

Radical Reactions

On the Role of Pre- and Post-Electron-Transfer Steps in the $\text{SmI}_2/\text{Amine}/\text{H}_2\text{O}$ -Mediated Reduction of Esters: New Mechanistic Insights and Kinetic Studies

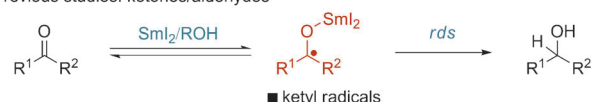
Michal Szostak,* Malcolm Spain, and David J. Procter*[a]

Abstract: The mechanism of the SmI_2 -mediated reduction of unactivated esters has been studied using a combination of kinetic, radical clocks and reactivity experiments. The kinetic data indicate that all reaction components (SmI_2 , amine, H_2O) are involved in the rate equation and that electron transfer is facilitated by Brønsted base assisted deprotonation of water in the transition state. The use of validated cyclopropyl-containing radical clocks demonstrates that the reaction occurs via fast, reversible first electron transfer, and that the electron transfer from simple $\text{Sm}(\text{II})$ complexes to aliphatic esters is rapid. Notably, the mechanistic details presented herein indicate that complexation between SmI_2 , H_2O and amines affords a new class of structurally diverse, thermodynamically powerful reductants for efficient electron transfer to carboxylic acid derivatives as an attractive alternative to the classical hydride-mediated reductions and as a source of acyl-radical equivalents for C–C bond forming processes.

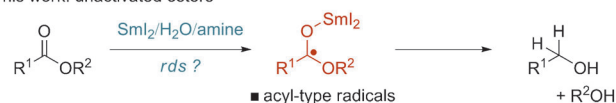
Samarium(II)-mediated generation of ketyl radicals has been the focus of intense research for more than three decades,^[1] and the SmI_2 -promoted reductions, which enable the synthesis of alcohols under conditions orthogonal to other reagents operating through single- and two-electron pathways,^[2,3] are a prominent class of these processes (Figure 1). Until recently, it had been thought that unactivated carboxylic acid derivatives were outside the reducing range of SmI_2 ,^[4] which prevented progression of the rich carbonyl chemistry of SmI_2 (e.g., reduction, cross-coupling, tandem bond-forming events) to acyl-type radicals generated from carboxylic acid derivatives under mild and chemoselective reaction conditions (Figure 1).

In 2011, we reported that the Sm^{II} reagent produced from SmI_2 , amine and H_2O is capable of reducing unactivated esters via radical intermediates,^[5] thus for the first time expanding the carbonyl chemistry of SmI_2 beyond ketones and alde-

■ Previous studies: ketones/aldehydes



■ This work: unactivated esters



• generalized mechanism of the Sm^{II} -mediated electron transfer to esters

Figure 1. Accepted and proposed mechanism of SmI_2 -mediated electron transfer to aldehydes, ketones, and carboxylic acid derivatives; rds = rate-determining step.

hydes.^[6] However, the mechanistic details of this process, including the critical role of amine and H_2O additives, remained unclear.^[6,7] As a better mechanistic understanding of the role of these additives could afford key insights for the development of new reductive processes, including chemoselective reduction of less reactive functional groups, such as nitriles, amides and amino acids, as well as the development of new C–C bond-forming reactions,^[8] we initiated a mechanistic investigation into the reduction of unactivated esters using $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$. The data described herein show two important features: 1) all reaction components (SmI_2 , amine, H_2O) are involved in the rate equation, and there is a direct correlation between the rate of ester reduction and pK_{BH^+} of amines; 2) the reaction occurs via fast, reversible first electron transfer, and the electron transfer from simple Sm^{II} complexes to aliphatic esters is rapid. Importantly, this study sets the stage for the use of $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$ complexes to generate acyl-type radicals from a plethora of carboxylic acid derivatives.

We started our investigation by conducting a range of kinetic studies (Table 1). *tert*-Butyl 3-phenylpropanoate (**1**) 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 Sm^{II} reduction conditions available for this substrate.^[5] Within experimental error, the reduction of **1** in the presence of $\text{SmI}_2/\text{Et}_3\text{N}/\text{H}_2\text{O}$ was found to be first order in all components of the reaction (Table 1). The rate constant of $1.4 \pm 0.1 \times 10^{-3} \text{ s}^{-1}$ was determined for the reduction of **1** under these reaction conditions. Taken together, these results suggest that all reaction components are involved in the rate equation, and that the reduction of **1** is a fast process.

