1,3-Asymmetric Induction in the Reduction of α -Alkyl β -Ketosulfoxides with DIBAL/ZnBr₂

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Abstract: The highly stereoselective reduction of chiral α -alkyl β -ketosulfoxides with DIBAL/ZnBr2 is governed by the configuration at the sulfur (1,3-induction) and not by that of the C- α (1,2-induction) as it has been previously reported. This fact considerably increases the scope of the Solladié's methodology to synthesize optically pure secondary carbinols. Those substituents decreasing the capability of the carbonyl oxygen to chelate the ZnBr2 induce a decrease in the stereoselectivity.

The reduction of β -ketosulfoxides in a predictably high stereoselective manner was reported by Solladié several years ago.¹ This methodology, which involves DIBAL and DIBAL/ZnCl₂ as reducing agents, has been successfully used in the synthesis of several interesting natural products² containing a methyl carbinol moiety in their structures. The stereochemical course of these reactions was wholly controlled by the sulfur configuration. Surprisingly, it has never been reported the extension of this methodology to the reduction of α -alkyl β -ketosulfoxides to prepare secondary, other than methyl, alkyl carbinols. This fact might be due to the results published by Bravo et al. indicating that the reduction of C- α instead of that of the sulfur.³ Therefore, in order to control the optical purity of the new chiral hydroxylic carbon, the reduction had necessarily to be carried out from C- α configurationally homogeneous alkylated β -ketosulfoxides. The low stereoselectivity of the reactions used to obtain these compounds (alkylation of β -ketosulfoxides⁴ or condensation of alkyl-*p*-tolylsulfoxides⁵), required the usually difficult separation of the C- α epimer mixtures before their reduction, which sharply decreased the synthetic interest of this methodology.

Although the results obtained by Bravo et al.³ were rationalized from the first model proposed by Solladié to explain the stereoselectivity of the DIBAL/ZnCl₂ reductions, which is based only on steric grounds¹ (A in Scheme 1), those were difficult to justify assuming our later model⁶ (B in Scheme 1), where the stereoselectivity is mainly governed by: i) the larger stability of a chair like versus a twist like transition states, and ii) the association of DIBAL with the lone electron pair at sulfur⁷ previous to its attack on the carbonyl, both factors being independent of the configuration at C- α .

The stereochemical results obtained in the reduction of cyclic β -ketosulfoxides^{6,8} which are α -alkyl substituted on their own, indicated that these reactions exhibit an 1,3-induction (sulfur control, as predicted model B) instead of 1,2-induction (α -carbon control, as predicted model A). A similar 1,3-asymmetric induction was observed in reduction of β -hydroxy α -alkyl ketones with catecholborane, whose evolution involved similar chelated species.⁹ All these facts prompted us to reinvestigate the reduction of acyclic α -alkyl β -ketosulfoxides with DIBAL in the presence of ZnX₂. This paper describes the results of our study.



The treatment of the β -ketosulfoxides R¹-CH₂-SO-Tol, 1-6¹⁰ [R¹=Me (1), *n*-Pr (2), *i*-Pr (3), *t*-Bu (4), Ph (5) and 4-OMe-C₆H₄ (6)] with the alkyl halides R²X (IMe, BrCH₂Ph or BrCH₂CH=CH₂) in the presence of NaH and tetrabutylammonium iodide in THF as solvent, afforded diastereoisomeric mixtures (ca. 60:40) of the α -alkyl β -keto sulfoxides 7-14¹¹ (Scheme 2), which were reduced with DIBAL/ZnBr₂¹² without previous separation. The results are collected in Table 1.



Scheme 2

Only two hydroxysulfoxides were obtained starting from the mixtures of the epimeric sulfoxides 7-11 (entries 1-5), being their ratios almost identical to those of the starting ketosulfoxides (evaluated from their 200 MHz ¹H-nmr spectra). This result suggested that the reduction of both diastereomeric ketosulfoxides had taken place in a highly stereoselective manner. In order to determine the configuration of the resulting hydroxysulfoxides, their mixtures were oxidized with MCPBA yielding two diastereomeric sulfones. This fact excluded the reduction as an 1,2-asymmetric induction process, which would yield a mixture of enantiomers.

As a demonstration that the stereoselectivity of these reactions is controlled by the configuration of the sulfur (i.e. 1,3-asymmetric induction), it was necessary to stablish the configurational assignments of the hydroxysulfoxides A and B, which were based on their ¹H-nmr data. Compounds 7A and 7B exhibit $J_{1,2}$ values of 2.5 and 9.1 Hz respectively, which are modified when DMSO-d₆ is used as solvent (4.5 and 7.1 Hz respectively). Comparison of these data with those of the methylsulfinyl (instead p-tolylsulfinyl) derivatives¹³ allowed us to assign the configuration (1*R*,2*S*,*R*_S) to compound 7A and (1*R*,2*R*,*R*_S) to 7B (Scheme 3). All the hydroxysulfoxides 8-11 named as A must exhibit the same configuration because all of them show small $J_{1,2}$ values in CDCl₃ (<2.6 Hz), which increases in DMSO-d₆ (up 4-5 Hz). The same must be true for the corresponding B epimers, which show larger values in CDCl₃ (>6Hz) decreasing in DMSO-d₆.¹⁴ This assignment indicates that the induced configuration is identical for alcohols A and B and therefore it is only

dependent on the configuration at sulfur. The conventional Raney Nickel desulfinilation of the mixture 8A+8B afforded 3-hexanol. The value of the rotary power of the obtained alcohol ($[\alpha]_D=+6$), evidenced the configuration (S),¹⁵ as it corresponds to (R) at the hydroxylic carbon of its precursor sulfoxide 8.



