JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Mechanism of SmI_2/Amine/H_2O-Promoted Chemoselective Reductions of Carboxylic Acid Derivatives (Esters, Acids, and Amides) to Alcohols

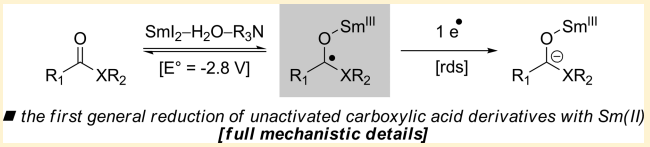
Michal Szostak,*[,†] Malcolm Spain,[‡] Andrew J. Eberhart,[‡] and David J. Procter*[,‡]

[†]Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States

[‡]School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, United Kingdom

Supporting Information

ABSTRACT: Samarium(II) iodide–water–amine reagents have emerged as some of the most powerful reagents ($E°$ = −2.8 V) for the reduction of unactivated carboxylic acid derivatives to primary alcohols under single electron transfer conditions, a transformation that had been considered to lie outside the scope of the classic SmI_2 reductant for more than 30 years. In this article, we present a detailed mechanistic investigation of the reduction of unactivated esters, carboxylic acids, and amides using SmI_2–water–amine reagents, in which we compare the reactivity of three functional groups. The mechanism has been studied using the following: (i) kinetic, (ii) reactivity, (iii) radical clock, and (iv) isotopic labeling experiments. The kinetic data indicate that for the three functional groups all reaction components (SmI_2, amine, water) are involved in the rate equation and that the rate of electron transfer is facilitated by base assisted deprotonation of water. Notably, the mechanistic details presented herein indicate that complexation between SmI_2, water, and amines can result in a new class of structurally diverse, thermodynamically powerful reductants for efficient electron transfer to a variety of carboxylic acid derivatives. These observations will have important implications for the design and optimization of new processes involving Sm(II)-reduction of ketyl radicals.



■ *the first general reduction of unactivated carboxylic acid derivatives with Sm(II)*
[full mechanistic details]

■ INTRODUCTION[1]

Samarium(II) iodide-mediated generation of ketyl radicals from aldehydes and ketones has been the focus of intensive research effort for more than three decades.[2] In particular, the use of SmI_2 enables synthesis of alcohols under conditions orthogonal to other reagents operating via single- and two-electron pathways,[3] and this process has been featured as a key step in numerous synthetic applications in which the exceptional chemoselectivity of SmI_2 proved beneficial over other available reductants.[4] The vast majority of processes involving generation of ketyl radicals with Sm(II) requires precomplexation of the lanthanide center with alcohol cosolvent to increase the redox potential of the system[5] or to promote protonation of the ketyl radical by a proton source placed in close proximity to the short-lived radical.[6] Numerous mechanistic studies have indicated the role of alcohols as crucial SmI_2-additives in reactions involving ketyl radicals (Figure 1).

Specifically, the pioneering findings by Kagan and co-workers on the reduction of 2-octanone with SmI_2–H_2O,[7] and the subsequent studies by Curran[8] and by Kamochi and Kudo[9] on the role of water in promoting reductions of dialkyl and aryl ketones, respectively, suggested that water may be a key additive to Sm(II) for the reduction of simple ketones (not shown). In 1999, Keck and co-workers systematically examined the effect of alcohol stoichiometry on the formation of Sm(II)–ROH complexes as demonstrated in a highly stereocontrolled reduction of β-hydroxy ketones using SmI_2–MeOH as the preferred reagent system (Figure 1A).[10] In 2002, Dahlén and Hilmersson[11] reported a breakthrough finding on the synergistic effect of water and amines on the reduction of simple dialkyl ketones using a reagent system previously described by Cabri and co-workers[12] and demonstrating a striking acceleration of the reaction rate in kinetic studies (Figure 1B). In 2004, Flowers and co-workers reported a study on the role of different alcohols in the reduction of acetophenone (Figure 1C).[13] In 2011, as an extension of mechanistic studies on the role of alcohols as additives to SmI_2 in the reduction of α,β-unsaturated nitriles, Hoz and co-workers reported a detailed investigation of the role of alcohols in the reduction of a sterically demanding ketone, norcamphor (Figure 1D).[14,15] In 2014, we reported mechanistic investigations on the reduction of six-membered lactones using SmI_2–H_2O with the key finding being the unusual effect of water on the stabilization of ketyl radical intermediates (Figure 1E).[16] The stabilizing effect of water as the Sm(II) additive was also demonstrated in a mechanistic study on the reduction of Meldrum's acids to β-hydroxy acids using SmI_2–H_2O as the key reagent system.[17] Recent work has also shown that alcohols serve as crucial additives to lanthanides(II) in several related processes involving ketyl radicals or equivalents.[18]

Special Issue: Mechanisms in Metal-Based Organic Chemistry

Received: August 11, 2014
Published: September 18, 2014

   dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988–12003

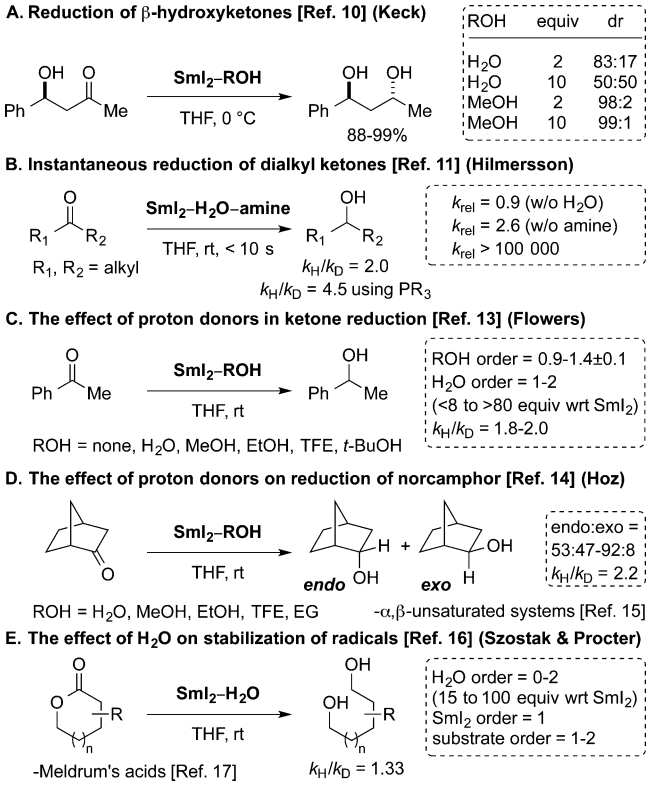


Figure 1. Previous mechanistic studies on electron transfer to carbonyl groups using Sm(II)-based reagents.

While the reduction of ketones and aldehydes to give the corresponding ketyl radicals is one of the useful reactions mediated by Sm(II),[2−4] until 2011 it had been thought that unactivated carboxylic acid derivatives (e.g., esters, carboxylic acids, amides) were outside the reducing range of Sm(II).[19] In 2011, we reported that the Sm(II) reagent produced from SmI_2, amine, and water is capable of reducing unactivated esters via radical intermediates, thus for the first time expanding the carbonyl chemistry of SmI_2 beyond the reduction of ketones and aldehydes.[20] In 2012, we reported the first general reduction of carboxylic acids with SmI_2 as an alternative to the classical hydride-mediated reductions.[21] In 2014, we reported the first general reduction of all types of amides (primary, secondary, tertiary) to the corresponding primary alcohols under mild conditions using the SmI_2−amine−water reagent.[22] Prior to our report, only a few methods for the reduction of amides to alcohols had been reported.[23] The excellent C−N/C−O cleavage chemoselectivity of this reaction (>90:10 in all cases examined) was proposed to result from complexation of the Lewis acidic Sm(III) to the nitrogen atom in the carbinolamine intermediate as well as from the mildly basic conditions of the reagent system favoring the carbinolamine intermediate collapse via alkoxide. The chemoselective reduction of nitriles[24] and cyclic esters[25] using SmI_2−amine−water[26] has also been reported.

The growing importance of SmI_2 in the reduction of carboxylic acid derivatives[20−22,24,25] prompted us to undertake a thorough mechanistic study of the formation of primary alcohols from unactivated esters, carboxylic acids, and amides using the SmI_2−amine−water system. In the literature, the vast majority of mechanistic studies on Sm(II) implicate the role of alcohols;[7−17] however, mechanistic studies on the synergistic effect of amine and water additives to Sm(II), including studies on the critical role of amine and water additives, are rare.[26a,b,e] Furthermore, these studies are almost exclusively limited to processes proceeding via an outer-sphere electron transfer.[26a,b] It is clear that a better mechanistic understanding of the role of the additives in the reduction of carboxylic acid derivatives could afford key insights for the development of new reductive processes (e.g., chemoselective reductions of complex functional groups, development of reductive bond forming reactions) and contribute to the 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 2).[2−4]

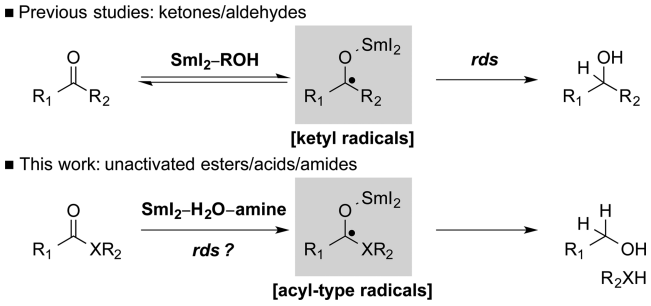
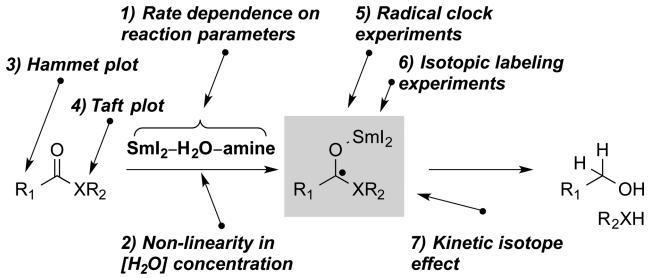


Figure 2. Accepted and proposed mechanism of SmI_2-mediated electron transfer to aldehydes, ketones, and carboxylic acid derivatives.

Herein, we present systematic kinetic and radical clock studies on the reduction of unactivated esters, acids and amides using SmI_2 (Chart 1). We demonstrate that for the three functional groups all reaction components (SmI_2, amine, water) are involved in the rate equation and that the rate of electron transfer is facilitated by base assisted deprotonation of water. Moreover, we demonstrate that the reactions occur via fast, reversible first electron transfer and that the electron transfer from simple SmI_2−water complexes (i.e., in the absence of amine) to carboxylic acid derivatives is rapid. In addition, we utilize reactivity studies to demonstrate that electronic (Hammett) and steric (Taft) effects significantly influence the rate of the reductions. Furthermore, we employ kinetic isotope effect experiments and ^{18}O labeling experiments to determine that proton transfer to carbon and hydrolysis (esters and amides) are not involved in the rate-determining step of the reductions.

Overall, the data suggest that reactions of esters, carboxylic acids, and amides proceed via a unified mechanism, in which the key step involves the second electron transfer step with amine

Chart 1. Methods Employed in the Current Study To Determine the Mechanism of the Reduction of Carboxylic Acid Derivatives Using Sm(II)



■ XR_2 = OR': Section A; XR_2 = OH: Section B; XR_2 = NR'R": Section C

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988−12003

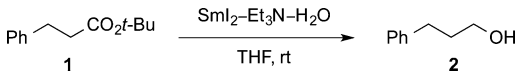
serving as an intramolecular base. The mechanistic details presented herein indicate that complexation between SmI_2, water, and amines results in a new class of structurally diverse, thermodynamically powerful reductants for efficient electron transfer to a variety of carboxylic acid derivatives. Importantly, these mechanistic studies provide substantial insights into the fundamental steps of the SmI_2-mediated reduction of carboxylic acid derivatives and could be critical for the design and optimization of processes involving reduction of ketyl radicals as a key step.

RESULTS AND DISCUSSION

Mechanism of Ester Reduction (Section A). In 2011, we reported the first general reduction of unactivated esters using SmI_2–amine–water.[20] This study provided a valuable foundation for the development of reductive processes involving other functional groups with SmI_2–amine–water;[21,22,24,25] however, the mechanistic details of this process, including the critical role of amine and water additives, remained unclear.

To gain preliminary insight into the mechanism of the reduction of carboxylic acid derivatives with SmI_2, we conducted a range of kinetic studies (Table 1). *tert*-Butyl 3-phenylpropanoate (**1**) was selected as a model substrate because its rate of reduction was found to be in a convenient range for kinetic studies and there was ample precedent for Sm(II) reduction conditions available for this substrate from our previous studies.[20] The reduction of **1** displayed a well-behaved kinetic profile throughout the course of the reduction. Kinetic profiles have been followed under the closest possible kinetic conditions relevant to the experimental conditions employed in synthetic studies.[20−22,24,25] The rates were determined by monitoring alcohol formation via GC or GC-MS analysis (cf., SmI_2 decay as in other studies) at low conversions to prevent significant background reactions due to oxidation to Sm(III)[5,6] and miscibility problems in heterogeneous reaction mixtures. The kinetics under pseudo-first-order conditions were determined by plotting ln[concentration] vs time, and the rate orders were determined by plotting ln(rate) vs ln(concentration). A similar procedure was followed for determining kinetics of the reduction of unactivated carboxylic acids[21] and amides[22] (vide infra). The selection of substrates for mechanistic studies was based on the reaction rate in order to determine kinetics under experimentally relevant reaction conditions.[20−22,24,25] Under the relevant experimental conditions, reactions mediated by Sm(II) and other lanthanides(II) cannot be monitored to higher conversions due to the sensitive nature of this class of reagents.[1−3,5,6] In attempts to conduct kinetics to higher conversions, we have detected significant background reactions due to oxidation to Sm(III) or miscibility problems. Within experimental error, the reduction of **1** in the presence of SmI_2–Et_3N–H_2O was found to be first order in all components of the reaction (Table 1). The rate constant of $(1.4 \pm 0.1) \times 10\ M^{-3}\ s^{-1}$ was determined for the reduction of **1** under these reaction conditions. Taken together, these results suggested that all reaction components were involved in the rate equation and that the reduction of **1** was a fast process.

