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COMMUNICATION

A general electron transfer reduction of lactones using $\text{SmI}_2\text{-H}_2\text{O}^\ddagger$

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Herein we describe a strategy for the selective, electron transfer reduction of lactones of all ring sizes and topologies using $\text{SmI}_2\text{-H}_2\text{O}$ and a Lewis base to tune the redox properties of the complex. The current protocol permits instantaneous reduction of lactones to the corresponding diols in excellent yields, under mild reaction conditions and with useful chemoselectivity. We demonstrate the broad utility of this transformation through the reduction of complex lactones and sensitive drug-like molecules. Sequential electron transfer reactions and syntheses of deuterated diols are also described.

Samarium diiodide (SmI_2 , Kagan's reagent) is the most convenient-to-use single electron transfer reagent available in the laboratory.¹ Of particular note is the ability of SmI_2 to operate through either one-electron or two-electron reductive pathways, or complex pathways involving both modes of activation. These pathways often proceed with exquisite control of structure and stereochemistry and are frequently utilised to furnish bond disconnections that are impossible to achieve with other reagents.² Although SmI_2 -mediated transformations of aldehydes and ketones have been widely employed to access alcohols and to initiate reductive couplings to form challenging C–C bonds, the analogous reactions of esters and lactones have long been thought to lie outside the reducing range of SmI_2 .^{1,2}

Recently, impressive progress has been made in the mechanistic understanding, development and application of proton donors and Lewis bases as additives for use with SmI_2 .³ These additives have played a key role in expanding the chemistry of SmI_2 by fine-tuning the redox properties of the reagent to enable a particular transformation or to target a specific group of substrates. In 2008, we reported that activation of SmI_2 by excess H_2O facilitated the unprecedented reduction of six-membered lactones through the formation of unusual ketyl-type radical intermediates (Fig. 1a).⁴ Attempts to extend the reaction to other lactones (using H_2O or other proton sources as activating additives)

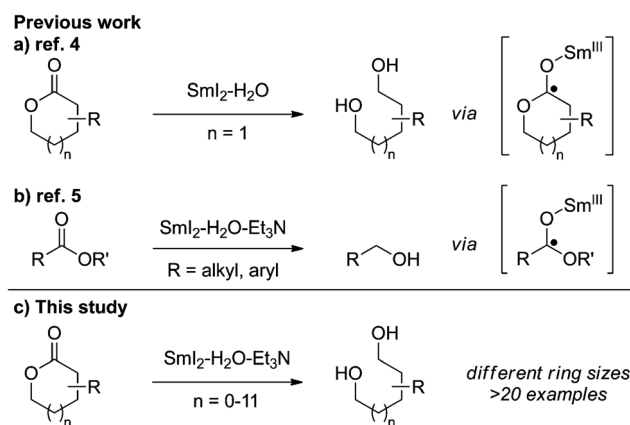


Fig. 1 Reduction of unactivated cyclic and acyclic esters using $\text{SmI}_2\text{-H}_2\text{O}$.

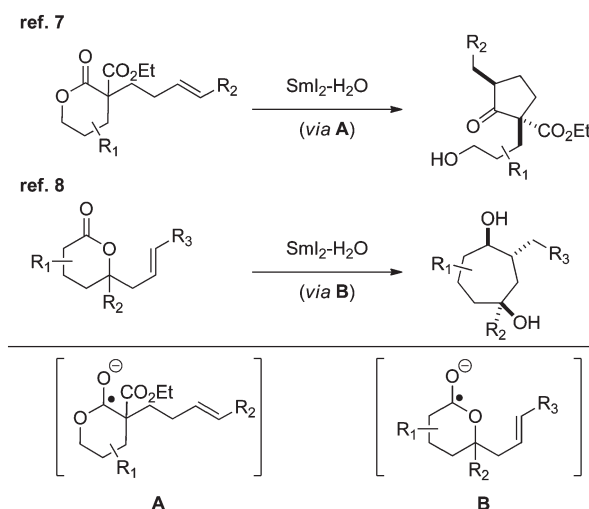


Fig. 2 Reductive cyclisations of ketyl radicals **A** and **B** generated in lactone reductions using $\text{SmI}_2\text{-H}_2\text{O}$.

