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Reduction of β-Hydroxyketones by $SmI_2/H_2O/Et_3N$

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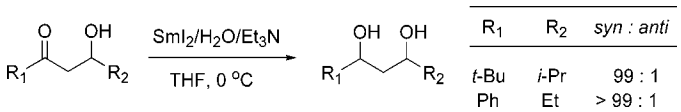
ABSTRACT



R_1	R_2	*syn* : *anti*
t-Bu	*i*-Pr	99 : 1
Ph	Et	> 99 : 1

Reduction of a series of β-hydroxyketones by $SmI_2/H_2O/Et_3N$ provided 1,3-diols in quantitative yields. The reactions were exceedingly clean with no byproduct formation, negating the need for further purification. Most reactions provided moderate to excellent diastereoselectivity with *syn*-diols as the major isomer in most instances.

The pioneering discovery by Inanaga[1] describing the use of HMPA in accelerating SmI_2-mediated reactions has resulted in widespread applications of the SmI_2−HMPA mixture. This combination is utilized in several reduction and reductive coupling reactions. Due to its ability to enhance reaction outcomes, HMPA is the preferred cosolvent in SmI_2-mediated reactions. There is, however, one serious drawback to the use of HMPA. It is a suspected human carcinogen and, therefore, extreme caution needs to be exercised during its use. Several nontoxic alternatives to HMPA have been reported recently. Cabri[2] and co-workers have explored the use of 1,1,3,3-tetramethylguanidine (TMG), 1,1,3,3-tetramethylurea (TMU) and Et_3N as cosolvents in halide-olefin coupling reactions. Curran[3] has reported the effects of water and DMPU in the reduction of ketones. These additives have proven to be useful in several reactions but unfortunately do not have the broad applicability of HMPA, and as a consequence, the search for an alternative is ongoing.

In this regard, the work reported by Hilmersson[4] and co-workers is of considerable significance. They have reported the use of an $SmI_2/H_2O/Et_3N$ mixture in the reduction of ketones. These reactions are instantaneous and provide excellent yields of reduced products. A comparison of the H_2O/Et_3N method and the HMPA/alcohol method in reduction of ketones indicates that H_2O/Et_3N is approximately 100 times faster. This method has also been applied in the reduction of α,β-unsaturated esters, imines, and conjugated olefins with excellent results.[5,6] These examples clearly show the utility of SmI_2/H_2O/amine mixtures in reduction of several functional groups. Moreover, they provide better yields and require much less time than the HMPA/alcohol systems. The workup and subsequent purification of products are straightforward since the byproducts precipitate during the course of the reaction. Therefore, the combination of amine and H_2O provides an excellent alternative to HMPA in SmI_2-based reactions.

Initial mechanistic studies show that water and Et_3N do not accelerate the reactions separately. The acceleration is a result of the Et_3N-H_2O mixture. Other amines such as *N*,*N*,*N*′,*N*′,-tetramethylethylenediamine (TMEDA) and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) have the same effect as Et_3N, while replacement of water by alcohols has a deleterious impact on the rates of reduction. It has been

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(1) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.
(2) Cabri, W.; Candiani, I.; Colombo, M.; Franzoi, L.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 949.
(3) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008.
(4) Dahlen, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, *43*, 7197.
(5) Dahlen, A.; Hilmersson, G. *Tetrahedron Lett.* **2003**, *44*, 2661.
(6) Dahlen, A.; Hilmersson, G. *Chem. Eur. J.* **2003**, *9*, 1123.