Table 1. Rate Constant and Reaction Orders for the Reduction of *tert*-Butyl 3-Phenylpropanoate Using SmI_2–Et_3N–H_2O



	rate order			
k^a [$M^{-3}s^{-1}$]	substrate[a]	SmI_2[b]	Et_3N[c]	H_2O[d]
1.4 × 10	0.96 ± 0.10	1.09 ± 0.10	1.18 ± 0.10	0.92 ± 0.10

[a] $[SmI_2]$ = 75 mM, $[H_2O]$ = 250 mM, $[Et_3N]$ = 150 mM, [ester] = 5–20 mM. [b] $[SmI_2]$ = 50–100 mM, $[H_2O]$ = 250 mM, $[Et_3N]$ = 150 mM, [ester] = 12.5 mM. [c] $[SmI_2]$ = 75 mM, $[H_2O]$ = 250 mM, $[Et_3N]$ = 75–250 mM, [ester] = 12.5 mM. [d] $[SmI_2]$ = 75 mM, $[H_2O]$ = 75–300 mM, $[Et_3N]$ = 150 mM, [ester] = 12.5 mM. T = 23 °C.

At this stage of the investigation into the reaction mechanism, we learned from a related reduction of six-membered lactones using SmI_2–H_2O,[16,17] a process concurrently under investigation in our laboratory, that the rate of the latter reaction is significantly dependent on the concentration of water cosolvent. Accordingly, we further explored the impact of H_2O on the reduction rate of **1** by monitoring the rate of the reduction over a 20-fold concentration range as depicted in Figure 3. In this study,

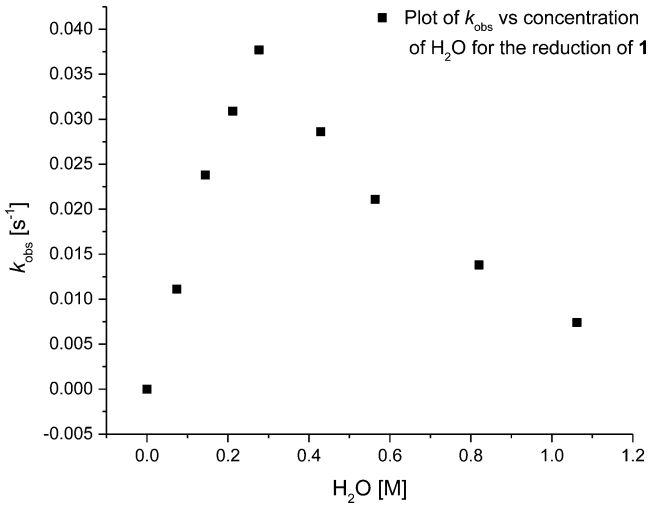


Figure 3. Plot of k_{obs} versus concentration of H_2O for the reduction of **1**. $[H_2O]$ = 0.075–1.2 M. $[SmI_2]$ = 75 mM, $[Et_3N]$ = 150 mM, [ester] = 12.5 mM, T = 23 °C.

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 1, consistent with saturation behavior (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 agreement with previous studies, H_2O is expected to show high affinity for Sm(II) and compete for coordination to Sm(II) with the carboxylic acid derivative.[13,14] Interestingly, the concentration of H_2O at which the decrease in the reaction rate is observed correlates with iodide displacement from the Sm(II) coordination sphere.[13c]

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 (morpholine, *n*-Bu_3N, Et_3N, *n*-$BuNH_2$, pyrrolidine: $v_{initial}$ = 2.4 × 10^{-4}; 3.9 × 10^{-5}; 5.0 × 10^{-4}; 6.8 × 10^{-3}; 8.8 × 10^{-3} mM s^{-1}, respectively).[27] Remarkably, a dramatic change in the reaction rate of over 2 orders of magnitude was found by simply using different amines for the reduction. Considering steric properties exerted by these amines, our findings bode well for the

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988–12003

chemoselective fine-tuning of Sm(II)−amine reductants to specific functional groups.

To elucidate the productivity difference in the SmI_2−amine−H_2O mediated reduction of esters, we utilized intermolecular competition studies (Table 2).[18c] Remarkably, in the series of eight methyl esters a reactivity range of over 3 orders of magnitude was observed, depending on steric and electronic properties of the α-carbon substituent at the ester group undergoing the reduction (entries 1−8). This effect is consistent with both electronic stabilization of ketyl-type radicals (entries 1−4) and steric inhibition of coordination to Sm(II) (entries 4−8). Moreover, several substrates with enhanced leaving group ability compared with the methyl ester were examined (entries 9−14). These results support the importance of electronic stabilization of ketyl radical intermediates in the reduction.[28] The data presented in Table 2 indicate high levels of chemoselectivity in the reduction of esters with SmI_2−Et_3N−H_2O.[2j]

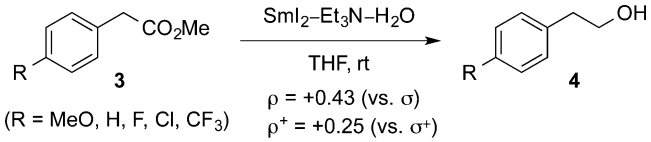
Table 2. Role of Steric and Electronic Effects on the Relative Rates for the Reduction of Esters

entry	CO_2Me	RV[a]
1	Ph	>100
2	Ph	9.14
3	Ph	4.29
4	C_9H_{19}	1.00
5	R, R = nC_5H_{11}	0.41
6		0.26
7	Ph, Me	0.91
8	*n*-Hex, *n*-Bu	0.05

entry	Ph 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
13[b]	R = OCH_2CF_3	1.72 (3.12)
14[b]	R = OCH_2CH_2OMe	1.76 (3.20)

[a]Relative reactivity values determined from product distribution by ^1H NMR or GC of crude reaction mixtures. [b]Relative reactivity values vs the corresponding ethyl esters are shown in parentheses. All data represent the average of at least two experiments.

Evidence for the electronic and steric stabilization of ketyl-type radical intermediates was further substantiated by Hammett (Figure 4)[29] and Taft correlation studies (Figure 5).[30] The Hammett correlation study, employing methyl esters of 4-phenylacetic acid (note that 4-substituted benzyl alcohols undergo reductive cleavage of benzyl heteroatom bonds),[26e] 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.[29] In addition, a good correlation was obtained by plotting $\log(k_{obs})$ vs Hammet−Brown σ^+ constants,[31] which may suggest that resonance effects are involved in stabilization of the reactive center. The Taft correlation study, obtained by plotting $\log(k_{obs})$ vs E_S in a series of aliphatic esters of hydrocinnamic acid showed a large positive slope of 0.83 (R^2 = 0.97). Overall, these results suggest that an anionic intermediate



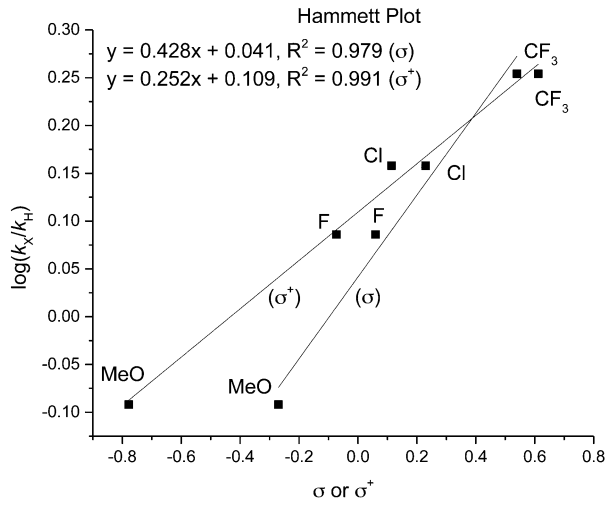
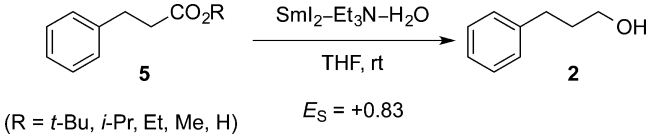


Figure 4. Plot of log k vs σ and σ^+ for the reduction of 4-phenylacetic acid methyl esters with SmI_2−Et_3N−H_2O. [Ester] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.



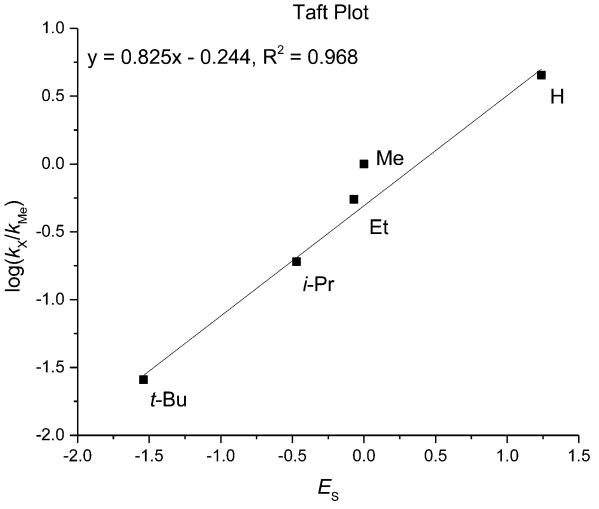


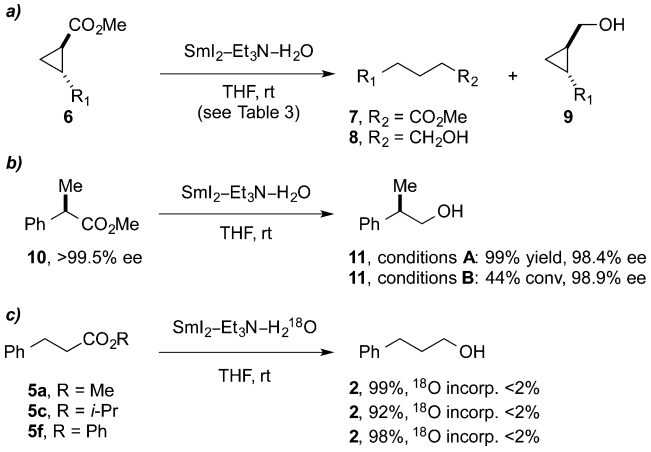
Figure 5. Plot of log k vs E_S for the reduction of hydrocinnamic acid esters with SmI_2−Et_3N−H_2O. [Ester] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988−12003

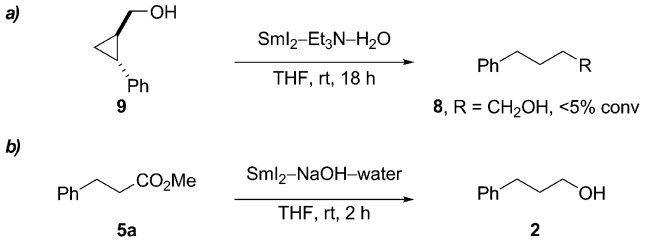
is formed in the transition state of the reaction and that a conformational change is taking place in the rate-determining step of the reaction. Note that the geometry and conformational preferences of ketyls, hydroxyalkyl radicals, and hydroxyalkyl carbanions indicate that ketyl radicals are planar.[32] As suggested by the Taft plot, the overall transformation from ketyl to hydoxyalkyl carbanion can be compared with a change in geometry similar to the ester hydrolysis (sp^2 to sp^3).[33]

Next, to gain independent evidence on the nature of the electron transfer steps, we carried out several studies employing mechanistic probes[34] and labeling experiments (Scheme 1 and Table 3): (1) Most importantly, *trans*-cyclopropane-containing radical clock (R_1 = Ph, approximated unimolecular rate constant k_{frag} = ca. 3×10^{11} s^{-1} at 25 °C)[35,36] was selected and subjected to the reaction conditions with a limiting amount of SmI_2 (Scheme 1a and Table 3, entries 1). The reaction resulted in rapid cyclopropyl ring opening to give acyclic ester **7** and alcohol **8** in 94:6 ratio. Cyclopropyl carbinol **9** was not detected in the reaction. (2) Several control experiments were performed (Scheme 1a, Table 3, entries 2–8).[37] The reaction with SmI_2–H_2O resulted in a facile opening, with no over-reduction to **8** or **9** observed. The reductive opening of radical clock was not observed with other Sm(II) reagents, including systems with higher redox potential (SmI_2–MeOH, SmI_2–LiCl, SmI_2–HMPA, and SmI_2–Et_3N). The reductive opening of cyclopropyl carbinol does not occur under the reaction conditions (Scheme 2a). (3) The reduction of the methyl ester of cyclopropanecarboxylic acid (Scheme 1a, Table 3, entries 9–11, R = H, approximated unimolecular rate constant k_{frag} = ca. 9.4×10^7 s^{-1} at 25 °C) with SmI_2–amine–H_2O afforded the corresponding acyclic alcohol and cyclopropyl carbinol in 96:4 ratio. This allows us 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}.[34−36] (4) Experiments utilizing chiral probe **10** (Scheme 1b) demonstrate that enolization does not occur in the process despite basic reaction conditions. (5) Control experiments using $H_2{}^{18}O$ (Scheme 1c) show that the reduction does not proceed via sequential ester hydrolysis/acid reduction mechanism. (6) Control experiments with a SmI_2–base system (Scheme 2b, modified Kamochi–Kudo conditions)[38] demonstrate that under optimized reaction conditions SmI_2–NaOH–H_2O reduces aliphatic esters in high yield. Overall, these findings strongly suggest that reductions of unactivated esters with SmI_2–amine–H_2O occur via fast, reversible electron transfer[39] and indicate that electron transfer using simple SmI_2–H_2O complexes (i.e., without amine) to aliphatic esters is rapid.[40]

