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Asymmetric Synthesis of β-Hydroxy Sulfones by Reduction of Chiral β-Keto Sulfones

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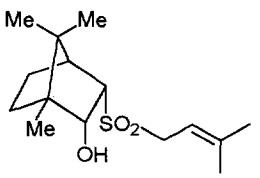
Abstract: Chiral β-keto sulfones **3** have been prepared from enantiomerically pure sulfinic acids **2** derived from (*R*)- and (*S*)-methylbenzylamine. Enantiospecific reduction of these ketosulfones **3** can be achieved using different hydrides affording β-hydroxy sulfones. Opposite configurations on the newly created stereocenter is obtained with DIBAL-H or LAH as reducing agents.

The chemistry of sulfones and their aplication in organic synthesis is a topic under increasing development, however, there is a lack in the use of chiral sulfones in asymmetric synthesis.[1] To the best of our knowledge, only the camphor derivative **1** has been used in the asymmetric synthesis of chrysanthemic acid with 25% ee.[2] We have focused our attention on the preparation of chiral β-keto sulfones **3** derived from chiral sulfinic acids **2**, obtained from (*R*)- and (*S*)-*N*-α-methylbenzylamine. The reduction of the carbonyl group would allow the asymmetric synthesis of β-hydroxy sulfones.[3] Previously, an excellent control of the stereoselective reduction of the carbonyl group has been achieved using chiral β-keto sulfoxides by the choice of the reducing agent.[1e,f,6] In this immolative strategy, the sulfoxide group is generally destroyed at the end of the synthesis and only a recoverable chiral sulfoxide has recently been described.[6d,e,f] The possibility of a removal of the sulfonyl moiety by an elimination procedure and therefore allowing recovery of the corresponding sulfinic acid makes chiral sulfones promising intermediates in asymmetric synthesis.



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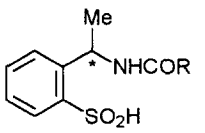
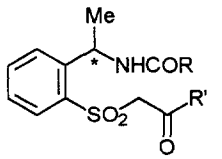
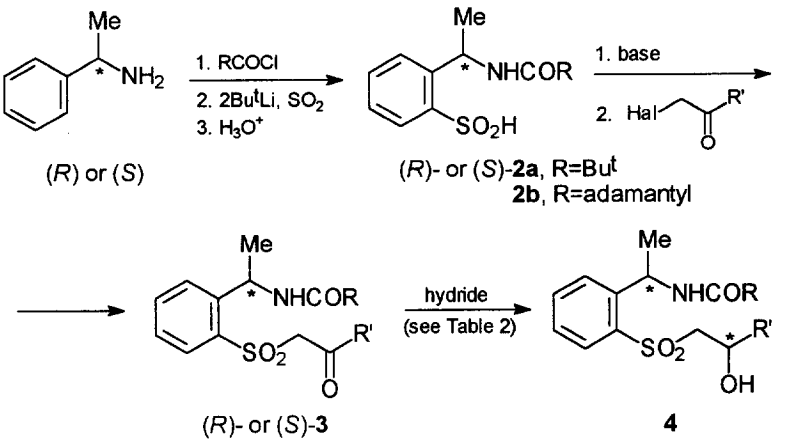


(*R*)- or (*S*)-**2**



(*R*)- or (*S*)-**3**

The starting sulfinic acids **2** have been prepared by acylation of (*R*)- and (*S*)-*N*-α-methylbenzylamine with pivaloyl or adamantylcarbonyl chlorides followed by ortho-lithiation with *tert*-butyllithium and treatment with sulfur dioxide[7] (Scheme 1). Subsequent treatment of **2** with the corresponding haloketone in basic media led to enantiomerically pure β-keto sulfones **3** (Scheme 1 and Table 1).



Scheme 1

Table 1. Preparation of β-Keto Sulfones **3**.

Haloketone	product					
	no.	R	R'	yield (%)[a]	mp (°C)[b] or R_f[c]	$[\alpha]_D^{25}$[d]
ICH_2COCH_3[e]	(*R*)-**3a**	Bu^t	CH_3	53	135-137	+19.9 (1.0)
$BrCH_2COPh$[f]	(*R*)-**3b**	Bu^t	Ph	65	55-57	+60.3 (2.1)
$BrCH_2COPh$	(*S*)-**3b**	Bu^t	Ph	65	0.22	-61.3 (2.1)
$BrCH_2COPh$[f]	(*R*)-**3c**	adamantyl	Ph	32	120-121	+13.7 (1.5)

[a] Isolated yield after column chromatography (silica gel) based on starting sulfinic acid **2**. [b] Hexane/CH_2Cl_2. [c] Hexane/EtOAc: 2/1. [d] $CHCl_3$, concentration in parenthesis. [e] NaH was used as base. [f] 0.15 M KOH/MeOH was used as base.

The reduction of sulfones **3** to the corresponding β-hydroxy sulfones **4** with different reducing agents at low temperature (-78° → -40°C) was studied (Scheme 1 and Table 2). The reduction of β-keto sulfones with *R* configuration **3a-3c** using DIBAL-H or $NaBH_4$, gave mainly the corresponding hydroxy sulfones with *R* configuration on the carbon bearing the hydroxy group (Table 2, entries 1, 3, 10, 11, and 13) whereas using other mixed hydrides the obtained configuration was mainly the opposite (Table 2, entries 2,4,5,6, and 12). On the other hand, when the β-keto sulfone with *S* configuration (S)-**3b** was reduced with DIBAL-H or LAH, mainly *S* or *R* configurations were observed on the carbon bearing the alcohol function respectively (Table 2, entries 8 and 9). It was also observed that lithium hydrides [LAH, super-hydride] gave much better diastereomer ratios than sodium ones ($NaBH_4$, N-selectride®). No influence on the diastereomeric ratios was observed when the *tert*-butyl on the amide moiety was changed by adamantyl (Table 2, entries 11, 12, and 13).

