

## A convenient pathway to Sm(II)-mediated chemistry in acetonitrile†‡

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In this communication we show that the instability of samarium diiodide ( $\text{SmI}_2$ ) in acetonitrile is a consequence of ionization of the reductant in this solvent. Samarium triflate ( $\text{Sm}(\text{OTf})_2$ ) is exceptionally stable in acetonitrile for periods over six months and can be used with appropriate additives to initiate a ketyl–olefin coupling reaction in high yield.

Since Kagan *et al.* introduced samarium diiodide ( $\text{SmI}_2$ ) to chemists in 1980, it has attained an importance reserved for few reagents.<sup>1</sup> Although once considered an esoteric reagent,  $\text{SmI}_2$  is now a standard reductant in most organic laboratories. The unique place held by  $\text{SmI}_2$  in the arsenal of synthetic chemists is a result of its ability to initiate numerous, fundamentally important reactions in organic synthesis that proceed through free radical intermediates.<sup>2</sup> The versatility of  $\text{SmI}_2$  can be attributed in part to its ease of preparation, storage, and stability in THF. Although the majority of Sm(II)-based reductions are carried out using  $\text{SmI}_2$  in THF, this solvent is relatively expensive and is capable of terminating radical reactions because it is a good hydrogen atom donor.<sup>3</sup> In fact, Göttlich and Noack have shown that THF may even inhibit some Sm-based reactions.<sup>4</sup> Other common solvents including acetonitrile (MeCN) have been used as media for reactions of  $\text{SmI}_2$  and in some cases provide access to reactions not possible in THF.<sup>5</sup> While  $\text{SmI}_2$  can be prepared in MeCN, the reductant degrades quickly and must be used upon preparation, limiting the utility of this reagent–solvent combination. During the past several years, we have been engaged in studies designed to understand the role of solvation in reactions of  $\text{SmI}_2$ , to extend the chemistry of Sm(II) reductants to a wider range of solvents. In the present study we sought to determine the following: what is the basis of degradation of  $\text{SmI}_2$  in MeCN? Can Sm(II) be stabilized in MeCN thus extending the range of Sm(II)?

Recent studies in our group and others have shown that conductance can be used to characterize the solution structure of Sm-based reductants.<sup>6</sup> To study the stability of Sm(II) in MeCN,  $\text{SmI}_2$  and samarium(II) triflate ( $\text{Sm}(\text{OTf})_2$ ) were prepared at concentrations of 2.5 mM and their conductance was measured.

Solutions of  $\text{SmI}_2$  were prepared through the combination of Sm metal and  $\text{I}_2$  and concentrations of 50 mM were obtained. These solutions were used immediately since they degraded over a period of 24 h. Solutions of  $\text{Sm}(\text{OTf})_2$  were initially prepared through the treatment of a combination of Sm metal,  $\text{Sm}(\text{OTf})_3$ , and catalytic iodine by sonication.<sup>7</sup> Solutions of  $\text{Sm}(\text{OTf})_2$  were obtained in concentrations of 90 mM. Concentrations of both solutions were determined by iodometric titration and UV–vis analysis of the molar absorptivities. Surprisingly, the conductance of  $\text{SmI}_2$  was considerably higher than that of  $\text{Sm}(\text{OTf})_2$  suggesting dissociation of ligands in the case of  $\text{SmI}_2$ .

To further explore this supposition, hexamethylphosphoramide (HMPA) was added to solutions of  $\text{SmI}_2$  and  $\text{Sm}(\text{OTf})_2$ . Since this additive is known to displace iodide from  $\text{SmI}_2$  leading to increased solution conductance, no further increase in conductance would be expected upon addition of HMPA if the reductant is already ionized. To examine the system, HMPA was added to  $\text{SmI}_2$  and  $\text{Sm}(\text{OTf})_2$  in MeCN and the conductance was measured (Fig. 1). Conductance was relatively high for both reductants in MeCN. This solvent is known to accommodate dissolution of ions, so it is likely that some ionization of both reductants is occurring.<sup>8</sup> Addition of HMPA to  $\text{Sm}(\text{OTf})_2$  showed a gradual increase in conductance consistent with displacement of triflate, whereas the conductance of the  $\text{SmI}_2$  solution decreased, then leveled off at 20 equivalents. The basis for the initial decrease in conductance of  $\text{SmI}_2$  upon the addition of small amounts of HMPA is unclear. However, it is likely that upon initial addition of HMPA, MeCN coordinated to Sm(II) is

