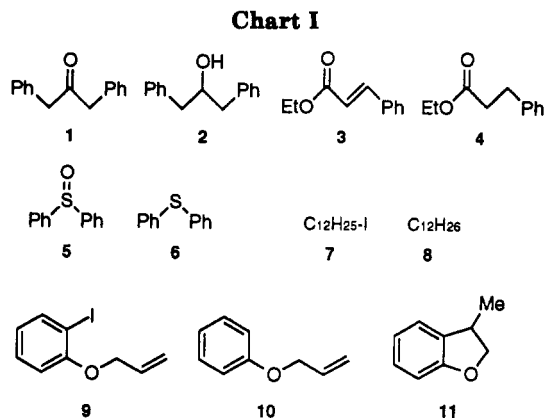# Additive and Solvent Effects on SmI2 Reductions: The Effects of Water and DMPU

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Samarium diiodide (SmI2)[2] has rapidly become one of the most popular reducing agents in organic synthesis because it is easy to prepare, it is reasonably soluble in many organic solvents, and it cleanly reduces a wide range of functional groups.[3,4] Mechanistic understanding of SmI2 reductions has lagged behind synthetic advances, but recent studies have provided a clearer picture of some SmI2 reductions.[5] Reductions with SmI2 are often conducted with an additive,[2] and the additive usually falls into one of two classes: (1) proton sources (water or low molecular weight alcohols) or (2) electron donors (HMPA,[6] DMPU,[7,8] inorganic bases[9]). The role of donor ligands is

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## Chart I



to increase the reducing power of Sm(II), and it has been thought that proton sources served only to protonate basic organometallic intermediates (samarium ketyls, alkoxides or enolates, or alkyl samariums).[2] In their seminal 1980 paper, Kagan and co-workers reported that water was the additive of choice for the SmI2 reduction of 2-octanone to 2-octanol.[2] We now present evidence that water serves not only as a proton source, but can also accelerate certain classes of samarium reductions. By implication, low molecular weight alcohols may serve a similar dual role. In an ancillary study, we have observed that DMPU is an effective additive for the reduction of an aryl iodide in MeCN but not THF. Related to these effects are observations that aqueous bases can promote reductions of recalcitrant substrates with SmI2.[9]

## Results and Discussion

In conducting kinetic experiments,[10] it became important for us to ensure that typical quenching procedures of SmI2 reductions were rapid and quantitative. Visual observations suggested that water was not only a poor quenching reagent for SmI2 (as expected[3]), but that it actually accelerated reductions after its addition. For example, addition of water (10–20 equiv) to THF solution of SmI2 induced a color change from the original deep blue to a deep purple reminiscent of SmI2 in THF/HMPA. This purple color persisted for a few hours. However, it completely faded within a few minutes in the presence of an alkyl iodide although the alkyl iodide itself did not decolorize SmI2 over a few hours in the absence of water. These observations prompted us to study in more detail the effects of water on SmI2 reductions. We chose five representative compounds as reactants for the reductions with SmI2 (Chart I): 1,3-diphenylacetone (1), ethyl cinnamate (3), diphenyl sulfoxide (5), 1-iodododecane (7), and o-allyloxyiodobenzene (9). The corresponding products of these reductions are also shown in Chart I. For the reduction of 9, products 10 and 11 formed in a ratio of 3/97,[11] and we only quantified the yield of 11.

Table I summarizes the results of all the experiments that we conducted. In general, the substrate was added to THF solutions of SmI2 (2 equiv) with and without water (15 equiv versus SmI2). After the indicated time period,

(10) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* 1993, *34*, 1717.

(11) (a) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* 1990, 773. (b) Molander, G. A.; Harring, L. S. *J. Org. Chem.* 1990, *55*, 6171. (c) Inanaga, J.; Ujikawa, O.; Yamaguchi, M. *Tetrahedron Lett.* 1991, *32*, 1737–1740. (d) Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* 1992, *114*, 6050.

