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Studies on the Mechanism, Selectivity, and Synthetic Utility of Lactone Reduction Using SmI_2 and H_2O

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Abstract: Although simple aliphatic esters and lactones have long been thought to lie outside the reducing range of SmI_2, activation of the lanthanide reagent by H_2O allows some of these substrates to be manipulated in an unprecedented fashion. For example, the SmI_2-H_2O reducing system shows complete selectivity for the reduction of 6-membered lactones over other classes of lactones and esters. The kinetics of reduction has been studied using stopped-flow spectrophotometry. Experimental and computational studies suggest that the origin of the selectivity lies in the initial electron-transfer to the lactone carbonyl. The radical intermediates formed during lactone reduction with SmI_2-H_2O can be exploited in cyclizations to give cyclic ketone (or ketal) products with high diastereoselectivity. The cyclizations constitute the first examples of ester-alkene radical cyclizations in which the ester carbonyl acts as an acyl radical equivalent.

Introduction

The rerouting of synthetic transformations through less-conventional intermediates opens up unexplored reaction space where new selectivity and reactivity may be discovered and exploited. For example, diverting fundamental transformations of the carbonyl group—transformations carried out routinely in academic and industrial laboratories—through intermediates with stabilities and reactivities different to those intermediates typically encountered during the conversion presents opportunities to identify new selective reactions of carbonyl compounds. Here we report a full account of our synthetic and mechanistic studies on a ring size-selective reduction of lactones using SmI_2[1]$-H_2O$[2] and report for the first time that radical intermediates formed during lactone reduction with SmI_2-H_2O can be exploited in cyclizations to give cyclic ketone products with high diastereoselectivity. The cyclization constitutes the first example of ester-alkene radical cyclizations in which the ester carbonyl acts as an acyl radical equivalent.[3]

During studies on a SmI_2-mediated stereoselective spirocyclization,[4] we found that exposure of spirocyclic lactone **1** to excess SmI_2 in THF, employing H_2O as a cosolvent, gave triol **2**. Although Kamochi and Kudo had described the reduction of carboxylic acids[5a] and aryl esters[5b] using SmI_2-H_2O, the reduction of unactivated aliphatic esters and lactones with SmI_2 had not been reported.[5] Spirocyclic lactones **3** and **5** also underwent reduction to give the corresponding triols in good yield. Importantly, the β-hydroxyl group present in these substrates was found to not play a crucial role[6] in the activation of the lactone carbonyl group, and less-functionalized 6-membered lactones also underwent reduction to the corresponding diols in good yield (Figure 1).

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[||] Pfizer Global R & D.

(1) Metal-mediated radical reactions: (a) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. Recent reviews on the use of SmI_2 in synthesis: (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G. A. *Org. React.* **1994**, *46*, 211. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (e) Skrydstrup, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345. (f) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (g) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (h) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (i) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. (j) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607.

(2) For a preliminary account of this work, see: (a) Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 1136We have recently reported the selective reductions and cyclizations of cyclic-1,3-diesters using SmI_2-H_2O: (b) Guazzelli, G.; De Grazia, S.; Collins, K. D.; Matsubara, H.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 7214.

(3) Cossy has described the radical cyclization of unsaturated esters using sodium-ammonia but proposes that radicals at a lower oxidation state (cf. **17** Scheme 3) are involved: (a) Cossy, J. Gille, B. Bellosta, V. *J. Org. Chem.* **1998**, *63*, 3141. Srikrishnaha's reported the anionic cyclization of unsaturated esters using lithium-ammonia: (b) Srikrishna, A.; Ramasastry, S. S. V. *Tetrahedron Lett.* **2004**, *45*, 379. See also ref 2b.

(4) (a) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811. (b) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345. (c) Guazzelli, G.; Duffy, L. A; Procter, D. J. *Org. Lett.* **2008**, *10*, 4291.

(5) Kamochi and Kudo have described the reduction of aryl carboxylic acid derivatives using the reagent: (a) Kamochi, Y.; Kudo, T. *Chem. Lett.* **1991**, 893. (b) Kamochi, Y.; Kudo, T. *Chem. Lett.* **1993**, 1495. Markó has recently exploited the SmI_2-mediated reduction of aryl esters in a deoxygenation procedure: (c) Lam, K.; Markó, I. E. *Org. Lett.* **2008**, *10*, 2773. Markó has recently exploited the SmI_2-mediated reduction of aryl esters in the removal of ester protecting groups: (d) Lam, K.; Marko, I. E. *Org. Lett.* **2009**, *11*, 2752.

