

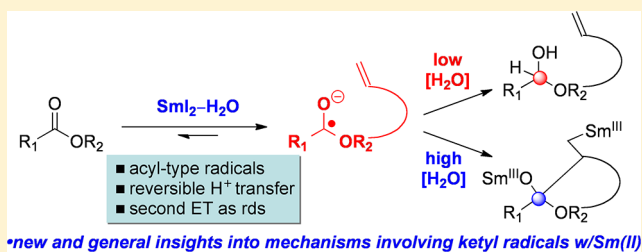
# Ketyl-Type Radicals from Cyclic and Acyclic Esters are Stabilized by $\text{SmI}_2(\text{H}_2\text{O})_n$ : The Role of $\text{SmI}_2(\text{H}_2\text{O})_n$ in Post-Electron Transfer Steps

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**S** Supporting Information

**ABSTRACT:** Mechanistic details pertaining to the  $\text{SmI}_2$ - $\text{H}_2\text{O}$ -mediated reduction and reductive coupling of 6-membered lactones, the first class of simple unactivated carboxylic acid derivatives that had long been thought to lie outside the reducing range of  $\text{SmI}_2$ , have been elucidated. Our results provide new experimental evidence that water enables the productive electron transfer from  $\text{Sm(II)}$  by stabilization of the radical anion intermediate rather than by solely promoting the first electron transfer as originally proposed. Notably, these studies suggest that all reactions involving the generation of ketyl-type radicals with  $\text{SmI}_2$  occur under a unified mechanism based on the thermodynamic control of the second electron transfer step, thus providing a blueprint for the development of a broad range of novel chemoselective transformations via open-shell electron pathways.



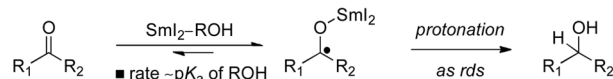
## INTRODUCTION

Water is a critical additive used to activate  $\text{SmI}_2$  toward numerous fully chemoselective reductions and reductive cyclizations involving ketyl-type radicals to furnish primary alcohols and complex carbocyclic ring systems with myriad applications in organic synthesis and selectivity unattainable using other reagents operating via either one- or two-electron pathways (Figure 1).<sup>1–3</sup> Historically, water has been used as a proton donor to enhance the regio-, chemo-, and diastereoselectivity of the reductive transformations mediated by  $\text{Sm(II)}$ .<sup>4</sup> The seminal mechanistic reports by Curran,<sup>5</sup> Flowers,<sup>6</sup> and Hoz<sup>7</sup> suggested that coordination of water to  $\text{Sm(II)}$ ,<sup>5</sup> increase of the redox potential,<sup>6b</sup> ligand displace-

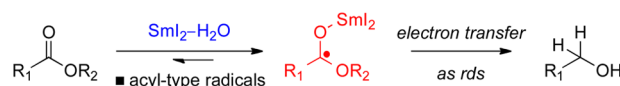
ment,<sup>6c</sup> and efficient protonation of radical anions<sup>7</sup> might play a crucial role in some of these transformations.<sup>8</sup> Although extensive empirical synthetic studies have shown that water is instrumental in enabling a broad range of valuable  $\text{Sm(II)}$ -mediated reactions,<sup>9</sup> the mechanistic details of the role of the water additive on the stabilization of the formed ketyl radicals,<sup>10</sup> a fact which determines the facility of electron transfer steps and dictates the reaction pathways,<sup>11</sup> are poorly understood. Moreover, there are contradicting reports regarding the mechanism of  $\text{Sm(II)}$ -mediated reactions of carbonyl groups,<sup>2</sup> which prevents a generalization of mechanism for the formation and reactivity of ketyl-type radicals using divalent lanthanides<sup>12</sup> and hampers the rational development of novel transformations mediated by the extremely useful  $\text{SmI}_2$  reagent.<sup>13</sup>

To understand the role of water in  $\text{Sm(II)}$ -mediated reductions, we examined in detail the mechanism of the reduction and cyclization of 6-membered lactones,<sup>14</sup> substrates which had long been thought to lie outside the reducing range of  $\text{SmI}_2$ <sup>15</sup> and have been shown to react with  $\text{SmI}_2$  only upon activation of the reagent with  $\text{H}_2\text{O}$ <sup>16</sup> (Scheme 1A). As a result of these studies, we report herein experimental evidence showing that (1) water enables the productive electron transfer from  $\text{Sm(II)}$  by enhancing the stabilization of the intermediate radical anion rather than solely promoting the first electron transfer step as we originally proposed;<sup>14a,b</sup> (2) there is a direct and nonlinear correlation between the rate of lactone reduction and the concentration of water, in contrast to what we originally proposed;<sup>14b</sup> (3) proton transfer is not involved in the rate-determining step of the reduction of lactones, and the same is also true for the reduction of simple ketones and

**A.** Previous studies: reduction of ketones/aldehydes



**B.** This work: reduction and reductive cyclization of esters



- +rate of the reduction and stability of ketyl radical is directly related to  $[\text{H}_2\text{O}]$
- +2nd electron transfer is the rds in reductions and reductive cyclizations
- +new mode of reactivity of lactones via C–O bond scission to carboxylic acids
- +proton transfer not the rds in reactions of simple ketones and aldehydes
- +unifying mechanism for reactions involving ketyl radicals using  $\text{SmI}_2(\text{ROH})_n$

**guidelines for the use of  $\text{SmI}_2$ - $\text{H}_2\text{O}$  complexes in the generation of ketyl radicals**

**Figure 1.** (a) Proposed mechanism for  $\text{SmI}_2$ -mediated electron transfer to aldehydes and ketones. (b) This study: mechanism of chemoselective electron transfer to esters using the  $\text{SmI}_2$ - $\text{H}_2\text{O}$  reagent.