**Table I. Water Effect on the Reductions of Substrates 1, 3, 5, 7, and 9 with SmI$_2$[a]**

| entry | reactant (R) | H$_2$O | reaction time, min | quench[b] method | product (P) | ratio[c] R/P |
|---|---|---|---|---|---|---|
| 1 | 1 | no | 10 | A | 2 | 6:94 |
| 2 | 1 | no | 10 | B | 2 | 26:74 |
| 3 | 1 | no | 10 | C | 2 | 100:0 |
| 4 | 1 | yes | 10 | C | 2 | 1:99 |
| 5 | 3 | no | 10 | C | 4 | 100:0 |
| 6 | 3 | yes | 10 | C | 4 | 0:100 |
| 7 | 5 | no | 1 | C | 6 | 66:34 |
| 8 | 5 | yes | 1 | C | 6 | 1:99 |
| 9 | 7 | no | 60 | C | 8 | 88:12 |
| 10 | 7 | yes | 60 | C | 8 | 29:71 |
| 11 | 9 | no | 300 | C | 11 | 80:20 |
| 12 | 9 | yes | 300 | C | 11 | 36:64[d] |

[a] Reactant/SmI$_2$/H$_2$O = 1:2.2:33 (15 equiv vs SmI$_2$); solvent, THF; [SmI$_2$] $\simeq$ 0.1 M. [b] Method A: 0.2 N HCl; method B: saturated NH$_4$Cl; method C: air/saturated NH$_4$Cl. [c] Determined by $^1$H NMR. [d] 10/11 = 5:95.

the reactions were quenched and the ratio of reduced product to recovered starting material was measured by $^1$H NMR. All reactions were very clean, and crude mass balances generally exceeded 90%.

The yield of 2 in the reduction of 1 was very sensitive to the method of quench. Reduction of 1 in the absence of water for 10 min, followed by quenching with water and standard workup provided 1 and 2 in a ratio of 6/94 (entry 1). Quenching of a water-free reduction with ammonium chloride gave 1/2 in a ratio of 26/74. When a water-free reduction of 1 was quenched by bubbling dry air through the mixture prior to standard ammonium chloride workup, we recovered only the starting ketone 1; product 2 was not formed (entry 3). Finally, when water was present in the medium (entry 4), we observed complete conversion to 2. The presence of water is clearly essential to the rapid conversion of 1 to 2, and "quenching" dry reactions with water only serves to promote this conversion. In contrast, dry air rapidly consumes unreacted SmI$_2$ (as judged by the fast decolorization), and this effective quenching procedure was adopted for the rest of the experiments. Despite the potential for oxygenation of organosamarium intermediates,[12] we observed no oxygenated products in any of the reactions in Table I.
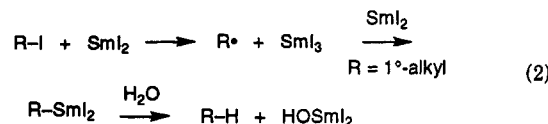
Substrates 3 and 5 behaved very similar to 1. Under dry reduction conditions with air quenching these substrates were recovered completely (3) or partly (5), but when water was present in the medium they were rapidly (10 min for 3; 1 min for 5) and cleanly converted to products (compare entry 5 with 6, and 7 with 8). For comparison, Kagan reported that reduction of 3 at 25 °C with SmI$_2$ (2 equiv of MeOH) took 1 day, while reduction of 5 (no proton source) took 3 days.[2] Inanaga reported that addition of 2.6 equiv of HMPA shortened the reduction time of 5 to 1 min.[13]

These results show that water is required for reductions of substrates 1, 3, and 5, and they are fully consistent with the usually accepted role of a proton donor.[3] Equation 1 illustrates the likely mechanism for the reduction of 1 with SmI$_2$. Reduction of 1 to form a samarium ketyl 12 is probably rapid and reversible,[5a] and the equilibrium may lie towards the side of the starting materials. In the absence of a proton donor, ketyl 12 is consumed very slowly (by dimerization to a pinacolate[14]). The addition of a
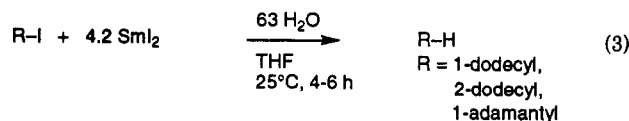
$$\underset{1}{\overset{O}{R}\overset{\Vert}{C}R} + SmI_2 \rightleftharpoons \underset{12}{\overset{OSmI_2}{R\overset{\cdot}{C}R}} \xrightarrow[SmI_2]{H_2O} \underset{13}{\overset{OSmI_2}{R\overset{H}{C}R}} + HOSmI_2 \quad (1)$$
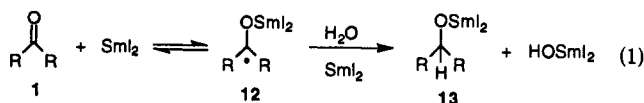
proton source opens a new pathway for 12. Proton transfer and reduction by a second equivalent of SmI$_2$ (in either order) provides samarium alkoxide 13, which is the immediate precursor of alcohol 2. Since ketyl 12 is replaced rapidly at equilibrium, this leads to rapid consumption of 1. These experiments neither prove nor disprove the role of water in accelerating SmI$_2$ reductions of the initial substrates because the role of water as an accelerator cannot be separated from its role as a proton source.