(6) (a) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172. (b) Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2002**, *124*, 6357.

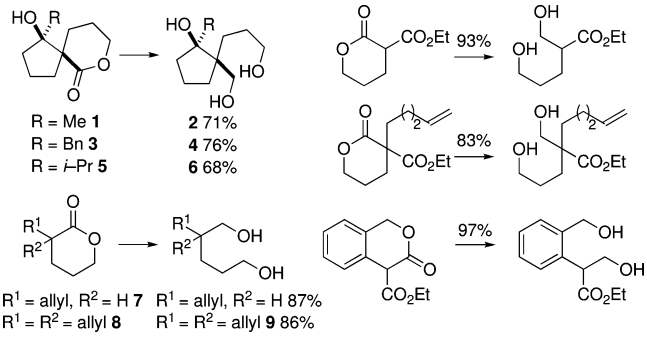
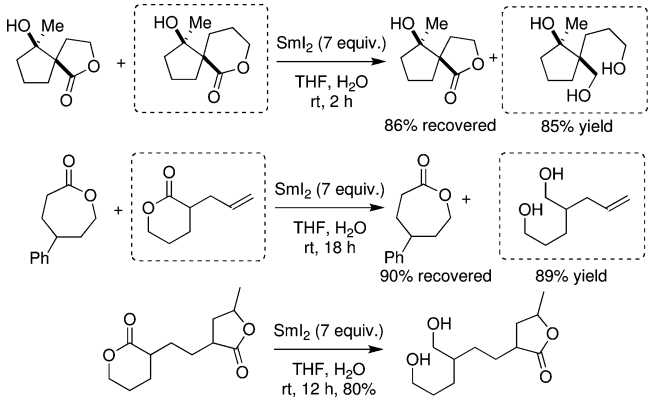


Figure 1. Reduction of 6-membered lactones to the corresponding diols/triols with SmI_2-H_2O. (Conditions: SmI_2 (7 equiv), THF, H_2O (150 equiv), rt, 3−30 h.)

Scheme 1. Selective Reductions of 6-Membered Lactones Using SmI_2-H_2O (1:1 Mixture of Substrates)



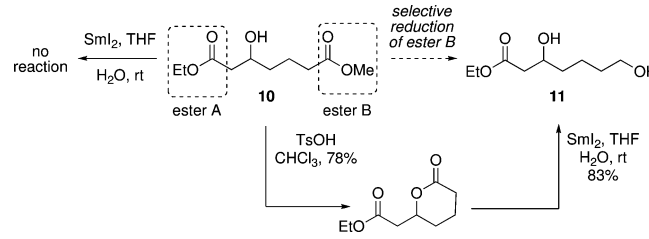
As shown in Figure 1, lactone reduction was possible in substrates bearing ester substituents. A series of competition experiments has been carried out to illustrate further the chemoselectivity observed with the SmI_2-H_2O reagent system. Mixtures of lactones were prepared and treated with SmI_2-H_2O. In all cases, no reduction products arising from 5, 7 and 8-membered lactones were observed while 6-membered lactones were reduced smoothly (Scheme 1). Modified SmI_2 reagent systems employing additives (HMPA, DMPU, LiBr)[1i] were also ineffective for the reduction of other lactones.

The enhanced reactivity of SmI_2, enabling the reduction of lactones, is due to activation of the reagent by the H_2O cosolvent. Hasegawa and Curran first proposed that H_2O accelerated reactions using SmI_2 by increasing the reduction potential of the reagent in addition to acting as a proton source.[7] Flowers has since shown that H_2O produces larger rate enhancements than alcohols in the reduction of acetophenone with SmI_2,[8a] and has used UV−vis spectra of SmI_2 with H_2O to illustrate that a unique reductant is formed at high concentrations of H_2O.[8a,b] Flowers has also shown that the reduction potential of SmI_2 (−1.3 V) increases to a maximum of −1.9 V on the addition of up to 500 equivalents of H_2O.[8]

Results and Discussion

The selectivity of the SmI_2-H_2O reagent system for 6-membered lactones suggests that selective lactonization can be used to 'switch-on' the reactivity of an ester carbonyl group, making it receptive to electron-transfer from Sm(II). To explore this idea, diester **10**, possessing ester groups with similar reactivity toward conventional hydride reducing agents, was prepared. (An ethyl ester group and a methyl ester group were chosen to facilitate monitoring of the selectivity of reactions involving **10**.) As expected, treatment of **10** with SmI_2-H_2O gave no reaction and **10** was recovered in quantitative yield. Selective lactonization of ester B upon treatment with acid, however, activated ester B toward reduction and treatment with SmI_2-H_2O gave diol **11** in 83% yield (Scheme 2). The overall sequence corresponds to a selective reduction of ester B in the presence of ester A.