To further explore the impact of H_2O , the reduction rate of **1** was monitored over a 20-fold concentration range as depicted

[a] Dr. M. Szostak, M. Spain, Prof. Dr. D. J. Procter
School of Chemistry, University of Manchester
Oxford Road, Manchester M13 9PL (UK)
Fax: (+44) 161-275-4939
E-mail: michal.szostak@manchester.ac.uk
david.j.procter@manchester.ac.uk

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Table 1. Rate constant and reaction orders for the reduction of **1** using the $\text{SmI}_2/\text{Et}_3\text{N}/\text{H}_2\text{O}$ system.^[a]

$\text{Ph-CH}_2\text{-CH}_2\text{-CO}_2\text{tBu} \xrightarrow[\text{THF, rt}]{\text{SmI}_2/\text{Et}_3\text{N}/\text{H}_2\text{O}} \text{Ph-CH}_2\text{-CH}_2\text{-OH}$				
	1		2	
$k^{[a]}$ [M ⁻³ s ⁻¹]	Substrate ^[a]	Rate order $\text{SmI}_2^{[b]}$	$\text{Et}_3\text{N}^{[c]}$	$\text{H}_2\text{O}^{[d]}$
1.4×10	0.96 ± 0.10	1.09 ± 0.10	1.18 ± 0.10	0.92 ± 0.10
[a] $[\text{SmI}_2] = 75 \text{ mM}$; $[\text{H}_2\text{O}] = 250 \text{ mM}$; $[\text{Et}_3\text{N}] = 150 \text{ mM}$; [ester] = 5–20 mM. [b] $[\text{SmI}_2] = 50\text{--}100 \text{ mM}$; $[\text{H}_2\text{O}] = 250 \text{ mM}$; $[\text{Et}_3\text{N}] = 150 \text{ mM}$; [ester] = 12.5 mM. [c] $[\text{SmI}_2] = 75 \text{ mM}$; $[\text{H}_2\text{O}] = 250 \text{ mM}$; $[\text{Et}_3\text{N}] = 75\text{--}250 \text{ mM}$; [ester] = 12.5 mM. [d] $[\text{SmI}_2] = 75 \text{ mM}$; $[\text{H}_2\text{O}] = 75\text{--}300 \text{ mM}$; $[\text{Et}_3\text{N}] = 150 \text{ mM}$; [ester] = 12.5 mM. $T = 23^\circ\text{C}$. See the Supporting Information.				

ed in Figure 2. In this study, a nonlinear rate dependence on H_2O was found. At lower concentrations (up to 300 mM), the rate was found to increase linearly with a slope corresponding to the rate order of one, consistent with saturation behavior

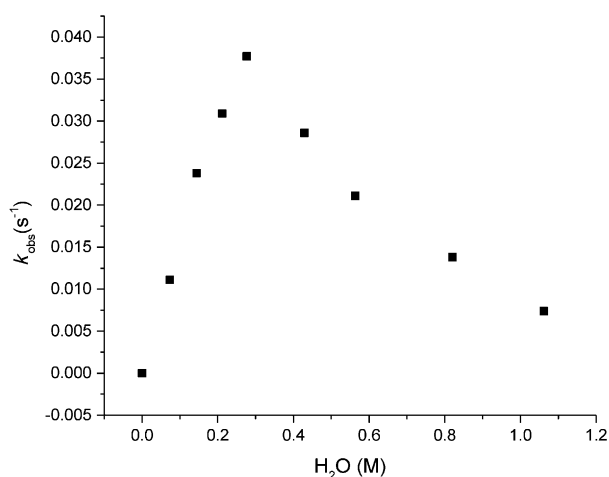


Figure 2. Plot of k_{obs} versus concentration of H_2O for the reduction of **1**. $[\text{H}_2\text{O}] = 0.075\text{--}1.2 \text{ M}$; $[\text{SmI}_2] = 75 \text{ mM}$; $[\text{Et}_3\text{N}] = 150 \text{ mM}$; [ester] = 12.5 mM; $T = 23^\circ\text{C}$.

