An Especially Convenient Stereoselective Reduction of β-Hydroxy Ketones to Anti 1,3 Diols Using Samarium Diiodide†

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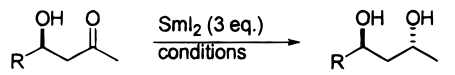
The 1,3 diol unit is an extremely common and recurring structural motif in many polypropionate- and polyacetate-derived natural products. Given the current availability of a number of enantio- and stereoselective methods for the construction of β-hydroxy carbonyl compounds, it is not surprising that one prominent pathway used for the construction of such arrays utilizes the reduction of β-hydroxy ketones. A number of processes have been developed for this purpose, invariably involving hydride reducing agents. For example, $Zn(BH_4)_2$ has been commonly used to access syn 1,3 diols from β-hydroxy ketones, presumably via formation of an intermediate zinc chelate, which undergoes reduction from the less sterically encumbered face.[1] DiMare has used a similar chelation strategy with protected β-hydroxy ketones in which a discrete Lewis acid complex is first established with $TiCl_4$, followed by introduction of a hydride reducing agent such as $BH_3{\cdot}Me_2S$, and Prasad has reported a syn-selective reduction using $(EtO)_3B$ and $NaBH_4$.[2] Similarly, boron aldolates can be induced to undergo chelate formation prior to workup and reduced stereoselectively with $LiBH_4$, as shown by Patterson.[3] Anti 1,3 diol units are most commonly accessed via the reduction of β-hydroxy ketones with tetramethylammonium triacetoxyborohydride, by a process believed to proceed via an internal delivery of hydride, as described by Evans.[4] Evans has also reported a modification of the Tishchenko reduction in which a complex prepared by SmI_2 reduction of benzaldehyde is used to reduce β-hydroxy ketones to an anti monobenzoate derivative,[5] wherein hydride transfer occurs via an intramolecular process in a Meerwein−Ponndorf−Verley sense.

Notable by their absence are methods based on sequential one-electron transfer, as opposed to hydride transfer. We became intrigued as to whether the structural features present in such β-hydroxy or β-alkoxy ketones might have a significant influence on the stereochemical outcome of such a sequence. One can readily imagine that chelated intermediates might be formed in "dissolving metal"-type reductions of such systems, particularly with oxophilic metals. We record herein the results of an investigation using SmI_2 in this role, which has led to the development of a very convenient, high-yielding, and stereoselective process.

We began with a simple β-hydroxy ketone substrate **1a** to survey potential reaction conditions and proton sources.[6] Addition of a THF solution of SmI_2 to a solution of **1a** in THF at 0 °C, containing 2 equiv of water as the proton source, led to a very fast reaction (complete within 10 min) that afforded a 96% isolated yield of the desired diol product as a 83:17 mixture of anti and syn isomers.[7] No reaction was observed at −78 °C or with *tert*-butyl alcohol as the proton source at 0 °C (Table 1). Use of an excess (10 equiv) of water led to a 1:1 mixture of diastereomers, again in good yield.

Table 1. Proton Source Varied



1a R = C_6H_5 **2a** R = C_6H_5

1b R = c-C_6H_{11} **2b** R = c-C_6H_{11}

entry	substrate	proton source	*T* (°C); *t*(h)	yield (%)	ratio
1	**1a**	H_2O (2 equiv)	0; 1	96	83:17
2	**1a**	H_2O (2 equiv)	−78; 1	sm	
3	**1a**	t-BuOH (2 equiv)	0; 1	sm	
4	**1a**	H_2O (10 equiv)	0; 1	88	50:50
5	**1a**	MeOH (2 equiv)	0; 1	95	98:2
6	**1a**	MeOH (10 equiv)	0; 1	99	>99:1
7	**1b**	MeOH (10 equiv)	0; 2.1	84	95:5
8	**1b**	MeOH (2 equiv)	0; 3	55	98:2
9	**1b**	MeOH (20 equiv)	0; 0.5	95	99:1
10	**1b**	MeOH (100 equiv)	0; 1	91	99:1

Much better results were obtained using MeOH as the proton source. In this case, the use of 2 equiv of MeOH at 0 °C led to a quantitative conversion to a 98:2 mixture of anti and syn isomers. However, unlike the water case, the use of excess methanol led to an improved result: with 10 equiv, a 99% isolated yield of the anti compound was obtained as a single isomer (HPLC analysis). We next examined another simple, but similar, substrate in which the phenyl ring was replaced by its saturated counterpart. In this case, the reaction was considerably more sluggish and less selective: with 10 equiv of MeOH, the reaction required 2.1 h for completion and gave an 84% yield of a 95:5 mixture of diastereomers. With 2 equiv of MeOH, the yield was only 55% after 3 h. For whatever reason, it thus appeared that the phenyl-containing substrate was an especially good one for this reduction; thus, the process of optimization was initiated again with the cyclohexyl substrate. It was found that the use of 20 equiv or so of MeOH was optimal for obtaining high yields and high diastereoselectivity. Thus, with 20 equiv of MeOH, reduction of this substrate was complete within 30 min to give a 95% yield and a 99:1 level of diasteroselectivity.