Received: April 11, 2014

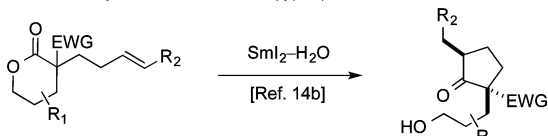
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Scheme 1. Previous Studies on the Reduction and Reductive Cyclization of Lactones using  $\text{SmI}_2\text{-H}_2\text{O}$ 

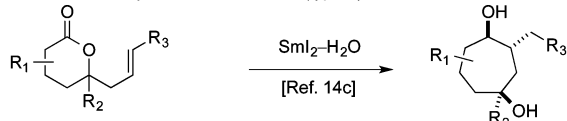
## A. Selective reduction of six-membered lactones



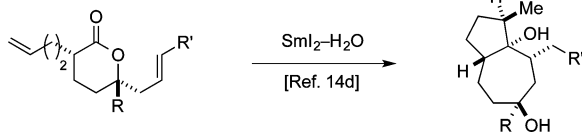
## B. Reductive radical cyclization of lactones (type I)



## C. Reductive radical cyclization of lactones (type II)



## D. Reductive radical cyclization cascades

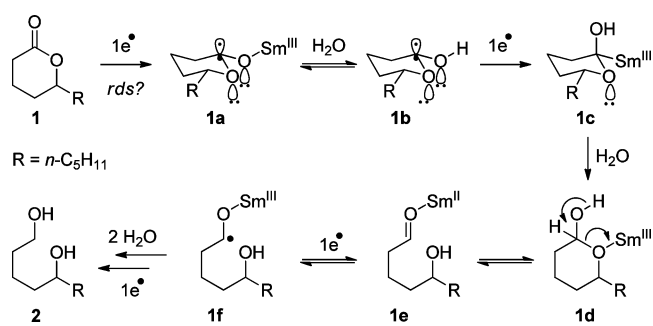


aldehydes, in contrast to what has been previously proposed,<sup>6a,8c</sup> (4) the rate of radical cyclizations mediated by  $\text{Sm(II)-H}_2\text{O}$  is directly related to the concentration of water; (5) second electron transfer is the rate-determining step in reductions and reductive cyclizations mediated by  $\text{SmI}_2\text{-H}_2\text{O}$ . Moreover, we reveal a novel mode of reactivity of cyclic esters involving a radical C–O bond scission mechanism. Overall, these results demonstrate that the concentration of water is instrumental for achieving high chemoselectivity in reductive processes mediated by the  $\text{SmI}_2\text{-H}_2\text{O}$  system and strongly imply that reactions involving generation of ketyl radicals under  $\text{Sm(II)}$  conditions occur under a unified mechanism based on thermodynamic control of the second electron transfer step. Most importantly, this study sets the stage for application of  $\text{SmI}_2\text{-H}_2\text{O}$  complexes to rationally design and exploit ketyl-type radicals formed from an array of carbonyl group precursors.

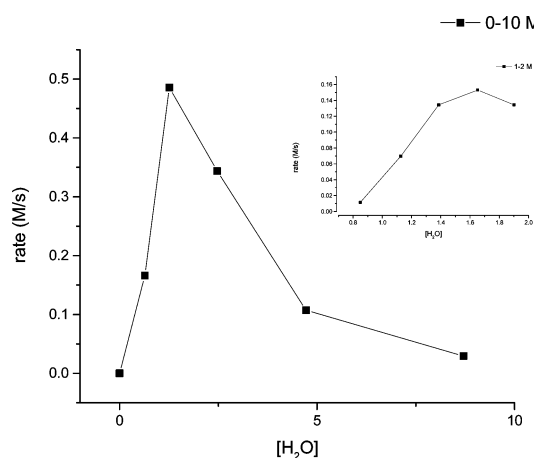
## RESULTS AND DISCUSSION

Recently, we reported that  $\text{H}_2\text{O}$  activates  $\text{Sm(II)}$  to allow the first reduction of unactivated 6-membered lactones thus enabling fully chemoselective electron transfer processes,<sup>14</sup> including reductive cyclizations<sup>14b</sup> and reductive cascades<sup>14c</sup> proceeding via unusual ketyl-radical intermediates generated directly from the lactone carbonyl groups (Scheme 1A–D). Although we originally proposed a mechanism that involved activation of the  $\text{Sm(II)}$  reagent by water to enable the rate determining initial electron transfer to the lactone carbonyl group (Scheme 2) aided by anomeric stabilization of the ketyl radical **1a** and featuring zero order dependence on water concentration,<sup>14a,b</sup> after continuous probing of the reaction pathway, several observations suggested that an alternative mechanism might be operative.