(300 mM). However, at higher concentrations (300–1200 mM), the rate decreased dramatically, consistent with substrate displacement from the inner coordination sphere of Sm^{II} . In contrast, a linear rate dependence on amine at these concentrations was found. In agreement with previous studies, H_2O is expected to show high affinity for Sm^{II} and compete for coordination to Sm^{II} with the ester substrate.^[9] Interestingly, the concentration of H_2O at which the decrease in the reaction rate was observed correlates with iodide displacement from the Sm^{II} coordination sphere.^[10]

To further elucidate the role of the amine component, the reduction rate of **1** was measured in the presence of a wide range of amines with varying steric and electronic properties (Table 2). Remarkably, a dramatic change in the reaction rate of over two orders of magnitude was found by simply using different amines for the reduction. Moreover, a good correlation between the reaction rate and basicity of amines was ob-

Table 2. Determined initial rate in the reduction of **1** using $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$ versus $\text{p}K_{\text{BH}^+}$.^[a]

Entry	Amine	v_{initial} [mM s ⁻¹]	$\text{p}K_{\text{BH}^+}^{[b]}$
1	morpholine	2.4×10^{-4}	9.0 ± 0.2
2	$n\text{Bu}_3\text{N}$	3.9×10^{-5}	10.0 ± 0.5
3	Et_3N	5.0×10^{-4}	10.6 ± 0.3
4	$n\text{BuNH}_2$	6.8×10^{-3}	10.7 ± 0.1
5	pyrrolidine	8.8×10^{-3}	11.3 ± 0.2

[a] $[\text{SmI}_2] = 75 \text{ mM}$; $[\text{H}_2\text{O}] = 250 \text{ mM}$; [ester] = 12.5 mM; [amine] = 150 mM; $T = 23^\circ\text{C}$. [b] Determined from ACD lab prediction algorithm.

tained.^[11] By plotting $\log(k_{\text{obs}})$ versus $\text{p}K_{\text{BH}^+}$, a linear correlation was found with a slope corresponding to 0.79, which corresponds very well to the value obtained in the reduction of alkyl halides via an *outer-sphere mechanism* using $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$ reported by Hilmersson (0.76; for a detailed comparison, see the Supporting Information).^[7e] This result strongly suggests that the role of the amine component is independent of the mechanistic pathway (inner- vs. outer-sphere electron transfer) and the relative redox potentials of both classes of substrates. Considering steric properties exerted by these amines, our findings bode well for the chemoselective fine tuning of Sm^{II} /amine reductants to specific functional groups.

Several additional studies give insight into the electron-transfer steps. 1) The reduction with $\text{SmI}_2/\text{amine}/\text{D}_2\text{O}$ gives the alcohol with $>95\%$ $[\text{D}]_2$ incorporation suggesting that anions are protonated in a series of electron transfers. 2) The kinetic isotope effect in the reduction of isopropyl 3-phenylpropanoate using $\text{SmI}_2/\text{Et}_3\text{N}/\text{H}_2\text{O}$ of 1.5 ± 0.1 , parallel runs, and 1.4 ± 0.1 , intramolecular competition,^[5] indicate that proton transfer is not involved in the rate-determining step.^[12] 3) UV/Vis spectrophotometric studies carried out on various $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$ systems show isosbestic points and absorbance changes upon addition of amines and H_2O to SmI_2 ,^[7d] which is consistent with the formation of distinct Sm^{II} reductants.

Next, we utilized intermolecular competition studies to elucidate the actual productivity difference in the $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$ -mediated reduction of esters (Table 3). In these experiments, an equimolar amount of two esters was reacted with limiting SmI_2 (typically, less than 2 equiv). The relative reactivity values were determined from the product distribution. This method allows to accurately measure the relative reactivity values of Sm^{II} -mediated reactions provided that the studied substrates do not participate in alternative reaction pathways.^[13] Methyl decanoate was chosen as an arbitrary standard. Remarkably, in the series of eight methyl esters, a reactivity range of over three orders of magnitude was observed, depending on the steric and electronic properties of the α -carbon substituent at the ester group undergoing the reduction (Table 3, entries 1–8). This effect is consistent with both electronic stabilization of ketyl-type radicals (Table 3, entries 1–4) and steric inhibition of coordination to Sm^{II} (entries 4–8). Moreover, several substrates with enhanced leaving-group ability compared to the methyl ester were examined (Table 3, entries 9–12). These results further support the importance of electronic effects for the stabilization of the ketyl-type radical intermediates and determining

Table 3. Steric and electronic influence on the relative rates for the reduction of esters.