However, the accelerating role of water in the reduction of alkyl and aryl iodides can readily be demonstrated. In such reactions, SmI$_2$ is though to reduce the iodides to radicals by irreversible dissociative electron transfer (eq 2).[5a] Thus, while water can function as a proton source to trap any samarium reagents that are formed, this protonation cannot influence the rate of reduction as it can in eq 1. Subsequent reactions of the initial radical depend on the group "R". When R = aryl or tertiary alkyl, radical/solvent or radical/radical reactions generally occur, though these can be superseded by fast radical rearrangements. However, when R = primary-alkyl, rapid reduction of the radical to an alkyl samarium reagent occurs, as shown in eq 2.

$$R{-}I + SmI_2 \longrightarrow R\cdot + SmI_3 \xrightarrow[R = 1°\text{-alkyl}]{SmI_2}$$

$$R{-}SmI_2 \xrightarrow{H_2O} R{-}H + HOSmI_2 \quad (2)$$

Reduction of 1-iodododecane (7) for 60 min under dry conditions provided 7 and 8 in a ratio of 88/12, while in the presence of water the ratio was 29/71 (entries 9, 10). Likewise, dry reduction of 9 provided 9 and 11 in a ratio of 80/20, while with water present, the ratio was 36/64 (entries 11, 12). These experiments show that water has a modest but significant accelerating effect on reductions of iodides by SmI$_2$.

Unfortunately, conducting the reactions of 7 and 9 for longer reaction times did not significantly increase the conversion ratios. This is apparently because the reduction of water by SmI$_2$ is competitive with the reduction of the iodide. The problem can be overcome by using excess SmI$_2$. Reductions of representative primary, secondary, and tertiary iodides with 4.2 equiv of SmI$_2$ in THF containing 63 equiv of water provided reduced products in virtually quantitative yields in 4–6 h (eq 3). This

$$R{-}I + 4.2\,SmI_2 \xrightarrow[\substack{THF \\ 25°C, 4{-}6\,h}]{63\,H_2O} \underset{\substack{R = 1\text{-dodecyl,} \\ 2\text{-dodecyl,} \\ 1\text{-adamantyl}}}{R{-}H} \quad (3)$$

reaction time is considerably shorter than Kagan's original procedure (THF, no additive, 24 h at 25 °C or 6 h at reflux), but considerably longer than procedures with HMPA. Of course, water is virtually free and is a positively healthy additive compared to HMPA.

Unlike the results obtained in THF, we found that the blue color of SmI$_2$ in MeCN is rapidly decolorized (several

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(14) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765.

**Table II. Reductions of *o*-(Allyloxy)iodobenzene (9) with SmI₂ in the Presence of DMPU or HMPA[a]**

| entry | additive | solvent | reaction time, min | ratio[b] % 9/11 |
|-------|----------|---------|--------------------|-----------------|
| 1 | DMPU | THF | 5 | 94:6[d] |
| 2[c] | DMPU | THF | 30 | 95:5[e] |
| 3 | DMPU | McCN | 5 | 12:88 |
| 4 | DMPU | MeCN | 30 | 0:100 |
| 5 | none | MeCN | 60 | 100:0 |
| 6 | HMPA | THF | 5 | 0:100[f] |
| 7 | HMPA | MeCN | 5 | 0:100 |