To elucidate the role of water in the  $\text{SmI}_2$ -mediated reduction of 6-membered lactones, a series of kinetic rate studies were performed. 5-Decanolide was selected as a model substrate because its rate of reduction is in a convenient range for kinetic studies and there is ample literature precedent for

Scheme 2. Proposed Mechanism of the Reduction of Lactones Using  $\text{SmI}_2\text{-H}_2\text{O}$ 

$\text{Sm(II)}$  reduction conditions available for this substrate.<sup>14b</sup> We started our investigation by monitoring the reduction of **1** with increasing concentrations of water (Figure 2). Previously, we



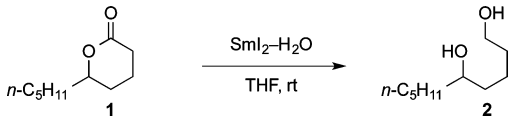
**Figure 2.** Plot of concentration of  $\text{H}_2\text{O}$  versus  $k_{\text{obs}}$  for the reduction of **1**.  $[\text{H}_2\text{O}] = 0\text{--}10\text{ M}$  (0–800 equiv).  $M = \text{mol/L}$ . The inset (independent runs) shows the same up to  $[\text{H}_2\text{O}] = 2\text{ M}$ .  $\text{SmI}_2 = (6\text{ equiv})$ , ester = (1 equiv),  $T = 23\text{ }^\circ\text{C}$ .

have shown that the reduction of 5-decanolide with  $\text{SmI}_2\text{-H}_2\text{O}$  is zero order in water within the concentration range of 100–180 equiv of water with respect to  $[\text{SmI}_2]$ .<sup>14b</sup> Previous studies have determined that water exhibits an unusual high affinity for  $\text{SmI}_2$  and displaces THF from the lanthanide(II) coordination sphere at low concentrations.<sup>8g,6b</sup> This range of concentrations was found to activate  $\text{Sm(II)}$  toward the lactone reduction, which is in agreement with the thermodynamic increase of the redox potential of  $\text{Sm(II)}$  in the ground state by the coordination of water ( $\text{SmI}_2$ :  $-1.5\text{ V vs Ag/AgNO}_3$  in THF;  $\text{SmI}_2(\text{H}_2\text{O})_n$ :  $-1.9\text{ V vs Ag/AgNO}_3$ ,  $n = 500\text{ equiv}$ , THF).<sup>6b</sup> In an extended study, we now found a nonlinear rate dependence on  $\text{H}_2\text{O}$  within the concentration range of 0–100 equiv with respect to  $[\text{SmI}_2]$  in the reduction of **1** (Figure 2). At lower concentrations (up to 25 equiv, 1.5 M) the rate was found to increase linearly with a slope, which is consistent with saturation of  $\text{Sm(II)}$  (15–25 equiv, 0.9–1.5 M). However, at higher concentrations (50 equiv, 3.0 M) the rate decreased dramatically (>10-fold decrease in rate; 4-fold change in  $[\text{H}_2\text{O}]$ ), consistent with substrate dissociation from the inner coordination sphere of  $\text{Sm(II)}$ . From a practical point of view, it is important to note that  $\text{SmI}_2$  has been shown to be stable at high concentration of water for periods in the order of days,<sup>5,6,14</sup> whereas the oxidation of  $\text{SmI}_2$  to  $\text{Sm(III)}$  in the

related but more reducing  $\text{SmI}_2$ , water, amine systems has been determined to occur in hours at room temperature.<sup>4,8e-j</sup> Note, although  $\text{SmI}_2$ - $\text{H}_2\text{O}$ -amine systems are strongly reducing,<sup>4a,b</sup> issues of chemoselectivity can arise in electron transfer to carbonyl groups.<sup>8e-j,16b,e,f</sup>

To probe the role of each reactant in the reduction of **1**, the rate orders for reaction components were determined at 15–25 equiv (with respect to  $[\text{SmI}_2]$ ) concentration of water (Table 1). The rate orders obtained in the previous study (100 equiv

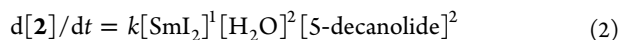
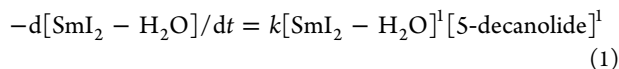
**Table 1. Reaction Orders for the Reduction of **1** Using the  $\text{SmI}_2$ - $\text{H}_2\text{O}$  System**



entry	$\text{H}_2\text{O}$ (equiv)	rate order			$k_{\text{H}}/k_{\text{D}}$
		substrate <sup>a</sup>	$\text{SmI}_2$ <sup>b</sup>	$\text{H}_2\text{O}$ <sup>c</sup>	
1	15–25	$2.2 \pm 0.1$	$1.1 \pm 0.1$	$2.1 \pm 0.1$	1.33
2	>100	$1.1 \pm 0.1$	$1.3 \pm 0.1$	0	1.5

<sup>a</sup> $[\text{SmI}_2] = 70 \text{ mM}$ ,  $[\text{H}_2\text{O}] = 15 \text{ equiv}$ ,  $[\text{ester}] = 0.05\text{--}0.15 \text{ mmol}$ ;  $[\text{SmI}_2] = 10 \text{ mM}$ ,  $[\text{H}_2\text{O}] = 150 \text{ equiv}$ ,  $[\text{ester}] = 45\text{--}70 \text{ equiv}$ . <sup>b</sup> $[\text{SmI}_2] = 50\text{--}70 \text{ mM}$ ,  $[\text{H}_2\text{O}] = 15 \text{ equiv}$ ,  $[\text{ester}] = 1 \text{ equiv}$ ;  $[\text{SmI}_2] = 5\text{--}10 \text{ mM}$ ,  $[\text{H}_2\text{O}] = 150 \text{ equiv}$ ,  $[\text{ester}] = 5 \text{ mM}$ . <sup>c</sup> $[\text{SmI}_2] = 70 \text{ mM}$ ,  $[\text{H}_2\text{O}] = 15\text{--}25 \text{ equiv}$ ,  $[\text{ester}] = 1 \text{ equiv}$ ;  $[\text{SmI}_2] = 10 \text{ mM}$ ,  $[\text{H}_2\text{O}] = 100\text{--}180 \text{ equiv}$ ,  $[\text{ester}] = 650 \text{ mM}$ . Values for entry 1 are listed first.