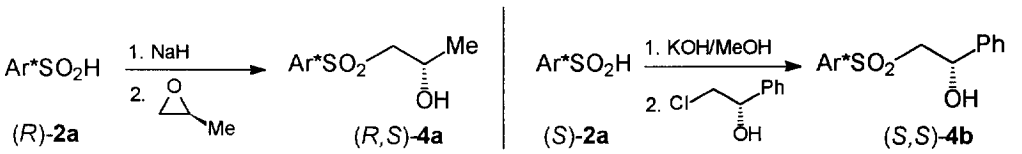
Diastereomeric ratios were determined by ^1H NMR (300 MHz) and the assignment of the configuration of the new created stereocenter was carried out by synthesis of enantiomerically pure β-hydroxy sulfones. The hydroxy sulfone with (*R,S*)-configuration (*R,S*)-**4a** was prepared by reaction of the sodium salt of sulfinic acid

Table 2. Diastereoselective Reduction of β-Keto Sulfones **3**.

Entry	keto sulfone	β-hydroxy sulfone					
		no.	R	R'	hydride[a]	yield (%)[b]	diastereomeric ratio *R/S*
1	(*R*)-**3a**	**4a**	Bu^t	CH_3	DIBAL-H	88	56:44
2	(*R*)-**3a**	**4a**	Bu^t	CH_3	LAH	52	25:75
3	(*R*)-**3b**	**4b**	Bu^t	Ph	DIBAL-H	58	78:22
4	(*R*)-**3b**	**4b**	Bu^t	Ph	LAH	80	10:90
5	(*R*)-**3b**	**4b**	Bu^t	Ph	$LiBHEt_3$	80	22:78
6	(*R*)-**3b**	**4b**	Bu^t	Ph	$NaBHBu^s_3$	40	43:57
7	(*R*)-**3b**	**4b**	Bu^t	Ph	$NaBH_4$	100	66:33
8	(*S*)-**3b**	**4b**	Bu^t	Ph	DIBAL-H	58	22:78
9	(*S*)-**3b**	**4b**	Bu^t	Ph	LAH	80	90:10
10	(*S*)-**3b**	**4b**	Bu^t	Ph	$NaBH_4$	100	33:66
11	(*R*)-**3c**	**4c**	adamantyl	Ph	DIBAL-H	54	90:10
12	(*R*)-**3c**	**4c**	adamantyl	Ph	LAH	62	17:83
13	(*R*)-**3c**	**4c**	adamantyl	Ph	$NaBH_4$	100	60:40

[a] 3 Equiv. of reducing agent were used. All reductions were carried out in dry THF except for $NaBH_4$, where EtOH was used as solvent. [b] Isolated crude yield. [c] Determined by ^1H NMR (300 MHz), see text.

(*R*)-**2a** with (*S*)-(-)-propylene oxide, whereas hydroxy sulfone with (*S,S*)-configuration (*S,S*)-**4b** was obtained by reaction of the potassium salt of (*S*)-**2a** with (*S*)-(+)-2-chloro-1-phenylethanol under refluxing DMF (Scheme 2).



Scheme 2

The chemical shifts and *J* values of the two α-hydrogens to the SO_2 group in compounds **4** are shown in Figure 1. The diastereomeric ratio can be obtained by integration of the methylene signals adjacent to the hydroxy group, whereas the absolute configuration of each diastereomer can be deduced by comparison of the ^1H NMR crude spectra with that of (*R,S*)-**4a** or (*S,S*)-**4b**.

In the reduction with DIBAL-H and LAH we observed similar results as described by Wills *et al.* starting from related β-keto sulfoxides[7] and, therefore, we also propose similar attacking models (Scheme 3).

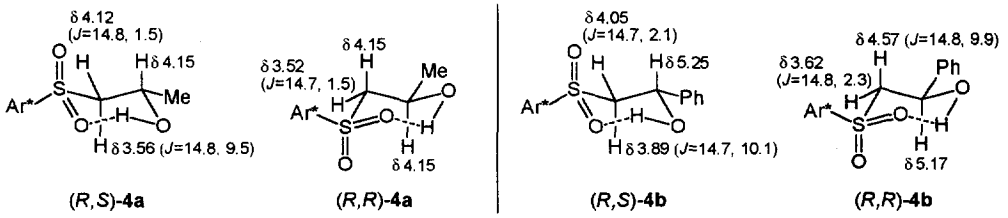
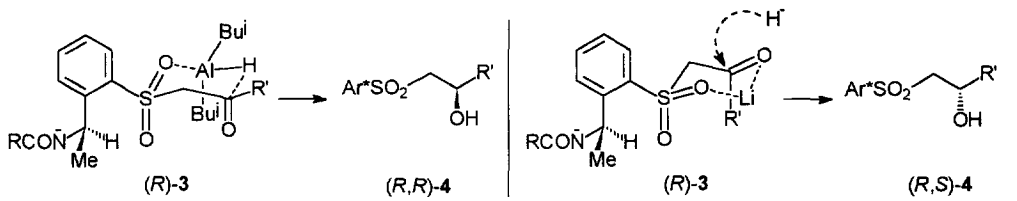


Figure 1

In the first case keto sulfone and DIBAL-H describe a chair-like conformation with the bulky hydride far from the methyl group on the stereogenic center. However, in the case of LAH and other lithium hydrides the chair is formed with the lithium at the same side of this methyl group and the hydride is delivered from the opposite side. Further studies on the use of other chiral sulfones and synthetic applications of the optically active β-hydroxy sulfones are now under way.[8]



Scheme 3

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