Scheme 2. Selective Lactonization to "Switch-On" the Reactivity of an Ester Carbonyl Group



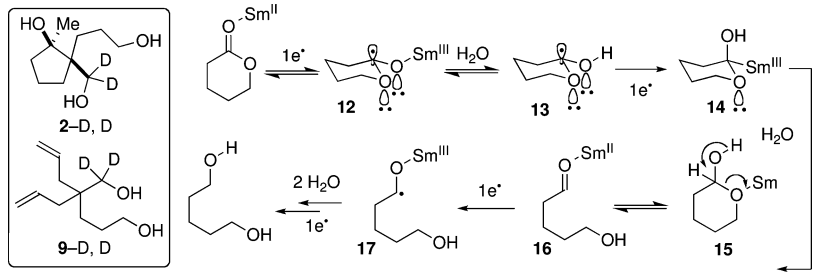
Studies to elucidate the mechanism of the reduction and to understand the ring size-selectivity observed have been carried out. The reduction of **1** and **8** with SmI_2-D_2O gave **2**-D, D and **9**-D, D, respectively, suggesting that anions are generated and protonated by H_2O during a series of single electron transfers. A possible mechanism for the transformation is given in Scheme 3. Activation of the lactone by coordination to Sm(II) and electron-transfer generates radical anion **12** that is then protonated.[8] A second electron transfer generates carbanion **14**[9] that is quenched by the H_2O cosolvent. Lactol **15** is in equilibrium with hydroxy aldehyde **16** and is reduced by a third electron-transfer from Sm(II) to give a ketyl radical anion **17**. A final electron-transfer from Sm(II) gives an organosamarium that is protonated by H_2O. The amount of SmI_2 (approximately 7 equiv) required experimentally is consistent with the amount predicted by the proposed mechanism (4 equiv).

A kinetic study was initiated to determine the role of each reactant in the lactone reduction. Rate studies were performed using stopped-flow spectrophotometry under pseudo-first-order conditions with substrate in excess. 5-Decanolide was chosen as a representative model substrate for kinetic studies and rates were obtained by monitoring the decay of the SmI_2-H_2O complex at 560 nm. A plot of observed rate constant (k_{obs}) with concentration for the reduction of 5-decanolide is shown in Figure 2. The rate constant for the reduction of 5-decanolide with SmI_2-H_2O was found to be $7.4 \pm 0.1 \times 10^{-3}$ M^{-1} s^{-1}. The rate order of 5-decanolide was 1.1 ± 0.1 (Figure 3) and the rate order of the SmI_2-H_2O complex was found to be 1, as determined by the fractional times method as well as the initial rates method (see Supporting Information).[10]

To determine the role of water under the concentrations used in the reactions, k_{obs} values for the reduction of 5-decanolide were monitored with increasing concentration of water from 100 to 180 equivalents with respect to [SmI_2] and no appreciable

(7) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008.
(8) (a) Chopade, P. R.; Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2004**, *126*, 44. (b) Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2005**, *127*, 18093. (c) Enemaerke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Chem. Commun.* **1999**, 343.
(9) For a discussion of the conformation of related radicals and organosamariums, see: Skrydstrup, T.; Jarreton, O.; Mazeas, D.; Urban, D.; Beau, J.-M. *Chem.—Eur. J.* **1998**, *4*, 655.
(10) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw Hill: New York, 1995; p 32.

Scheme 3. Mechanism of the Reduction of Lactones Using SmI_2-H_2O



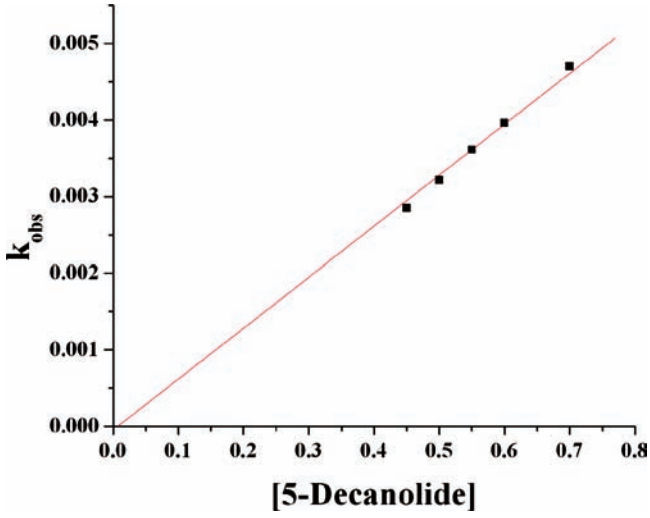


Figure 2. Plot of k_{obs} vs [5-decanolide]. $SmI_2 = 10$ mM, $H_2O = 150$ equiv, 5-decanolide = 45−70 equiv, $T = 30.0 \pm 0.1$ °C. Rate constant = $7.4 \pm 0.1 \times 10^{-3}$ M^{-1} s^{-1}.