with respect to  $[\text{SmI}_2]$ <sup>14b</sup> are depicted in Table 1 for comparison purposes. Within experimental error, the reduction of **1** with  $\text{SmI}_2$ - $\text{H}_2\text{O}$  was found to be second order in lactone, first order in  $\text{SmI}_2$ , and second order in  $\text{H}_2\text{O}$  at lower concentration of water. The rate order of two for the lactone most likely results from the formation of a dimeric  $\text{SmI}_2$ -lactone complex with the substrate serving as one of the  $\text{Sm}(\text{II})$  ligands.<sup>16d</sup> The rate order of one for  $\text{SmI}_2$  and of two for water, indicates that the mechanism of the reduction changes with increasing concentration of water (Table 1); that is, at low concentration,  $\text{H}_2\text{O}$  is involved in the rate-determining step of the reaction; at high concentration water promotes the reaction only by the formation of a thermodynamically stronger reductant by activating  $\text{SmI}_2$  toward the electron transfer (eq 1: reduction of **1** at high concentration of water;<sup>14a,b</sup> eq 2: reduction of **1** at low concentration of water).



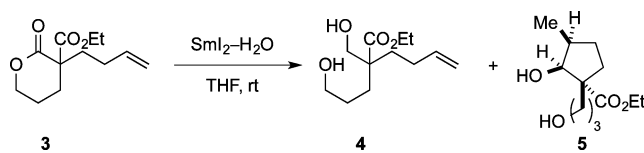
Moreover, the kinetic isotope effect was measured for the reduction of **1** at the same concentration of water (Table 1). The obtained value  $k_{\text{H}}/k_{\text{D}}$  of 1.33, parallel runs, indicates that proton transfer is not involved in the rate-determining step of the reaction.<sup>17</sup>

Importantly, the nonlinear dependence on water concentration in the reduction of **1** was further confirmed by monitoring the reduction of **1** with  $\text{SmI}_2$ - $\text{H}_2\text{O}$  under the standard experimental reaction conditions utilizing preformed solutions of  $\text{SmI}_2$  and  $\text{SmI}_2$  powder, which validates that the observed dependence is not related to the heterogeneous nature of  $\text{SmI}_2$  stock solutions<sup>1c,d</sup> (see the Supporting Information (SI) for detailed reaction profiles). Moreover, a nonlinear dependence on water concentration was observed in

the reduction of an acyclic, unactivated pfp ester (pentafluorophenyl 3-phenylpropanoate) under identical  $\text{SmI}_2$ - $\text{H}_2\text{O}$  reaction conditions (see the SI for detailed reaction profiles), thus suggesting that the observed effect is general. Overall, these results indicate that synthetically useful changes in the rate of electron transfer steps can be achieved by simply modifying the concentration of water additive.<sup>18</sup>

To further test the impact of water on the rate of reduction of ketyl radicals, we exposed the 6-membered lactone **3** bearing a tethered olefin to the  $\text{SmI}_2$ - $\text{H}_2\text{O}$  conditions under a range of water concentrations (Table 2, Figure 3).<sup>19</sup> The bimolecular

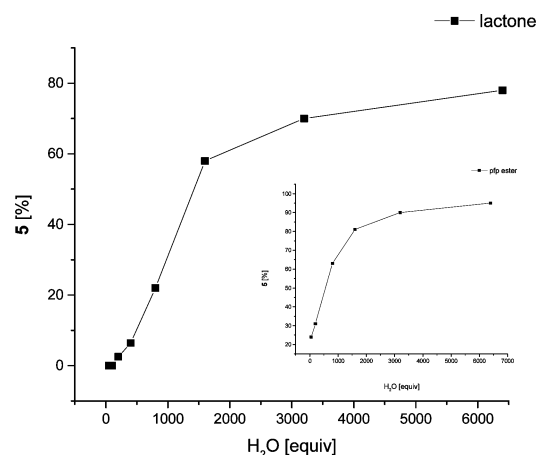
**Table 2. Effect of Concentration of Water on the Rate of Reduction of Acyl-Type Radicals Derived from Lactone **3**<sup>a</sup>**



entry	$\text{H}_2\text{O}$ (equiv)	4:5	$[\text{SmI}_2]$	$[\text{H}_2\text{O}]$	rate [ $10^7 \times \text{M}^{-1} \text{ s}^{-1}$ ]
1	0	>98:2	0.053		>21.3
2	25	>98:2	0.053	0.22	>21.3
3	50	>98:2	0.053	0.44	>21.3
4	100	>98:2	0.053	0.88	>21.3
5	200	97:3	0.052	1.73	14.30
6	400	94:6	0.050	3.33	7.21
7	800	77:23	0.048	6.40	1.60
8	1600	42:58	0.042	11.20	0.39
9	3200	30:70	0.035	18.67	0.28
10	6400	22:78	0.026	27.75	0.25
11	800	81:19	0.025	3.33	3.92
12	800	86:14	0.015	2.00	9.41