We next examined protected derivatives of such β-hydroxy ketones, specifically the OBn and OTBS compounds. Here it was found that these materials were essentially inert, in marked contrast to the free hydroxy compounds. No reduction was observed even after prolonged periods at 0 °C, and a limited study at higher temperatures revealed a slow and nonselective reduction at THF reflux, consistent with the limited literature available for ketone reductions using SmI_2. *It is thus clear that the β-OH moiety is responsible not only for the stereoselectivity observed but also for a very dramatic rate enhancement in these reductions.*

† Portions of this work have been previously disclosed: Keck, G. E. Brockway, C. A.; Wager, T. T.; Sell, T. 216th ACS National Meeting, Boston, MA, Aug 1998; Paper ORG #609.

‡ Undergraduate research participant.

(1) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 2, 6074.

(2) Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; Dimare, M. *J. Org. Chem.* **1996**, *61*, 868. (b) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923.

(3) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, *797*.

(4) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(5) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

(6) Selective reduction of ketones that lack an α substituent is especially problematic; for a recent case study, see: Watanabe, H.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **1998**, *39*, 8313.

(7) Structural assignments were based upon independent synthesis and also spectral analysis of the derived acetonides using the method of Rychnovsky: Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251.

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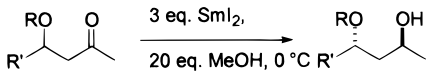
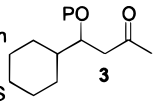
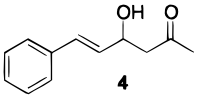
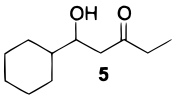
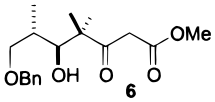
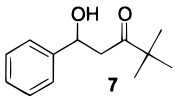
Table 2. Reduction of β-Hydroxy Ketones



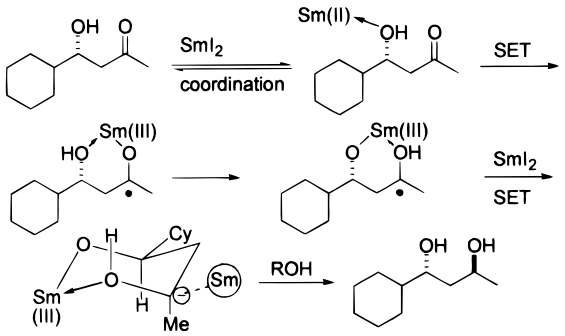
Entry	Substrate	Yields	Ratio
1	P=OBn  **3**	start mat	---
2	P=TBS	start mat	---
3	 **4**	95%	97:3
4	 **5**	86%	84:16
5[a]		71%	93:7
6[b]	 **6**	83%	>91:9
7[c]	 **7**	96%	50:50
8	 **8**	67%	50:50

[a] This reaction was performed at −20 °C for 20 h. This reaction was also performed on 1.0 mmol of ketone at −20 °C for 48 h, which gave 92:8 diastereoselectivity and 86% yield. [b] 12 equiv of water was used in this reaction. [c] 60 equiv of MeOH was used in this reaction.

Results for other substrates (summarized in Table 2 above with reaction conditions, isolated yields, and anti/syn ratios indicated) suggest that this procedure will prove generally useful. In all cases examined to date, anti selectivity is realized irrespective of the nature of, or absence of, α-alkyl substituents. The β-keto ester substrate **6** is reduced without incident and without β-elimination or lactonization; in this case, better results were obtained with water as an additive than with MeOH.[8]

The mechanistic details of these reactions are still obscure, as is the precise nature of the samarium(II) species involved. The results clearly indicate a role for the free hydroxyl of substrate in facilitating reduction, even in the presence of a large excess of another alcohol. It may well be that the pathway involves initial association of samarium with the free hydroxyl, followed by what would now be an intramolecular electron transfer to the keto group. It is difficult to envision that the levels of stereoselectivity obtained are realized without the intervention of some reasonably well organized structure, especially with the substrates which lack α substituents. Formation of a chelated species between the hydroxyl, Sm^{3+}, and the ketyl oxygen seems eminently plausible; after protonation of the samarium ketyl, the carbinol radical undergoes a second rapid electron transfer to give a samarium carbanion that would be protonated to yield the diol. If this is in fact the overall sequence of events, then to rationalize the stereochemical outcome would seem to demand that the samarium and its associated ligands are effectively much larger than the α′ ketone substituent, leading to an equatorial disposition of samarium and hence an axial orientation for the α′ substituent. It was found that reduction of the *tert*-butyl substrate **7** yielded a 1:1 mixture of diastereomers, suggesting, in terms of this working model, that the samarium and its associated ligands are approximately as sterically demanding as the *tert*-butyl group. It is also clear that a β-substituent is necessary to obtain useful levels of diastereoselectivity in that reductions of substrate **8** (containing a primary alcohol) were nonselective. Finally, it was found that α-hydroxy ketones are not suitable substrates for use in these reactions; in these cases the known reductive cleavage of the α-hydroxy substituent proved to be faster than the desired ketone reduction (Scheme 1).

Scheme 1



One especially attractive feature of the process is experimental simplicity and ease of execution, particularly when compared to reductions using tetramethylammonium triacetoxyborohydride. However, this reduction protocol currently lacks the extensive database now available for that procedure, and care should be taken to ensure that the products obtained in any particular application are actually the anti materials expected on the basis of the cases examined to date.

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra.

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(8) In this case, since we have not been able to identify a suitable analytical HPLC separation to date, we can only place a lower limit on the stereoselectivity by NMR analysis, but it is clear by comparison to independently synthesized syn/anti mixtures obtained by $NaBH_4$ and $Zn(BH_4)_2$ reductions that this substrate is reduced with a high degree of stereoselectivity.