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Stereoselective catalytic Tishchenko reduction of β-hydroxyketones using scandium triflate

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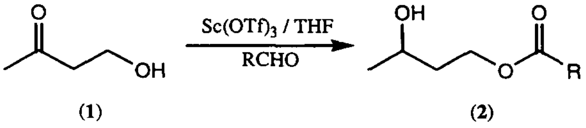
Abstract

A number of aliphatic and aromatic β-hydroxyketones were reduced to 1,3-diol monoesters by aldehydes in the presence of a catalytic amount of scandium triflate. Chiral substrates were reduced with high 1,3-*anti* diastereoselectivity. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: scandium; scandium compounds; reduction; aldols; diastereoselection.

The 1,3-diol unit is important in the chemistry of natural products such as the polyketide Rifamycin[1] and polyether antibiotics such as Lonomycin A.[2] A versatile source of 1,3-diols is the reduction of β-hydroxyketones which themselves are synthesised from silyl enol ethers and aldehydes via the Mukaiyama aldol reaction.[3] A large number of such reductive methods produce the *syn* diol[4–11] while the Tishchenko reduction[12,13] has produced the *anti* diastereoisomer. Possibly the most successful of these methods is that of Evans and Hoveyda[12] which utilises SmI_2 as catalyst and gives high yield and diastereoselectivity. However, SmI_2 has the disadvantage of being air sensitive and is not readily recoverable from the product mixture. Also, naturally-occurring samarium contains significant quantities of a radioactive isotope.[14] We report here the surprising observation that the Tishchenko reduction of β-hydroxyketones is also catalysed by scandium triflate, a water- and air-tolerant compound which has received much attention as a Lewis acid catalyst.[15]



Scheme 1.

Our early experiments (Scheme 1) were concerned with the selection of aldehydes as stoichiometric reducing agents. When a mixture of 4-hydroxybutan-2-one **1** and isobutyraldehyde was treated with

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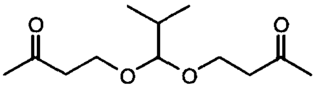
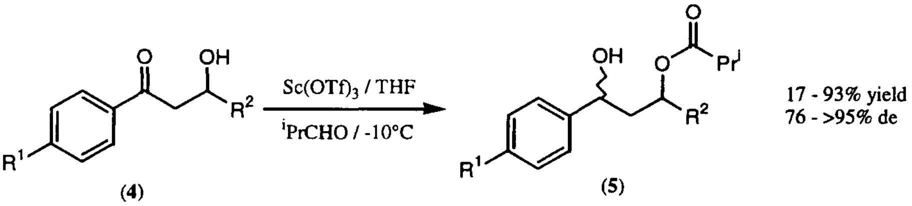
10% $Sc(OTf)_3$ in THF at room temperature, the Tishchenko product **2** (R=^{i}Pr) was formed along with ca. 50% of acetals such as **3**. In an attempt to reduce the concentration of hydroxyketone present, and thereby inhibit acetal formation, a solution of the hydroxyketone was added over 2.5 h to a mixture of isobutyraldehyde and $Sc(OTf)_3$. This led to the formation of **2** in >95% yield. The use of propionaldehyde and dihydrocinnamaldehyde as stoichiometric reducing agents gave similar results, whereas the use of benzaldehyde and crotonaldehyde which contain less hydridic aldehyde hydrogens was unsuccessful.



(3)

We then turned our attention to the diastereoselective reduction of chiral substrates. A number of racemic aromatic hydroxyketones **4** (Scheme 2) were synthesised from silyl enol ethers[16] and aldehydes via the Mukaiyama reaction.[3] These were reduced with isobutyraldehyde in the presence of 10% $Sc(OTf)_3$ at −10°C (Table 1).[17] For these secondary alcohols, no acetal formation was observed and the slow addition protocol was found to be unnecessary. No evidence was found for transesterification of the 1,3-diol monoester product under these conditions. At higher temperatures, lower diastereoselectivities in the reduction were obtained.



Scheme 2.