[a] 9/SmI₂/additive = 1:3.1–3.3:26–27 (8 equiv vs SmI₂). Quenching method B (See Table I). [b] Determined by ¹H NMR. [c] Conducted under argon. [d] 10/11 = 45:55. [e] 10/11 = 61:39. [f] 10/11 = 4:96.

seconds) by water. Thus, water will probably not be a useful additive in MeCN. In surveying other potential alternatives to HMPA in MeCN, we found that DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) is much more efficient in MeCN[8d] than in THF. Table II shows the results of a series of reductions of iodide 9 in THF and MeCN. Iodide 9 is not efficiently reduced by SmI₂ in MeCN without an additive. While DMPU is not an effective additive in THF,[15] it is quite effective in MeCN. However, HMPA still accelerates the reduction of 9 in MeCN significantly better than DMPU.

These results suggest that water has underrecognized potential as a safe, convenient additive for accelerating SmI₂ reductions. A potential complicating factor with less reactive substrates is the slow reduction of water by SmI₂. Though it has not yet been demonstrated, low molecular weight alcohols may also accelerate reductions of SmI₂, and our results suggest that traditional reduction procedures might be beneficially modified simply by dramatically increasing the amount of alcohol that is added. Our visual experiments show that SmI₂ reduces alcohols even more slowly than it reduces water. Care must be used when quenching SmI₂ reductions with water, since significant amounts of additional product may actually be formed in the quenching process as the addition of water accelerates the reduction. Though water clearly

accelerates the reductions of alkyl and aryl iodides, the origin of this accelerating effect is not obvious. The presence of water (or a related proton source) is essential for the rapid reduction of carbonyls and related substrates, though its role in these reactions could well be simply as a proton source to drive the reduction forward.

## Experimental Section

**General.** 1,2-Diphenylacetone, ethyl cinnamate, and phenyl sulfoxide (Aldrich) were used for the reactions without further purification. 1-Iodododecane was prepared by the reaction of 1-dodecanol tosylate with sodium iodide. *o*-(Allyloxy)iodobenzene was obtained by allylation of *o*-iodophenol. THF was distilled from sodium–benzophenone under N₂. MeCN was distilled from CaH₂ under N₂. DMPU (Aldrich) was stored with molecular sieves 4A under N₂. HMPA (Aldrich) was distilled from CaH₂ and stored with molecular sieves 4A under N₂. SmI₂ solution was prepared from Sm (Aldrich) and iodine in an appropriate solvent.[2] Product identifications were accomplished by direct comparisons of ¹H NMR (300 MHz) spectra of reaction products with those of authentic samples (commercial or prepared).

**Reactions with SmI₂ in the Presence of Additives. Water Effect:** To a N₂-prepurged mixture of substrate (0.356–0.358 mmol) and water (210 μL, 11.7 mmol) was added 0.1 M SmI₂ in THF (8 mL, 0.8 mmol). The mixture was stirred for 1–60 min followed by either addition of 0.2 N HCl (method A), saturated NH₄Cl (method B), or bubbling of air followed by saturated NH₄-Cl (method C). The mixture was extracted with ether and the extract was washed with 5% Na₂S₂O₃ and brine and dried with MgSO₄. The residue obtained by concentration was analyzed by ¹H NMR. **DMPU or HMPA Effect:** To SmI₂ (0.1 M SmI₂ in THF, 6 mL, 0.6 mmol or 0.05 M SmI₂ in MeCN, 10 mL, 0.5 mmol) was added the solution of 9 (0.193–0.194 mmol in 1 mL of THF or 0.155 mmol in 1 mL of MeCN) followed by DMPU (0.6 mL, 4.96 mmol for THF; 0.5 mL, 4.13 mmol for MeCN) or HMPA (0.85 mL, 4.89 mmol for THF; 0.7 mL, 4.02 mmol for MeCN). The mixture was stirred for 5–30 min followed by saturated NH₄Cl quenching. Subsequently, this was extracted with pentane–ether (1/1) and the extract was washed with water (×2), 5% Na₂S₂O₃, and brine, and dried with MgSO₄. Then, ¹H NMR analysis of the crude products was performed.

(15) Addition of DMPU to a solution of 9 and SmI₂ resulted in a deep purple heterogeneous mixture. This suggests that the reduced effectiveness of DMPU in THF may be due in part to formation of an insoluble SmI₂/DMPU complex.