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Solvent-Dependent Diastereoselectivities in Reductions of β-Hydroxyketones by SmI_2

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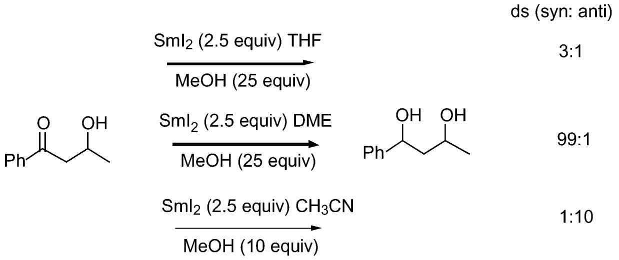
ABSTRACT



The reductions of a series of β-hydroxyketones by SmI_2 were examined in THF, DME, and CH_3CN using methanol as a proton source. Reductions in THF and DME typically lead to the syn diastereomer with DME providing higher diastereoselectivities. Reductions in CH_3CN provided the anti diastereomer predominantly. This study reveals that solvation plays an important role in substrate reduction by SmI_2.

The unique place held by SmI_2 in the arsenal of synthetic chemists is a result of its versatility in mediating numerous fundamentally important reactions in organic synthesis, including reductions, reductive couplings, and tandem reactions.[1,2] Since the introduction of SmI_2 by Kagan in 1980,[3] the solvent of choice has been tetrahydrofuran (THF). While THF is a reasonable solvent for many reactions, it is also a good hydrogen atom donor[4] and can terminate certain radical reactions.[5] Other solvents, including tetrahydropyran (THP),[6] acetonitrile (CH_3CN),[7] and even benzene,[8] have been reported as media for reactions, but each has certain features that limit their use.

From a mechanistic vantage point, little is known about the role of solvation in SmI_2-mediated reactions. Examination of crystal structure data for SmI_2 in nitriles,[9] dimethoxyethane (DME),[10] and THF[11] shows that there is substantial structural diversity for SmI_2-solvates with six-, seven-, and eight-coordinate complexes reported in the literature. The diversity of SmI_2-solvates and the likely variable affinity of different solvents for Sm(II) lead to the supposition that the solvent milieu will have an impact on the reactivity of SmI_2 and

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potentially alter product distributions. To test this hypothesis, SmI_2 was characterized in THF, CH_3CN, and DME and the reduction of a series of β-hydroxyketones was examined. This study reveals that solvation plays an important role in substrate reduction by SmI_2.

Solutions of SmI_2 in THF, CH_3CN, and DME were prepared by reaction of I_2 with excess Sm metal. The solutions were stored in a drybox until used. Concentrations of SmI_2 in each solvent were determined by iodometric titration. The solubilities of SmI_2 in THF and CH_3CN were 0.1 and 0.05 M, respectively. Solubility in DME was initially 0.1 M, but precipitation was evident after a few days. The solution of SmI_2 in DME was allowed to stand, and the concentration was monitored as a function of time and reached a steady state of 0.02 M after a few days. Sonication in a cleaning bath temporarily dissolved precipitated SmI_2-DME.

Next, vapor pressure osmometry (VPO) was utilized to determine the solution MW of SmI_2 in DME. This study showed that SmI_2 is clearly monomeric in DME with an aggregation number of 1.09 ± 0.02. This finding was consistent with previous studies showing that SmI_2 is a solvated monomer in THF[12] and CH_3CN.[13]

To characterize SmI_2 further in the three solvents, UV−vis spectroscopy was utilized. The spectra are displayed in Figure 1. The spectrum of SmI_2 in THF shows the typical absorptions at 350, 418, 557, and 618 nm. The spectrum of SmI_2 in CH_3CN shows broad absorptions at 440 and 680 nm. The DME solvate of SmI_2 more closely resembles the spectrum in THF, although there are some differences. The low-energy bands are slightly blue-shifted, with the highest wavelength band having a higher intensity.

A recent paper by Dorenbos assigned the absorption bands in Sm(II) complexes to f to d ($4f^n$ to $4f^{n-1}5d^1$) transitions.[14] The analysis in the Dorenbos work was based on the spectra of lanthanides generated in inorganic salts in the solid state. Though care must be taken in comparing the electronic transitions in solutions with the solid state, the apparent changes in the absorption maxima as well as the relative intensity of these peaks in different solvents suggest that the transition energy and probability are affected by solvation of Sm(II). The X-ray crystal structures of SmI_2 in these solvents indicate that the solvent shell geometry is different in each solvent.[9−11] If the solvent can perturb the accessible d orbitals of Sm(II), it is reasonable to assume that the change in solvent shell geometry and affinity could lead to unique d-orbital pertubation, resulting in f to d transitions of different energy and probability. Nonetheless, examination of the spectra in Figure 1 clearly shows that each SmI_2-solvate is unique.

