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Substrate-Directable Electron Transfer Reactions. Dramatic Rate Enhancement in the Chemoselective Reduction of Cyclic Esters Using SmI_2-H_2O: Mechanism, Scope, and Synthetic Utility

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Supporting Information

ABSTRACT: Substrate-directable reactions play a pivotal role in organic synthesis, but are uncommon in reactions proceeding via radical mechanisms. Herein, we provide experimental evidence showing dramatic rate acceleration in the Sm(II)-mediated reduction of cyclic esters that is enabled by transient chelation between a directing group and the lanthanide center. This process allows unprecedented chemoselectivity in the reduction of cyclic esters using SmI_2-H_2O and for the first time proceeds with a broad substrate scope. Initial studies on the origin of selectivity and synthetic application to form carbon−carbon bonds are also disclosed.

The use of directing groups is a powerful strategy to control the enantio- and diastereoselectivity as well as site selectivity of valuable synthetic reactions by providing highly ordered transition states through multiple-point substrate−reagent interactions.[1] Since the pioneering work reported by Henbest in 1957,[2] considerable effort has been devoted to the development of substrate-directable reactions that proceed via closed-shell pathways.[3] However, considerably fewer studies have employed directing groups in an alternative mechanistic manifold involving sequential electron transfers using low-valent metal reagents, including Sm(II) reductants (Figure 1A).[4] In this regard, several elegant approaches to control stereochemical aspects of electron transfer steps exist;[5] however, a strategy based on a chelate-controlled activation of inert functional groups toward productive electron transfer by coordination of low-valent, often highly oxophilic, hard Lewis acidic metals remains vastly unexplored.[6,7]

Herein, we provide experimental evidence showing dramatic rate acceleration in the Sm(II)-mediated reduction of cyclic esters that is enabled by transient chelation between directing groups and the lanthanide center.[8] Using kinetic experiments we quantify the effect of directing groups on the rate of the electron transfer in a set of cyclic esters previously unreactive toward the reagent system (Figure 1B) and establish, for the first time, that inert functional groups can be activated toward highly chemoselective electron transfer from a SmI_2 complex[9] by the use of a directing group effect (Figure 1C).

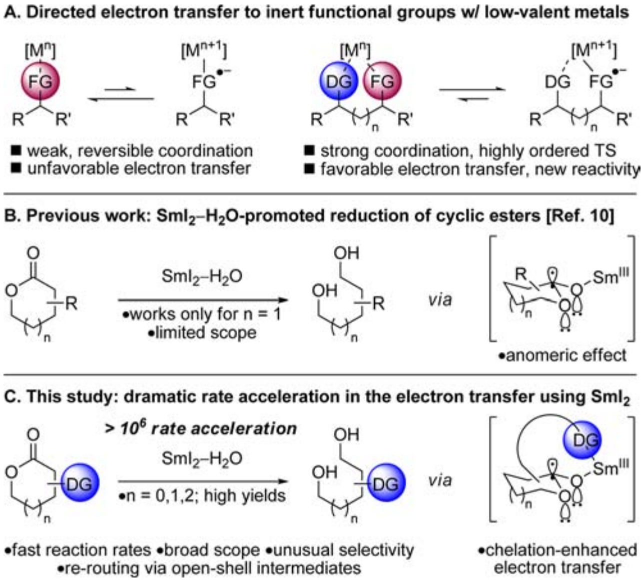

Figure 1. (a) Directing group strategy toward electron transfer. (b) Previous work: chemoselective reduction of lactones with SmI_2. (c) This study: rate acceleration in the chelation-enabled electron transfer to cyclic esters using SmI_2-H_2O.

Recently, we reported the reduction of cyclic esters using SmI_2.[10] Prior to this work it had been thought that simple aliphatic esters were outside the reducing range of SmI_2.[6,7] The reaction showed unprecedented chemoselectivity in that the SmI_2-H_2O complex was completely selective for six-membered lactones over other classes of esters and lactones, which was ascribed to the anomeric stabilization of the ketyl radical intermediate in a six-membered ring system (Figure 1B).[11] However, the reaction was very limited in scope in that it tolerated only sterically accessible six-membered lactones. When expanding the scope of this transformation, we hypothesized that positioning a suitable directing group within close proximity to the formed radical anion would stabilize this intermediate by chelation and facilitate the electron transfer in the rate determining step of the reaction. Importantly, we recognized that, if successful, this process would constitute one of the first substrate directable electron transfer reactions,

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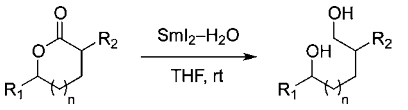
which could deliver unique chemoselectivity impossible to achieve by existing one- or two-electron mechanisms.