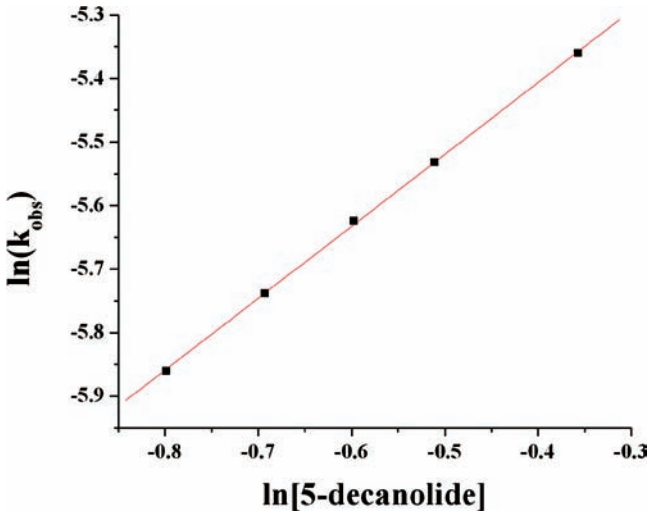
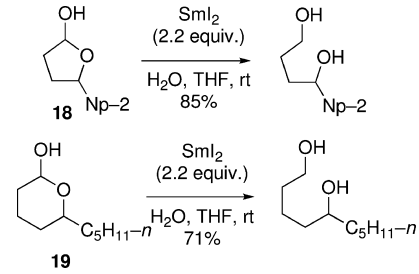


Figure 3. Plot of $\ln(k_{obs})$ vs ln[5-decanolide]. $SmI_2 = 10$ mM, $H_2O = 150$ equiv, 5-decanolide = 45−70 equiv, $T = 30.0 \pm 0.1$ °C. Rate order = 1.1 ± 0.1.

increase in the rate values were observed over this range (see Supporting Information). A deuterium isotopic study was carried out to further analyze the role of H_2O in the system. The rate of 5-decanolide reduction was monitored using 150 equiv of D_2O in place of H_2O. This study provided a k_H/k_D value of 1.5. The impact of deuterium is likely the result of a secondary kinetic isotope effect due to differential coordination of H_2O and D_2O with Sm(II). Typically, primary deuterium isotope

Scheme 4. Investigating the Origin of the Ring Size-Selectivity



effects consistent with proton transfer are greater than 2.[11] Furthermore, the lack of influence of H_2O concentration under the reaction conditions on the rate of reduction shows that proton transfer is not involved in the rate equation.

Overall, these kinetic studies show that the initial electron transfer from the SmI_2-H_2O complex to substrate is the rate limiting step as shown in eq 1.

$$-\mathrm{d}[SmI_2-H_2O]/\mathrm{d}t = k[SmI_2-H_2O][\text{5-decanolide}] \quad (1)$$

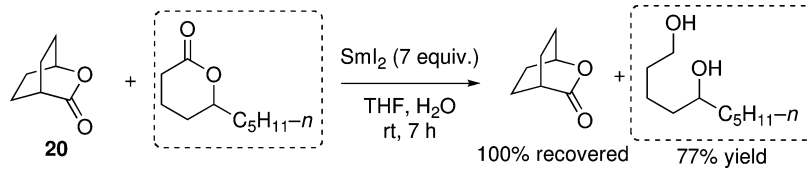
The complete selectivity of the reducing system for 6-membered lactones over 5, 7 and 8-membered lactones appears to have its origin in the rate of the initial electron-transfer to the lactone carbonyl. This is illustrated by the observation that lactols **18** and **19**, intermediates in the reductions, are both rapidly reduced, in high yield, by SmI_2-H_2O (Scheme 4).