Scheme 1. Experiments Designed To Investigate Mechanism of the Reduction of Unactivated Esters using SmI_2–Et_3N–H_2O: (a) Radical Clock Studies; (b) Racemization Studies; (c) ^{18}O Incorporation Studies



Scheme 2. Additional Control Experiments: (a) Reductive Opening of Cyclopropyl Carbinol; (b) Reduction Using SmI_2–NaOH–H_2O (Kamochi–Kudo Conditions)



Mechanism of Carboxylic Acid Reduction (Section B). Following our successful use of the SmI_2–amine–H_2O reagent for the reduction of unactivated esters,[20] in 2012, we reported the first general reduction of unactivated carboxylic acids using

Table 3. Radical Clock Experiments in the Reduction of Esters Using SmI_2–Et_3N–H_2O and SmI_2–H_2O Reagents

entry	R_1	SmI_2 (equiv)	Et_3N (equiv)	H_2O (equiv)	time[a]	conv[b] (%)	**7**[b] (%)	**8**[b] (%)	**9**[b] (%)
1	Ph	4	24	24	<1 min	80	75	5	<2
2	Ph	8	48	48	2 h	>98	<2	>98	<2
3	Ph	8		200	2 h	53	53		<2
4	Ph	4	48		2 h	<2[c]			<2
5	Ph	4			72 h	<2			<2
6[d]	Ph	4			2 h	dec.			<2
7[e]	Ph	4			2 h	<2			<2
8[f]	Ph	4			2 h	<2			<2
9[g]	H	2	24	24	2 h	62.8	34.2	26.6	2.0
10[g]	H	8	48	48	2 h	>98	<2	93.6	6.4
11[h]	H	8		200	2 h	<2			<2

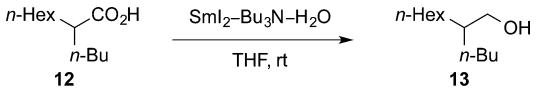
[a]Quenched with air after the indicated time. [b]Determined by ^1H NMR or GC-MS of crude reaction mixtures and comparison with authentic samples. In all entries, >90% combined yield of **7** and **8** based on the recovered starting material. In all entries, when <2% is indicated, **9** was not detected. [c]66:34 ratio of ester to acid. [d]HMPA, 24 equiv, was used. [e]LiCl, 48 equiv, was used. [f]MeOH, 370 equiv, was used (4/1 v/vol). [g]Morpholine was used instead of Et_3N. [h]<2% conv. using SmI_2, 8 equiv and H_2O, 800 equiv at rt for 2 h.

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988–12003

SmI_2.[21] It should be noted that in contrast to other functional groups addressed in this study, the reduction of unactivated carboxylic acids had been previously described by Kamochi and Kudo using SmI_2–base systems;[38] however, this process was low yielding and limited in scope. The successful application of Sm(II) systems other than SmI_2–amine–water to the reduction of carboxylic acids suggested the following: (1) this functional group is more accessible to efficient electron transfer from Sm(II) than other carboxylic acid derivatives; and (2) high chemoselectivity in the reduction of carboxylic acids can be achieved using Sm(II). This proved to be the case in our synthetic studies.[21]

As in the studies on the mechanism of the reduction of esters with SmI_2–amine–water, we started our investigation by conducting kinetic experiments (Table 4). The reduction of 2-butyloctanoic acid (**12**) using Bu_3N as the amine ligand was selected as a model reaction because the rate of reduction of **12** was found to be in a convenient range for kinetic studies under these conditions. It should be noted that all kinetic experiments in this study were performed under experimental conditions similar to those employed in synthetic studies to gain insight into the mechanism under experimentally relevant conditions.[20−22,24,25] Variations between kinetics performed under pseudo-first-order and preparative experimental conditions under have been reported.[16,33,39] Reaction conditions available for the reduction of unactivated carboxylic acids with a variety of SmI_2–amine–water systems have been published.[21]

Table 4. Rate Constant and Reaction Orders for the Reduction of 2-Butyloctanoic Acid Using SmI_2–Bu_3N–H_2O



	rate order			
k^a [M^{-4} s^{-1}]	substrate[a]	SmI_2[b]	Bu_3N[c]	H_2O[d]
2.5×10^2	0.93 ± 0.10	1.93 ± 0.10	0.94 ± 0.10	1.01 ± 0.10

[a][SmI_2] = 75 mM, [H_2O] = 250 mM, [Bu_3N] = 150 mM, [acid] = 5–20 mM. [b][SmI_2] = 50–75 mM, [H_2O] = 200 mM, [Bu_3N] = 125 mM, [acid] = 10.5 mM. [c][SmI_2] = 75 mM, [H_2O] = 250 mM, [Bu_3N] = 75–250 mM, [acid] = 12.5 mM. [d][SmI_2] = 75 mM, [H_2O] = 75–112 mM, [Bu_3N] = 150 mM, [acid] = 12.5 mM. Negative rate order (−0.48) for [H_2O] = 112–225 mM. T = 23 °C.

Within experimental error, the reduction of **12** with SmI_2–Bu_3N–H_2O was found to be first order in acid, second order in SmI_2, first order in amine, and first order in water at lower concentration of water (Table 4). The rate constant of $(2.5 \pm 0.1) \times 10^2$ M^{-4} s^{-1} was determined for the reduction of **12** under these conditions. In summary, these results suggested that all reaction components were involved in the rate equation. The rate order of two for SmI_2 most likely results from the formation of a dimeric SmI_2 complex with a dimerization process promoted by water or amine,[26a,b] or formation of the Sm(III) carboxylate under the reaction conditions.[38] The rate order of two for SmI_2 may also suggest that the reduction proceeds in two steps with the latter being rate determining.[39] The rate order of one for amine, acid, and water indicates that the mechanism of the reduction of carboxylic acids bears similarities to the mechanism of the reduction of esters under these reaction conditions.

Interestingly, the reduction of **12** was found to display a nonlinear rate dependence on water concentration (linear increase up to 112 mM) with a dramatic decrease of the rate at higher concentrations (112–225 mM). As such, the reduction of carboxylic acids is significantly more sensitive to changes in the concentration of water than the reduction of esters (vide supra),[6,13−15] which can be explained by the higher Lewis basicity of the carboxylic acid/carboxylate ligand in the transition state of the reaction.[41] This effect is consistent with substrate displacement from the inner coordination sphere of Sm(II) and previous studies.[13c,26d,16] The rate dependence on the amine component in the reduction of **12** was found to follow a similar order as the rate of the reduction of esters (*n*-Bu_3N, Et_3N, pyrrolidine: $v_{initial}$ = 9.1×10^{-3}; 1.3×10^{-2}; 1.6×10^{-2} mM s^{-1}, respectively).[27] The kinetic data are consistent with the role of the steric and electronic properties of the amines in enhancing the redox potential of the Sm(II) reductant, as well as with the increased negative charge of the reductant by coordination of an anionic carboxylate ligand. Finally, control experiments indicated that water is required for the reduction of carboxylic acids under these conditions (<2% conversion in the absence of water), which rules out the role of carboxylic acid acting as a proton source in the reduction.[42] However, the recent findings should also be considered.[43]

Having determined kinetics of the reduction of carboxylic acids, we turned our attention to intermolecular competition studies to gain insight into the productivity difference in the SmI_2–amine–water mediated reduction of carboxylic acids using a set of eight carboxylic acids as a benchmark for comparison with the reduction of esters under otherwise identical reaction conditions (Table 5; cf. Table 2).[18c]

Table 5. Role of Steric and Electronic Substitution on the Relative Rates of Reduction of Carboxylic Acids

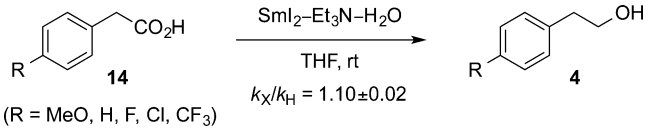
entry	CO_2H	RV[a]
1	Ph	5.73
2	Ph	1.48
3	Ph	1.47
4	C_9H_{19}	1.00
5	R, R = nC_5H_{11}	0.83
6		0.58
7	Ph, Me	0.87
8	*n*-Hex, *n*-Bu	0.17

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

Remarkably, in the series of eight derivatives a change of the reactivity range from 3 orders of magnitude (esters, Table 2) to 1 order of magnitude (acids, Table 5) was observed, consistent with the flattening out effect in the reduction rate of carboxylic acids using SmI_2–amine–water observed during the kinetic studies. Moreover, the reduction of 4-phenylacetic acids using SmI_2–amine–water (Hammett study, Table 6)[29] showed a flat k_X/k_H of 1.10 ± 0.02, providing further evidence for the relative insensitivity of the reduction rate of carboxylic acids to electronic

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988−12003

Table 6. Effect of Substitution on the Relative Rates for the Reduction of 4-Phenylacetic Acids Using SmI_2–Et_3N–H_2O[a]



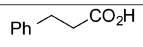
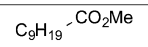
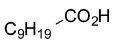
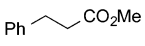
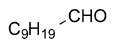
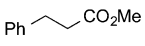
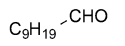
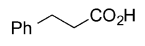
(R = MeO, H, F, Cl, CF_3)

entry	R	σ	RV[b]
1	CF_3	0.54	1.08
2	Cl	0.23	1.09
3	F	0.06	1.12
4	H	0	1.00
5	MeO	−0.27	1.10

[a]Conditions: [acid] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C. [b]Relative reactivity values determined from product distribution by ^{1}H NMR or GC of crude reaction mixtures.

and steric components on the substrate, consistent with the formation of a negatively charged intermediate and strong coordination to Sm(II) during the transition state of the reaction. Finally, to test the role of electronic activation in the relative rates of the reduction of carboxylic acids, we performed competition experiments with electronically differentiated esters and aldehydes (Table 7). The data in Table 7 indicate that the

Table 7. Effect of Electronic Activation on the Relative Rates of Reduction of Esters, Carboxylic Acids, and Aldehydes Using SmI_2–Et_3N–H_2O

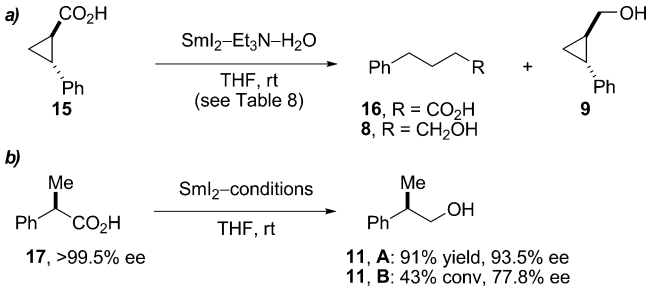
entry	acid/aldehyde	ester/acid	RV[a]
1			3.59
2			1.51
3			8.39
4			9.89

[a]Relative reactivity values determined from product distribution by ^{1}H NMR or GC of crude reaction mixtures. All data represent the average of at least two experiments.

chemoselectivity of the reduction of esters and carboxylic acids can be significantly influenced by a judicious choice of the electronics of the substrate, which may have important consequences from a synthetic perspective. Moreover, the data in Table 7 suggest that the reduction of aldehydes under these conditions is under thermodynamic control, which could be due to the reversibility of the first electron transfer or formation of hydrated hemiacetals.[44] Relative rates for the reduction of carboxylic acids,[21] esters,[20] and aldehydes[11] have been published.

Next, experiments employing mechanistic probes were carried out to establish reversibility of the electron transfer[34,40] in the reduction of carboxylic acids with SmI_2–amine–water and the potential for racemizaton of a chiral α-stereocenter under the reaction conditions (Scheme 3 and Table 8): (1) Most importantly, *trans*-cyclopropane-containing radical clock **15** was subjected to the reaction conditions with a limiting amount of SmI_2 (Scheme 3a and Table 8, entry 1).[35,36] The reaction resulted in rapid cyclopropyl ring opening to give acyclic acid **16** and alcohol **8** in 78:22 ratio. Cyclopropyl carbinol **9** was not detected in the reaction. (2) Several control experiments were

Scheme 3. Experiments Designed To Investigate the Mechanism of the Reduction of Unactivated Carboxylic Acids using SmI_2–Et_3N–H_2O: (a) Radical Clock Studies; (b) Racemization Studies[a]



[a]Conditions: **A**: Et_3N (48 equiv), H_2O (48 equiv); **B**: NaOH(aq) (16 equiv, 4 N).

performed (Scheme 3a, Table 8, entries 2–7).[37] The reaction with excess of SmI_2 resulted in a full reduction to **8** (entry 2). The reaction with SmI_2–H_2O resulted in a facile opening, with no over-reduction to **8** or **9** observed (entry 3), and the rate dependence on water concentration was consistent with the previous studies (entry 5).[16,17] The reductive opening of the radical clock was not observed with SmI_2, SmI_2–amine, or SmI_2–MeOH systems (entries 4–5, 7). (3) Experiments utilizing chiral probe **17** (Scheme 3b) demonstrate that enolization does not occur to a significant extent in the reduction (the rate of ET is faster than the rate of enolization); however, note that the presence of a chiral α-stereocenter is not compatible with the reduction using SmI_2–NaOH (Scheme 3b, conditions B). The data in Table 8 strongly suggest that the reaction proceeds via reversible electron transfer and indicate that electron transfer using simple SmI_2–H_2O complexes (i.e., without amine) to aliphatic acids is rapid. In summary, these findings strongly suggest that reductions of unactivated acids with SmI_2–amine–H_2O occur via a similar mechanism to the reduction of unactivated esters with the major difference being a flattening out of the reaction rate due to the presence of a negatively charged carboxylate intermediate.

