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SYNTHESIS AND CONJUGATE ADDITIONS TO (E)-γ-ALKOXY-α-SUBSTITUTED-α,β-UNSATURATED SULFONES

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Summary: *(E)-γ-hydroxy-α,β-unsaturated sulfones have been readily functionalized at α-position via protection of hydroxyl group, metalation with n-BuLi and subsequent reaction with electrophiles. The conjugate addition of organolithiums to (E)-γ-methoxymethoxy-α-trimethylsilyl-α,β-unsaturated phenyl sulfones in* Et_2O *is highly syn-stereoselective.*

The stabilization of a carbanionic center by an adjacent sulfonyl group is the basis of the wide usefulness of vinylsulfones as Michel acceptors[1]. For instance, Isobe has nicely used the conjugate addition of organolithium reagents to γ-alkoxy-α-trimethylsilyl-α,β-unsaturated sulfones, to synthesize fragments for maytansine[2] and okadaic acid syntheses[3]. The addition reaction using such substrates, having a γ-chiral centre, is highly *syn* or *anti* stereoselective depending on the nature of the γ-alkoxysubstituent[4]. However the typical method of synthesis of this kind of α,β-unsaturated sulfones, based on a Peterson olefination[4,5] with α-alkoxyaldehydes, yields usually mixtures of both E- and Z-diastereomers, although the latter preponderates. Recently we have reported a practical one-step method to the stereoselective preparation of (E)-γ-hydroxy-α,β-unsaturated phenyl sulfones (1) from aldehydes[6] (scheme 1). We herein describe the easy functionalization of these vinylsulfones at the α position and the behaviour of the corresponding (E)-α-silyl-α,β-unsaturated sulfones as Michel acceptors in the reaction with organolithiums.

Trisubstituted olefins **2**-**8** were prepared from α,β-unsaturated sulfones **1** by a straightforward two steps sequence (scheme 1). First, the hydroxyl group was protected as MOM derivative ($CH_2(OMe)_2$, P_2O_5)[7] followed by kinetic metalation with n-BuLi (1.1 equiv., THF, -78°C, 30 min) to give the corresponding α-sulfonyl carbanion[8], which reacts with a wide variety of electrophiles to afford compounds **2**-**8** in 57-84% overall yields (table 1). In all cases compounds 2 to 8 were obtained as a single diastereomer of (E) configuration[9].

Scheme 1

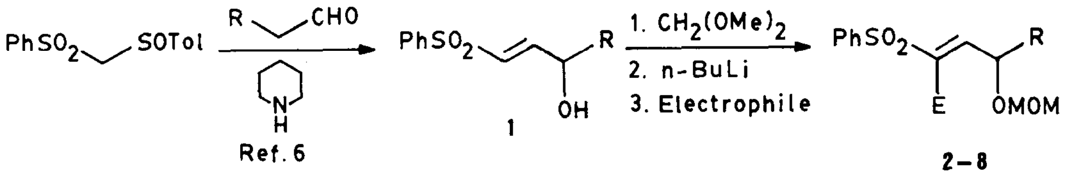


Table 1: α-functionalization of olefins 1

Entry	R	Electrophile	(React. conditions)	E	Compound	Yield(%)[a]
1	Me	D_2O	(10eq., -78°C, 2h.)	D	2	78
2	Me	IMe	(3eq., 0°C, 3h.)	Me	3	80
3	Me	PhCHO	(1.3eq., -78°C, 1h.)	PhCH(OH)	4	57[b]
4	Me	n-PrCOMe	(1.2eq., 0°C, 2h.)	n-PrC(OH)Me	5	73[b]
5	Me	$ClCO_2Et$	(1.2eq., -78°C, 1h.)	CO_2Et	6	76
6	Me	$MeSO_2SMe$	(1.2eq., -78°C. 3h.)	SMe	7	80
7	Me	ClTMS	(4eq., -78°C, 2h.)	TMS	**8a**	76
8	Et	ClTMS	(4eq., -78°C, 2h.)	TMS	**8b**	84
9	*i*-Pr	ClTMS	(4eq., -78°C, 2h.)	TMS	**8c**	62
10	$BnOCH_2CH_2$	ClTMS	(4eq., -78°C, 2h.)	TMS	**8d**	74