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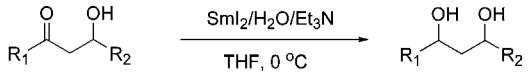
Table 1. Reduction of β-Hydroxyketones by $SmI_2/H_2O/Et_3N$



R_1 = Me, *t*-Bu, Ph; R_2 = Me, Et, *i*-Pr, *t*-Bu, Ph

entry	R_1	R_2	ds (syn:anti)[a]
1	*t*-Bu	Me	12:1
2	*t*-Bu	Et	29:1
3	*t*-Bu	*i*-Pr	99:1
4	*t*-Bu	*t*-Bu	4:1
5	*t*-Bu	Ph	1.5:1
6	Ph	Me	99:1
7	Ph	Et	>99:1
8	Ph	*i*-Pr	>99:1
9	Ph	*t*-Bu	1:41
10	Ph	Ph	2.6:1
11	Me	*t*-Bu	99:1
12	Me	Ph	1:2

[a] Substrate (β-hydroxyketone, 1 mmol) was placed in a flame-dried round-bottom flask and dissolved in 10 mL of anhydrous THF, and the solution was cooled to 0 °C. A mixture of SmI_2 (2.5 equiv) in THF, triethylamine (5 equiv), and deaerated water (6.25 equiv) was added dropwise to the reaction mixture. The reaction mixture was allowed to stir at 0 °C until the color of the reaction changed from blue to yellow.

proposed that rapid precipitation of $Sm(OH)_3$ and a tertiary ammonium salt, $Et_3NH^+ I^-$, provides the driving force for the reduction.[6]

To expand the applicability of the $SmI_2/H_2O/Et_3N$ reagent and to determine its general utility in important single-electron-transfer-promoted reactions, the reduction of β-hydroxyketones to 1,3-diols was studied. The seminal work of Keck has shown that the reduction of β-hydroxyketones is sensitive to proton donor source and temperature.[7] Recent work in our laboratory has shown that solvation also plays an important role in determining the stereochemical outcome of these reductions.[8] A limited survey of the effects of substitution and solvent on reduction of β-hydroxyketones in three solvents showed that, in most cases, DME provided superior diastereoselectivities over THF (both solvents leading to the syn product), whereas reductions in CH_3CN led to *anti*-1,3-diols. Since the nature of substitution in substrates is known to influence outcomes in $SmI_2/H_2O/Et_3N$-mediated reactions,[6] a series of β-hydroxyketones were synthesized to examine the role of substituents in detail.

Table 1 contains the series of β-hydroxyketones examined in this study. The β-hydroxyketones were synthesized by the aldol reaction of ketones and aldehydes or the L-proline-catalyzed asymmetric aldol reaction.[9] Substrates were subjected to reduction using $SmI_2/H_2O/Et_3N$. These reactions were performed at 0 °C in an inert atmosphere of N_2, and all reactions were completed within 5 min of addition of the Sm(II) reductant. The diastereoselectivity was determined by gas chromatography, and the stereochemistry of the 1,3-diols was determined utilizing the protocol described by Rychnovsky.[10] The results are shown in Table 1.

All reactions were quantitative, and the precipitation of byproducts $Sm(OH)_3$ and $HNEt_3^+ I^-$ made purification quite simple. Filtration of the precipitate and rotary evaporation of solvent provided clean product, and no further purification was necessary. Inspection of the results in Table 1 shows a number of interesting trends. Most reactions provided the syn diastereomer predominantly, although two cases (entries 9 and 12) provided the anti diastereomer as the major product. When R_2 was Ph, the diastereoselectivity decreased dramatically, whereas Me, Et, and *i*-Pr substituents resulted in good to excellent diastereoselectivity.

Comparison with other reported protocols using SmI_2 reveals some interesting trends and differences among SmI_2-based approaches to the reduction of β-hydroxyketones. When R_1 = *t*-Bu and R_2 = Ph (entry 5, Table 1), poor diastereoselectivities were obtained using $SmI_2/H_2O/Et_3N$ and SmI_2/MeOH in THF[7] or DME[8] suggesting that this substitution pattern may be inherently difficult to reduce diastereoselectively. When R_1 = Me and R_2 = Ph (entry 12, Table 1), excellent diastereoselectivities providing the anti diastereomer were obtained with SmI_2/MeOH in THF and DME, whereas reduction by $SmI_2/H_2O/Et_3N$ provided only modest selectivity for the anti diastereomer. Substrates in entries 1, 6, and 11 of Table 1 are reduced with greater diastereoselectivity by $SmI_2/H_2O/Et_3N$ than SmI_2 in THF/MeOH.