<sup>a</sup>Conditions:  $\text{SmI}_2$  (6 equiv), THF,  $\text{H}_2\text{O}$ , 23 °C.  $[\text{SmI}_2] = 0.015\text{--}0.053 \text{ M}$ .  $[\text{H}_2\text{O}] = 0.22\text{--}27.75 \text{ M}$ . See SI for full experimental details.

rate constant for the reduction of the ketyl-type radical was obtained by using an approximated unimolecular rate constant  $k_{\text{S-exo}} = \text{ca. } 2.3 \times 10^5 \text{ s}^{-1}$  for the validated 5-exo alkyl radical clock.<sup>19,20</sup> As expected no reaction occurred in the absence of water.<sup>14a</sup> Remarkably, the rate of reduction of the ketyl-type

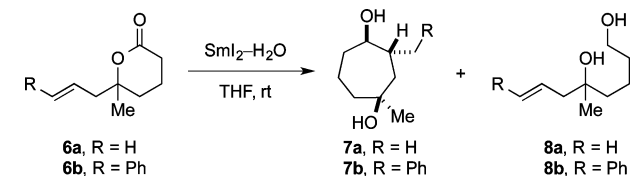


**Figure 3.** Cyclization of acyl-type radical derived from **3** as a function of concentration of water. The inset shows the same for a pfp ester (pentafluorophenyl 2-benzylhex-5-enoate).  $\text{SmI}_2$  (6 equiv),  $\text{H}_2\text{O}$  (0–6400 equiv),  $T = 23 \text{ }^\circ\text{C}$ . See SI for full experimental details.

radical obtained from **3** to give **4** was found to decrease linearly with increasing concentration of water, in contrast to the rates expected from the thermodynamic redox potentials determined for Sm(II)–H<sub>2</sub>O complexes in the ground state.<sup>6b</sup> Control experiments at different concentrations of SmI<sub>2</sub> with a constant amount of water show that the rate of reduction increases at lower concentration of SmI<sub>2</sub>.<sup>19b</sup> Furthermore, the study of the role of water on the reduction of a ketyl-radical derived from an unactivated acyclic pfp ester bearing a tethered olefin poised for the 5-exo cyclization (pentafluorophenyl 2-benzylhex-5-enoate, see SI for details) demonstrates that the rate of the reduction decreases linearly with increasing concentration of water. Based on these results, complete chemoselectivity for the 5-exo cyclization or reduction can be achieved by simply modifying the concentration of water additive (see SI for additional discussion).

We likewise investigated the effect of water on the rate of reduction of lactones **6** bearing a tethered olefin at the 5-position (Table 3). Positioning an alkene tether alpha to the

**Table 3. Effect of Concentration of Water on the Rate of Reduction of Acyl-Type Radicals Derived from Lactones 6<sup>a</sup>**



entry	R	H <sub>2</sub> O (equiv)	7:8	[H <sub>2</sub> O]	rate [10 <sup>5</sup> × M <sup>-1</sup> s <sup>-1</sup> ]
1	H	200	66:34	2.02	19.42
2	H	800	91:9	7.36	4.14
3 <sup>b</sup>	H	2200	95:5	20.07	2.30
4	Ph	200	93:7	2.54	2.27
5	Ph	800	99:1	8.95	0.35

<sup>a</sup>Conditions: SmI<sub>2</sub> (6 equiv), THF, H<sub>2</sub>O, 23 °C; [SmI<sub>2</sub>] = 0.063–0.080 M. <sup>b</sup>Ref 14c. All entries, >85% yield based on recovered substrate. See SI for full experimental details.

oxygen atom on the lactone scaffold allows access to seven-membered polyoxygenated carbocycles by cyclizations of the radical anion intermediates derived from the SmI<sub>2</sub>–H<sub>2</sub>O reduction.<sup>14c</sup> The results in Table 3 clearly indicate that a significant effect of water concentration on the rate of reduction of the radical derived from **6** is observed. Importantly, the same order of the water effect as in the case of 2-tethered lactones is observed (i.e., faster reduction rate at lower concentration). Remarkably, the rate of reduction of the acyl-type radical is directly related to the electronic properties of the olefin  $\pi$ -acceptor,<sup>21</sup> thus providing strong indication that the first electron transfer to the lactone carbonyls is reversible in these systems and that the reductive coupling occurs via a late transition state.<sup>22</sup> As expected from the relative rates of radical cyclizations,<sup>19a</sup> the reduction of lactones **6** is slower than the corresponding 2-tethered analogues under the same concentration of water.