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resulted in low or no reactivity. Our interest in new strategies for synthesis involving atypical intermediates accessed using SmI_2 and protic additives has also led us to develop the first reduction of aliphatic esters and acids using SmI_2 (Fig. 1b).⁵ Key to the success of this transformation was the finding that the addition of a Lewis base to $\text{SmI}_2\text{-H}_2\text{O}$ afforded a powerful single electron

Table 1 Reduction of unactivated lactones with $\text{SmI}_2\text{-H}_2\text{O-Et}_3\text{N}$

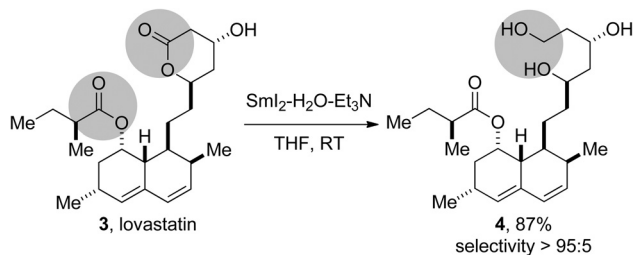
Entry	1	Lactone	Yield (%)	Entry	1	Lactone	Yield (%)
1	1a		97	9	1i		99
2	1b		98	10	1j		87
3	1c		93	11	1k		97
4	1d		87	12	1l		92
5	1e		99	13	1m		99
6	1f		85	14	1n		88
7	1g		92	15	1o		93
8	1h		90	16	1p		99

reductant that allowed efficient transformation of simple acyclic esters *via* acyl radical equivalents (Fig. 1b).

We hypothesised that a similar $\text{SmI}_2\text{-H}_2\text{O}$ -amine system could facilitate the direct manipulation of lactones that are unreactive to our previously reported $\text{SmI}_2\text{-H}_2\text{O}$ conditions (Fig. 1a).⁶ Specifically, capitalising on the finely-tuned redox properties of the $\text{SmI}_2\text{-H}_2\text{O}$ -amine complex, we reasoned that lactones of other ring sizes, lactones featuring steric hindrance close to the carbonyl group and conformationally-locked, bridged lactones could be selectively activated towards the reduction (Fig. 1c).^{1,2,5} We have already demonstrated that ketyl-type radicals derived from six-membered lactone templates readily participate in unprecedented, stereoselective reductive

couplings and radical cascades to afford complex molecular architectures (Fig. 2).⁷⁻⁹ Straightforward access to ketyl intermediates from other ring-sizes of lactone would significantly expand the scope of the reductive coupling of lactones using $\text{SmI}_2\text{-H}_2\text{O}$ in organic synthesis.

As predicted, the addition of triethylamine to $\text{SmI}_2\text{-H}_2\text{O}$ gave a reagent system capable of reducing a broad range of lactone substrates (Table 1).¹⁰ Six-, five-, seven-, eight- and sixteen-membered lactones (entries 1–7) and sterically-hindered substrates, whose reduction typically proved problematic with our original $\text{SmI}_2\text{-H}_2\text{O}$ system (see, Table ESI-1 in ESI†¹¹ for comparison between the two systems and additional examples), were amenable to the current protocol and provided the desired diols



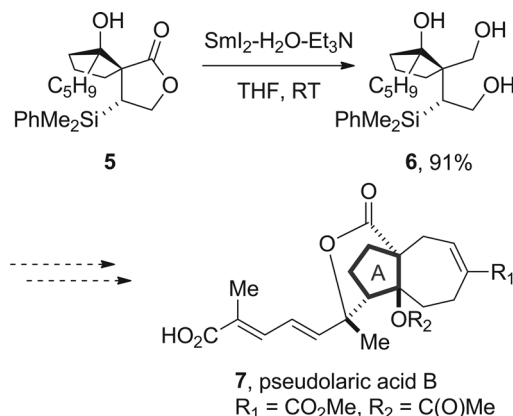
Scheme 1 Selective reduction of lovastatin using $\text{SmI}_2\text{-H}_2\text{O-Et}_3\text{N}$.