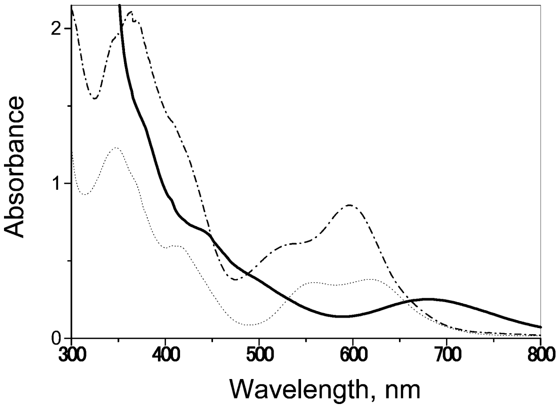

Figure 1. UV−vis spectra of SmI_2 in THF (dot), DME (dash−dot), and CH_3CN (solid).

The final characterization of reductants utilized cyclic voltammetry (CV) to estimate the redox potential of SmI_2 in DME. Potentials for SmI_2 in THF and acetonitrile have been reported and are −1.58 ± 0.04[12] and −1.44 ± 0.05 V[13] (vs saturated $Ag/AgNO_3$), respectively. The potential of SmI_2 in DME was measured employing a glassy carbon electrode, a saturated $Ag/AgNO_3$ reference, and a platinum wire auxiliary electrode. The electrolyte was either LiI or tetra-*n*-butylammonium hexafluorophosphate. The $E_{1/2}$ of SmI_2 in DME was found to be −1.62 ± 0.05 V. The CV is similar to those generated in THF and CH_3CN. Comparison of SmI_2 in all three solvents shows very little difference between them in terms of their thermodynamic reducing power (within experimental error).

The characterization of SmI_2 in THF, CH_3CN, and DME is consistent with the following: (1) SmI_2 is monomeric in all three solvents; (2) dissolution of SmI_2 in each solvent provides unique UV−vis spectra; and (3) the $E_{1/2}$ values are nearly the same within experimental error. The affinity of solvent for Sm(II) and the ability of various functional groups to displace solvent (or I^-) and interact with Sm(II) through chelation can potentially alter the *energies* of intermediates and activated complexes along the reaction coordinate, resulting in different product distributions.[15]

To address this issue, the reduction of a series of β-hydroxyketones was examined in all three solvents. The seminal work of Keck showed that the reduction of β-hydroxyketones by SmI_2 is sensitive to substitution, proton source, and temperature.[16] On the basis of these findings, it was proposed that these substrates may be sensitive to changes in the solvent milieu as well. Initial experiments utilized 25 equiv of MeOH (based on $[SmI_2]$) as a proton source in all three solvents. The diastereoselectivity of the reductions were determined using GC and ^1H NMR, and the identities of the diastereomers were established using the protocol reported by Rychnovsky.[17] The results are shown in Table 1. Examination of the data shows some very interesting trends. In global terms, reductions in THF and

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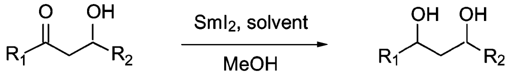
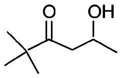
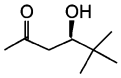
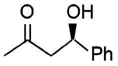
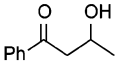
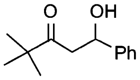
Table 1. Reduction of β-Hydroxyketones by SmI_2 in THF, CH_3CN, and DME



entry	substrate	*syn* : *anti*		
		THF (yield, %)[a,b]	equiv MeOH[c] - CH_3CN (yield, %)[a]	DME (yield, %)[a,b]
1		3 : 1 (q)	2 - 1 : 5 (68) 5 - 1 : 5 (75) 10 - 1 : 3 (79) 15 - 1 : 3 (82) 25 - 1 : 3 (78)	15 : 1 (q)
2		9 : 1 (q)	10 - 1 : 3 (72) 25 - 1 : 2 (75)	> 99 : 1 (q)
3		1 : 99 (99)[d] > 1 : 99 (q)	10 - 1 : 5 (89) 25 - 1 : 2 (76)	> 1 : 99 (q)
4		3 : 1 (q)	10 - 1 : 10 (75) 25 - 1 : 5 (84)	> 99 : 1 (q)
5		50 : 50 (96)[d] 55 : 45 (q)	10 - 1 : 3 (75) 25 - 1 : 2 (84)	50 : 50 (q)

[a] GC yields. [b] MeOH (25 equiv, based on [SmI_2]) was used in the THF and DME studies. [c] Variable concentrations of MeOH were used in the acetonitrile studies. [d] From ref 16.

DME show the same trends, while reductions in CH_3CN always provide the anti 1,3-diol as the major diastereomer. Quantitative reductions were obtained in THF and DME, while good yields (70−80%) were obtained in CH_3CN. Use of greater amounts of SmI_2 in CH_3CN did not provide significantly better yields in the reductions.