Mechanism of Amide Reduction (Section C). Building upon our experience in using Sm(II) reagents,[20,21] in 2014 we reported the first general reduction of amides to alcohols with SmI_2–amine–water.[22] The reaction was particularly significant because of the uncommon C–O/C–N cleavage selectivity for all types of amides (primary, secondary, tertiary) and the exceptionally mild reaction conditions that allow direct conversion of amides to alcohols under standard laboratory conditions.[45] Prior to our report, only a few methods for the reduction of amides to alcohols had been reported, and none of them displayed the generality of the SmI_2-mediated process.[23] Perhaps not surprisingly in light of the low electrophilicity of amide bonds,[46] during the development of the reaction we found that the reduction of amides is significantly more challenging than the reduction of other carboxylic acid derivatives. We hypothesized that detailed mechanistic studies would shed light on this process and allow for further optimization of the reaction conditions reported in our initial communication. From the outset, we realized that the key question pertained to the generality of the reduction mechanism, an answer to which could potentially provide insights into the use of similar reaction conditions to maximize the synthetic efficiency of the process. For comparison purposes, the discussion on the mechanism of amide reduction

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988–12003

Table 8. Radical Clock Experiments in the Reduction of Carboxylic Acids Using SmI_2–Et_3N–H_2O and SmI_2–H_2O Reagents

entry	SmI_2 (equiv)	Et_3N (equiv)	H_2O (equiv)	time[a]	conv[b] (%)	**16**[b] (%)	**8**[b] (%)	**9**[b] (%)	yield[b] (%)
1	2	24	24	<1 min	44	34	9.5	<2	44
2	8	48	48	2 h	>98		96	<2	96
3	8		200	2 h	15	15		<2	15
4	8			2 h	<2			<2	<2
5	8	48		2 h	<2			<2	<2
6	8		48	2 h	8.3	8.3		<2	8
7[d]	8		615 (MeOH)	2 h	<2[d]			<2	<2

[a]Quenched with air after the indicated time. [b]Determined by ^{1}H NMR or GC-MS of crude reaction mixtures and comparison with authentic samples. In all entries, when <2% is indicated, **9** was not detected. [d]MeOH instead of H_2O was used (4/1 v/vol).

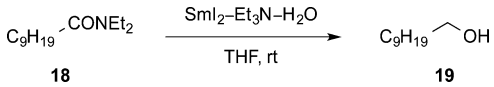
follows the same format as the discussion of the reduction of unactivated esters and carboxylic acids.

We started our investigation by conducting a range of kinetic studies (Table 9). *N*,*N*-Diethyldecanamide (**18**) was selected as a model substrate because its rate of reduction was found to be in a convenient range for kinetic studies. The reduction of *N*,*N*-diethyldecanamide displayed a well-behaved kinetic profile throughout the course of the reaction. Reaction conditions for the reduction of amides using SmI_2–amine–water have been published.[22] Within experimental error, the reduction of **18** with SmI_2–Et_3N–H_2O was found to be first order in SmI_2, first order in amine, and first order in H_2O at low concentration of water. The reaction displayed half-order dependence on amide concentration. The rate constant of $(1.7 \pm 0.1) \times 10^{-1}$ M^{-1} s^{-1} was determined for the reduction of **18** under these reaction conditions. The observed rate order for the amide most likely results from the formation of a complex between the Lewis basic substrate and the reagent,[26e,41] in which the amide competes for coordination with amine/water at the Sm(II) center; however, formation of amide dimers could also contribute to the observed rate order.[47] The rate order of one for SmI_2, amine, and water indicates that the mechanism of the reduction of amides bears significant similarities to the reduction of unactivated esters and carboxylic acids under these reaction conditions. In addition, the reduction of **18** also displays a nonlinear rate dependence on water concentration (linear increase up to 112 mM) with a dramatic decrease of the rate at higher concentrations (112–225 mM), which is analogous to the effect of the concentration of water on the rate of the reduction of carboxylic acids (vide supra).[6,13–15] This effect is consistent with the coordination of the substrate to the Sm(II) center. Moreover, the rate dependence on the amine component in the reduction of **18** follows a similar order as for the reduction of esters and acids (Et_3N, pyrrolidine: $v_{initial}$ = 5.4×10^{-4}; 5.6×10^{-3} mM s^{-1}, respectively).[27] Taken together, these results strongly suggest that the role of amine and water components in the reduction of esters, acids, and amides in this Sm(II) reducing system shares significant similarities between the substrates and is not significantly influenced by the relative redox potentials and coordination abilities of the substrates. Considering steric properties of amines with varying pK_{BH^+} values,[27] these observations suggest that chemoselective fine-tuning of Sm(II)–amine reductants to specific functional groups should be possible.[2j] The relative reactivity of functional groups with SmI_2–amine–water systems has been published.[20–22]

To elucidate how steric and electronic parameters influence the rate of amide reduction, we conducted a set of intramolecular competition experiments across a selected series of benchmark substrates with varying electronic and steric properties (Table 10).[18c] All values presented in Table 10 are normalized versus decanamides. Interestingly, the study revealed significant differences in the reduction rate between primary (10-fold difference in reactivity), secondary, and tertiary amides (>100-fold difference in reactivity across the five benchmark substrates), with the largest relative difference observed for secondary amides. This effect is similar to the flattening out effect observed in the reduction of unactivated carboxylic acids under the same reaction conditions.

Next, Taft[30] and Hammett[29] correlation studies were carried out to gain additional insight into the mechanism of amide reduction (Figures 6–9). Taft correlation (Figure 6) was obtained by plotting $\log(k_{obs})$ vs E_S in a series of *N*-mono and *N*,*N*-disubstituted 3-phenylpropanamides and showed large

Table 9. Rate Constant and Reaction Orders for the Reduction of *N*,*N*-Diethyldecanamide using SmI_2–Et_3N–H_2O



18 19

	rate order			
k[a] [M^{-1} s^{-1}]	substrate[a]	SmI_2[b]	Et_3N[c]	H_2O[d]
1.7×10^{-1}	0.50 ± 0.10	0.93 ± 0.10	0.94 ± 0.10	0.84 ± 0.10

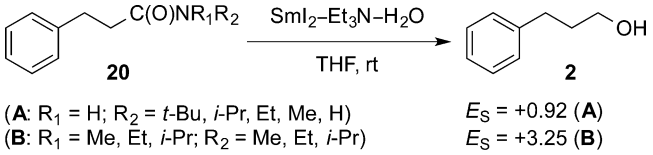
[a][SmI_2] = 75 mM, [H_2O] = 250 mM, [Et_3N] = 150 mM, [amide] = 5–20 mM. [b][SmI_2] = 50–75 mM, [H_2O] = 200 mM, [Et_3N] = 125 mM, [amide] = 10.5 mM. [c][SmI_2] = 75 mM, [H_2O] = 250 mM, [Et_3N] = 75–250 mM, [amide] = 12.5 mM. [d][SmI_2] = 75 mM, [H_2O] = 75–112 mM, [Et_3N] = 150 mM, [amide] = 12.5 mM. Negative rate order (−0.37) for [H_2O] = 112–225 mM. T = 23 °C.

Table 10. Effect of Steric and Electronic Substitution on the Relative Rates of Reduction of Amides Using SmI_2–Et_3N–H_2O

entry		R = NH_2 RV[a]	R = NHBu RV[a]	R = NEt_2 RV[a]
1		3.57	>100	>100
2		3.39	6.18	5.33
3		2.10	2.38	2.24
4		0.52	0.29	0.42

[a]Relative reactivity values determined from product distribution by ^{1}H NMR or GC of crude reaction mixtures. All values are normalized vs $C_9H_{19}COR$.

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988–12003



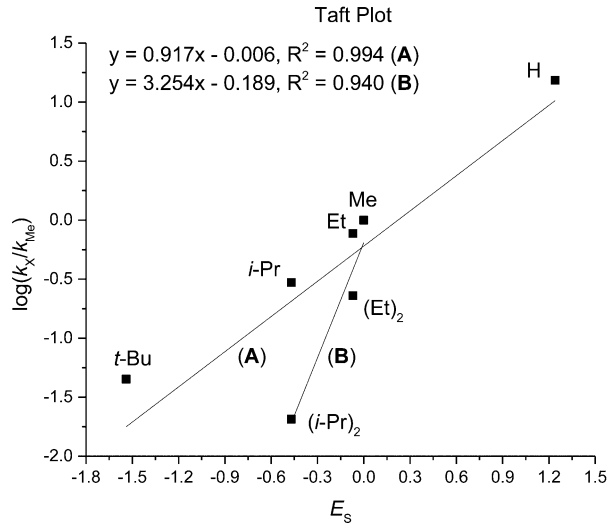
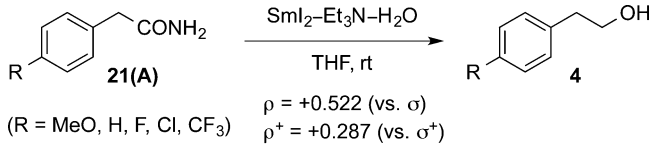


Figure 6. Plot of log k vs E_S for the reduction of *N*-mono and *N*,*N*-disubstituted 3-phenylpropanamides with SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.

positive slopes of 0.92 (R^2 = 0.99) and of 3.25 (R^2 = 0.94) for the reduction of secondary and tertiary amides, respectively. This can be compared with a positive slope of 0.97 determined earlier for the reduction of aliphatic esters of hydrocinnamic acid. Taken together, these findings indicate that steric factors play a significant role in the reduction of carboxylic acid derivatives with SmI_2–amine–water. The slow reaction rate caused by inhibition of Sm(II)-coordination to carbonyl groups due to steric factors has been previously reported.[16b]

Hammett correlation studies (Figures 7–9) were conducted for various para-substituted 2-phenylacetamides and showed large positive ρ-values of 0.52 (R^2 = 0.98) (Figure 7) and of 0.60 (R^2 = 0.90) (Figure 9) for the reduction of primary and tertiary amides, respectively, which can be compared with the ρ-value of 0.43 determined for the reduction of methyl esters of 4-phenylacetic acid determined earlier, and a small positive ρ-value of 0.13 (R^2 = 0.99) (Figure 8) for the reduction of secondary amides under identical reaction conditions. Previously, it has been shown that 4-substituted benzyl alcohols undergo reductive cleavage of benzyl heteroatoms.[26e] In the reduction of *para*-trifluoromethyl-substituted primary amides, a competing defluorination reaction was observed under these reaction conditions,[26f] and these substrates were not included. In addition, typically good correlations were obtained by plotting log(k_{obs}) vs Hammet–Brown σ^+ constants for the reduction of amides with SmI_2–amine–water,[31] which suggests that resonance effects are involved in stabilization of the reactive center. In summary, Hammett correlation studies in the reduction of amides suggest the following: (1) an anionic intermediate is formed in the transition state of the reaction; (2) the reaction of primary and tertiary amides bears analogies to the reduction of unactivated esters under the SmI_2–amine–water conditions in terms of electronic stabilization of the anionic intermediate in the transition state of the reaction; and (3) the reaction of secondary amides bears similarities to the reduction of unactivated carboxylic acids under the SmI_2–amine–water conditions in that an additional negative charge is present in the transition state of the reaction (i.e., N–H deprotonation or formation of carboxylate occurs prior to the rate-determining step of the reaction).



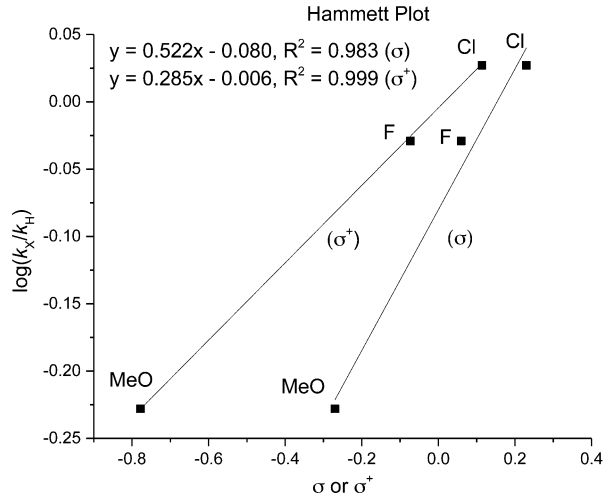
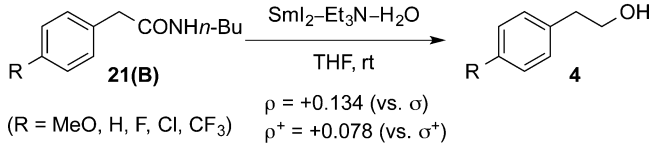


Figure 7. Plot of log k vs σ and σ^+ for the reduction of 2-phenylacetamides with SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.



