4): 3418, 2928, 2856 cm^{-1}. HRMS calcd for $C_{10}H_{18}O$: 154.1358, found 154.1351. LRMS (EI) m/e: 154 (15), 111 (100), 98 (76).

2-Methylbicyclo[4.4.0]decan-1-ol (2g). 2-(4-Pentenyl)-cyclohexan-1-one (**1g**, 0.076 g, 0.45 mmol), yield 0.065 g (85%) as a 2:1:1 mixture of diastereomers: bp 85 °C (0.1 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 1.95–1.09 (m, 17 H), 0.91 (d, J = 7.3 Hz, 1.5 H), 0.82 (d, J = 6.8 Hz, 0.75 H), 0.78 (d, J = 6.8 Hz, 0.75 H). ^{13}C NMR (75 MHz, $CDCl_3$): (major) δ 73.08, 39.54, 37.44, 36.40, 28.96, 28.82, 28.66, 26.06, 21.64, 20.15, 15.18; (minor) 73.80, 73.19, 44.06, 43.96, 32.40, 30.52, 29.18, 28.21, 27.41, 27.38, 26.14, 24.77, 23.18, 21.35, 20.86, 20.41, 14.51, 14.35. IR (CCl_4): 3430, 2916, 2844 cm^{-1}. HRMS calcd for $C_{11}H_{20}O$: 168.1514, found 168.1510. LRMS (EI) m/e: (major) 168 (31), 125 (14), 111 (100), 98 (54); (minor I) 168 (30), 125 (19), 111 (100), 98 (47); (minor II) 168 (28), 125 (12), 111 (100), 98 (50).

(1*R,2*R**,6*R**)-1,2,6-Trimethylcyclohexan-1-ol (2i).** 3-Methyl-7-octen-2-one (**1i**, 0.144 g, 1.03 mmol), yield 0.130 g (89%) as a 6:1 mixture of diastereomers, bp 90 °C (25 mmHg). ^1H NMR (300 MHz, $CDCl_3$): (major) δ 1.71–1.05 (m, 9 H), 1.12 (s, 3 H), 0.91 (d, J = 7.1 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 74.06, 38.60, 36.74, 30.52, 29.95, 24.85, 20.04, 15.34, 14.32; (minor) 75.32, 43.97, 32.73, 25.91, 15.12, 13.17. IR (CCl_4): 3424, 2931 cm^{-1}. HRMS calcd for $C_9H_{18}O$: 142.1358, found 142.1358. LRMS (EI) m/e: (major) 142 (14), 85 (100), 72 (19), 57 (15), (minor) 142 (14), 85 (100), 72 (31), 57 (22).

(1*R,2*R**,5*S**)-1,2,5-Trimethylcyclohexan-1-ol (2j).** 3-Methyl-7-octen-2-one (**1j**, 0.141 g, 1.01 mmol), yield 0.124 g (86%) as a 4:1 mixture of diastereomers, bp 95 °C (25 mmHg). ^1H NMR (300 MHz, $CDCl_3$): (major) δ 1.98–0.95 (m, 9 H), 1.09 (s, 3 H), 0.87 (d, J = 7.3 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): (major) δ 72.98, 42.41, 38.58, 29.15, 28.48, 28.19, 27.83, 22.35, 15.99; (minor) 73.21, 51.22, 42.22, 34.91, 32.20, 30.74, 22.38, 20.13, 14.92. IR (CCl_4): 3425, 2919 cm^{-1}. HRMS calcd for $C_9H_{18}O$: 142.1358, found 142.1338. LRMS (EI) m/e: 142 (4), 127 (9), 109 (7), 85 (100).

(1*R,5*S**,7*R**)-7-Methylbicyclo[3.2.1]octan-1-ol (2k).** 3-(2-Propenyl)cyclohexan-1-one (**1k**, 0.102 g, 0.739 mmol), yield 0.091 g (88%) as a 17:1 (endo/exo) mixture of diastereomers, mp 118–123 °C. ^1H NMR (300 MHz, $CDCl_3$): (major) δ 2.13–0.87 (m, 13 H), 0.94 (d, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): (major) δ 78.83, 47.10, 41.28, 34.50 (2 C), 33.00, 31.13, 19.14, 11.70. IR (CCl_4): 3335, 2928, 2856 cm^{-1}. LRMS (EI) m/e: (major) 140 (6), 97 (100), 70 (28), 55 (23); (minor) 140 (1), 97 (100). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.19; H, 11.32.