For 6-membered lactones, we believe that reduction generates a radical anion intermediate **12** that is stabilized by interaction with the lone-pairs on both the endocyclic and exocyclic oxygens.[12] Such interactions are known to be more pronounced in 6-membered rings than in other, conformationally more labile, ring systems. It appears that the greater stability of the radical anion **12**, compared to analogous radicals formed from the reduction of 5, 7 and 8-membered lactones, promotes the initial reduction step.[13] This hypothesis is supported by the observation that 2-oxabicyclo[2,2,2]octan-3-one **20**, from which an intermediate radical-anion would be unable to adopt the chair conformation necessary for optimal stabilization, is not reduced by SmI_2-H_2O (Scheme 5).

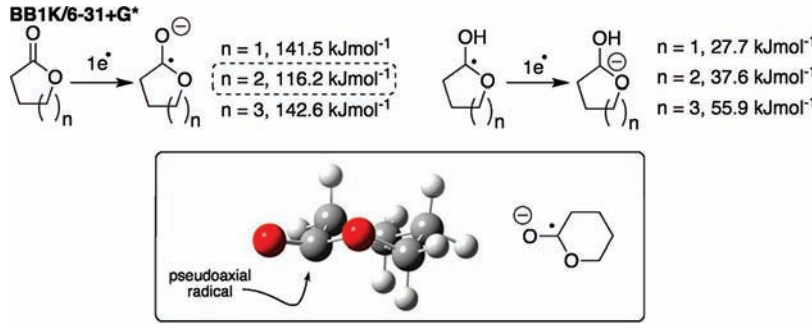
Calculated, *relative* reaction energies, not taking into account the impact of Sm(II) and Sm(III) ions, lend further support to

(11) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw Hill: New York, 1995; pp 217−218.
(12) Axial radicals are preferred due to the anomeric effect. For selected examples, see: (a) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609. (b) Giese, B.; Dupuis, J. *Tetrahedron Lett.* **1984**, *25*, 1349. (c) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.
(13) Relief of ring strain is a less-satisfactory explanation, see: (a) Leitao, M. L. P.; Pilcher, G.; Meng-Yan, Y. J.; Brown, J. M.; Conn, A. D. *J. Chem. Thermodynamics* **1990**, *22*, 885. (b) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117.

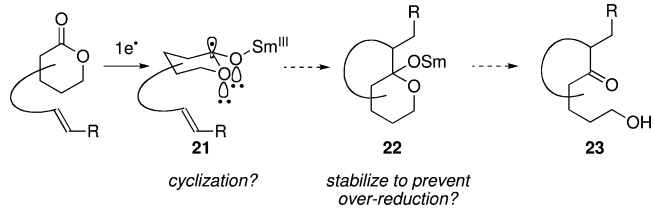
Scheme 5. Support for the Importance of a Radical Anomeric Effect (1:1 Mixture of Substrates)



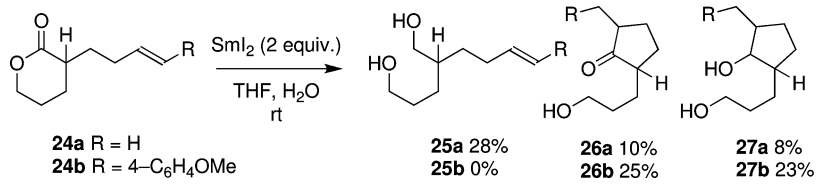
Scheme 6. Calculations on the Reduction of Lactones Using SmI_2-H_2O



Scheme 7. Potential to Intercept the Radical-Anions from Lactone Reduction



Scheme 8. Preliminary Studies on the Cyclization of Lactones Using SmI_2-H_2O



the importance of the first electron-transfer to the lactone carbonyl group. Calculations suggest that the first electron-transfer to the lactone carbonyl is endothermic (>100 kJ mol^{-1}) in all cases. The relative reaction energy of this step for 6-membered lactones, however, is calculated to be 116 kJ mol^{-1}, about 25−26 kJ mol^{-1} lower than those involving 5- and 7-membered rings (Scheme 6). (The relative reaction energy for the first electron-transfer to bicyclic lactone **20** is calculated to be 147.4 kJ mol^{-1}). The second electron transfer is lower in energy and similar for all systems, agreeing with kinetic studies showing that the first electron-transfer is the rate-determining step. The calculated lowest energy conformation of the radical anion derived from a 6-membered anion suggests that the radical does indeed adopt a pseudoaxial orientation apparently enjoying stabilization by an anomeric effect. Activation of the lactone by coordination to Sm(II) and electrostatic stabilization of the product radical-anion by coordination to Sm(III)[14] is likely to render these reductions more favorable than the calculated, relative reaction energies suggest.