Scl	heme	3
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Table 1. Hydroxysulfoxides ratio obtained in reduction of α -alkyl β -ketosulfoxides with DIBAL in the presence of 1.4 eq. of ZnBr₂.

Entry		R ²	Substrate	epimeric	Hydroxysulfoxides ratio			Yield(%)
				ratio	Α	В	С	
	Me	Me	7a+7b	66:34	66	34		91
2	n-Pr	Me	8a+8b	60:40	60	40		98
3	n-Pr	Bn	9a+9b	55:45	60	40		73
4	n-Pr	Allyl	10a+10b	60:40	60	40		77
5	<i>i</i> -Pr	Me	11a+11b	70:30	69	31		93
6	<i>t-</i> Bu	Me	12a+12b	60:40	60	35	5	98
7	t-Bu	Me	12a+12b	60:40 ^{a)}	60	31	9	98
8	<i>t</i> -Bu	Me	12a+12b	60:40 ^{b)}	60	37	3	98
9	Ph	Me	13a+13b	55:45	57	14	29	85
10	Ph	Me	13a+13b	55:45ª)	59	6	35	85
11	Ph	Mie	13a+13b	55:45 ^b)	61	25	14	89
12	4-OMePh	Me	14a+14b	54:46	64	28	8	87
13	4-OMePh	Me	14a+14b	54:46 ^{a)}	60	25	15	92
14	4-OMePh	Me	14a+14b	54:46 ^{b)}	60	31	9	90

^{a)} 1.4 eq. of ZnCl₂. ^{b)} 5.0 eq. of ZnBr₂.

The presence of a third hydroxysulfoxide, C, was detected in the mixtures obtained from 12 (entries 6-8) and 13 (entries 9-11). In these cases only one of the epimeric starting ketosulfoxides evolved with very high stereoselectivity. From the values of $J_{1,2}$ measured for epimers C (1.2 Hz), which are not affected by the solvent, we could assign them the configuration $(1S,2R,R_S)^{13}$ (Scheme 3), which indicated that C derives from $(2R,R_S)$ epimers. ¹⁶ As it can be seen, the amount of C is minimized when a large excess of ZnBr₂ is used (compare entries 6 and 8 or 9 and 11). Steric effects could be responsible for the more difficult chelation of the $(2R,R_S)$ -12 epimer. On the contrary, if we start from the phenylderivative mixture 13, C isomer is the major alcohol derived from the $(2R,R_S)$ -ketosulfoxide using ZnCl₂ as catalyst (entry 10). The amount of B diastereoisomer increases with ZnBr₂ (entry 9) and becomes greater using a large excess of this Lewis acid (entry 11). If we take into account that the chelation of 2-methylsulfinyl-1-phenylethanone with ZnCl₂ is not easily attained, ¹⁷ these results suggest that with this catalyst, 13 evolves mainly through the non-chelated species. The change of Lewis acid must increase the share of the chelated species, which are major when an excess of ZnBr₂ is used. We prepared the p-methoxyphenyl derivative 14 in order to demonstrate that the low chelation capability of the carbonyl oxygen determines an imperfect chelation. The epimeric mixture was treated in the same conditions as 13 and the results (compare entries 12-14 with 9-11) are very eloquent.

Therefore we can conclude that the reduction of α -alkyl-B-ketosulfoxides with DIBAL in the presence of ZnX₂ (bromide better than chloride) is a 1,3-asymmetric induction process controlled by the configuration at sulfur. Deviations of this rule are a consequence of an imperfect chelation of the substrate.¹⁸ In these cases, the increase of the amount of catalyst improve the stereoselectivity in the expected sense.

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- 10. These compounds were obtained by reaction of the esters R¹-COOEt (R¹=Me, n-Pr, i-Pr, t-Bu, Ph and 4- $OMe-C_6H_4$) with (R)-methyl p-tolylsulfoxide, following the procedure previously reported for compounds 4 and 5 (J.L. García Ruano, A. Martín and J.H. Rodriguez, Tetrahedron Lett. 1991, 32, 3195). Compounds 1-3 and 6 were prepared using similar conditions.
- 11. The yields were higher than 90% in methylation and 70% in the other alkylation reactions.
- 12. The experimental procedure described in reference 7 was slightly modified by adding the mixture of the ketosulfoxides and ZnBr2 over the THF solution of DIBAL.
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- 16. The lower selectivity observed in the reduction of the $(2R,R_S)$ -ketosulfoxides is in accordance with the results obtained from B-hydroxyketones (see reference 9). It could be a consequence of the different stability of the chelated species depending on the relative configuration of the chiral centers.
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 18. The erroneous generalization of Bravo in reference 3 (diasteroselectivity controlled only by the
- stereochemistry of the substituted α -carbon, 1,2-induction), achieved from the study of the reduction of fluorinated ketosulfoxides, may be due to the reaction conditions thereby used (ZnCl₂, 1 eq.) as well as to the presence of fluorine atoms, which are able to compete with sulfinyl group in the chelation and decrease the electronic density on the carbonylic oxygen. In fact, the reduction of a 61:39 mixture of the C- α epimers of CH₂F-CO-CH(CH₃)-SO-pTol (substrate studied by Bravo in reference 3) carried out in the conditions indicated in this paper (ZnBr₂, 5 eq.), yields a 66:22:12 mixture of alcohols **A**, **B** and **C** (see Scheme 3). The appearance of C diastereomer (compare with entry 1 in Table 1) is a consequence of the above mentioned fluorine atom effect on chelation. However, B predominates over C, as it could be expected on assuming our chelated model.

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