Pergamon

Tetrahedron Letters 40 (1999) 1227–1228

TETRAHEDRON
LETTERS

1,4 Asymmetric Induction in the Carbonyl Reduction of a γ-Ketosulfoxide.

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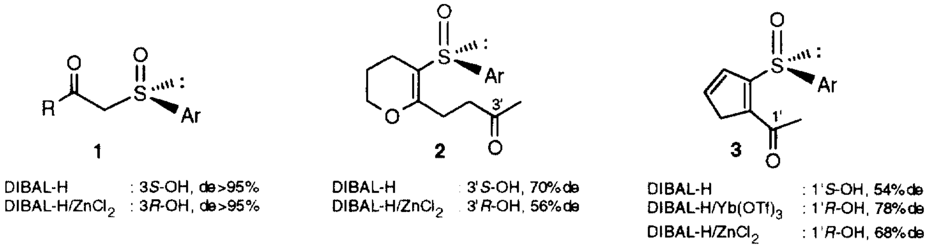
Received 4 November 1998; accepted 30 November 1998

Abstract: a chiral sulfoxide induced high stereoselectivity in the DIBAL-H reduction of a methyl ketone located in the γ position as a result of a 1,4-asymmetric induction. Addition of a lanthanide triflate or cerium chloride completely reversed the stereoselectivity.

The stereoselective sulfoxide directed reduction of β-ketosulfoxides **1** is now a well known and useful method of preparing enantiomerically pure hydroxylic compounds in the desired configuration.[1] The high level of asymmetric induction has been related to an intramolecular hydride transfer from DIBAL-H (chelated to the oxygen sulfoxide) or in presence of a chelating Lewis acid such as $ZnCl_2$, the formation of a chelate.[2]

Only a few reports concern the reduction of ketosulfoxides in which the sulfoxide group is in a more remote position from the carbonyl: Iwata reported a 1,6-asymmetric induction[3] in the DIBAL-H reduction of the ε-ketosulfoxide **2** (Scheme 1) and more recently Arai[4] presented a case of 1,4- asymmetric induction with the γ-ketosulfoxide **3**. In both cases, the cyclic structures of **2** and **3** allowed good interaction between the ketone and the sulfoxide which could explain the observed stereoselectivity. In the case of DIBAL-H reduction of **3**[4] , the addition of $Yb(OTf)_3$ or $ZnCl_2$ has a similar effect: inversion of the configuration of the carbinol, a result in sharp contrast with our previous studies[5] on the DIBAL-H reduction of β-hydroxy-γ-ketosulfoxides where $Yb(OTf)_3$ had no effect on the configuration of the carbinol.



Scheme 1

We report in this paper results concerning the DIBAL-H reduction of an acyclic γ-ketosulfoxide **6.** The (+)-(*R*)-3-(*p*-tolylsulfinyl)-propionic acid **4** was obtained in 70% yield by addition of lithium bromoacetate to

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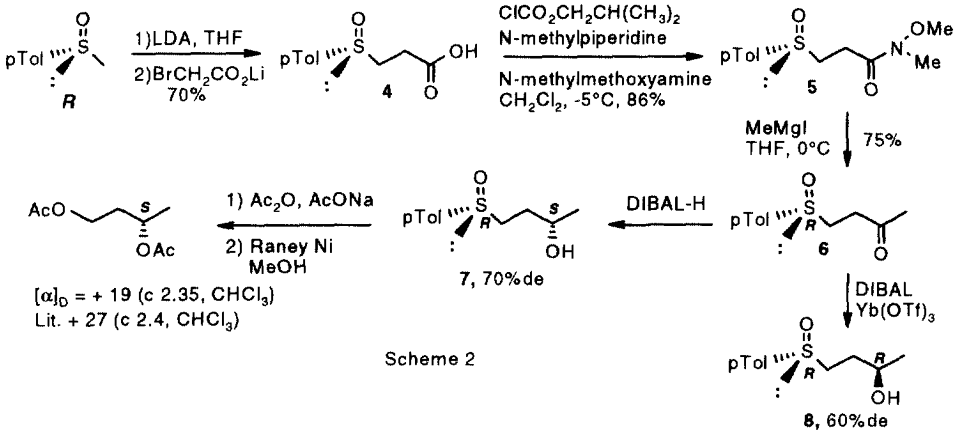
PII: S0040-4039(98)02572-6

the anion of (+)-(*R*)-methyl-*p*-tolyl sulfoxide[6] (scheme 2). Condensation of the acid **4** to N-methylmethoxyamine in the presence of N-methylpiperidine and *iso*-butylchloroformate afforded the Weinreb derivative **5** in 86% yield. Finally the γ-ketosulfoxide **6** was obtained by Grignard addition to **5** in 75% yield.



Scheme 2

Table I. Reduction of the γ-ketosulfoxide 6

Reducing agent / additive	**solvent/temp./time**	**isolated yield**	**7 / 8[7]**
$NaBH_4$ (1eq.)	EtOH / -78°C / 4h	75%	50 / 50
Dibal-H (1.1eq.)	THF / -78°C / 1.5h	85%	80 / 20
Dibal-H (1.1eq)	**THF / -105°C / 1.5h**	**85%**	**85 / 15**
Dibal-H (1.5eq.)/ZnI_2 (1.1eq.)	THF / -78°C / 3h	84%	69 / 31
Dibal-H (1.5eq.)/$MgBr_2$ (1.1eq.)	THF / -78°C / 5h	75%	56 / 44
Dibal-H (2.5eq.)/$YbTf_3$ (1.1eq.)	**THF / -78°C / 5h**	**40%**	**20 / 80**
Dibal-H (3eq.)/$YbTf_3$ (0.5eq.)	THF / -78°C / 5h	56%	30 / 70
Dibal-H (4eq.)/$NdTf_3$.(1.1eq.)	THF / -78°C / 2h	75%	25 / 75
Dibal-H (3eq.)/$CeCl_3$ (1.1eq.)	**THF / -78°C / 4h**	**66%**	**25 / 75**
Dibal-H, BHT[9]	Toluene / -60°C /3h	62%	35 / 65

The main features concerning reduction of the γ-ketosulfoxide **6** (Table I) are the following: DIBAL-H gave a high stereoselectivity which decreases in presence of ZnI_2 but the configuration of the main stereoisomer is unchanged in contrast with the reduction of β-ketosulfoxides. Ytterbium triflate, neodynium triflate and cerium chloride gave good stereoselectivity but with an opposite configuration for the main isomer.

In conclusion, a chiral sulfoxide induced high stereoselectivity in the DIBAL-H reduction of a methyl ketone located in the γ position as a result of a 1,4-asymmetric induction. Addition of a lanthanide triflate or cerium chloride completely reversed the stereoselectivity.

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7) The diastereomeric ratio was determined by ^1H NMR from the non equivalent methyl groups of the TBDMS derivatives of **7** and **8**. The absolute configuration *R*(S),*S* of the γ-hydroxysulfoxide **7** was determined by chemical correlation with the known (+)-(*S*)-1,3-diacetoxybutane[8] by Pummerer reaction and desulfurization with Raney Nickel.

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9) 2,6-di-*tert*-butyl-4-methylphenol.