

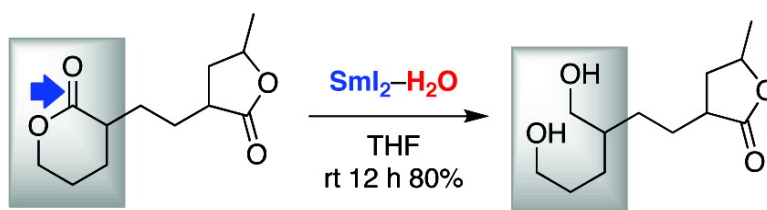
Communication

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A Ring Size-Selective Reduction of Lactones Using SmI_2 and H_2O

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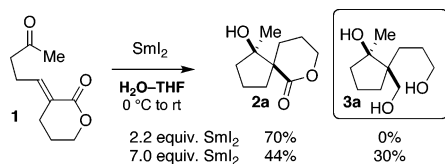
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The discovery of reagent systems that allow the selective manipulation of functional groups is crucial for advancements in synthesis. Of particular value are reagent systems that allow functional groups with apparently similar reactivities to be distinguished by the re-routing of transformations through less-conventional intermediates. Here we report that the reducing system $\text{SmI}_2\text{-H}_2\text{O}$ not only differentiates between the carbonyl groups of esters and lactones but also shows complete ring size-selectivity² for six-membered lactones.

During studies on a SmI_2 -mediated¹ stereoselective spirocyclization we found that the treatment of methyl ketone **1** with SmI_2 in THF, employing H_2O as a cosolvent, gave spirocyclic lactone **2a** as a single diastereoisomer in 70% yield.³ When an excess of SmI_2 was used, triol **3a** was obtained in 30% yield in addition to the expected lactone **2a** (Scheme 1). Although Kamochi and Kudo have described the reduction of carboxylic acids^{4a} and aryl esters^{4b} using $\text{SmI}_2\text{-H}_2\text{O}$ the reduction of unactivated aliphatic esters or lactones with SmI_2 has not been reported.

Scheme 1. Sequential Spirocyclization–Reduction Using $\text{SmI}_2\text{-H}_2\text{O}$



Treatment of lactone **2a** with $\text{SmI}_2\text{-H}_2\text{O}$ at room temperature gave triol **3a** in 71% (Figure 1) thus showing **2a** to be an intermediate in the production of **3a** from **1**. Spirocyclic lactones **2b** and **2c** also underwent reduction to give the corresponding triols in good yield. Importantly, the β -hydroxyl group present in these substrates was found not to be playing a crucial role⁵ in the activation of the lactone carbonyl group and less-functionalized six-membered lactones also underwent reduction to the corresponding diols with yields ranging from 72% to 90% (Figure 1).

We have carried out a series of experiments to illustrate the chemoselectivity observed with the $\text{SmI}_2\text{-H}_2\text{O}$ reagent system. Mixtures of esters and lactones were prepared and treated with $\text{SmI}_2\text{-H}_2\text{O}$. In all cases, no reduction products arising from esters or five, seven, and eight-membered lactones were observed while six-membered lactones were reduced smoothly (Scheme 2). Modified SmI_2 reagent systems employing additives (HMPA, DMPU, LiBr)¹¹ were also ineffective for the reduction of other lactones.

The enhanced reactivity of SmI_2 observed in our studies 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.⁶

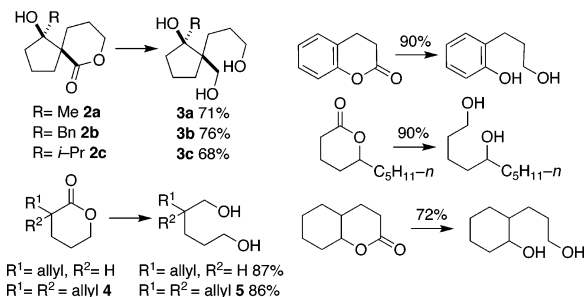
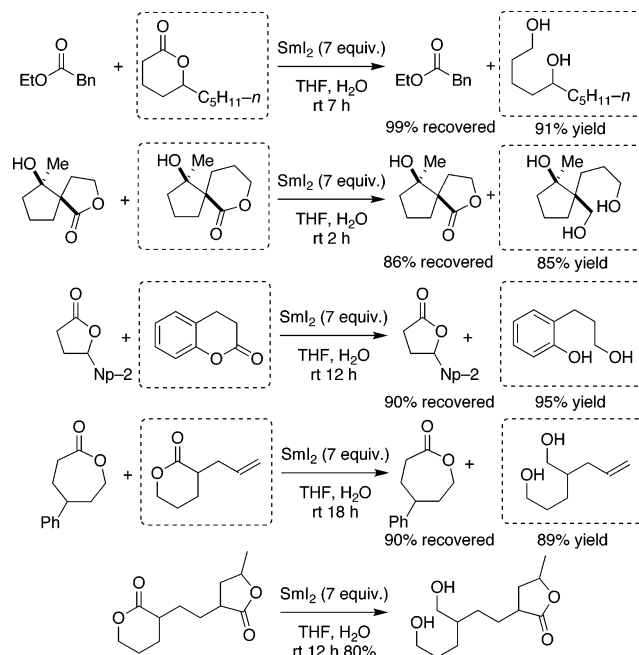


Figure 1. Reduction of six-membered lactones to the corresponding diols/triols with $\text{SmI}_2\text{-H}_2\text{O}$. Conditions: SmI_2 (7 equiv), THF, H_2O (150 equiv), room temp, 3–30 h.