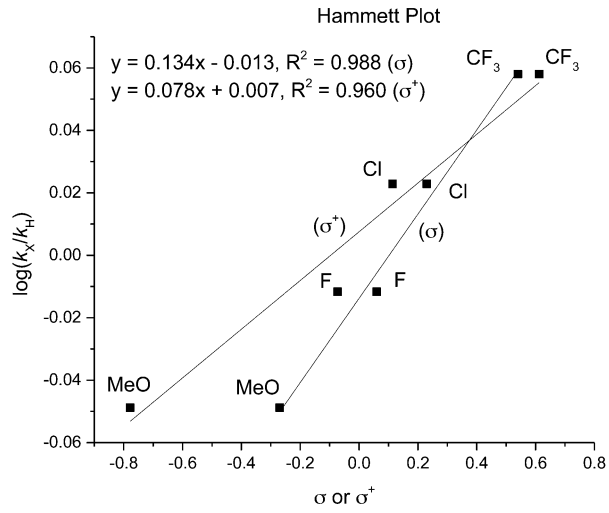


Figure 8. Plot of log k vs σ and σ^+ for the reduction of *N*-alkyl 2-phenylacetamides with SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988–12003

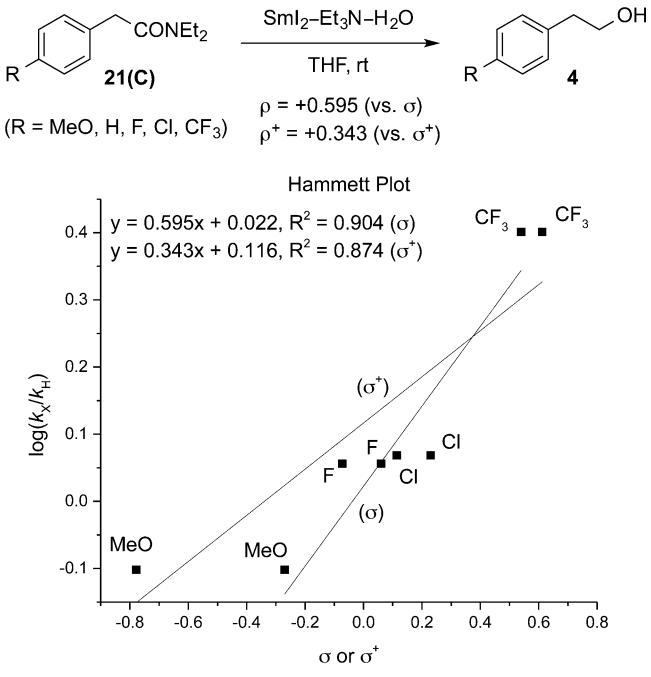
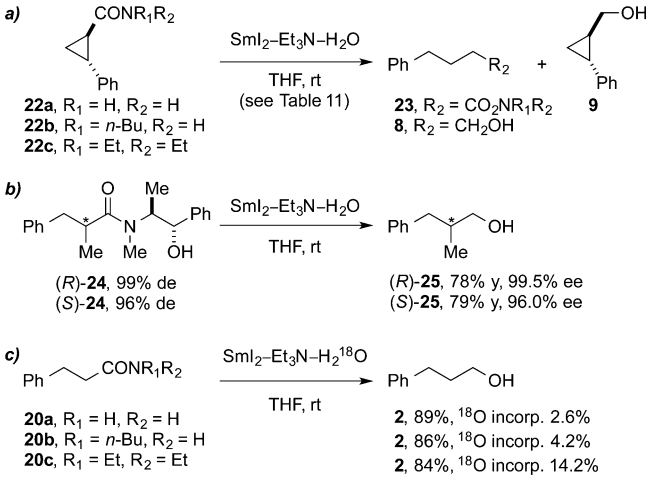


Figure 9. Plot of log k vs σ and σ^+ for the reduction of *N*,*N*-dialkyl 2-phenylacetamides with SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.

Studies employing mechanistic probes[34,40] and labeling experiments were conducted to elucidate the nature of the electron transfer steps and to probe the potential for racemization and hydrolysis under the reaction conditions (Scheme 4 and Table 11): (1) Most importantly, *trans*-

Scheme 4. Experiments Designed To Investigate the Mechanism of the Reduction of Unactivated Amides Using SmI_2–Et_3N–H_2O: (a) Radical Clock Studies; (b) Racemization Studies; (c) ^{18}O Incorporation Studies



cyclopropane-containing radical clock **22** was subjected to the reaction conditions with a limiting amount of SmI_2 (Scheme 4a and Table 11, entries 1–3).[35,36] The reaction resulted in rapid cyclopropyl ring opening to give acyclic amides **23** and alcohol **8** in 78:22, 85:15, and 92:8 ratio (primary, secondary, and tertiary amides, respectively). Cyclopropyl carbinol **9** was not detected in the reaction. (2) Several control experiments were performed (Scheme 4a, Table 11, entries 4–12).[37] The reaction with excess SmI_2 resulted in a full (primary and secondary) and significant (tertiary) reduction to **8** (entries 4–6). The reaction with SmI_2–H_2O resulted in cyclopropyl opening, with no over-reduction to **8** or **9** observed (entries 7–9); note that reactions in entries 4–10 have not been optimized. The reductive opening of the radical clock was not observed with the SmI_2–THF system (entries 10–12). (3) Experiments utilizing chiral probe **24** (Scheme 4b)[22,23c] demonstrate that enolization does not occur in the reduction despite basic reaction conditions. (4) Control experiments using $H_2{}^{18}O$ (Scheme 4c) show that amide and/or iminium hydrolysis are not the major reaction pathways with the extent of ^{18}O incorporation consistent with the relative stability of the iminium intermediates.[48]

The data in Table 11 strongly suggest that the reduction of amides proceeds via a reversible electron transfer and indicate that electron transfer using simple SmI_2–H_2O complexes (i.e., without amine) to unactivated amides is feasible, but this process is slower than that from Sm(II) to the corresponding esters and carboxylic acids as would be expected on the basis of the relative electrophilicity of the carbonyl groups. In summary, these findings demonstrate that reductions of unactivated amides with SmI_2–amine–H_2O occur via a similar mechanism to the reduction of unactivated esters and carboxylic acids with the major difference being a flattening out of the reaction rate due to steric factors (primary amides), the presence of a negatively charged intermediate (secondary amides), and inhibition of coordination of Sm(II) center (tertiary amides).

Additional Radical Clock Experiments. Previous studies have shown that different Sm(II)-based reducing systems are capable of efficiently promoting electron transfer to the carbonyl groups of carboxylic acid derivatives.[20–22,24,25] As shown in Tables 3, 8, and 11, SmI_2–water was one of the examined systems that promoted the reductive opening of cyclopropyl radical clocks; however, under the reaction conditions, further reduction to the alcohol was not observed, consistent with the higher chemoselectivity of the reagent (cf., SmI_2–Lewis base–water reagents).[2j]

To compare the reactivity of SmI_2–water and SmI_2–amine–water reagents and to gain insights into the relative rates of the first electron transfer[34,35] a set of competition studies was designed and carried out (Table 12). The relative reactivity values were determined from the product distribution of the C–C cleavage products.[18c] In these experiments, further reduction to the alcohol is typically not observed or results from the reduction of the more reactive carboxylic acid derivative as shown in Tables 2, 5, and 10. The studied substrates do not participate in alternative reaction pathways. This method allows us to accurately measure the relative energy barriers for the first electron transfer to carboxylic acid derivatives and stability of the resulting radicals using various Sm(II)-based systems.

As shown in Table 12 (entries 1–4), comparison of the relative reactivity toward the first electron transfer of esters with varying steric (entries 1–2) and electronic (entries 3–4) properties reveals the following: (1) the radical formed from a *tert*-butyl ester is significantly less stable than the radical formed from a methyl ester using SmI_2–amine–water (entry 1); however, the stability of these radicals is similar when using SmI_2–water (entry 2); (2) the stability of radicals formed from a methyl and a pfp ester is similar when using SmI_2–amine–water (entry 3); however, the radical formed from a methyl ester is significantly less stable when using SmI_2–water (entry 4). These effects are consistent with the stabilization of ketyl radicals with SmI_2–amine–water relative to SmI_2–water and the fact that SmI_2–

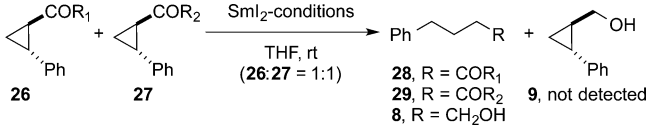
dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988–12003

Table 11. Radical Clock Experiments in the Reduction of Amides Using SmI_2–Et_3N–H_2O and SmI_2–H_2O Reagents

entry	22	SmI_2 (equiv)	Et_3N (equiv)	H_2O (equiv)	time[a]	conv[b] (%)	23[b] (%)	8[b] (%)	yield[b] (%)
1	**22a**	2	24	24	<1 min	54	78	22	54
2	**22b**	2	24	24	<1 min	50	85	15	50
3	**22c**	2	24	24	<1 min	51	92	8	51
4	**22a**	8	72	72	18 h	>98	<2	>98	99
5	**22b**	8	72	72	18 h	>98	3	97	97
6	**22c**	8	72	72	18 h	>98	59	41	99
7	**22a**	8		200	2 h	39	>98	<2	39
8	**22b**	8		200	2 h	4	>98	<2	4
9	**22c**	8		200	2 h	10	>98	<2	10
10	**22a**	8			18 h	<5			<5
11	**22b**	8			18 h	<5			<5
12	**22c**	8			18 h	<5			<5

[a]Quenched with air after the indicated time. [b]Determined by ^1H NMR or GC-MS of crude reaction mixtures and comparison with authentic samples. In all entries, **9** was not detected (<2.0%). Combined yield of **23** and **8**. Conversion = (100 − SM).

Table 12. Radical Clock Experiments Designed To Investigate the Rate of Initial Electron Transfer to Sterically and Electronically Differentiated Carboxylic Acid Derivatives Using SmI_2–Et_3N–H_2O and SmI_2–H_2O Reductants



entry	R_1	R_2	conditions[a]	28[b] (%)	29[b] (%)	8[b] (%)	$k_{26/27}$
1	OMe	O*t*Bu	A	42	4	<5	11.5
2	OMe	O*t*Bu	B	82	41	<5	2.0
3	OMe	Opfp	A	7.5	8.5	8.5	0.44
4	OMe	Opfp	B	<2	26	20	<0.04
5	OMe	OH	A	29	24	<5	1.25
6	OMe	OH	B	60	6	<5	10.3
7	OMe	OH	C	21	67	<5	0.31
8	OMe	NH_2	A	3	44	20	0.04
9	OMe	NH_2	B	54	40	<5	1.35
10	OH	NH_2	A	15	29	16	0.52
11	OH	NH_2	B	19	34	<5	0.57

[a]Conditions: A, SmI_2 (2 equiv), Et_3N (24 equiv), H_2O (24 equiv); B, SmI_2 (8 equiv), H_2O (200 equiv); C, SmI_2 (2 equiv), NaOH (12 equiv), H_2O (24 equiv). Quenched with air after the indicated time. In all entries, preformed Sm(II) system was used. [b]Determined by ^1H NMR or GC-MS of crude reaction mixtures and comparison with authentic samples. In all entries, **9** was not detected (<2.0%).

amine–water systems are typically more sterically encumbered than SmI_2–alcohol reagents. Moreover, these findings demonstrate that the difference in rates in the reduction of methyl and pfp esters with SmI_2–amine–water may result from a decreased energy of activation (favoring the pfp ester) for the second electron transfer.

Examination of the relative rates for the first electron transfer to carboxylic acids (entries 5–7) reveals dramatic differences in reactivity between SmI_2–amine–water (entry 5), SmI_2–water (entry 6), and SmI_2–NaOH (entry 7) systems. The results are summarized as follows: (1) using SmI_2–amine–water, the ketyl radical formed from the ester is slightly more stable than the ketyl radical formed from acid; however after deprotonation to carboxylate, the ketyl stability significantly increases via inductive effect (cf. Table 7); (2) using SmI_2–water, the ketyl-type radical formed from the ester is significantly more stable than the ketyl-type radical formed from the acid; (3) using SmI_2–NaOH, the ketyl-type radical formed from the ester is significantly less stable than the ketyl-radical formed from the acid, which indicates that the formation of an anion stabilizes the ketyl. This in turn indicates that under SmI_2–amine–water conditions the carboxylic acid is partially deprotonated during the first electron transfer step (cf. Hammett studies and kinetic experiments in Table 5).

Finally, comparison of the relative rates for the first electron transfer to amides versus esters (entries 8–9) and acids (entries 10–11) using SmI_2–amine–water and SmI_2–water systems reveals the following features: (1) the stability of ketyl radicals formed from amides is much higher than that of radicals formed from esters using SmI_2–amine–water (entry 8); however, these radicals are similar in stability when using SmI_2–water (entry 9); (2) radicals formed from carboxylic acids are similar in stability to radicals formed from amides using SmI_2–amine–water (entry 10) and SmI_2–water systems (entry 11). These observations are consistent with the stabilization of ketyl-type radicals with SmI_2–amine–water and the Lewis basicity of the carboxylic acid derivative. Overall, the findings presented in Table 12 are consistent with the thermodynamic nature of the first electron transfer step under the examined reaction conditions.