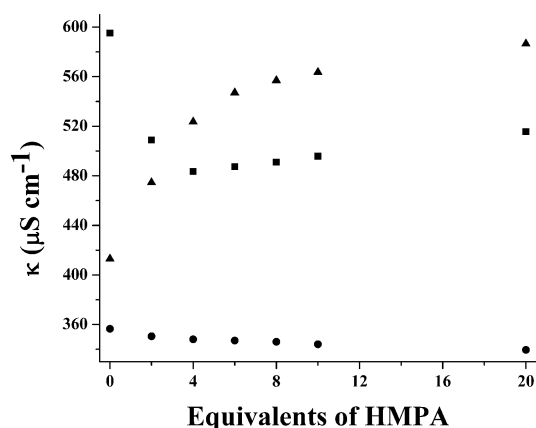


Fig. 1 Plot of the conductivity of 2.5 mM  $\text{SmI}_2$  and  $\text{Sm}(\text{OTf})_2$  in MeCN with increasing amounts of HMPA (●– $\text{Bu}_4\text{NI}$ , ▲– $\text{Sm}(\text{OTf})_2$ , ■– $\text{SmI}_2$ ).

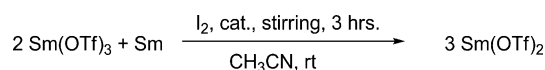
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displaced. The expulsion of solvent to the outer sphere may open coordination sites, strengthening the interaction of the iodide and Sm(II). As increasing amounts of HMPA are added, iodide is further displaced. Regardless of the basis for the observed changes in conductance, the results are consistent with ionization of SmI<sub>2</sub> in MeCN. Conversely, Sm(OTf)<sub>2</sub> exhibits behavior analogous to the behavior of SmI<sub>2</sub> in THF (see ESI†).<sup>6b</sup> Unlike SmI<sub>2</sub> which rapidly degrades in MeCN, Sm(OTf)<sub>2</sub> maintained its concentration and was stable for longer periods of time in an inert atmosphere. We propose that the instability of SmI<sub>2</sub> is a consequence of its ionization in MeCN. Furthermore, the conductance data obtained for Sm(OTf)<sub>2</sub> suggest that its stability is a consequence of the structural integrity of the complex in MeCN. While this finding is interesting, how does the reactivity of Sm(OTf)<sub>2</sub> in MeCN compare to SmI<sub>2</sub> in THF? Furthermore, is Sm(OTf)<sub>2</sub> sufficiently reactive in MeCN to be synthetically useful?

One of the problems with our present synthesis of Sm(OTf)<sub>2</sub> is that it requires the use of high intensity ultrasound. To be broadly applicable, it is important to develop a straightforward synthesis. Several methods for the synthesis of Sm(OTf)<sub>2</sub> have been developed in THF and involve the addition of an organolithium or organomagnesium reagent to Sm(OTf)<sub>3</sub>.<sup>9</sup> Unfortunately, these approaches do not work in MeCN since the organometallic reagents react with the solvent. A number of other approaches have been developed for the synthesis of Sm(OTf)<sub>2</sub> in other solvents, but often require the use of reagents that are difficult to prepare or require extended periods of time.<sup>10</sup> After examining numerous preparations, we found that stirring samarium(III) triflate with samarium metal in the presence of a catalytic amount of iodine (5–20 mol%) in acetonitrile over a three hour period provided a dark green color solution of Sm(OTf)<sub>2</sub> in nearly quantitative yield as shown in Scheme 1. In all cases, the reagent was obtained with concentrations up to 0.09 M (as determined by iodometric titration). It is important to note that the reaction did not take place in the absence of iodine. The exact role of iodine in this reaction is not known, but it could facilitate the reaction by cleaning the surface of the metal or it could generate SmI<sub>2</sub>, which in turn reduces samarium(III) triflate. Careful examination of the UV–vis spectrum of solutions of Sm(OTf)<sub>2</sub> show no trace of SmI<sub>2</sub> (see ESI†). The Sm(OTf)<sub>2</sub> generated from this process was stable and maintained its concentration for over six months in an inert atmosphere.