in good yields after short reaction times (entries 3, 8–9). To further explore the substrate scope, we tested the reduction of a variety of saturated and unsaturated lactones (entries 10–16). Importantly, the reduction shows good functional group tolerance: olefin and aryl-containing substrates (entries 5, 10–14), bicyclic lactones, and sterically-demanding lactones with more complex carbon skeletons (entries 15–16), all gave diol products in high yield. Notably, all reductions using $\text{SmI}_2\text{-H}_2\text{O-NEt}_3$ demonstrated considerably higher reaction rates and gave superior yields to reductions using our previously reported protocol with $\text{SmI}_2\text{-H}_2\text{O}$.

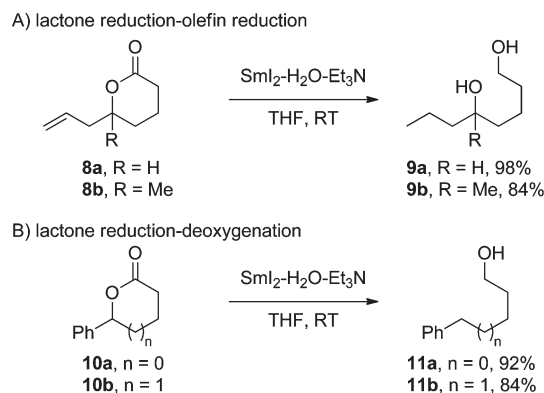
Mild reaction conditions and selectivity are important features of the reduction and make our method complementary to existing procedures.¹² To demonstrate the selectivity possible, we subjected lovastatin, a cholesterol-lowering drug bearing a six-membered lactone and an acyclic ester in a sensitive carbocyclic skeleton, to our reaction conditions (Scheme 1). We were delighted to find that the reduction using $\text{SmI}_2\text{-H}_2\text{O-Et}_3\text{N}$ proceeded with complete selectivity for the lactone moiety. No products resulting from alternative reduction pathways were detected. Furthermore, the mild conditions associated with the protocol permitted the isolation of the desired product in high yield.¹³

The ultimate test for any new method is its application in the synthesis of complex natural products.¹⁴ In this context, we have exploited lactone reduction using $\text{SmI}_2\text{-H}_2\text{O-Et}_3\text{N}$ in the selective synthesis of a model of the functionalized A ring of pseudolaric acid B (Scheme 2). Reduction of the 5-membered lactone **5**,¹⁵ a lactone prone to retro-aldol reaction, gave the diol **6** in an excellent 91% yield with full retention of stereochemical integrity. It is worth noting that conventional methods of reduction resulted only in decomposition products, demonstrating the potential of our method for the manipulation of sensitive molecules.

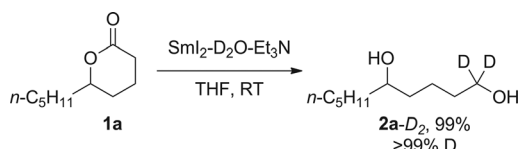
We next explored the potential of using lactones as substrates for sequential processes mediated by electron transfer (Scheme 3). Although tandem, one-pot and sequential reactions proceeding *via* ionic and radical mechanism have attracted considerable interest in the last decade, tandem reactions based on electron transfer processes and involving two different functional groups have received less attention.^{16,17} The one-pot reduction of multiple functional groups has obvious potential for streamlining synthetic routes. For example, lactones **8** (containing unactivated olefins) and lactones **10** (bearing aromatic rings at the δ -position) underwent sequential reduction to give fully saturated diols (after lactone and olefin reduction) and primary alcohols (after lactone reduction and deoxygenation), respectively. These one-pot reactions provide attractive alternatives to multi-step procedures.¹⁸



Scheme 2 Lactone reduction in the synthesis of a model of the A ring of pseudolaric acid B.