Kinetic Isotope Effects.[49] Several types of deuteration and kinetic isotope studies with carboxylic acid derivatives using SmI_2–amine–water have been conducted.[20−22] A summary of these studies is presented in Table 13. Deuteration and KIE studies suggest that anions are protonated in a series of electron transfers and that proton transfer to carbon is not involved in the

Table 13. Summary of Deuterium Incorporation and Kinetic Isotope Effect Studies in the Reduction of Esters, Carboxylic Acids, and Amides Using SmI_2–Et_3N–H_2O

entry	substrate	D^2 [%]	k_H/k_D
1[a]	$PhCH_2CH_2CO_2i$-Pr	>97	1.4
2[b]	$PhCH_2CH_2CO_2H$	96.0	1.1
3[c]	$PhCH_2CH_2CONH_2$	83.2	1.4
4[c]	$PhCH_2CH_2CONHn$-Bu	94.7	1.3
5[c]	$PhCH_2CH_2CONEt_2$	96.9	1.3

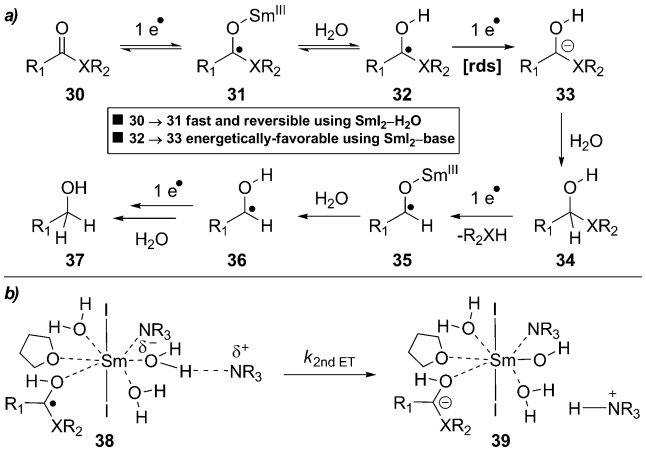
[a]Reference 20. [b]Reference 21. [c]Reference 22. KIE determined from intramolecular competition experiments or parallel runs. D^2 incorporation determined from reactions using D_2O instead of H_2O. See ref 16a for additional details.

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988−12003

rate-determining step of the reduction of unactivated esters, carboxylic acids, and amides with SmI_2–amine–water.[16,20−22]

Proposed Mechanism. The mechanistic studies presented in this manuscript indicate that reductions of unactivated esters, carboxylic acids, and amides with SmI_2–amine–water proceed via a generalized mechanism featuring the following steps: (1) reversible coordination, protonation, and first electron transfer steps; (2) rate-limiting second electron transfer step; (3) rapid hemiacetal/hemiaminal collapse and reduction to the alcohol product (Scheme 5). Several other features of the presented

Scheme 5. (a) Proposed Mechanism for the Reduction of Carboxylic Acid Derivatives Using SmI_2–H_2O–Amine Complexes and (b) Mechanism Describing the Final Step of the Electron Transfer to Carboxylic Acid Derivatives Using SmI_2–Et_3N–H_2O



mechanism are noteworthy: (i) inner-sphere electron transfer process that is inhibited by large concentrations of water and facilitated by Brønsted basic amines in the case of all three functional groups; (ii) rate-determining step that can be fine-tuned by steric and electronic properties of the carboxylic acid-derived substrate; (iii) change of the substrate ground state redox potential by coordination of the carbonyl group to the Lewis acidic SmI_2-reductant allowing efficient electron transfer.

The synthetic and mechanistic experiments indicate that in the reductions of carboxylic acid derivatives with SmI_2–amine–water, the reactive complex between SmI_2, water, and amine must be present in significant quantities.[26a] Within this complex, one molecule of amine participates in partial deprotonation of water, 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. The use of SmI_2–amine–water is advantageous over other Sm(II) systems due to the high redox potential of the reagent, which allows the reduction of traditionally unreactive functional groups under single electron transfer conditions.[2j] From a practical point of view, the pK_{BH^+} dependent deprotonation of H_2O in SmI_2–amine–H_2O complexes can have a profound impact on achieving high levels of chemoselectivity in the reductions of various substrates.

A summary of observed reaction orders for the reduction of carboxylic acid derivatives using SmI_2–H_2O–Et_3N is presented in eqs 1−3, which can be compared with the reduction of alkyl halides using SmI_2–H_2O–Et_3N (eq 4),[26b] deoxygenation of benzyl alcohols using SmI_2–H_2O–Et_3N at low concentrations of substrate and water (eq 5),[26e] and the reduction of six-membered lactones using SmI_2–H_2O at low concentration of water (eq 6).[16a] A summary of determined mechanistic parameters for the reduction of all three functional groups is presented in Chart 2.

$$d[\text{alcohol}]/dt = k[SmI_2]^1[H_2O]^1[Et_3N]^1[\text{ester}]^1 \quad (1)$$

$$d[\text{alcohol}]/dt = k[SmI_2]^2[H_2O]^1[Et_3N]^1[\text{acid}]^1 \quad (2)$$

$$d[\text{alcohol}]/dt = k[SmI_2]^1[H_2O]^1[Et_3N]^1[\text{amide}]^{0.5} \quad (3)$$

$$d[\text{R—H}]/dt = k[SmI_2]^2[H_2O]^0[Et_3N]^1[\text{R—X}]^1 \quad (4)$$

$$d[\text{R—CH}_2\text{H}]/dt = k[SmI_2]^1[H_2O]^1[Et_3N]^1[\text{RCH}_2\text{—OH}]^1 \quad (5)$$

$$d[1,5\text{-diol}]/dt = k[SmI_2]^1[H_2O]^2[\text{lactone}]^2 \quad (6)$$

Chart 2. Summary of Methods Employed in the Current Study To Determine the Mechanism of Reduction of the Three Functional Groups

parameter	esters	acids	amides
rate orders	+	+	+
non-linearity in [H_2O]	+	+	+
Hammett correlation	+	+[a]	+
Taft correlation	+	+	+
radical clock opening	+	+	+
^{18}O labeling[b]	-	nd	-
D_2 labeling[c]	+	+	+
KIE[d]	-	-	-

[a]Flat correlation was observed. [b]"–" sign indicates that ^{18}O incorporation was not observed. nd = not determined. [c]D_2 incorporation was observed. [d]"–" sign indicates that a significant primary KIE to carbon was not observed.

Recent findings demonstrate that reductions of carboxylic acids (SmI_2–amine–water)[20−22] and other carbonyl derivatives (SmI_2–water)[16] using distinct Sm(II) reductants share common mechanistic features, the most important being the thermodynamic character of the first electron transfer step and a nonlinear rate dependence on the water concentration.[2j,40] The recent advances in the understanding of processes mediated by SmI_2–amine–water complexes[26] should be considered in conjunction with other recent studies on the mechanisms of SmI_2-mediated reactions[13−15] in the future development of new SmI_2-promoted transformations.

■ CONCLUSIONS

We have described a detailed investigation into the mechanism of the SmI_2-mediated reduction of carboxylic acid derivatives (esters, acids, and amides) to alcohols. With minor differences noted in the manuscript, the overall mechanism for the transformation of all three functional groups is similar. Our data are consistent with the formation of distinct Sm(II) reductants by complexation between Sm(II), amine, and H_2O. The reduction appears to proceed after deprotonation of a molecule of H_2O by amine and to involve a reversible first electron transfer step. Our data demonstrate that a set of novel Sm(II) reductants that can be fine-tuned by the pK_{BH^+} of the amine component is available for challenging electron transfer

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988−12003

reactions to carboxylic acid derivatives. Most crucially, this work is one of the few studies showing that Sm(II) additives (e.g., H_2O, amine−H_2O) contribute to the stabilization of ketyl radical intermediates rather than to simply increasing the redox potential of the Sm(II) reductant. We fully expect that these findings will contribute to the development of new electron transfer reactions. The work in this direction is ongoing in our laboratories, and these results will be reported shortly.

EXPERIMENTAL SECTION

General Methods. All products and staring materials used in this study are commercially available or have been previously reported.[20−22] The products were identified using ^{1}H NMR, GC, and GC-MS analysis and comparison with authentic samples. The reaction progress was quantified by ^{1}H NMR or GC-MS analysis using internal standards after workup unless stated otherwise. Characterization data for all alcohol products have been previously reported. All experiments were performed using standard Schlenk techniques under argon atmosphere. All solvents were purchased at the highest commercial grade and used as received or after purification by passing through activated alumina columns or distillation from sodium/benzophenone under nitrogen. All solvents were deoxygenated by freeze−pump−thawing or sparging with argon prior to use. Samarium(II) iodide was prepared as described previously.[45] Samarium metal was purchased as −40 mesh and stored at room temperature in a closed container on a bench prior to use. 1,2-Diiodoethane was stored at 4 °C and used after purification as described previously.[45] All other chemicals were purchased at the highest commercial grade and used as received. Reaction glassware was oven-dried at 140 °C for at least 24 h or flame-dried prior to use, allowed to cool under vacuum, and purged with argon (three cycles). Other general methods have been published.[5b]

Procedure A. Kinetic Studies. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.10 M) was added followed by Et_3N and H_2O with vigorous stirring, which resulted in the formation of the characteristic dark brown color of the SmI_2−Et_3N−H_2O complex. A solution of substrate (stock solution in THF) was added, and the reaction mixture was vigorously stirred under argon. Small aliquots (typically, 0.25 mL) were removed from the reaction mixture at set time intervals, immediately quenched by bubbling air through the reaction mixture, diluted with diethyl ether (2.0 mL) and HCl (0.1 *N*, 0.25 mL), and analyzed by GC or GC-MS to obtain yield and product distribution using internal standard and comparison with authentic samples: Agilent HP-5MS (19091S-433) (length 30 m, internal diameter 0.25 mm, film 0.25 μm), He as the carrier gas, flow rate 1 mL/min, initial oven temp 90 °C, 10 °C/min ramp, after 90 °C hold for 3 min to 220 °C, then hold at 220 °C for 5 min. Ester kinetics: product = 11.50 min; starting material = 12.55 min; standard = 12.45 min. Acid kinetics: product = 14.73 min; starting material = 16.09 min; standard = 14.94 min. Amide kinetics: product = 9.39 min; starting material = 15.29 min; standard = 13.69 min.

Procedure B. Relative Reactivity Studies. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.20 mmol, 2.0 equiv, 0.10 M) was added followed by Et_3N (0.33 mL, 24 equiv) and H_2O (0.043 mL, 24 equiv) with vigorous stirring, which resulted in the formation of the characteristic dark brown color of the SmI_2−Et_3N−H_2O complex. A preformed solution of two substrates (each 0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred until decolorization to white had occurred. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and HCl (1 *N*, 30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL); the organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion and yield using internal standard and comparison with authentic samples.

Procedure C. Radical Clock Studies. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.20−0.80 mmol, 2.0−8.0 equiv, 0.10 M) was added followed by Et_3N and H_2O with vigorous stirring, which resulted in the formation of the characteristic dark brown color of the SmI_2−Et_3N−H_2O complex. A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred for the indicated time. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture. Workup and analysis was performed as described for method B. In all other cases, the Sm(II) reagent was preformed by adding the specified additive to the SmI_2 solution prepared as described above and stirring until the color characteristic to a particular Sm(II) complex had appeared (SmI_2−H_2O, burgundy red; SmI_2−MeOH, dark brown; SmI_2−HMPA, purple; SmI_2−LiCl, green; SmI_2−Et_3N, dark blue).

Procedure D. Epimerization Studies. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.80 mmol, 8.0 equiv, 0.10 M) was added followed by Et_3N and H_2O with vigorous stirring, which resulted in the formation of the characteristic dark brown color of the SmI_2−Et_3N−H_2O complex. A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred for 2−18 h. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture. Workup and analysis was performed as described for method B. Enantiomeric excess was determined after chromatographic purification on silica gel. HPLC analysis: ester and acid reduction (chiralpak IA 28C, hexanes/*i*-PrOH 99/1, 1.0 mL/min, 220 nm), t_R (minor) = 18.42 min, t_R (major) = 19.48 min; amide reduction, *R* (chiracel OD-H, hexanes/*i*-PrOH 95/5, 1.0 mL/min, 220 nm), t_R (minor) = 8.75 min, t_R (major) = 10.39 min; amide reduction, *S* (chiracel OD-H, hexanes/*i*-PrOH 95/5, 1.0 mL/min, 220 nm), t_R (major) = 9.23 min, t_R (minor) = 11.12 min.

Procedure E. $H_2{}^{18}O$ Incorporation Studies. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.80 mmol, 8.0 equiv, 0.10 M) was added followed by Et_3N and H_2O with vigorous stirring, which resulted in the formation of the characteristic dark brown color of the SmI_2−Et_3N−H_2O complex. A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred for 2−18 h. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture. Workup and analysis was performed as described for method B. ^{18}O incorporation was determined by HRMS analysis after workup.

Procedure F. Reagent Stoichiometry Studies. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.45 mmol, 4.5 equiv, 0.10 M) was added followed by Et_3N (4−24 equiv) and H_2O (4−24 equiv) with vigorous stirring, which resulted in the formation of the characteristic dark brown color of the SmI_2−Et_3N−H_2O complex. A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred for 24 h. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture; a small aliquot (1.0 mL) was removed from the reaction mixture, diluted with diethyl ether (2 mL) and HCl (0.1 *N*, 0.25 mL), and analyzed by GC-MS to obtain product distribution using correction for response factors obtained by analyzing known quantities of the starting materials and products.