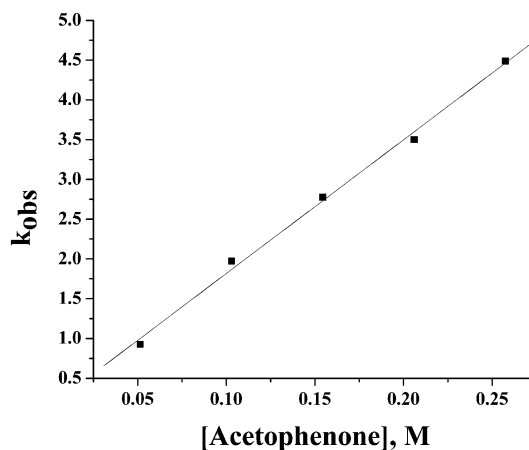
**Scheme 1** Generation of samarium(II) triflate.

With a routine synthesis of Sm(OTf)<sub>2</sub> in MeCN in hand, we next examined the rate of substrate reduction to compare the reactivity of Sm(OTf)<sub>2</sub> with SmI<sub>2</sub>. Acetophenone and benzyl bromide were used as model substrates since there is a great deal of rate data available for their reduction by SmI<sub>2</sub> in THF, allowing for comparison among the different Sm-based reductants and solvents.<sup>11</sup> All rate studies were carried out under pseudo first-order conditions by monitoring the decay of the absorption of Sm(II) *via* stopped-flow spectrophotometry. Table 1 contains the rate data for these experiments and Fig. 2 contains a representative rate study for the reduction of acetophenone by Sm(OTf)<sub>2</sub> in

**Table 1** Rate data for reduction of benzyl bromide and acetophenone by SmI<sub>2</sub> and Sm(OTf)<sub>2</sub> in MeCN and THF

Reagent–substrate system	Solvent	$k$ (M <sup>-1</sup> s <sup>-1</sup> ) <sup>a</sup>	Substrate rate order
SmI <sub>2</sub> –benzyl bromide	MeCN	$1.12 \pm 0.05 \times 10^{-1}$	$1.05 \pm 0.06$
	THF	$1.80 \pm 0.03$	$1.0 \pm 0.1$
Sm(OTf) <sub>2</sub> –benzyl bromide	MeCN	$1.22 \pm 0.02 \times 10^{-1}$	$0.99 \pm 0.02$
	THF	$4.9 \pm 0.1 \times 10^{-1}$	$0.97 \pm 0.02$
SmI <sub>2</sub> –acetophenone	MeCN	$1.76 \pm 0.2 \times 10^{-1}$	$0.95 \pm 0.09$
	THF	$7.0 \pm 1.0$	$1.0 \pm 0.03$
Sm(OTf) <sub>2</sub> –acetophenone	MeCN	$1.6 \pm 0.1 \times 10^1$	$0.95 \pm 0.05$
	THF	$3.29 \pm 0.2 \times 10^1$	$1.07 \pm 0.11$

<sup>a</sup> All rate data were determined under pseudo first-order conditions: [Sm(II)] = 5 mM; [substrate] = 50–250 mM.



**Fig. 2** Plot of  $k_{\text{obs}}$  versus [acetophenone] for the reduction of acetophenone by 5 mM Sm(OTf)<sub>2</sub> in MeCN at 25 °C. Rate constant =  $1.6 \pm 0.1 \times 10^1$  M<sup>-1</sup> s<sup>-1</sup>.

MeCN. In all cases, reductions were first order in substrate and Sm(II) reductant showing that the initial electron transfer is rate-limiting.

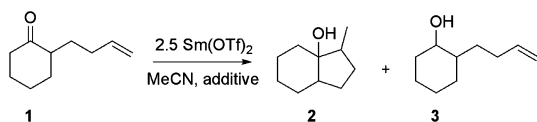
Careful inspection of the rate data provides a number of interesting comparisons. For the reduction of benzyl bromide, the rates of reaction are faster in THF than MeCN. Reduction of benzyl bromide by SmI<sub>2</sub> is 16 times faster in THF than MeCN whereas reduction by Sm(OTf)<sub>2</sub> is 4 times faster in THF than MeCN. The differences in rates of reaction between the two reductants are modest. Reduction in MeCN occurs at nearly the same rate (within experimental error). Kinetic studies on the reduction of acetophenone by SmI<sub>2</sub> and Sm(OTf)<sub>2</sub> show more pronounced differences. Reduction of acetophenone by SmI<sub>2</sub> is nearly 40 times faster in THF than MeCN whereas reduction by Sm(OTf)<sub>2</sub> is twice as fast in THF. Surprisingly, reduction of acetophenone by Sm(OTf)<sub>2</sub> is significantly faster than SmI<sub>2</sub> with the reaction being nearly two orders of magnitude faster in MeCN and about five times faster in THF. This finding suggests that Sm(OTf)<sub>2</sub> is slightly more oxophilic than SmI<sub>2</sub>.