While ease of reduction, workup, and in some cases higher diastereoselectivities are obtained in reductions of β-hydroxyketones with $SmI_2/H_2O/Et_3N$ in THF compared to SmI_2/MeOH, it is important to assess various mechanistic scenarios responsible for reaction outcomes so that practitioners can make judicious choices best suited to their system of interest. The reduction of ketones by SmI_2 in the presence of proton sources likely proceeds through a House-type mechanism,[11] and recent mechanistic work has shown that the rate-limiting step is the first proton transfer to the initially formed ketyl radical anion.[12,13] While reduction of β-hydroxyketones may be somewhat more complex since the presence of an internal proton source (β-OH) may also act as a donor, initial rate studies are also consistent with the initial proton transfer to the ketyl radical anion as the rate-limiting step.[14] The radical produced after protonation of the ketyl is reduced to a carbanion by a second equivalent of Sm(II). The stereodefining step in the present reductions is likely to be the final proton transfer to the carbanion.

There is strong synthetic and mechanistic evidence to support the presence of chelation along the reaction coordinate of Sm(II)-mediated reduction and reductive coupling

(7) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172.
(8) Chopade, P. R.; Davis, T. A.; Prasad, E.; Flowers, R. A., II. *Org. Lett.* **2004**, *6*, 2685.
(9) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 239.
(10) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251.
(11) House, H. O. In *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972.
(12) Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2001**, *42*, 5565.
(13) Chopade, P. R.; Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2004**, *126*, 44.
(14) Chopade, P. R. Ph.D. Dissertation, Texas Tech University, Lubbock, TX, 2004.

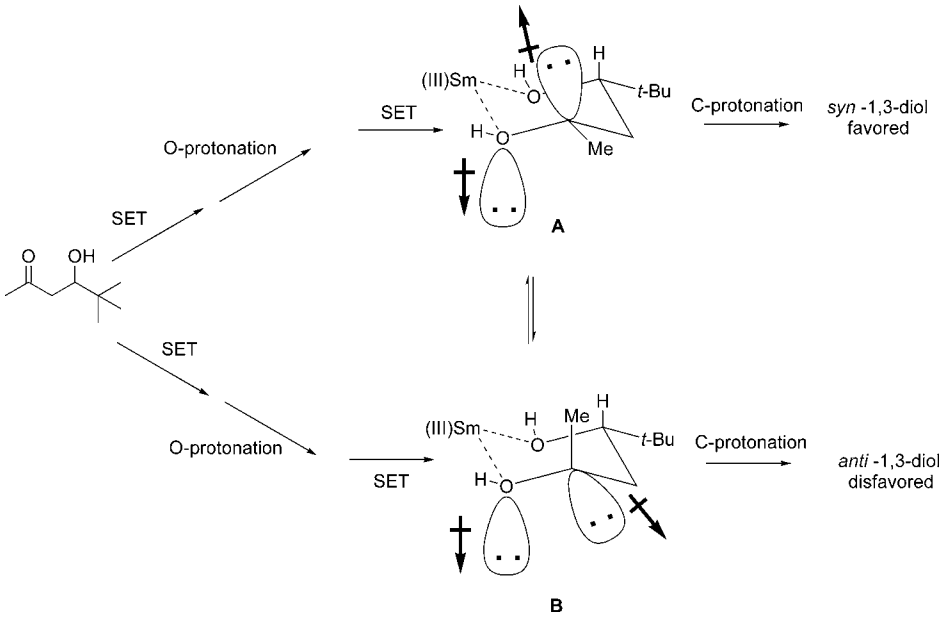


Figure 1. Electrostatic interaction between lone pairs on carbanion intermediate and neighboring oxygen.