Procedure G. Reductions Using SmI_2−NaOH. An oven-dried vial containing a stir bar was charged with sodium hydroxide, placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution) was added followed by substrate (0.10 mmol, 1.0 equiv, stock solution in THF) and H_2O with vigorous stirring, which resulted in the formation of the characteristic dark green color of the SmI_2−NaOH−H_2O complex. A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred for the indicated time. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture, and the reaction mixture was diluted with CH_2Cl_2 (30 mL) and HCl (1 *N*, 30 mL). The aqueous layer was extracted with

dx.doi.org/10.1021/jo5018525 | J. Org. Chem. 2014, 79, 11988−12003

CH_2Cl_2 (3 × 30 mL); the organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion and yield using internal standard and comparison with authentic samples.

Procedure H. Determination of Deuterium Incorporation and Kinetic Isotope Effect. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.80 mmol, 8.0 equiv, 0.10 M) was added followed by Et_3N and D_2O (deuterium incorporation) or an equimolar mixture of D_2O and H_2O (kinetic isotope effect) with vigorous stirring, which resulted in the formation of a characteristic dark brown color of the SmI_2–Et_3N–H_2O complex. A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred for 2–18 h. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture. Workup and analysis was performed as described for Method B. Deuterium incorporation was determined after chromatographic purification on silica gel (^1H NMR, 500 MHz, $CDCl_3$).

Characterization Data. Characterization data for all alcohol products have been previously reported.[20−22] ^1H and ^{13}C NMR data for the alcohol products used in the current study are presented below for characterization purposes.

Benzyl Alcohol (Table 2, entry 1). ^1H NMR (500 MHz, $CDCl_3$) δ 1.75 (br, 1 H), 4.60 (s, 2 H), 7.19−7.24 (m, 1 H), 7.26−7.31 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.4, 127.0, 127.7, 128.6, 140.9.

Phenethyl Alcohol (Table 2, entry 2). ^1H NMR (500 MHz, $CDCl_3$) δ 1.65 (br, 1 H), 2.78 (t, J = 7.0 Hz, 2 H), 3.76 (t, J = 6.5 Hz, 2 H), 7.13−7.17 (m, 3 H), 7.21−7.25 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.2, 63.7, 126.5, 128.6, 129.1, 138.5.

3-Phenylpropan-1-ol (Table 2, entry 3). ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (br, 1 H), 1.79−1.87 (m, 2 H), 2.64 (t, J = 7.6 Hz, 2 H), 3.61 (t, J = 6.4 Hz, 2 H), 7.09−7.24 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 34.3, 62.3, 125.9, 128.4, 128.5, 141.8.

Decan-1-ol (Table 2, entry 4). ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, J = 6.9 Hz, 3 H), 1.15−1.33 (m, 15 H), 1.47−1.53 (m, 2 H), 3.57 (t, J = 6.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.8, 29.3, 29.5, 29.6, 29.7, 31.9, 32.8, 63.1.

rac-((1S,4R)-4-Pentylcyclohexyl)methanol (Table 2, entry 5). ^1H NMR (300 MHz, $CDCl_3$) δ 0.75−0.91 (m, 7 H), 1.02−1.27 (m, 10 H), 1.38 (br, 1 H), 1.71 (d, J = 8.7 Hz, 4 H), 3.37 (d, J = 6.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.6, 29.5, 32.2, 32.7, 37.4, 37.8, 40.7, 68.8.

1-Adamantanemethanol (Table 2, entry 6). ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (br, 1 H), 1.43−1.46 (m, 6 H), 1.55−1.70 (m, 6 H), 1.90−1.95 (m, 3 H), 3.13 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 34.5, 37.2, 39.0, 73.9.

2-Methyl-3-phenylpropan-1-ol (Table 2, entry 7). ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.9 Hz, 3 H), 1.33 (br, 1 H), 1.79−1.94 (m, 1 H), 2.36 (dd, J = 8.0, 13.5 Hz, 1 H), 2.69 (dd, J = 6.2, 13.4 Hz, 1 H), 3.37−3.50 (m, 2 H), 7.07−7.25 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 37.8, 39.7, 67.7, 125.9, 128.3, 129.2, 140.6.

2-Butyloctan-1-ol (Table 2, entry 8). ^1H NMR (500 MHz, $CDCl_3$) δ 0.79−0.85 (m, 6 H), 1.09−1.14 (br, 1 H), 1.16−1.29 (m, 16 H), 1.35−1.42 (m, 1 H), 3.47 (d, J = 5.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 23.1, 26.9, 29.1, 29.8, 30.6, 30.9, 31.9, 40.5, 65.8.

2-(4-(Trifluoromethyl)phenyl)ethanol (Figure 4, entry 1). ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (br, 1 H), 2.95 (t, J = 6.6 Hz, 2 H), 3.92 (t, J = 6.6 Hz, 2 H), 7.37 (d, J = 8.1 Hz, 2 H), 7.59 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.9, 63.2, 122.5, 125.5 (q, J^3 = 3.8 Hz), 129.3 (q, J^2 = 32.5 Hz), 129.4, 142.8; ^{19}F (376 MHz, $CDCl_3$) δ −62.4.

2-(4-Chlorophenyl)ethanol (Figure 4, entry 2). ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (br, 1 H), 2.86 (t, J = 6.6 Hz, 2 H), 3.87 (t, J = 6.6 Hz, 2 H), 7.19 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.5, 63.5, 128.7, 130.4, 132.3, 137.0.

2-(4-Fluorophenyl)ethanol (Figure 4, entry 3). ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (br, 1 H), 2.77 (t, J = 6.6 Hz, 2 H), 3.77 (t, J = 6.6 Hz, 2 H), 6.93 (t, J = 8.7 Hz, 2 H), 7.12 (dd, J = 5.7, 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.3, 63.5, 115.4 (d, J^2 = 21.2 Hz), 130.4 (d, J^3 = 7.7 Hz), 134.2 (d, J^4 = 3.2 Hz), 161.7 (d, J^1 = 242.8 Hz); ^{19}F (376 MHz, $CDCl_3$) δ −116.8.

2-(4-Methoxyphenyl)ethanol (Figure 4, entry 4). ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (br, 1 H), 2.84 (t, J = 6.6 Hz, 2 H), 3.82 (s, 3 H), 3.85 (t, J = 6.6 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 7.17 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.3, 55.3, 63.8, 114.1, 130.0, 130.4, 158.3.

4-Phenylbutan-1-ol (Scheme 1, entry 1, 8). ^1H NMR (300 MHz, $CDCl_3$) δ 1.44−1.67 (m, 4 H), 1.71 (br, 1 H), 2.56 (t, J = 7.8 Hz, 2 H), 3.55 (t, J = 6.6 Hz, 2 H), 7.06−7.13 (m, 3 H), 7.16−7.23 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 32.3, 35.7, 62.8, 125.8, 128.3, 128.5, 142.4.

*rac-((1R,2R)-2-Phenylcyclopropyl)methanol (Scheme 1a, **9**).* ^1H NMR (500 MHz, $CDCl_3$) δ 0.82−0.91 (m, 2 H), 1.34−1.41 (m, 1 H), 1.65 (br, 1 H), 1.72−1.76 (m, 1 H), 3.49−3.57 (m, 2 H), 6.99 (dd, J = 1.5, 7.5 Hz, 2 H), 7.07 (tt, J = 1.5, 7.0 Hz, 1 H), 7.18 (t, J = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.3, 25.3, 66.6, 125.7, 125.9, 128.4, 142.5.

*(R)-2-Phenylpropan-1-ol (Scheme 1b, **11**).* ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (d, J = 7.0 Hz, 3 H), 1.33 (br, 1 H), 2.84−2.91 (m, 1 H), 3.63 (d, J = 7.0 Hz, 2 H), 7.14−7.18 (m, 3 H), 7.24−7.28 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 42.5, 68.7, 126.7, 127.5, 128.7, 143.7.

*(R)-2-Methyl-3-phenylpropan-1-ol (Scheme 4b, **25**).* ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, J = 6.5 Hz, 3 H), 1.36 (br, 1 H), 1.84−1.93 (m, 1 H), 2.36 (dd, J = 8.0, 13.0 Hz, 1 H), 2.69 (dd, J = 6.5, 13.5 Hz, 1 H), 3.39−3.49 (m, 2 H), 7.09−7.14 (m, 3 H), 7.19−7.23 (m, 2 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 37.8, 39.7, 67.7, 125.9, 128.3, 129.2, 140.6.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Kinetic plots, ^1H and ^{13}C NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: michal.szostak@rutgers.edu.

*E-mail: david.j.procter@manchester.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPRSC and the Leverhulme Trust for support. M.S. thanks Rutgers University for support during the preparation of this manuscript.

■ REFERENCES

(1) For a preliminary communication on the mechanism of ester reduction, see: Szostak, M.; Spain, M.; Procter, D. J. *Chem.—Eur. J.* **2014**, *20*, 4222.

(2) (a) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis using Samarium Diiodide: A Practical Guide*; RSC Publishing: Cambridge, U.K., 2010. Recent reviews on SmI_2: (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (c) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (d) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (e) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H. U. *Synlett* **2004**, 422. (f) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140. (g) Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. *Chem. Soc. Rev.* **2010**, *39*, 4103. (h) Beemelmanns, C.; Reissig, H. U. *Chem. Soc. Rev.* **2011**, *40*, 2199. (i) Szostak, M.; Procter, D. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7737. (j) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Soc. Rev.* **2013**, *42*, 9155. (k) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959.

(3) Reviews on metal-mediated radical reactions: (a) Szostak, M.; Procter, D. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9238. (b) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (c) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63.

(d) Justicia, J.; Àlvarez de Cienfuegos, L.; Campaña, A. G.; Miguel, D.; Jakoby, V.; Gansäuer, A.; Cuerva, J. M. *Chem. Soc. Rev.* **2011**, *40*, 3525. (e) Streuff, J. *Synthesis* **2013**, *45*, 281. (f) Murphy, J. *J. Org. Chem.* **2014**, *79*, 3731. Recent studies on mechanisms of SET-mediated reactions: (g) Findlay, N. J.; Park, S. R.; Schoenebeck, F.; Cahard, E.; Zhou, S.; Berlouis, L. E. A.; Spicer, M. D.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 15462. (h) Cahard, E.; Schoenebeck, F.; Garnier, J.; Cutulic, S. P. Y.; Zhou, S.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3673. (i) Doni, E.; Mondal, B.; O'Sullivan, S.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 10934. (j) Doni, E.; O'Sullivan, S.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2239. (k) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Gansäuer, A.; Barchuk, A.; Keller, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041. (l) Paradas, M.; Campaña, A. G.; Jiménez, T.; Robles, R.; Oltra, J. E.; Buñuel, E.; Justicia, J.; Cárdenas, D. J.; Cuerva, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 12748. (m) Gansäuer, A.; Behlendorf, M.; Cangönül, A.; Kube, C.; Cuerva, J. M.; Friedrich, J.; van Gastel, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3266. (n) Gansäuer, A.; Klatte, M.; Brändle, G. M.; Friedrich, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 8891. (o) Morcillo, S. P.; Miguel, D.; Resa, S.; Martín-Lasanta, A.; Millán, A.; Choquesillo-Lazarte, D.; García-Ruiz, J. M.; Mota, A. J.; Justicia, J.; Cuerva, J. M. *J. Am. Chem. Soc.* **2014**, *136*, 6943.

(4) (a) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991. (b) Hudlicky, M. *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, U.K., 1984. (c) Seyden-Penne, J. *Reductions by Alumino and Borohydrides in Organic Synthesis*; Wiley: New York, 1997. (d) Andersson, P. G.; Munslow, I. J. *Modern Reduction Methods*; Wiley-VCH: Weinheim, Germany, 2008. (e) Addis, D.; Das, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6004.

(5) (a) Dahlén, A.; Nilsson, Å.; Hilmersson, G. *J. Org. Chem.* **2006**, *71*, 1576. (b) Szostak, M.; Spain, M.; Procter, D. J. *J. Org. Chem.* **2014**, *79*, 2522 and references cited therein.

(6) For reviews on additives to SmI_2, see: (a) Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Commun.* **2012**, *48*, 330. (b) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. (c) Kagan, H. B.; Namy, J. L. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: New York, 1999; p 155.

(7) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(8) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008.

(9) Kamochi, Y.; Kudo, T. *Chem. Lett.* **1993**, 1495.

(10) (a) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172. (b) Keck, G. E.; Wager, C. A. *Org. Lett.* **2000**, *2*, 2307. (c) Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, *4*, 3131.

(11) (a) Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, *43*, 7197. (b) Dahlén, A.; Hilmersson, G. *Chem.—Eur. J.* **2003**, *9*, 1123. See also: (c) Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2001**, *42*, 5565.

(12) Cabri, W.; Candiani, I.; Colombo, M.; Franzoi, L.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 949.

(13) (a) Chopade, P. R.; Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2004**, *126*, 44. See also: (b) Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2005**, *127*, 18093. (c) Sadasivam, D. V.; Teprovich, J. A., Jr.; Procter, D. J.; Flowers, R. A., II *Org. Lett.* **2010**, *12*, 4140. (d) Flowers, R. A., II *Synlett* **2008**, 1427.

(14) Upadhyay, S. K.; Hoz, S. *J. Org. Chem.* **2011**, *76*, 1355.