In view of the paucity of mechanistic studies on the role of directing groups in electron transfer processes, we began our examination by determining the effect of various directing groups on the rate of the reduction of five-, six-, and seven-membered lactones (Table 1). Experiments were carried out using stopped-flow spectrophotometry under pseudo-first-order conditions. Rates were obtained by monitoring the decay of the SmI_2-H_2O complex at 560 nm. Plots of the observed rate constants against concentration for the reduction of cyclic esters are shown in the Supporting Information (SI).

Table 1. Observed Rate Constants and Reaction Orders for the Reduction of Lactones Using SmI_2-H_2O[a]



entry	n	R_1, R_2	k [M^{-1} s^{-1}]	rate order	
				lactone	SmI_2
1	0	H, H	$<1.0 \times 10^{-5}$	–	–
2	1	H, H	0.014 ± 0.001	0.8 ± 0.03	1.0
3	2	H, H	3.0×10^{-4}	–	–
4	0	H, CO_2Et	419 ± 45	1.1 ± 0.1	1.0
5	1	H, CO_2Et	610 ± 10	1.0 ± 0.1	1.0
6	2	H, CO_2Et	0.91 ± 0.05	1.3 ± 0.1	1.0
7	0	H, CO_2*t*-Bu	0.32 ± 0.03	1.0 ± 0.1	1.0
8	0	H, C(OH)R	0.34 ± 0.03	2.2 ± 0.2	1.0
9	0	H, CONHCy	$>1.0 \times 10^{4}$	–	–
10	1	H, Ph	0.012 ± 0.001	0.9 ± 0.1	1.0
11	1	C_5H_{11}, H	0.007 ± 0.001	1.1 ± 0.1	1.0

[a] Conditions: $[SmI_2] = 10$ mM; $H_2O = 150$ equiv; lactone = 10–50 equiv, $T = 30.0 \pm 0.1$ °C. Entry 8, R = C_5H_{10}. See SI for full experimental details.

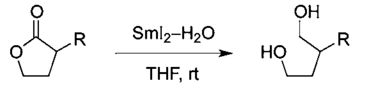
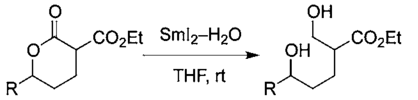
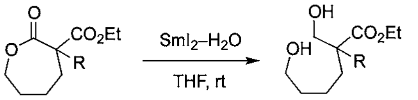
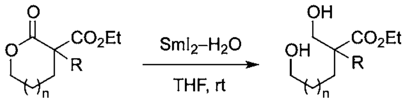
The reduction of a simple six-membered lactone (entry 2, $k = 0.014$ M^{-1} s^{-1}) was found to be much faster than that of the corresponding five- and seven-membered lactones (entries 1 and 3, $k < 0.1 \times 10^{-5}$ M^{-1} s^{-1}, lower limit value, and $k = 3 \times 10^{-4}$ M^{-1} s^{-1}, respectively). In agreement with our previous findings,[10,11] these rate constants can be explained by anomeric stabilization of the radical anions. The slow rate for reduction of five- and seven-membered lactones prohibits their use in chemoselective Sm(II)-mediated transformations (the natural decay of SmI_2 of 4.4×10^{-4} s^{-1}).[8] *Remarkably, dramatic rate acceleration ranging from 4 to 7 orders of magnitude is observed in all three ring systems by using an ester directing group in the α-position of lactone substrates* (entries 4–6).[12] The acceleration is consistent with efficient chelation of the SmI_2-H_2O reductant. Intriguingly, it appears that a high concentration of water does not prohibit the Sm(II) chelation (*vide infra*), although previous studies have shown that water displaces Lewis basic oxygens from the coordination sphere of Sm(II).[13] A range of other directing groups results in a very significant acceleration of the rate of the reduction, from 4 to 9 orders of magnitude, demonstrating that the effect is not limited to simple esters (entries 7–9). The reduction of an α-phenyl-substituted lactone (entry 10) demonstrates that chelation of Sm(II) is the major factor contributing to the rate enhancement. The low rate of reduction of 5-alkyl-substituted lactone (entry 11, ca. 2 times slower than that of the unsubstituted analogue) suggests that the reaction is sensitive to steric hindrance around the lactone carbonyl group. Finally, the rate constants measured for several α-aryl-containing substrates (see SI for details and additional discussion) confirm the importance of steric factors in the coordination of Sm(II) and further demonstrate the unique properties of SmI_2-H_2O over other Sm(II) reducing systems.[9]