(1*R,2*R**,5*S**)-2-Methylbicyclo[3.3.1]nonan-1-ol (2l).** 3-(3-Butenyl)cyclohexan-1-one (**1l**, 0.156 g, 1.03 mmol), yield 0.104 g (66%), GC analysis of the crude reaction mixture indicated a 17:1 mixture of diastereomers. The major diastereomer was isolated in 66% yield following flash chromatography, mp 83–85 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.12 (br s, 1 H), 2.00–1.94 (m, 1 H), 1.74–1.46 (m, 11 H), 1.40 (br s, 1 H), 1.32–1.21 (m, 1 H), 0.94 (d, J = 5.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.02, 44.91, 42.11, 34.00, 32.41, 32.00, 30.97, 30.08, 22.63, 15.47. IR (CCl_4): 3419, 2904 cm^{-1}. LRMS (EI) m/e: 154 (4), 111 (18), 97 (100). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.50; H, 11.51.

(1*R,2*S**)-1-[(2-Hydroxy-2-methyl-1-cyclopentyl)-methyl]cyclohexan-1-ol (4a).** The following is a representative procedure for cyclization of substrate **1a** followed by nucleophilic addition (Table II). To a suspension of SmI_2 (2.254 mmol) in 16 mL of THF was added 3.6 mL (20.7 mmol) of HMPA. The resulting solution was allowed to stir for 5 min, followed by the addition of 6-hepten-2-one (**1a**, 0.110 g, 0.98 mmol) in 20 mL of THF over 20 min. During this time a precipitate had formed that immediately went into solution upon addition of a solution of cyclohexanone (0.147 g, 0.150 mmol) in 3 mL of THF. After an additional 30 min the reaction was quenched (saturated aqueous $NaHCO_3$), and following usual workup and flash chromatography the title compound was isolated in 80% yield (0.166 g, 0.783 mmol), mp 104–105 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.93 (br s, 2 H), 2.04–1.97 (m, 1 H), 1.75–1.13 (m, 18 H), 1.07 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.85, 71.41, 43.79, 41.02, 39.79, 35.84, 31.06, 25.80, 22.41, 22.05, 21.81, 19.44. IR (CCl_4): 3323, 2928, 2857 cm^{-1}. HRMS calcd for $C_{13}H_{24}O_2$: 212.1776, found 212.1775. LRMS (EI) m/e: 212 (<1), 99 (53), 81 (100).

2-(2-Hydroxy-2-phenylethyl)-1-methylcyclopentan-1-ol (4b). **1a** (0.103 g, 0.92 mmol), yield 0.168 g (83%) as a 3:1 mixture of diastereomers. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.20 (m, 5 H), 4.86 (dd, J = 5.6, 4.8 Hz, 0.75 H), 4.65 (dd, J = 10.5, 2.4 Hz, 0.25 H), 3.64 (br s, 2 H), 2.03–1.19 (m, 9 H), 1.18 (s, 0.75 H), 1.16 (s, 2.25 H). ^{13}C NMR (75 MHz, $CDCl_3$): (major) δ 144.52, 128.24, 127.03, 125.84, 79.70, 72.60, 44.87, 41.29, 38.43, 30.01, 22.14, 19.84; (minor) 145.42, 128.27, 127.22, 125.64, 79.02, 74.77, 48.90, 41.01, 39.77, 30.29, 22.41, 19.61. IR (CCl_4): 3415, 2925 cm^{-1}. HRMS calcd for $C_{14}H_{20}O_2$: 220.1463, found 220.1451. LRMS (EI) m/e: (major) 220 (<1), 202 (24), 107 (76), 96 (100), 82 (92), 79 (74), 77 (76); (minor) 220 (<1), 202 (26), 107 (82), 96 (100), 81 (98), 79 (93), 77 (93).