(15) For mechanistic studies on α,β-unsaturated systems and benzophenones, see: (a) Yacovan, A.; Bilkis, I.; Hoz, S. *J. Am. Chem. Soc.* **1996**, *118*, 261. (b) Tarnopolsky, A.; Hoz, S. *J. Am. Chem. Soc.* **2007**, *129*, 3402. (c) Amiel-Levy, M.; Hoz, S. *J. Am. Chem. Soc.* **2009**, *131*, 8280. (d) Tarnopolsky, A.; Hoz, S. *Org. Biomol. Chem.* **2007**, *5*, 3801. (e) Farran, H.; Hoz, S. *J. Org. Chem.* **2009**, *74*, 2075. (f) Farran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 4875. (g) Kleiner, G.; Tarnopolsky, A.; Hoz, S. *Org. Lett.* **2005**, *7*, 4197. See also: (h) Yella, R.; Hoz, S. *Org. Lett.* **2014**, *16*, 3876. (i) Halder, S.; Hoz, S. *J. Org. Chem.* **2014**, *79*, 2682. (j) Yella, R.; Hoz, S. *Org. Lett.* **2013**, *15*, 5262. (k) Rao, C. N.; Hoz, S. *J. Org. Chem.* **2012**, *77*, 4029. (l) Rao, C. N.; Hoz, S. *J. Org. Chem.* **2011**, *76*, 9438.

(16) (a) Szostak, M.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 8459. Study of the mechanism of SmI_2–H_2O-mediated lactone reduction facilitated by a directing group effect: (b) Szostak, M.; Spain, M.; Choquette, K. A.; Flowers, R. A., II; Procter, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 15702.

(17) Szostak, M.; Lyons, S. E.; Spain, M.; Procter, D. J. *Chem. Commun.* **2014**, *50*, 8391.

(18) (a) Jensen, C. M.; Lindsay, K. B.; Taaning, R. H.; Karaffa, J.; Hansen, A. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2005**, *127*, 6544. (b) Hansen, A. M.; Lindsay, K. B.; Antharjanam, P. K. S.; Karaffa, J.; Daasbjerg, K.; Flowers, R. A., II; Skrydstrup, T. *J. Am. Chem. Soc.* **2006**, *128*, 9616. (c) Taaning, R. H.; Lindsay, K. B.; Schiøtt, B.; Daasbjerg, K.; Skrydstrup, T. *J. Am. Chem. Soc.* **2009**, *131*, 10253. (d) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2265. (e) Cividino, P.; Py, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2007**, *72*, 485. (f) Burchak, O. N.; Philouze, C.; Chavant, P. Y.; Py, S. *Org. Lett.* **2008**, *10*, 3021. (g) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459. (h) Masson, G.; Philouze, C.; Py, S. *Org. Biomol. Chem.* **2005**, *3*, 2067. (i) Gilles, P.; Py, S. *Org. Lett.* **2012**, *14*, 1042. (j) Szostak, M.; Sautier, B.; Spain, M.; Behlendorf, M.; Procter, D. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12559. For the effect of alcohols on the reactivity of TmI_2, see: (k) Szostak, M.; Spain, M.; Procter, D. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7237.

(19) Selected studies on determination of the redox potential of Sm(II), see: (a) Shabangi, M.; Flowers, R. A., II *Tetrahedron Lett.* **1997**, *38*, 1137. (b) Enemærke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Chem. Commun.* **1999**, 343. (c) See ref 5b.

(20) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Commun.* **2011**, *47*, 10254.

(21) Szostak, M.; Spain, M.; Procter, D. J. *Org. Lett.* **2012**, *14*, 840.

(22) Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 2268.

(23) (a) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhard, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378. (b) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623. (c) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (d) Balaraman, E.; Gnanaprakasam, B.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2010**, *132*, 16756. (e) Ito, M.; Ootsuka, T.; Watari, R.; Shiibashi, A.; Himizu, A.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 4240. (f) John, J. M.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 10377. (g) Krackl, S.; Someya, C. I.; Enthaler, S. *Chem.—Eur. J.* **2012**, *18*, 15267.

(24) Szostak, M.; Sautier, B.; Spain, M.; Procter, D. J. *Org. Lett.* **2014**, *16*, 1092.

(25) Szostak, M.; Collins, K. D.; Fazakerley, N. J.; Spain, M.; Procter, D. J. *Org. Biomol. Chem.* **2012**, *10*, 5820.

(26) For other selected studies on SmI_2–water–amine, see: (a) Dahlén, A.; Hilmersson, G.; Knettle, B. W.; Flowers, R. A., II *J. Org. Chem.* **2003**, *68*, 4870. (b) Dahlén, A.; Hilmersson, G. *J. Am. Chem. Soc.* **2005**, *127*, 8340. (c) Davies, T. A.; Chopade, P. R.; Hilmersson, G.; Flowers, R. A., II *Org. Lett.* **2005**, *7*, 119. (d) Ankner, T.; Hilmersson, G. *Org. Lett.* **2009**, *11*, 503. (e) Ankner, T.; Hilmersson, G. *Tetrahedron* **2009**, *65*, 10856. (f) Wettergren, J.; Ankner, T.; Hilmersson, G. *Chem. Commun.* **2010**, *46*, 7596. (g) Ankner, T.; Stålsmeden, A. S.; Hilmersson, G. *Chem. Commun.* **2013**, *49*, 6867.

(27) (a) Graton, J.; Laurence, C.; Berthelot, M.; Le Questel, J. Y.; Besseau, F.; Raczynska, E. D. *J. Chem. Soc., Perkin Trans. 2* **1999**, 997. (b) Graton, J.; Berthelot, M.; Laurence, C. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2130. (c) Graton, J.; Besseau, F.; Berthelot, M.; Raczynska, E. D.; Laurence, C. *Can. J. Chem.* **2002**, *80*, 1375.

(28) Reduction potential of thioesters is lower than that of corresponding esters: $E_{OR} = -3.0$ V vs SCE; $E_{SR} = -2.6$ V vs SCE. (a) Weïwer, M.; Olivero, S.; Duñach, E. *Tetrahedron* **2005**, *61*, 1709. (b) Belotti, D.; Cossy, J.; Pete, J. P.; Portella, C. *J. Org. Chem.* **1986**, *51*, 4196. (c) See also ref 18b.

(29) (a) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96. (b) Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191.

(30) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(31) (a) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979. (b) Chapman, N. B.; Shroter, J. *Advances in Linear Free Energy Relationships*; Plenum, Press: London, 1972.

(32) (a) Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1656. (b) Kefalidis, C. E.; Perrin, L.; Maron, L. *Eur. J. Inorg. Chem.* **2013**, 4042.
(33) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2005.
(34) (a) Renaud, P., Sibi, M., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001. (b) Chatgilialoglu, C., Studer, A., Eds. *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Wiley-Blackwell: Chichester, U.K., 2012. (c) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; Wiley-VCH: Weinheim, Germany, 1996. (d) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717. (e) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, J. *Synlett* **1992**, 943.
(35) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.
(36) Tanko and co-workers have demonstrated that the rate of radical anion radical clocks is similar to that of the corresponding neutral radicals: (a) Stevenson, J. P.; Jackson, W. F.; Tanko, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 4271. (b) Tanko, J. M.; Gillmore, J. G.; Friedline, R.; Chahma, M. *J. Org. Chem.* **2005**, *70*, 4170. (c) Tanko, J. M.; Li, X.; Chahma, M.; Jackson, W. F.; Spencer, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 4181. (d) Chahma, M.; Li, X.; Phillips, J. P.; Schwartz, P.; Brammer, L. E.; Wang, Y.; Tanko, J. M. *J. Phys. Chem. A* **2005**, *109*, 3372.
(37) For examples of the reductive opening of α-cyclopropyl radicals using Sm(II), see: (a) Williams, D. B. G.; Blann, K.; Caddy, J. *Org. Prep. Proced. Int.* **2001**, *33*, 565. (b) Breitler, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 11168 and references cited therein. (c) See also ref 2j.
(38) (a) Kamochi, Y.; Kudo, T. *Chem. Lett.* **1991**, 893. (b) Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* **1991**, *32*, 3511. (c) Kamochi, Y.; Kudo, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3049.
(39) Under pseudo-first-order conditions, the observed rate law is consistent with conclusions described in the manuscript. (a) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill: New York, 2002. (b) Atkins, P.; de Paula, J. *Atkins' Physical Chemistry*; Oxford University Press: Oxford, U.K., 2006. (c) Halpern, A. M.; McBane, G. C. *Experimental Physical Chemistry: A Laboratory Textbook*; W. H. Freeman: New York, 2006. (d) Arnaut, L.; Formosinho, S.; Burrows, H. *Chemical Kinetics: From Molecular Structure to Chemical Reactivity*; Elsevier: Amsterdam, 2007. For additional discussion, see:. (e) Murdoch, J. R. *J. Chem. Educ.* **1981**, *58*, 32. (f) Laidler, K. J. *J. Chem. Educ.* **1988**, *65*, 250. (g) Birk, J. P. *J. Chem. Educ.* **1970**, *47*, 805. (h) Edwards, J. O.; Greene, E. F.; Ross, J. *J. Chem. Educ.* **1968**, *45*, 381. (i) Leidler, K. J.; Glasstone, S. *J. Chem. Educ.* **1948**, *25*, 383.
(40) Selected examples of reversibility of electron transfer to carbonyl compounds using Sm(II) and other reductants: (a) Baron, R.; Kershaw, N. M.; Donohoe, T. J.; Compton, R. G. *J. Phys. Org. Chem.* **2009**, *22*, 247. (b) Heintz, M.; Devaud, M.; Hebri, H.; Dunach, E.; Troupel, M. *Tetrahedron* **1993**, *49*, 2249. (c) Wagenknecht, J. H.; Goodin, R. D.; Kinlen, P. J.; Woodard, F. E. *J. Electrochem. Soc.* **1984**, *131*, 1560. (d) Wagenknecht, J. H.; Eberson, L.; Utley, J. H. P. In *Organic Electrochemistry*; Hammerich, O., Lund, H., Eds.; CRC Press: Boca Raton, FL, 2000; Chapter 12, p 453. (e) Hou, Z.; Fujita, A.; Zhang, Y.; Miyano, T.; Yamazaki, H.; Wakatsuki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 754. Reversibility of electron transfer in outer sphere processes: (f) Deacon, G. B.; Shen, Q. *J. Organomet. Chem.* **1996**, *506*, 1. (g) Evans, W. J.; Ulibarri, T.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 219. (h) Fedushkin, I. L.; Bochkarev, M. N.; Dechert, S.; Schumann, H. *Chem.—Eur. J.* **2001**, *7*, 3558. Amides: (i) Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660. (j) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887. (k) Traoré, M.; Mietton, F.; Maubon, D.; Peuchmaur, M.; Hilário, F. F.; de Freitas, R. P.; Bougdour, A.; Curt, A.; Maynadier, M.; Vial, H.; Pelloux, H.; Hakimi, M. A.; Wong, Y. S. *J. Org. Chem.* **2013**, *78*, 3655. Esters, ketones: (l) Honda, T.; Ishikawa, F. *Chem. Commun.* **1999**, 1065. (m) Honda, T. *Heterocycles* **2011**, *83*, 1. (n) Xu, Q.; Cheng, B.; Ye, X.; Zhai, H. *Org. Lett.* **2009**, *11*, 4136. Aldehydes: (o) Takahashi, S.; Kubota, A.; Nakata, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4751. (p) Helm, M. D.; Da Silva, M.; Sucunza, D.; Findley, T. J. K.; Procter, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9315. (q) Helm, M. D.; Da Silva, M.; Sucunza, D.; Helliwell, M.; Procter, D. J. *Tetrahedron* **2009**, *65*, 10816. (r) Fazakerley, N. J.; Helm, M. D.; Procter, D. J. *Chem.—Eur. J.* **2013**, *19*, 6718. (s) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964. (t) Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764. (u) Yeoman, J. T. S.; Cha, J. Y.; Mak, V. W.; Reisman, S. E. *Tetrahedron* **2014**, *70*, 4070.
(41) Laurence, C.; Gal, J. F. *Lewis Basicity and Affinity Scales: Data and Measurement*; Wiley-Blackwell: Chichester, U.K., 2009.
(42) Selected examples of the use of carboxylic acids as ligands to SmI_2: (a) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945. (b) Inanaga, J.; Ujikawa, O.; Handa, Y.; Otsubo, K.; Yamaguchi, M. *J. Alloys Compd.* **1993**, *1*−*2*, 197. (c) Hagiwara, H.; Suka, Y.; Nojima, T.; Hoshi, T.; Suzuki, T. *Tetrahedron* **2009**, *65*, 4820. See also: (d) Kamochi, Y.; Kudo, T. *Tetrahedron* **1992**, *48*, 4301.
(43) Szostak, M.; Spain, M.; Procter, D. J. *Org. Lett.* **2014**, *16*, 5052.
(44) For selected examples of in situ protection of aldehydes as hemiacetals in Sm(II) reductions, see: (a) Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* **2000**, *41*, 341. (b) Austad, B. C.; Calkins, T. L.; Chase, C. E.; Fang, F. G.; Horstmann, T. E.; Hu, Y.; Lewis, B. M.; Niu, X.; Noland, T. A.; Orr, J. D.; Schnaderbeck, M. J.; Zhang, H.; Asakawa, N.; Asai, N.; Chiba, H.; Hasebe, T.; Hoshino, Y.; Ishizuka, H.; Kajima, T.; Kayano, A.; Komatsu, Y.; Kubota, M.; Kuroda, H.; Miyazawa, M.; Tagami, K.; Watanabe, T. *Synlett* **2013**, *24*, 333.
(45) For a comprehensive study on the preparation of SmI_2, see: Szostak, M.; Spain, M.; Procter, D. J. *J. Org. Chem.* **2012**, *77*, 3049.
(46) Greenberg, A., Breneman, C. M., Liebman, J. F., Eds. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Wiley: Hoboken, NJ, 2000.
(47) Shirota, H.; Ushiyama, H. *J. Phys. Chem. B* **2008**, *112*, 13542.
(48) Crugeiras, J.; Rios, A.; Riveiros, E.; Richard, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 15815.
(49) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.