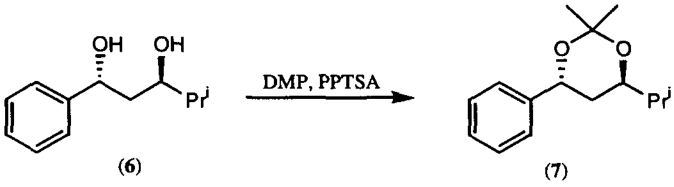
Reductive cleavage of **5** with $LiAlH_4$ gave the corresponding diols **6**. Integration of the ^1H NMR spectra (in particular the multiplets at ~5.05 and ~4.90 ppm corresponding to the benzylic proton) allowed quantification of diastereomeric excess. For comparison, the spectra of 50:50 *syn:anti* diol mixtures (prepared from $LiAlH_4$ reduction of the β-hydroxyketones **4**) were also recorded.

Table 1
Catalytic Tishchenko reduction at −10°C

	R^1	R^2	Time/h	Yield/%[a]	d.e./%[b]
1	H	Me	48	83	>95
2	H	^{i}Pr	48	93	>95
3	H	CH_2CH_2Ph	72	17	>95
4	Cl	Me	48	93	76
5	Cl	^{i}Pr	48	55	78
6	Cl	CH_2CH_2Ph	72	40	88
7	OMe	Me	120	57	88
8	OMe	^{i}Pr	120	38	80
9	OMe	CH_2CH_2Ph	120	59	94

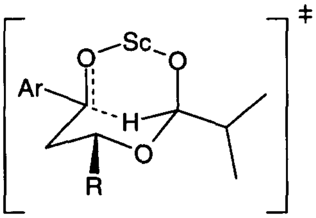
[a] Isolated yield; [b] Determined by ^1H NMR analysis of the corresponding diol

The relative stereochemistry of the products was determined by the method of Rychnovsky et al.[18] For example, the diol **6** (Table 1, entry 2) was converted to its acetonide **7** by stirring in dimethoxypropane in the presence of a catalytic amount of pyridinium *p*-toluenesulphonate for 2 h (Scheme 3). The ^{13}C NMR spectrum of **7** showed resonances at δ 24.72 and 25.40 ppm corresponding to the acetonide methyl groups of *anti*-**7** in a twist-boat conformation.[18] For comparison, the acetonide formed from the 50:50 *syn*:*anti* diol mixture of **6** displayed additional ^{13}C resonances at 19.20 and 30.71 ppm corresponding to *syn*-**7** in a chair conformation. This shows that the product in entry 2 was predominantly *anti*. Comparison of ^1H NMR spectra of the other diols indicated that the *anti* diastereoisomer was the major product in all cases.



Scheme 3.

The *anti* selection can be rationalised on the basis of the Meerwein–Pondorff–Verley-type transition-state proposed by Evans where the substituents are maintained in equatorial positions **8**.[12]



It would appear from the yield data that the electron-withdrawing group on the aromatic ring renders the carbonyl a better hydride acceptor. We will report a kinetic investigation of this phenomenon in due course. The low yield for entry 3, while consistent over several experiments, cannot be fully rationalised.

In conclusion, we have developed a catalytic Tishchenko reduction of β-hydroxyketones using scandium triflate. Both aromatic and aliphatic substrates have been successfully reduced. There is a high level of diastereoselectivity in the case of chiral substrates. We are currently engaged in the development of an enantioselective version of this reaction and in the investigation of mechanistic detail.

Acknowledgements

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17. Typical procedure: $Sc(OTf)_3$ (50 mg, 0.1 mmol) was placed in a 25 ml round-bottomed flask and dry THF was added under an atmosphere of argon. The β-hydroxyketone (1 mmol) was then added and the system was cooled to −10°C with stirring. Isobutyraldehyde (1.5 mmol) was then added. After the appropriate time diethyl ether was added (10 ml) and the mixture was washed with water (2×5 ml). The product was then purified by column chromatography [hexane:ethyl acetate (4:1)].
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