We considered that radical-anion intermediates **21** (cf. **12**) on the reaction path might be trapped by an alkene tethered to the lactone scaffold.[15] Provided that the proposed hemiketal intermediate **22** could be prevented from collapsing, the interception of radical-anions **21** to give cyclic ketones **23** would correspond to an unprecedented acyl radical-type cyclization of lactones (Scheme 7).

We began by investigating the behavior of lactones **24**, bearing alkene radical acceptors, in the presence of SmI_2-H_2O. Although diol **25a** was the major product from the reduction of the lactone **24a**, we were pleased to also isolate cyclopentanone **26a** and cyclopentanol **27a**, as mixtures of diastereoisomers and in low yield (Scheme 8). Treatment of lactone **24b**, containing a more reactive alkene radical acceptor, gave a higher yield of cyclization products **26b** and **27b** (48%). Importantly, diol **25b** was not isolated. These early experiments illustrated the feasibility of carrying out ester-alkene radical cyclizations using lactones and SmI_2-H_2O.[2b,16]

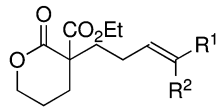
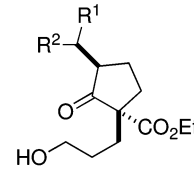
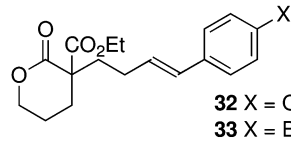
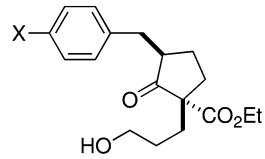
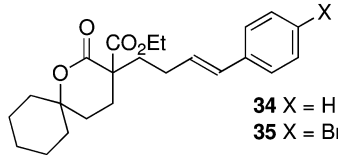
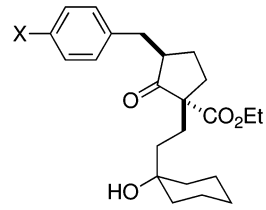
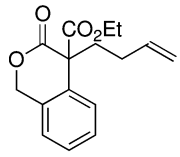
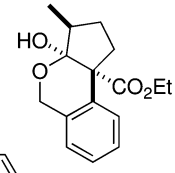
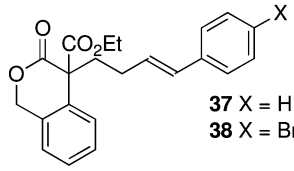
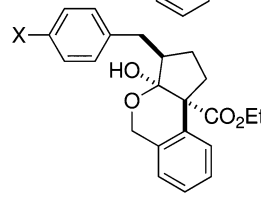
We envisaged that the introduction of a Lewis basic group capable of coordination to Sm(III), for example an adjacent ester substituent, would stabilize the hemiketal intermediates (cf. **22**)

(14) Farran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 4875.

(15) Calculations suggested that the cyclization of the first radical (*cf.* **12** in Scheme 3) and of the second radical (*cf.* **17** in Scheme 3) on the reaction pathway should both be possible. See Supporting Information.

(16) For an imide-alkene cyclization, see: Taaning, R. H.; Thim, L.; Karaffa, J.; Campaña, A. G.; Hansen, A.-M.; Skrydstrup, T. *Tetrahedron* **2008**, *64*, 11884.

Table 1. Lactones as Acyl Radical-Equivalents in Cyclizations Using SmI_2-H_2O

lactone substrates	ketone (hemi–ketal) products[a]
 **28** $R^1 = R^2 = H$ **29** $R^1 = R^2 = Me$ **30** $R^1 = Ph$, $R^2 = H$ **31** $R^1 = Ph$, $R^2 = Ph$	 **39** 56%,[b] 9:1 dr **40** 40%,[b] 33:1 dr **41** 60%, dr 12:1 **42** 72% dr>95:5
 **32** X = OMe **33** X = Br	 **43** 69% dr 7:1 **44** 73%, dr 8:1[c]
 **34** X = H **35** X = Br	 **45** 56%, dr>95:5 **46** 71%, dr>95:5
 **36**	 **47** 93%, dr 22:1
 **37** X = H **38** X = Br	 **48** 89%, dr>95:5 **49** 75%, dr 11:1[d]

[a] Diastereoisomeric ratios were determined by ^1H NMR. Reaction conditions: SmI_2 (5 equiv), H_2O (500 equiv), THF, rt, 5 min. [b] Yields are based on recovered starting material (see Supporting Information). 10−15% of cyclopentanol was also obtained. [c] Relative stereochemistry of the major diastereoisomer was determined by NOE experiments on a derivative (see Supporting Information). [d] Relative stereochemistry of the major diastereoisomer was confirmed by X-ray crystallography.