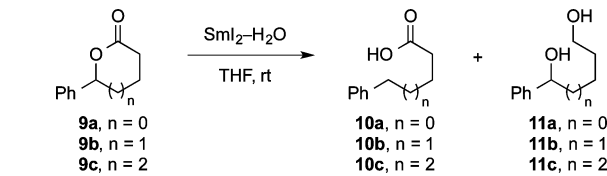
Taken together, the results outlined in Tables 1–3 strongly suggest that the reduction of acyl-type radicals by SmI<sub>2</sub>–H<sub>2</sub>O is favored by a concentration of water at which Sm(II) is activated toward the reduction;<sup>6a,b</sup> however, the coordination sphere of Sm(II) cannot be saturated with the water additive.<sup>6c</sup> The concentration of H<sub>2</sub>O at which the maximum rate of the reduction is observed correlates with iodide displacement from

the Sm(II) coordination sphere.<sup>6c</sup> Notably, high concentration of water favors reductive cyclizations due to the competing coordination of water to the Sm(II), despite a much higher thermodynamic redox potential of the SmI<sub>2</sub>–H<sub>2</sub>O reagent in a process that is formally analogous to an outer-sphere electron transfer.<sup>23,9n,o</sup>

With a working mechanism in place, we sought to further elucidate the impact of water on the electron transfer steps. In particular, we recognized that providing an alternative reaction pathway to the straight reduction/cyclization should allow validation of the findings obtained from the 5-exo radical clocks. Specifically, we hypothesized that lactones bearing a radical-stabilizing group at the 5-position could undergo C–O bond scission<sup>24</sup> depending on the reaction conditions, thus providing further insight into the role of water in the stabilization of ketyl-type radical intermediates.

To this end, phenyl bearing lactones **9** were prepared and subjected to the SmI<sub>2</sub>–H<sub>2</sub>O reaction conditions at a range of water concentrations (Table 4). In the original studies<sup>14a,b</sup> we

**Table 4. Effect of Concentration of Water on the Stability of Acyl-Type Radicals Derived from Lactones 9<sup>a</sup>**



entry	n	H <sub>2</sub> O (equiv)	time (h)	10:11	conv. (%)	[H <sub>2</sub> O]
1	0	200	5	41:59	35	1.93
2	0	800	5	77:23	9 <sup>b</sup>	6.99
3	1	200	5	34:66	96	1.93
4	1	800	5	72:28	92	6.99
5	2	200	5	96:4	>98	1.93
6	2	800	5	99:1	>98	6.99

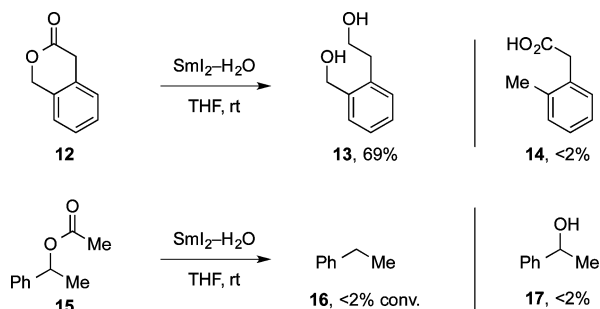
<sup>a</sup>Conditions: SmI<sub>2</sub> (8 equiv), THF, H<sub>2</sub>O, 23 °C, 5 h; [SmI<sub>2</sub>] = 0.070–0.077 M. <sup>b</sup>92% yield, 10:11 = 79:21, using a SmI<sub>2</sub>–MeOH–amine system. All entries, >95% yield based on recovered substrate. See SI for full experimental details.

found that similarly alkyl substituted 5- and 7-membered lactones could not be reduced to diols by SmI<sub>2</sub>–H<sub>2</sub>O, which we ascribed to the slower rate of the initial electron transfer to the lactone carbonyl groups. Remarkably, we now determined that 5-, 6-, and 7-membered lactones **9** decorated with a radical stabilizing group undergo efficient electron transfer from SmI<sub>2</sub>–H<sub>2</sub>O to give, depending on ring-size and concentration of water, the C–O fragmentation products in good to high selectivity and yields. At lower concentration of water (Table 4, entries 1, 3, and 5) the radicals were found to undergo fast reduction, leading to a decreased C–O scission selectivity, which mirrors the effect of the concentration of water outlined above in the 5-exo cyclization reactions. In contrast, at high concentration of water (Table 4, entries 2, 4, and 6), C–O fragmentation is the predominant reaction pathway. Crucially, by providing an alternative reaction pathway to the reduction of simple alkyl analogues (i.e., fragmentation), it is clear that other ring sizes of lactones than 6-membered serve as viable precursors to unusual acyl-type radicals. We note that this finding significantly expands the utility of SmI<sub>2</sub>–H<sub>2</sub>O to effect electron transfer to traditionally unreactive substrates. Moreover, the results presented in Table 4 provide yet another

indication of the fast reversible electron transfer to the lactone carbonyl groups in these systems.

Several control experiments were conducted to gain information on the stability of ketyl radical intermediates in the C–O fragmentation substrates (Scheme 3 and see SI for

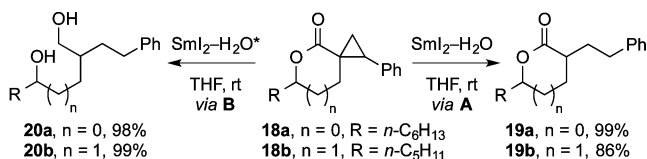
### Scheme 3. Mechanistic Probes for the Fragmentation of Acyl-Type Radicals Using $\text{SmI}_2\text{-H}_2\text{O}$



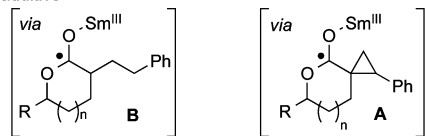
more details). In particular, we found that the conformationally constrained lactone **12** bearing a fused aromatic ring and an acyclic benzyl ester **15** do not undergo productive C–O bond scission. These results are explained by the lack of electronic overlap required for the fragmentation<sup>25</sup> and lower stability of the acyl-type radical intermediate in acyclic systems in which radical stabilization from an anomeric effect<sup>26</sup> cannot be achieved, respectively. These control reactions further reveal the unique chemoselectivity profile of  $\text{SmI}_2\text{-H}_2\text{O}$  reductants.