reactions of β-substituted ketones, and this is likely to be important in the reductions described above.[7,15−17] The majority of the reactions examined in the present case provide the syn diastereomer as the major product. After analysis of numerous chelation models, the results of the reductions described herein are consistent with the importance of electrostatic interactions in defining the final stereochemistry of the 1,3-diol product (Figure 1). Reaction of a β-hydroxyketone with $SmI_2/H_2O/Et_3N$ through two electron transfers (from 2 equiv of SmI_2) and one proton transfer (from H_2O) leads to two potential intermediates shown as **A** and **B** in Figure 1. Protonation of **A** leads to the formation of the *syn*-1,3-diol, whereas protonation of **B** leads to the formation of the *anti*-1,3-diol. In **A**, the electron lone pair of the oxygen and the lone pair of the adjacent carbanion are nearly antiperiplanar and as a result the electrostatic repulsion between them is not significant. Conversely, in **B**, the lone pairs are only separated by approximately 60°, leading to increased electrostatic repulsion. On the basis of this analysis, the transition state (TS) from **A** is of lower energy than the TS from **B**.

A different explanation for the syn stereoselectivity is possible as well. The axially oriented radical precursor of **A** is expected to be stabilized due to favorable overlap of the singly occupied orbital and the nonbonding orbital on the neighboring oxygen. Upon reduction of the radical, coplanarity of the nonbonding orbitals on the carbon and neighboring oxygen, while Coulombically favorable, leads to an unfavorable orbital interaction.[18] This intermediate (resembling **A**) could be protonated quickly by water in the system before configurational change takes place at the carbon center. Alternatively, distortion of the intermediate due to the interaction between the lone pair of the carbanion and the samarium (as shown for **A** in Figure 1) could move the nonbonding orbitals on carbon and oxygen out of plane, providing stabilization as well.

The mechanistic scenarios described above do not explain the change in diastereoselectivity when R_2 = Ph. After careful analysis, it is our hypothesis that the electron-deficient Sm^{3+} cation could possibly interact with the π-system of the benzene ring (Figure 2). Since this interaction is only possible in **B**, it could act to stabilize **B** depending on the substituent at R_1 and as a result provide an alternative

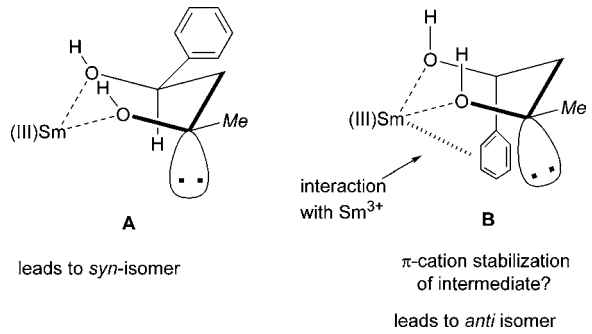


Figure 2. Depiction of possible intermediate leading to poor stereoselectivity or reversal of stereoselectivity when R_2 = Ph.

(15) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1998**, *63*, 812.
(16) Kawatsura, M.; Hosaka, K.; Matsuda, F.; Shirahama, H. *Synlett* **1995**, 729.
(17) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2002**, *124*, 6357.
(18) Skrydstrup, T.; Jarreton, O.; Mazéas, D.; Urban, D.; Beau, J.-M. *Chem. Eur. J.* **1998**, *4*, 655.

mechanistic (stereodifferentiating) pathway for the reduction. Additional detailed mechanistic studies on a variety of substrates will be necessary to further test this hypothesis.

In conclusion, reduction of a series of β-hydroxyketones by $SmI_2/H_2O/Et_3N$ in THF provided good to excellent selectivity for the *syn*-diol with a wide range of substrates. All reductions provided quantitative yields and were completed within a few minutes. Furthermore, precipitation of byproducts eliminates the need for further purification, thus simplifying the workup compared to standard Sm(II)-based reductions. Analysis of various transition state models proceeding through chelation control are consistent with the importance of electrostatic interactions controlling the diastereoselectivity of the 1,3-diol in most instances. Regardless of the exact mechanistic details of the present reductions, the data presented herein show the utility and ease of the $SmI_2/H_2O/Et_3N$ reducing system in the reduction of β-hydroxyketones. Examination of the use of this novel reducing system in reductive coupling reactions is currently underway, and 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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