The rate orders of substrates and SmI_2 were determined by the fractional times method and/or the initial rates method. Previous studies demonstrated that in a related reduction of 5-decanolide under the same experimental conditions the rate order of H_2O is zero.[11a] In the present study, we found that, in all cases, the rate order of SmI_2 was one. The substrate rate order studies showed the rate order of one (within experimental error) for all studied substrates except for the alcohol-containing ester, which showed the rate order of two (entry 8, within experimental error). The obtained rate orders are consistent with the proposed mechanism for the reduction of cyclic esters using SmI_2-H_2O.[11] The rate order of two for the alcohol-containing ester most likely results from the formation of a dimeric SmI_2–alcohol complex with the alcohol serving as one of the Sm(II) ligands.[12,13]

Having identified the effect of directing groups, we investigated the synthetic scope of the reduction using SmI_2-H_2O (Table 2). Typically a 2-fold excess of reagent was used to ensure that the reactions were complete. In general, the substrates were selected to demonstrate the ring-size chemoselectivity of the process, emphasize functional group tolerance, and probe the ease of reduction of five- to seven-membered lactones that could potentially be used as radical precursors for stereocontrolled C–C bond formation.[11a–f] In the event, a wide range of lactone-bearing ester and amide directing groups furnished the corresponding diols in good to excellent yields (entries 1–15). Importantly, over-reduction of acyclic directing groups was not observed under the reaction conditions, thus demonstrating the high chemoselectivity of the process. Moreover, the method tolerates functional groups that can be reduced under single electron transfer conditions, including aromatic rings, benzyl ethers, nitriles, acetates, and terminal olefins.[7d] Remarkably, under these reaction conditions, the reductive 5-exo cyclization is not observed (entries 13–15), showing that the directed reduction of acyl-type radicals is rapid.[14] Overall, these synthetic studies demonstrate that highly chemoselective electron transfer to lactones of ring sizes other than six can be readily achieved and open the door to the use of a wide range of cyclic esters in radical transformations with the SmI_2-H_2O reagent.

We have carried out initial studies to elucidate the mechanism of the reduction (see SI). (1) The reduction of six-membered lactone **1e** with limiting SmI_2 gives the corresponding lactol (86%, 52:48 dr). (2) The reduction of **1e** with SmI_2-D_2O gives the lactol with >98% D^1 incorporation (96.0% D^2 incorporation in the reduction of **1f**), indicating that anions are protonated during a series of electron transfer steps.[11a,15,16] (3) The kinetic isotope effects for the lactol and diol formation ($k_H/k_D = 1.27 \pm 0.1$ and 1.24 ± 0.1, respectively) suggest that proton transfer is not involved in the rate determining step of the reaction. (4) In the reduction of 5-decanolide under various SmI_2 conditions lactol is not detected, suggesting that α-ester stabilizes the tetrahedral intermediate. (5) The reaction shows full chemoselectivity over alkyl iodides and aryl esters[7e] (favoring the cyclic ester) as well as aliphatic ketones and aldehydes (favoring the latter).

Table 2. Chelation-Enabled Reduction of Lactones Using SmI_2-H_2O[a]

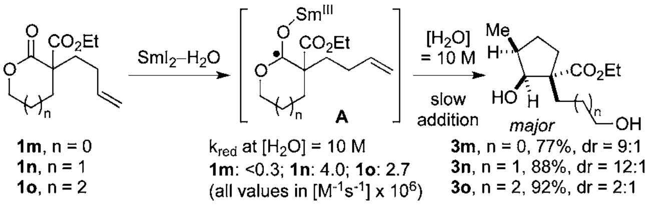
entry	lactone	diol	yield, %
			
1	**1a**, R = CO_2Et	**2a**	83
2	**1b**, R = CO_2t-Bu	**2b**	87
3[b]	**1c**, R = C(O)NHCy	**2c**	94
4[b]	**1d**, R = C(O)NHPh	**2d**	77
			
5	**1e**, R = H	**2e**	96
6	**1f**, R = C_5H_{11}	**2f**	72
7	**1g**, R = Ph	**2g**	68
			
8	**1h**, R = H	**2h**	87
9	**1i**, R = Bn	**2i**	85
10	**1j**, R = $(CH_2)_3CN$	**2j**	92
11	**1k**, R = $(CH_2)_4OAc$	**2k**	95
12	**1l**, R = $(CH_2)_4Ph$	**2l**	99
			
13	**1m**, n = 0, R = $(CH_2)_2CH{=}CH_2$	**2m**	79
14	**1n**, n = 1, R = $(CH_2)_2CH{=}CH_2$	**2n**	87
15	**1o**, n = 2, R = $(CH_2)_2CH{=}CH_2$	**2o**	88

[a]Conditions: SmI_2 (6–8 equiv), THF, H_2O, 23 °C. [b]C_7H_{15} derivatives at C_5 were used. See SI for full experimental details.