The viability of the mechanism involving fast reversible electron transfer to lactone carbonyls was further probed using validated cyclopropane radical clock substrates (Scheme 4).

### Scheme 4. Radical Clock Experiments in the Reduction of Cyclic Esters using $\text{SmI}_2\text{-H}_2\text{O}$



\* $\text{Et}_3\text{N}$  used as additive



The reaction of 5- and 6-membered lactones **18** (approximated unimolecular rate constant  $k_{\text{frag}} = \text{ca. } 3 \times 10^{11} \text{ s}^{-1}$  at  $25^\circ\text{C}$ )<sup>19a,20</sup> with a limiting amount of  $\text{SmI}_2\text{-H}_2\text{O}$  resulted in a rapid cyclopropyl ring-opening to give the 2-phenethyl lactones **19**. The corresponding cyclopropyl diol and phenethyl diol were not detected in these reactions. Furthermore, the reaction of 5- and 6-membered lactones **18** using a more thermodynamically powerful  $\text{Sm(II)}$  system containing amine as a Lewis basic additive<sup>4,8e–j</sup> resulted in the selective formation of the phenethyl diols **20** after less than 1 h reaction time. Hilmersson determined that the system using  $\text{Et}_3\text{N}$  as a Lewis basic additive shows a half-life of approximately 24 h (vide supra).<sup>8i</sup> Control reactions with the corresponding cyclopropyl diols under  $\text{Sm(II)}$  conditions resulted in full recovery of the cyclopropyl starting material (not shown, see SI). Moreover, the reaction of

pentafluorophenyl 2-phenylcyclopropanecarboxylate resulted in selective cyclopropyl opening (see SI). Taken together, these results strongly suggest that the reduction of esters using  $\text{SmI}_2\text{-H}_2\text{O}$  occurs via a fast reversible first electron transfer. Moreover, the C–C bond fragmentation shows that the stability of the resulting radicals is sufficient to allow follow-up transformations in cyclic and acyclic esters other than six-membered lactones, which considerably broadens the utility of  $\text{SmI}_2\text{-H}_2\text{O}$  complexes for the generation of acyl-type radicals from bench-stable carboxylic acid derivatives.

Finally, we recognized that the mechanism of the reduction of lactones using  $\text{SmI}_2$  reductants as elucidated in the current study is likely to be operative in other  $\text{Sm(II)}$ -mediated electron transfer reactions involving carbonyl groups. Although previously it has been correctly noted that the rate of the reaction of ketones bearing tethered olefins under  $\text{Sm(II)}$  conditions is fast relative to unsubstituted ketones,<sup>19c</sup> several recent reports suggested that the rate-determining step in the  $\text{Sm(II)}$ -mediated reduction of ketones might involve protonation.<sup>6a,8e,17</sup> In light of the evidence garnered in the current study, we considered that a dramatic change of the reaction pathway between esters and other carbonyl derivatives is unlikely. To test the validity of this hypothesis, we measured KIE for the reduction of several aldehydes, ketones, and other carboxylic acid derivatives using  $\text{Sm(II)}$  (Table 5; see SI for additional studies).

**Table 5. Kinetic Isotope Effects in the Reduction of Carbonyl Derivatives Using  $\text{SmI}_2\text{-H}_2\text{O}$ <sup>a</sup>**

entry	substrate	$\text{SmI}_2$ (equiv)	$\text{H}_2\text{O}$ (equiv)	$k_{\text{H}}/k_{\text{D}}$
1	$\text{PhCH}_2\text{CH}_2\text{CHO}$	3	100	$1.4 \pm 0.1$
2	$\text{PhCH}_2\text{CH}_2\text{C(O)Me}$	3	100	$1.5 \pm 0.1$
3	$\text{PhCO}_2\text{Me}$	6	200	$1.4 \pm 0.1$
4	$\text{PhCO}_2\text{H}$	6	200	$1.4 \pm 0.1$
5	$\text{PhC(O)Me}$	3	100	$1.8 \pm 0.1$
6	$\text{PhCHO}$	3	100	$2.0 \pm 0.1$

<sup>a</sup>Conditions:  $\text{SmI}_2$  (3–6 equiv), THF,  $\text{H}_2\text{O}$ ,  $23^\circ\text{C}$ . See SI for full experimental details.