In comparison to SmI_2 in THF, reduction of β-hydroxyketones (entries 1, 2, and 4, Table 1) by SmI_2 in DME provided significantly higher diastereoselectivities. The eight-coordinate solvate provided by the bidentate DME could potentially increase the steric demands of the reductant enough to provide the observed increase in diastereoselectivity.

Although reduction of all substrates by SmI_2 in CH_3CN provides anti diastereoselectivity, the selectivity was modest using 25 equiv of MeOH. The different stereochemical outcome for reductions in CH_3CN indicated the possibility of an alternate mechanistic pathway for the SmI_2-mediated conversion in this solvent. Another factor that could potentially have mechanistic implications is the presence of the proton source, MeOH. Proton sources are known to have an impact on the stereochemical outcome of numerous SmI_2-based reactions,[16,18] and recent mechanistic studies have shown that proton donor concentration can have an impact on the mechanistic pathway of the reduction.[19,20]

To examine the interplay between MeOH and solvent on SmI_2, UV−vis spectra of the reductant in each solvent was monitored in the presence of increasing amounts of MeOH. In THF and DME, no changes were visible in the spectra upon addition of up to 200 equiv of MeOH. Conversely, addition of MeOH to SmI_2 in CH_3CN (Figure 2) showed changes with as little as 2 equiv of the proton donor, suggesting coordination of the alcohol to Sm.[21] These findings indicate that MeOH has a much higher affinity for the oxophilic Sm in CH_3CN. In THF and DME, higher concentrations of MeOH are required to displace bulk solvent from the inner sphere of Sm.[20]

Since coordination of MeOH to SmI_2 could disrupt chelation of β-hydroxyketones, a number of reductions were run at lower concentration of the proton donor in CH_3CN. In all cases, it was found that 10 or fewer equivalents of MeOH provided higher diastereoselectivities in CH_3CN than

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(18) (a) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190−3198. (b) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811−4814.

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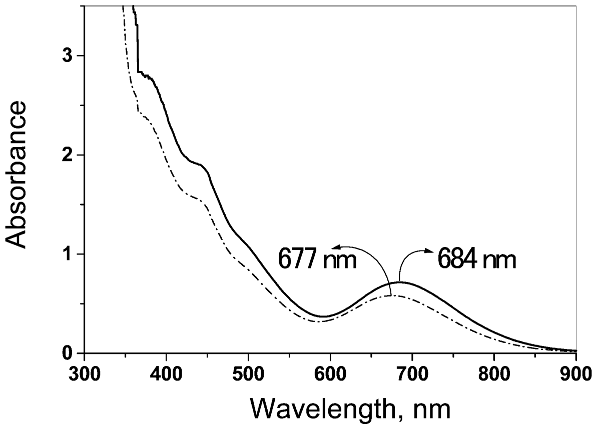

Figure 2. Uv−vis spectra of samarium diiodide (5 mM) (solid) and samarium diiodide in the presence of 2 equiv of methanol (dash dot) in acetonitrile.

the original experiments conducted with 25 equiv (Table 1). Although the diastereoselectivities in CH_3CN are still modest, reduction of 3-hydroxy-1-phenylbutane-1-one (entry 4, Table 1) to the corresponding diol provides a syn:anti ratio of 1:10.

In summary, physical characterization of SmI_2 by a variety of techniques has shown that its dissolution in THF, DME, and CH_3CN provides a unique reductant in each, presumably through differences in solvation. The impact of changes in the solvent milieu was examined through the reduction of a series of β-hydroxyketones using MeOH as a proton source. The same trends in diastereoselectivity were apparent in THF and DME, with the latter solvent generally providing better selectivity. Reductions in CH_3CN provided anti diols in good yields, and smaller amounts of MeOH were found to give better diastereoselectivities. Further characterization of SmI_2 by UV−vis spectroscopy showed evidence for coordination of MeOH to Sm in CH_3CN, but not in THF or DME. Although the discreet mechanistic details are not clear at this point, the SmI_2−MeOH complex is proposed to play a role in different reactivity patterns displayed in CH_3CN.

The affinity of solvent for SmI_2 likely plays a direct role in the ability of various substrates or additives (alcohols) to displace solvent from the metal and interact with it through direct coordination to the inner sphere. If this supposition is correct, the data communicated herein shows that different combinations of solvent, additive, and substrate could have an impact on the outcome of SmI_2-mediated reactions. Mechanistic (rate) studies are currently being carried out to examine the details of these reactions to provide synthetic chemists with the knowledge necessary to make judicious choices in solvent and additive to effect desired outcomes in these reactions. The results of these studies will be reported in due course.

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Supporting Information Available: General methods, experimental protocols, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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