(1*R,2*R**)-1-Methyl-2-[(phenylthio)methyl]cyclopentan-1-ol (4c).** **1a** (0.112 g, 1.00 mmol), yield 0.172 g (77%), bp 120 °C (0.05 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.26 (m, 5 H), 3.14 (dd, J = 12.4, 6.1 Hz, 1 H), 2.84 (dd, J = 12.4, 8.6 Hz, 1 H), 2.18 (s, 1 H), 2.13–2.08 (m, 2 H), 1.81–1.25 (m, 5 H), 1.29 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.40, 129.00, 128.88, 125.90, 80.33, 48.54, 40.95, 34.73, 29.55, 22.65, 19.95. IR (CCl_4): 3458, 2949, 1562 cm^{-1}. HRMS calcd for $C_{13}H_{18}OS$: 222.1078, found

222.1090. LRMS (EI) m/e: 222 (20), 123 (12), 110 (100).

(1R*,2S*)-1-Methyl-2-(2-oxopropyl)cyclopentan-1-ol Acetate (4d). **1a** (0.096 g, 0.86 mmol) was cyclized and trapped with acetic anhydride (5 equiv, 6 h at 25 °C), yield 0.145 g (85%), bp 80 °C (0.05 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.67 (dd, J = 15.9, 3.6 Hz, 1 H), 2.46–2.35 (m, 1 H), 2.17 (dd, J = 15.9, 10.5 Hz, 1 H), 2.08 (s, 3 H), 1.95–1.79 (m, 3 H), 1.87 (s, 3 H), 1.71–1.44 (m, 2 H), 1.26 (s, 3 H), 1.06–0.92 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.08, 170.39, 88.75, 44.59, 44.02, 38.03, 29.87, 28.61, 21.93, 20.78, 19.20. IR (CCl_4): 2948, 1732, 1710 cm^{-1}. HRMS calcd for $C_{11}H_{18}O_3$: 198.1256, found 198.1248. LRMS (EI) m/e: 198 (2), 138 (100), 113 (62), 95 (90), 81 (67), 80 (51), 71 (51).

(1R*,2S*)-1-(2-Hydroxy-2-methylcyclopent-1-yl)-2-propanone (4e). **1a** (0.093 g, 0.83 mmol) was cyclized and trapped with acetic anhydride (2 equiv, 5 min at 0 °C) to yield **4e** (0.096 g, 74%). In addition, a 12% yield of **4d** was isolated, bp 80 °C (0.05 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.34 (br s, 1 H), 2.54–2.38 (m, 2 H), 2.18–2.10 (m, 1 H), 2.09 (s, 3 H), 1.89–1.42 (m, 5 H), 1.16–1.02 (m, 1 H), 0.99 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.55, 78.85, 45.52, 44.85, 40.96, 30.27, 29.89, 23.15, 20.70. IR (CCl_4): 3424, 2948, 1704 cm^{-1}. HRMS calcd for $C_9H_{16}O_2$: 156.1150, found 156.1140. LRMS (EI) m/e: 156 (1), 138 (23), 113 (64), 95 (35), 71 (100).

(1R*,2S*)-2-(Hydroxymethyl)-1-methylcyclopentan-1-ol (4f). **1a** (0.102 g, 0.91 mmol), yield 0.082 g (69%) as a 15:1 mixture of diastereomers, bp 90 °C (0.05 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64–3.56 (m, 2 H), 2.84 (br s, 2 H), 2.12–1.98 (m, 1 H), 1.82–1.46 (m, 5 H), 1.19 (s, 3 H), 1.18–1.08 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): (major) δ 80.41, 63.64, 50.62, 41.03, 25.69, 22.10, 20.25; (minor) δ 80.56, 50.23, 41.09, 29.33, 29.00, 22.61. IR (CCl_4): 3424, 2948 cm^{-1}. HRMS calcd for $C_7H_{14}O_2$: 131.1072 (M + 1), found 131.1064. LRMS (EI) m/e: 115 (9), 112 (35), 97 (68), 58 (100).

(1R*,2S*)-2-[2-(N,N-Dimethylamino)ethyl]-1-methylcyclopentan-1-ol (4g). **1a** (0.109 g, 0.97 mmol), yield 0.121 g (73%), bp 95 °C (0.05 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34–2.20 (m, 2 H), 2.17 (s, 6 H), 1.74–1.36 (m, 10 H), 1.03 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.00, 59.89, 50.99, 45.11, 40.79, 30.24, 26.81, 22.52, 19.63. IR (CCl_4): 3220, 2937, 1534 cm^{-1}. HRMS calcd for $C_{10}H_{21}NO$: 171.1623, found 171.1608.