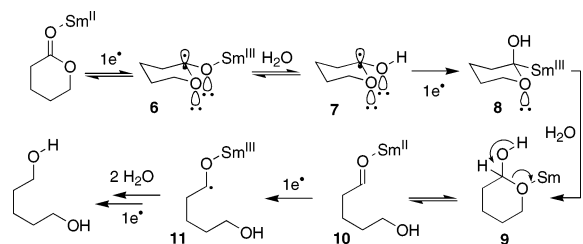
Scheme 2. Selective Reductions of Six-Membered Lactones



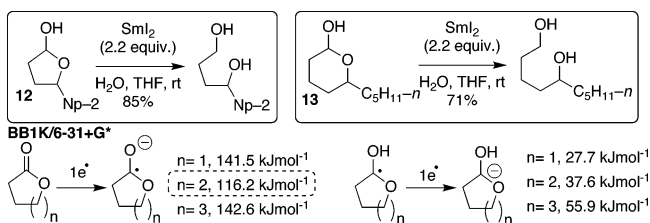
Flowers has since shown that H_2O produces larger rate enhancements than alcohols in the reduction of acetophenone with SmI_2 ,^{7a} and has used UV–vis spectra of SmI_2 with H_2O to illustrate that a unique reductant is formed at high concentrations of H_2O .^{7a,b} Flowers has also shown that the reduction potential of SmI_2 (–1.3 V) increases to a maximum of –1.9 V on the addition of up to 500 equiv of H_2O .⁷

We have carried out preliminary studies to elucidate the mechanism of the reduction and to understand the ring size-selectivity observed. The reduction of **2a** and **4** with $\text{SmI}_2\text{-D}_2\text{O}$ gave **3a-D,D** and **5-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.

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Scheme 3. Mechanism for the Reduction of Lactones Using $\text{SmI}_2\text{-H}_2\text{O}$ 

Activation of the lactone by coordination to Sm(II) and electron-transfer generates radical anion **6** that is then protonated.⁸ A second electron transfer generates carbanion **8** that is quenched by the H_2O cosolvent. Lactol **9** is in equilibrium with hydroxy aldehyde **10** and is reduced by a third electron-transfer from Sm(II) to give a ketyl radical anion **11**. A final electron-transfer from Sm(II) gives an organosamarium **11** 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). The complete selectivity of the reducing system for six-membered lactones over five, seven, and eight-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 **12** and **13**, intermediates in the reductions, are both rapidly reduced, in high yield, by $\text{SmI}_2\text{-H}_2\text{O}$ (Scheme 4).

Scheme 4. Investigating the Origin of the Selectivity

For six-membered lactones, we believe that reduction generates a radical anion intermediate **6** that is stabilized by interaction with the lone-pairs on both the endocyclic and exocyclic oxygens.⁹ Such interactions are known to be more pronounced in six-membered rings than in other, conformationally more labile, ring systems. It appears that the greater stability of the radical anion **6**, compared to analogous radicals formed from the reduction of five, seven, and eight-membered lactones, promotes the initial reduction step.¹⁰ This hypothesis is supported by the observation that 2-oxabicyclo[2.2.2]octan-3-one, where an intermediate radical-anion would be unable to adopt the chair conformation necessary for stabilization, is not reduced. Calculations lend further support and suggest the first electron-transfer to the lactone carbonyl is endothermic ($> 100 \text{ kJ mol}^{-1}$) in all cases. The reaction energy of this step for six-membered lactones, however, is calculated to be 116 kJ mol^{-1} ,

about $25\text{--}26 \text{ kJ mol}^{-1}$ lower than those involving five and seven-membered rings (Scheme 4).¹¹ The second electron transfer is lower in energy and similar for all systems, suggesting the first electron-transfer is the rate-determining step.

In summary, the first reduction of lactones to diols using $\text{SmI}_2\text{-H}_2\text{O}$ 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 six-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. In addition to the selectivity of the reagent system, SmI_2 is commercially available, or convenient to prepare,¹ easy to handle, and does not require any toxic cosolvents or additives, making the transformation an attractive addition to the portfolio of reductions. We are currently harnessing the intermediate radicals formed during the reduction and exploiting the ring size-selective transformation in new strategies for synthesis; for example, selective lactonization will be exploited to “switch on” the reactivity of one ester group in the presence of others.

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Supporting Information Available: Additional experiments, experimental conditions, characterization data, and details of calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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