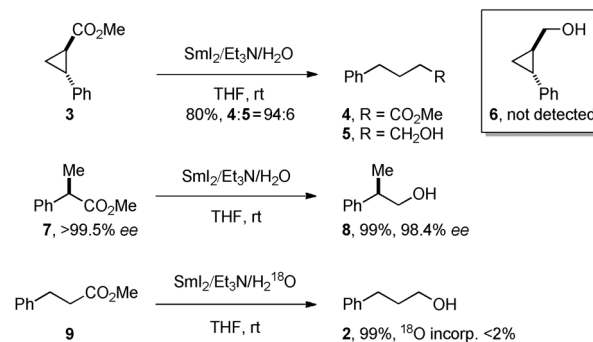
Entry	CO_2Me	RV ^[a]
1		> 100
2		9.14
3		4.29
4		1.00
5		0.41
6		0.26
7		0.91
8		0.05
Entry	$\text{Ph-CH}_2\text{-C(O)XR}$	RV ^[a]
9	R = OMe	1.00
10	R = OPh	6.88
11	R = Opfp	9.15
12	R = SEt	5.78

[a] Relative reactivity values (RV) determined from product distribution by ¹H NMR and/or GC analyses of crude reaction mixtures. All data represent the average of at least two experiments. pfp = pentafluorophenyl.

the redox potential of the substrates.^[14] Importantly, the data presented in Table 3 indicate high levels of chemoselectivity in the reduction of esters with $\text{SmI}_2/\text{Et}_3\text{N}/\text{H}_2\text{O}$.

Evidence for the electronic and steric stabilization of ketyl-type radical intermediates was further substantiated by Hammett and Taft correlation studies (see the Supporting Information). The Hammett correlation study, employing methyl esters of 4-substituted phenylacetic acids,^[15] showed a large positive ρ value of 0.43 ($R^2=0.98$), which can be compared with the ρ value of 0.49 for ionization of phenylacetic acids in H_2O at 25 °C.^[16] The Taft correlation study,^[17] obtained by plotting $\log(k_{\text{obs}})$ versus E_s in a series of aliphatic esters of hydrocinamic acid showed a large positive slope of 0.97 ($R^2=0.97$). Overall, these results suggest that an anionic intermediate is formed in the transition state of the reaction, and that a conformational change similar in geometry to the ester hydrolysis, tetrahedral intermediate, is taking place in the rate-determining step of the reaction.^[18]

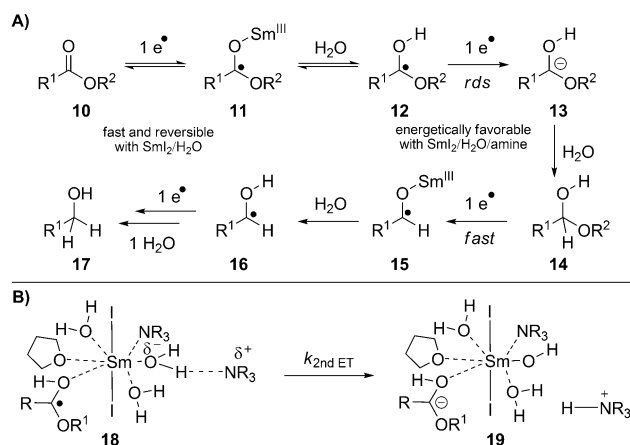
Finally, to gain independent evidence on the role of electron-transfer steps, we carried out several studies employing mechanistic probes (Scheme 1 and the Supporting Information). Most importantly, we recognized that implementation of a suitable radical clock should allow the detection of reversible reaction pathways.^[19] To this end, the *trans*-cyclopropane-containing radical clock **3** (approximated unimolecular rate constant $k_{\text{frag}} \approx 3 \times 10^{11} \text{ s}^{-1}$ at 25 °C)^[20] was selected and subjected to the reaction conditions with a limiting amount of SmI_2 (Scheme 1). The reaction resulted in rapid cyclopropyl-ring opening to give acyclic ester **4** and alcohol **5** in 94:6 ratio. Cy-



Scheme 1. Studies designed to investigate the mechanism of reduction of unactivated esters using $\text{SmI}_2/\text{Et}_3\text{N}/\text{H}_2\text{O}$.