(1R*,2S*)-2-(2-Methyl-2-hydroxycyclopent-1-yl)acetic Acid (4h). **1a** (0.096 g, 0.86 mmol) yield 0.089 g (65%), mp 65–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (bs, 2 H), 2.44 (dd, J = 16.1, 7.8 Hz, 1 H), 2.27 (dd, J = 16.1, 6.8 Hz, 1 H), 2.32–2.20 (m, 1 H), 1.98–1.62 (m, 6 H), 1.12 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.78, 79.88, 45.85, 40.70, 34.91, 30.03, 22.68, 20.31. IR (CCl_4): 3401, 2959, 1704, 1540 cm^{-1}. HRMS calcd for $C_8H_{14}O_3$: 158.0943, found 158.0927. LRMS (EI) m/e: 143 (4), 140 (33), 125 (40), 112 (77), 111 (41), 98 (79), 97 (69), 71 (100).

High R_f Dimer. **1f** (0.080 g, 0.526 mmol) in 3 mL of THF (0.18 M) was added to 1.315 mmol of SmI_2 in 9 mL of THF and 1.5 mL of HMPA. Usual workup and flash chromatography afforded 0.031 g of the high R_f diastereomer and 0.030 g of the low R_f diastereomer. Combined yield 0.061 g (76%), mp 187–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (br s, 2 H), 1.88–0.99 (m, 32 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.39, 49.49, 45.00, 27.70, 27.26, 26.80, 23.97, 23.33, 21.05, 20.30. IR (CCl_4): 3419, 2928, 2856 cm^{-1}. HRMS calcd for $C_{20}H_{34}O_2$: 288.2453 (M − H_2O), found 288.2455.

Low R_f Dimer. Mp 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90–1.06 (m, 34 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.33, 51.18, 44.90, 27.95, 27.61, 26.44, 23.97, 23.36, 21.10, 20.24. IR (CCl_4): 3407, 2916, 2856 cm^{-1}. HRMS calcd for $C_{20}H_{34}O_2$: 306.2559, found 306.2534.

Table III General Procedure. Following the general procedure for cyclization of olefinic ketones **1**, substrates **1d**, **1b**, and **1k** were treated under the provisions outlined in Table III. Usual workup followed by Kugelrohr distillation afforded the products reported as determined by fused silica capillary GC, ^{1}H NMR, and ^{13}C NMR analyses.

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Supplementary Material Available: Proton and carbon NMR of new compounds (47 pages). Ordering information is given on any current masthead page.

New Type of Cyclization of α,β,χ,ψ-Unsaturated Dioic Acid Esters through Tandem Conjugate Additions by Using Lithium N-Benzyl-N-(trimethylsilyl)amide as a Nitrogen Nucleophile

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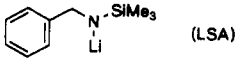
Treatment of dimethyl (2*E*,6*E*)-2,6-octadienedioate with lithium *N*-benzyl-*N*-(trimethylsilyl)amide (LSA) gave 5-*exo*-*trig* ring closure products, methyl 3-(*N*-benzylamino)-2-(methoxycarbonyl)cyclopentane-1-acetates, through tandem conjugate additions. The related 6-*exo*-*trig* cyclization proceeded stereoselectively to give ethyl *c*-3-(*N*-benzylamino)-*t*-2-(ethoxycarbonyl)cyclohexane-1-acetate. In contrast with the 5- and 6-*exo*-*trig* cyclization, no 7-*exo*-*trig* cyclization occurred. The 5-*exo*-*trig* cyclization products were converted into 2-(methoxycarbonyl)-2-cyclopentene-1-carboxylic acid methyl ester in an excellent yield. 5-*exo*-*trig* cyclization of the unsymmetrical dienedioate consisting of crotonate and (*E*)-2-methyl-2-butenoate units proceeded regioselectively through conjugate addition of LSA to the crotonate part. Similar regioselectively was observed in the case of 5-*exo*-*trig* cyclization of the dienedioate possessing crotonate and (*E*)-3-methyl-2-pentenoate units. Total syntheses of the physiologically active cyclopentane monoterpenes (±)-dihydronepetalactone and (±)-isohydronepetalactone has been accomplished by this cyclization strategy. In addition, it has been demonstrated that LSA is a more efficient nitrogen nucleophile than LDA to cyclize ω-halo-α,β-unsaturated esters.

When a crotonic acid ester is treated with a metal amide derived from a secondary amine, the reactions expected are (1) deprotonation of the γ-position to give the dienolate, (2) conjugate addition to give the β-amino acid ester, and (3) carboxamide formation. Recently, we have reported that lithium *N*-benzyl-*N*-(trimethylsilyl)amide (LSA) is an excellent nucleophile adding only in a 1,4-manner to crotonate derivatives.[2] Furthermore, the



(LSA)

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