To initially examine whether Sm(OTf)<sub>2</sub> in MeCN can be used as a synthetically viable alternative to SmI<sub>2</sub> in THF, the ketyl–olefin cyclization of 2-but-3-enyl-cyclohexane-1-one (**1**) was examined (Scheme 2) in the presence and absence of the additives HMPA and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU). The results of these experiments are shown in Table 2.

**Table 2** Reaction of **1** with Sm(OTf)<sub>2</sub> in MeCN

Additive, equiv	Time	Yield <b>2</b> , % ( <i>cis</i> : <i>trans</i> ) <sup>a</sup>	Yield <b>3</b> , % <sup>a</sup>
none	2 d	NR	
HMPA, 10	10 m	96 ± 2 (1 : 100)	<1
DMPU, <sup>b</sup> 10	2 d	72 ± 2 (1 : 50)	6
DMPU, <sup>b</sup> 10, <i>t</i> -BuOH, 3	12 h	96 ± 2 (1 : 13)	<1

<sup>a</sup> NMR yields. <sup>b</sup> 3 equiv of Sm(OTf)<sub>2</sub>, NR = no reaction.

**Scheme 2** Reaction of Sm(OTf)<sub>2</sub> with **1**.

Reduction of **1** by Sm(OTf)<sub>2</sub> led to complete recovery of starting material after 2 days. Addition of 10 equiv of HMPA gave an instantaneous reaction and provided a nearly quantitative yield of cyclized product **2**. The diastereoselectivity of the reaction was relatively high and consistent with reactions employing SmI<sub>2</sub>–HMPA in THF.<sup>12</sup> Next, we examined the use of DMPU as a replacement for HMPA. Curran and Hasegawa have previously shown that DMPU is useful as an additive in MeCN, but not THF (due to precipitation).<sup>13</sup> Addition of 10 equiv of DMPU led to a high yield and good diastereoselectivity of **2**. Addition of less than 10 equiv of DMPU provided a higher degree of reduced product **3**.<sup>6b</sup> Although reactions employing DMPU proceeded to completion, they took considerably longer to complete than reactions containing HMPA. Next, the proton donor, *t*-butanol (*t*-BuOH) was added to reactions containing HMPA and DMPU.<sup>12</sup> This additive had no impact on the yield, diastereoselectivity, or rate of the reaction with HMPA as reported previously for SmI<sub>2</sub> in THF.<sup>12b</sup> Interestingly, addition of *t*-BuOH to the reaction containing DMPU had a significant impact on the rate and yield with reaction complete in 12 h in nearly quantitative yield. Unfortunately, there was a concomitant decrease in the diastereoselectivity of the reaction. These initial studies show that Sm(OTf)<sub>2</sub> in MeCN provides a viable alternative to SmI<sub>2</sub> in THF for a radical-based bond-forming reaction.

In conclusion, these studies demonstrate that changing ligands on Sm(II) can have a large impact on its stability in different solvents. Conductance studies show that the instability of SmI<sub>2</sub> in MeCN is likely a result of ionization of the reductant. The lower degree of ionization of Sm(OTf)<sub>2</sub> in MeCN provides a very stable reductant whose reactivity and concentration can be maintained for extended periods of time in an inert atmosphere. The preparation of Sm(OTf)<sub>2</sub> in MeCN is straightforward and rate studies show that this reductant–solvent combination provides reactivity patterns similar to SmI<sub>2</sub> for the reduction of benzyl bromide. In comparison to SmI<sub>2</sub> in MeCN, Sm(OTf)<sub>2</sub> reduces acetophenone significantly faster. Reaction of a model ketyl-olefin

coupling demonstrates that Sm(OTf)<sub>2</sub>–MeCN containing HMPA or DMPU can be employed as an alternative to SmI<sub>2</sub> in THF. We are currently exploring the impact of ligands and solvent milieu on the reactivity of other Sm(II)-based reductants with the goal of extending the reactivity and selectivity of these reagents. The results of these studies will be reported in due course.

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