thus preventing collapse to the cyclopentanone and over-reduction to cyclopentanol products. Cyclization of a range of lactones **28**−**38** bearing a carboethoxy group α to the lactone carbonyl group gave cyclopentanone products **39**−**49** in moderate to high diastereoisomeric excess (7:1 dr to >95:5 dr) with no over reduction to the corresponding cyclopentanols (Table 1). The cyclization of substrates possessing aryl substituents on the alkene proceeded in excellent yield while substrates bearing unactivated alkenes also underwent efficient cyclization in some cases. In addition to preventing over-reduction, the α-ethoxycarbonyl group in lactones **28**−**38** promotes reduction of the lactone carbonyl by coordination to Sm(II) and improves the diastereoselectivity of the cyclizations through organization of the transition structures by coordination to the radical-anion intermediate (*vide infra*).

The relative stereochemistry of the major cyclization products was determined by NOE studies on a derivative of **44** (see Supporting Information) and by X-ray crystallographic analysis of **49**.[17]

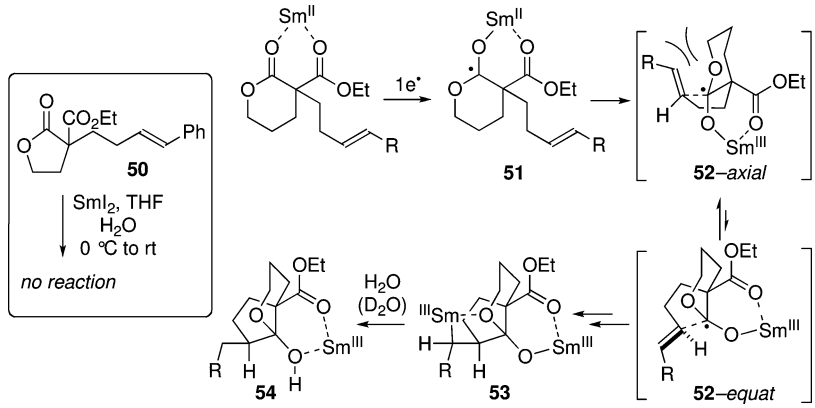
In line with our previous observations on the selectivity of the SmI_2-H_2O reagent system, no products resulting from reduction of the ethyl ester substituents were observed. In addition, five-membered lactone substrate **50** (Scheme 9) (analogous to six-membered lactone **30**) was recovered unchanged after exposure to SmI_2-H_2O, reaffirming the ring size-selectivity of lactone reduction and confirming that cyclization of these substrates is initiated by reduction of the lactone carbonyl rather than by reduction of the alkene.

A possible mechanism for the cyclizations is given in Scheme 9. Activation of the lactone by coordination to Sm(II) and electron-transfer generates radical anion **51** (cf. **21** in Scheme 7). Cyclization of equatorial radical **52**-*equat* through an electronically favored[18] *anti*-transition structure then gives organosamarium **53**, after reduction of the radical formed upon cyclization. Chelated hemiketal product **54** appears to be stable under the reaction conditions thus preventing collapse to the ketone and over reduction to give cyclopentanol products (Scheme 9).

(17) For X-ray crystallographic data and CCDC number, see Supporting Information.

(18) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

Scheme 9. Possible Mechanism of Lactone Cyclization Using SmI_2-H_2O



The reduction of **30** with SmI_2-D_2O gave **41-**D in 65% yield. Interestingly, **41-**D was obtained as a 7:1 diastereoisomeric mixture at the benzylic position, suggesting that one diastereoisomeric benzylsamarium predominates prior to protonation in the final stage of the reaction. The preference for one diastereoisomeric benzylsamarium may arise from coordination to the ring oxygen (cf. **53**, Scheme 9).