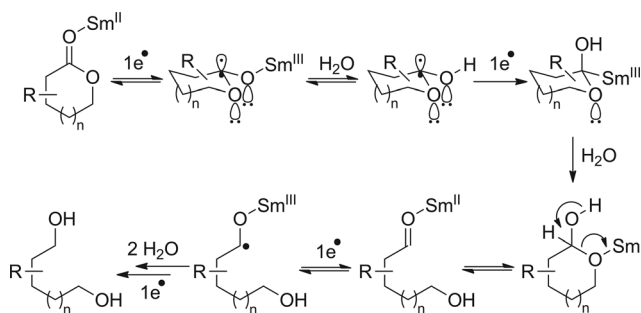
Scheme 3 Sequential reactions of lactones using $\text{SmI}_2\text{-H}_2\text{O-Et}_3\text{N}$.



Scheme 4 Synthesis of deuterated alcohols from lactones using $\text{SmI}_2\text{-D}_2\text{O-Et}_3\text{N}$.

Since the reduction involves aqueous conditions, with $\text{SmI}_2\text{-H}_2\text{O}$ playing a key mechanistic role in the protonation of anions formed during the course of the reaction, in a preliminary study, we have investigated the potential of using deuterium oxide as an inexpensive and non-toxic deuterium source (Scheme 4).¹⁹ As expected, the corresponding deuterated diol **2a-D₂** was formed from **1a** in quantitative yield, with >99% deuterium incorporation, establishing a new approach to the introduction of deuterium at the α -position of aliphatic alcohols.

A plausible mechanism for the lactone reduction is presented in Scheme 5. Activation of the lactone carbonyl by coordination to $\text{SmI}_2\text{-H}_2\text{O}$ and electron transfer generates the first radical anion that is then protonated. A subsequent series of electron and proton transfers gives a final anionic intermediate that is protonated by H_2O to furnish diol. The first ketyl radical intermediate generated by electron transfer from SmI_2 to the lactone carbonyl group has the potential to be utilised in reductive couplings (see Fig. 2).



Scheme 5 Mechanism of lactone reduction using $\text{SmI}_2\text{-H}_2\text{O-Et}_3\text{N}$.

Preliminary observations on the mechanism and features of lactone reduction, are listed below (see, ESI ‡ for details¹¹): (a) A primary kinetic isotope effect $k_{\text{H}}/k_{\text{D}}$ of 1.2 was determined for six-membered lactone **1a** indicating that proton transfer is not involved in the rate limiting step. (b) As illustrated in Scheme 4, the reduction of **1a** with $\text{SmI}_2\text{-D}_2\text{O}$ gave **2a-D**₂, suggesting that anions are generated and protonated by H_2O during a series of single electron transfers. (c) Complete selectivity for lactone **1a** is observed in competition experiments with primary aliphatic esters suggesting that initial electron transfer is rate-limiting. (d) The reaction of six-membered lactone **1a** is instantaneous (reaction complete in <30 s). (e) The relative rates of the reduction of 5-, 6-, 7-membered lactones are: $6 > 7 > 5$. (f) Both additives (H_2O and amine) are required for the reaction, with no reactivity observed in the absence of water and insignificant conversions detected in the absence of amine. (g) The optimal ratio of $\text{SmI}_2\text{-H}_2\text{O-amine}$ required to form the active complex is 1 : 1 : 2. This is consistent with literature precedent.¹⁰ (h) Amines other than Et_3N can be used in the reaction to deliver the products in comparable yields. (i) In agreement with our previous observations, water is the proton source of choice when compared to the use of other protic co-solvents known to strongly coordinate to SmI_2 .

In summary, we have introduced an approach for the selective reduction of lactones of all sizes and topologies using $\text{SmI}_2\text{-H}_2\text{O}$ as a single electron reductant. The value of this transformation has been highlighted by the selective manipulation of complex and/or sensitive molecules and by the orchestration of one-pot sequential reactions. We expect that this method will be of broad utility for the selective reduction of lactones under mild conditions. Application of the radical-anion intermediates formed in the reduction in reductive C–C bond formation will be described shortly.

Acknowledgements

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