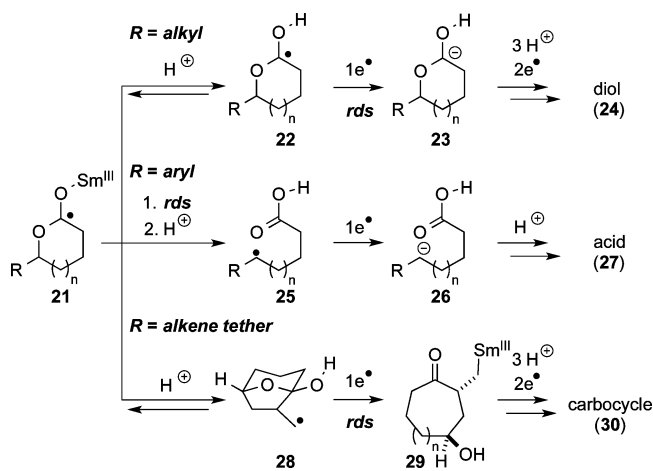
In most cases studied, a KIE between 1.4 and 1.5 was found, which is consistent with proton transfer to carbon not being involved in the rate-determining step of these reactions. The impact of deuterium is likely to result from a solvent secondary kinetic isotope effect due to the differential coordination of  $\text{D}_2\text{O}$  and  $\text{H}_2\text{O}$  to  $\text{Sm(II)}$ .<sup>27</sup> Interestingly, in the case of aromatic carbonyl derivatives, a higher KIE of 1.8–2.0 was obtained.<sup>28</sup> Although we cannot rule out that for this specific group of substrates the KIE values indicate a rate determining proton transfer to carbon, we suggest that these are secondary KIEs resulting from a combination of a differential coordination of  $\text{D}_2\text{O}/\text{H}_2\text{O}$  to  $\text{Sm(II)}$  (vide supra), the increased Lewis acidity of  $\text{Sm(III)}$  and increased stability of aryl ketyl radicals.<sup>29</sup> In reported examples of the hydrolysis of phenyl esters using deuterium oxide a KIE of up to 1.8 was found as a result of the secondary deuterium isotope effects.<sup>27</sup> Moreover, it has been well-established in numerous literature examples that aryl ketones and aldehydes are subject to divergent reaction pathways from their aliphatic counterparts upon exposure to  $\text{Sm(II)}$  and other single electron transfer reductants (i.e., aryl ketyls undergo predominantly pinacol or aryl cross-coupling reactions).<sup>1–3</sup> Overall, the examples documented above highlight that to date the only type of  $\text{Sm(II)}$ -mediated

reactions that has been conclusively shown to proceed via a rate determining protonation is the reduction of  $\alpha,\beta$ -unsaturated carbonyl acceptors ( $k_H/k_D$  of 6.0–7.6).<sup>7c</sup> Furthermore, care needs to be taken when interpreting KIE results when using Sm(II)–D<sub>2</sub>O reagent systems.<sup>17</sup>

From a practical perspective the finding that Sm(II) mediated transformations of carbonyl compounds proceed under one generalized mechanism can have a profound impact on designing novel synthetically valuable reductive transformations using Sm(II). In particular, these studies should facilitate the development of reductive cascades using substrates bearing multiple reactive sites,<sup>30</sup> in which the selectivity is tuned by simply adjusting the properties of a functional group/intermediates to make them more thermodynamically accessible for the reduction. We note that several examples of such cascades have been published; however, a rationale for the selectivity has been elusive.<sup>31</sup>

Scheme 5 depicts a revised mechanism for lactone reduction. As discussed above, we propose a pathway involving reversible

**Scheme 5. Revised Mechanistic Pathways for the Reactivity of Acyl-Type Radicals Generated from Lactones Using SmI<sub>2</sub>–H<sub>2</sub>O**



fast electron transfer and water-assisted stabilization of the formed ketyl radicals as key features. The feasibility of this mechanism is supported by the experiments outlined above. Furthermore, based on the results reported herein we postulate that a mechanism involving the rate determining second electron transfer is operative in other Sm(II)-mediated reactions of ketyl radicals. This mechanism is consistent with numerous examples of single electron transfer reactions of carbonyl groups,<sup>32</sup> including reactions mediated by SmI<sub>2</sub>.<sup>33</sup>

## CONCLUSIONS

In summary, we have elucidated the mechanism of the SmI<sub>2</sub>–H<sub>2</sub>O-mediated reduction and cyclization of lactones, the first class of simple unactivated carboxylic acid derivatives which for three decades have been thought to lie outside the reducing range of SmI<sub>2</sub> and have been shown to react with SmI<sub>2</sub> only upon activation of the reagent with H<sub>2</sub>O.<sup>34,35</sup> The results presented in this study indicate that a significant revision of the originally proposed mechanism is required. We have provided experimental evidence that water, an extremely valuable additive for Sm(II), enables the productive electron transfer from Sm(II) by stabilizing the radical anion intermediate, rather

than by solely promoting the first electron transfer, and have demonstrated that the reduction of simple carbonyl compounds with Sm(II) is unlikely to involve a rate determining protonation.

The two key conclusions obtained from this study are that (1) the transformations involving generation of ketyl-type radicals using SmI<sub>2</sub>–H<sub>2</sub>O are governed by thermodynamic control of the second electron transfer step and (2) low concentration of water facilitates the reduction of ketyl radicals, which is in contrast to the thermodynamic potential of the SmI<sub>2</sub>–H<sub>2</sub>O reductant in the ground state and results from an outer-sphere electron transfer step at high concentration of water. Notably, the results of our investigation suggest that a wide range of novel precursors should become available for Sm(II)-mediated reductive processes, including reductions, cross-couplings, and cascade transformations. Moreover, we have demonstrated that the generation of ketyl-type radicals from lactones and acyclic esters with SmI<sub>2</sub> occurs under a unified mechanism, which should enable the rational design of Sm(II)-mediated reactions of ketyl radicals. We hope that our studies on the role of water as an additive for Sm(II) will contribute to the discovery of new reactions involving the generation of ketyl- and acyl-type radicals by this reagent.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, compound characterization data and details of kinetic 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.

## ACKNOWLEDGMENTS

We acknowledge the EPSRC, GSK and The Leverhulme Trust for financial support.

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