To examine the mechanistic proposal in Scheme 9, a kinetic study was performed to determine the role of each reactant. Rate studies were performed under pseudo-first-order conditions similar to those employed for 5-decanolide. Lactone ester **30** was chosen as a representative model substrate for kinetic studies and rates were obtained by monitoring the decay of the SmI_2-H_2O complex at 560 nm. Reduction of **30** was too fast to be studied under pseudo-first-order conditions at room temperature, so the rate studies were carried out at 0.0 ± 0.1 °C. A plot of observed rate constant (k_{obs}) with concentration for the reduction of lactone ester **30** is shown in Figure 4. The rate constant for the reduction of lactone ester **30** with SmI_2-H_2O was found to be $3.14 \pm 0.18 \times 10^1$ M^{-1} s^{-1}. The rate order of lactone ester **30** was 1.06 ± 0.01 (Figure 4) and the rate order of the SmI_2-H_2O complex was found to be 1, as determined by the fractional times method as well as the initial rates method (see Supporting Information).[10]

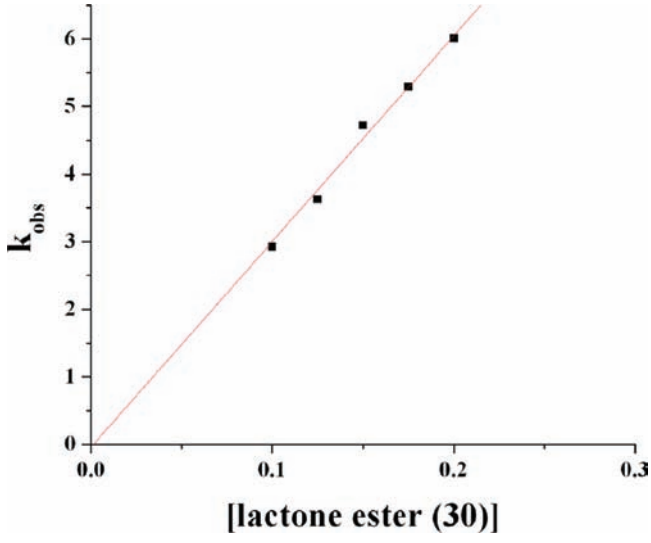


Figure 4. Plot of k_{obs} vs [lactone ester **30**]. SmI_2 = 10 mM, Water = 150 equiv, lactone ester **30** = 10−20 equiv, $T = 0.0 \pm 0.1$ °C. Rate constant = $3.14 \pm 0.18 \times 10^1$ M^{-1} s^{-1}.

A deuterium isotope study was carried out to further analyze the role of H_2O in this system. The rate of reduction of **30** was monitored using 150 equiv of D_2O in place of H_2O. This study provided a k_H/k_D value of 1.27. The impact of deuterium is likely the result of a secondary kinetic isotope effect due to differential coordination of H_2O and D_2O with Sm(II) as shown for 5-decanolide (*vide supra*).

These kinetic studies show that the initial electron transfer from the SmI_2-H_2O complex to substrate **30** is the rate limiting step as shown in eq 2. The significantly faster rate of reduction of **30** is likely due to two factors: (1) chelation of SmI_2 (formation of **51** in Scheme 9), and (2) rapid cyclization of the initially formed radical anion with the pendant alkene.

$$-\mathrm{d}[SmI_2-H_2O]/\mathrm{d}t = k[SmI_2-H_2O][\text{substrate}] \qquad (2)$$

Previous mechanistic studies have shown that esters β to a reducible functional group substantially increase the rate of reduction through a chelation-controlled pathway.[6b] More recent mechanistic studies have shown that ketones containing a pendant alkene are reduced 2−3 orders of magnitude faster than the parent substrate.[19] Overall, the present kinetic studies and previous mechanistic work on structurally similar systems are fully consistent with the mechanistic hypothesis set out in Scheme 9.

Conclusion

The first reduction of lactones to diols using SmI_2-H_2O has been carried out. The reagent system is selective for the reduction of lactones over esters, furthermore, it displays complete ring size-selectivity in that only 6-membered lactones are converted to the corresponding diols. Experimental and computational studies suggest the selectivity originates from the initial electron-transfer to the lactone carbonyl and that anomeric stabilization of the radical-anion formed is an important factor in determining reactivity. In addition to the selectivity of the reagent system, SmI_2 is commercially available, or convenient to prepare, easy to handle, operates at ambient temperature, and does not require toxic cosolvents or additives, making the transformation an attractive addition to the portfolio of reductions. Lactones can also be used in reductive C−C bond formation through cyclization of the radicals formed by one electron reduction, generating cyclic ketones (or ketals) often with high diastereoselectivity. The cyclizations constitute the

(19) Sadasivam, D. V.; Antharjanam, P. K. S.; Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2008**, *130*, 7228.

first examples of ester-alkene radical cyclizations in which the ester carbonyl acts as an acyl radical equivalent.

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Supporting Information Available: Experimental procedures, characterization data and ^{1}H and ^{13}C spectra, X-ray crystallographic data, details of calculations and rate studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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