clopropylcarbinol **6** was not detected in the reaction. Several control experiments were performed (see the Supporting Information). 1) The reaction of **3** with $\text{SmI}_2/\text{H}_2\text{O}$ (8 equiv, RT, 2 h) resulted in a facile opening to ester **4**, with no over-reduction to **5** or **6** observed. 2) The reduction of the methyl ester of cyclopropanecarboxylic acid (approximated unimolecular rate constant $k_{\text{frag}} \approx 9.4 \times 10^7 \text{ s}^{-1}$ at 25 °C)^[20] with excess $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$ afforded the corresponding acyclic alcohol and cyclopropylcarbinol in 96:4 ratio. This allows to estimate the rate of reduction of ketyl-type radicals with Sm^{II} to be comparable to a unimolecular reaction with k of about 10^8 s^{-1} .^[21] 3) The reductive opening of radical clock **3** was not observed with other Sm^{II} reagents, including systems with higher redox potential (SmI_2/MeOH , SmI_2/LiCl , SmI_2/HMPA (HMPA = hexamethylphosphoramide), and $\text{SmI}_2/\text{Et}_3\text{N}$).^[4b] Finally, experiments utilizing chiral probe **7** (Scheme 1) were carried out and demonstrate that enolization did not occur in the process despite basic reaction conditions, whereas control experiments using H_2^{18}O (Scheme 1 and the Supporting Information) show that the reduction did not proceed via a sequential ester hydrolysis/acid reduction mechanism. Overall, these findings strongly suggest that the reduction of unactivated esters with $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$ occurs through fast, reversible electron transfer, and, in contrary to the current paradigm,^[1,2] show that electron transfer from simple $\text{SmI}_2/\text{H}_2\text{O}$ complexes to aliphatic esters is rapid.^[22]

A mechanism that best fits the kinetic and reactivity studies presented herein features the following steps (Scheme 2):^[24] 1) Formation of the reactive complex between SmI_2 , H_2O , and amine, in which one or more molecules of H_2O and amine are coordinated to the Sm^{II} center.^[23] Within this complex, one molecule of amine participates in partial deprotonation of H_2O , resulting in a formal negative charge at oxygen and an overall increase of the redox potential of the Sm^{II} reductant in the transition state; 2) reversible ester coordination, protonation and first electron transfer steps; 3) rate-limiting second electron-transfer step; 4) inner-sphere electron-transfer process that is inhibited by large concentrations of H_2O and facilitated by Brønsted basic amines; and 5) rate-determining step that can be fine-tuned by steric and electronic properties of the ester substrate. The formation of a partial negative charge at oxygen was further supported by our finding that under optimized reaction conditions, $\text{SmI}_2/\text{NaOH}/\text{H}_2\text{O}$ ^[25] reduces aliphatic



Scheme 2. A) Proposed mechanism. B) Final steps of the reduction of esters using $\text{SmI}_2/\text{Et}_3\text{N}/\text{H}_2\text{O}$.

esters in high yield. From a practical point of view,^[26] the $\text{p}K_{\text{BH}^+}$ -dependent elongation of the hydrogen bond from H_2O in $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$ complexes can have a profound impact on the chemoselectivity of electron transfer to carboxylic acid derivatives.

In summary, we have presented a series of kinetic and reactivity experiments that probe the mechanism of the reduction of unactivated esters by using $\text{SmI}_2/\text{amine}/\text{H}_2\text{O}$. Our data are consistent with the formation of distinct Sm^{II} reductants by complexation between Sm^{II} , amine, and H_2O . The ester reduction appears to proceed after deprotonation of a molecule of H_2O by amine and to involve a reversible first electron-transfer step. Most crucially, our results demonstrate that a set of new Sm^{II} reductants that can be fine-tuned by the $\text{p}K_{\text{BH}^+}$ of the amine component is now available for challenging electron-transfer reactions to carboxylic acid derivatives. Equally importantly, this work shows that the major role of additives (e.g., H_2O , amine/ H_2O) is to stabilize the ketyl intermediates. We fully expect that these findings will serve as a foundation to enable the development of new electron-transfer reactions. Work in this direction using Sm^{II} systems is ongoing in our laboratories, and these results will be reported shortly.

Acknowledgements

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Keywords: electron donors • electron transfer • radicals • reduction • reductive coupling

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