Importantly, the SmI_2-H_2O system has been shown to tolerate other functional groups that are incompatible with Sm(II)-Lewis bases.[6,7] (6) The use of water is critical for the observed reactivity (no reaction is observed in the absence and at low concentration of water). (7) Other additives (LiCl, HMPA, MeOH, amine/Et_3N) do not promote the reaction efficiently, which is consistent with the coordination of water to Sm(II) to enhance the redox potential of the reagent and to stabilize the formed radical anion.[13]

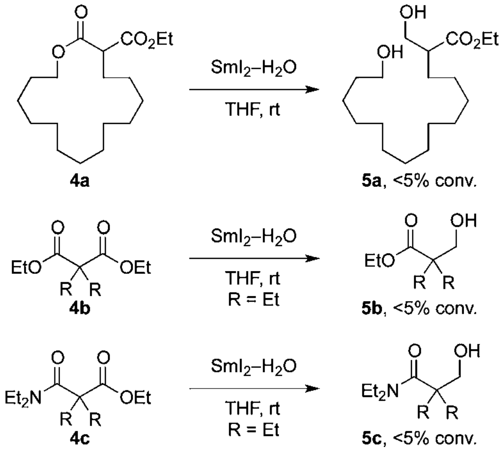
It is particularly noteworthy that the radical intermediates formed in the first electron transfer can be exploited in radical cyclizations by simply modifying the reaction conditions (slow addition protocol, see SI) (Scheme 1). Cyclic esters having five- to seven-membered rings undergo efficient radical cyclization to give cyclopentanols containing three contiguous stereocenters in good yields and in general high diastereoselectivities.[17] Moreover, by approximating the rate constant for cyclization of the 5-hexenyl radical (2.3×10^5 s^{-1})[14] we were able to estimate the relative rate constant for the reduction of acyl-type radicals **A** at the 10 M concentration of H_2O (Scheme 1). The obtained values are in good agreement with the anomeric stabilization of ketyl-type radicals in these systems and demonstrate that a plethora of reductive cyclizations (cf. reductions) can be achieved in these systems.

Scheme 1. Reductive Cyclizations of Lactones Using SmI_2-H_2O Enabled by the Directing Group Effect

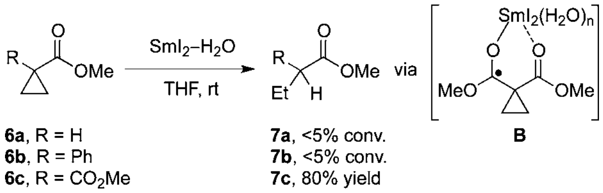


Finally, we have preliminary results pertaining to the origin of chemoselectivity in the directed reduction of cyclic esters using SmI_2-H_2O (Schemes 2 and 3). The reduction of a flexible 16-membered lactone under the same reaction conditions was unproductive, demonstrating that the release of strain may play a role in the chemoselectivity of the reaction (Scheme 2). The reduction of activated ester groups in acyclic diesters and malonate monoamides was not observed under the reaction conditions despite their well-established capacity to accept electrons from SmI_2–THF systems (Scheme 2).[18] Finally, the reaction of a series of radical clocks with SmI_2-H_2O points to the crucial role of directing groups to stabilize the formed radical anions (Scheme 3),[19,20] which is in agreement with the kinetic rate studies and the proposed mechanism.

Scheme 2. Investigating the Origin of Selectivity in the Reduction of Lactones Using SmI_2-H_2O



Scheme 3. Investigating the Directing Group Effect on the Stability of Ketyl-Type Radicals



In summary, the results presented herein demonstrate that the presence of a suitably placed directing group dramatically accelerates the rate of the reduction of cyclic esters with SmI_2–

H_2O. Remarkably, the reagent system is fully chemoselective for the reduction of lactones over esters and has been exploited in reductive carbon−carbon bond formation to rapidly build-up molecular complexity. Importantly, the current study is one of the few examples of substrate-directable reactions proceeding via sequential one-electron mechanisms. We believe that these findings will have an important impact for the activation of inert functional groups via open-shell reaction pathways. Application of this strategy to other substrate-directable electron transfer reactions is underway in our laboratory and will be described shortly.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization data, and details of rate studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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