[a] *Overall yield (from 1) in pure product after flash chromatography.* [b] *Obtained as a 1:1 mixture of both 1,4 diasteromers.*

Scheme 2

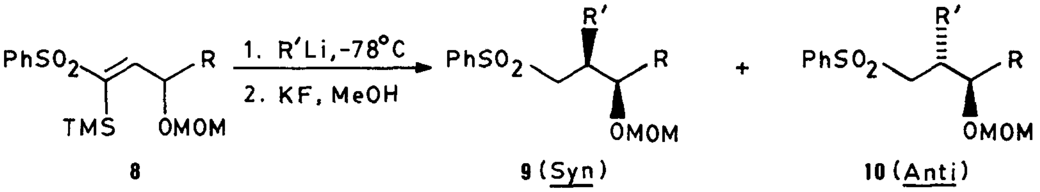


Table 2: Conjugate addition of organolithiums to α,β-unsaturated sulfones 8

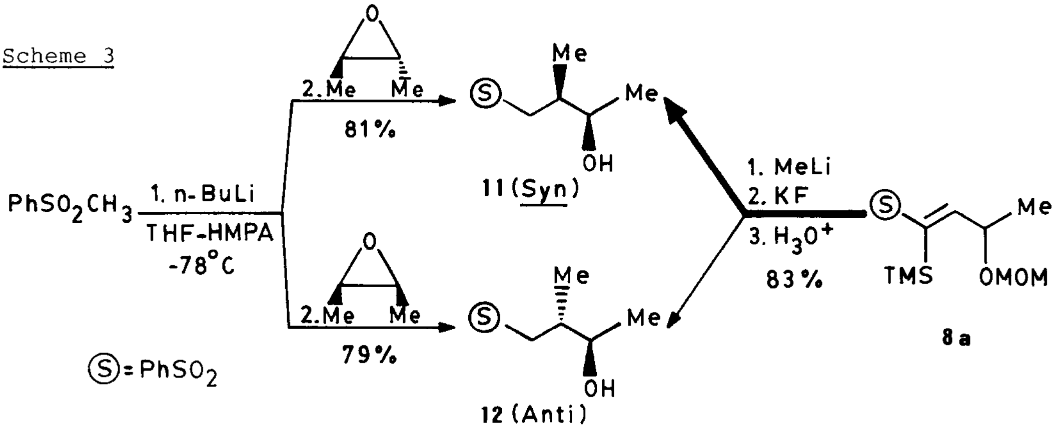
Entry	Compound	R	R'	Solvent	*Syn:Anti*[a]	Yield (%)[b]
1	8a	Me	*n*-Bu	Hexane	88:12	25[c]
2	8a	Me	*n*-Bu	THF	89:11	85
3	8a	Me	*n*-Bu	THF-HMPA[d]	76:24	81
4	8a	Me	*n*-Bu	Et_2O	94:6	84
5	8a	Me	Me	THF	93:7	91
6	8a	Me	Me	Et_2O	96:4	92
7	8a	Me	Ph	Et_2O	84:16	83
8	8a	Me	*t*-Bu	Et_2O	>98:2	88
9	8b	Et	Me	Et_2O	>98:2	92
10	8c	*i*-Pr	Me	Et_2O	>98:2	85
11	8c	*i*-Pr	*n*-Bu	Et_2O	>98:2	85
12	8c	*i*-Pr	*t*-Bu	Et_2O	>98:2	74
13	8d	$BnOCH_2CH_2$	Me	Et_2O	>98:2	83

[a] *Products ratio (9:10) determined by ^1H-NMR in the crude mixture.* [b] *Yield in pure products (9+10) after flash chromatography.* [c] *Determined by ^1H-NMR, 75% of starting material (8a) was also observed.* [d] *Ratio THF:HMPA = 5:1.*

Unsaturated sulfones **8** react rapidly with organolithiums (1.1 equiv.) in THF or Et_2O. The reaction is essentially complete before 15 minutes (scheme 2). After removing the trimethylsilyl group from the adducts (by treatment with KF in methanol[4]) the ratios of **9** and **10** were analyzed by ^{1}H-NMR and the results summarized in table 2. In all cases the conjugate addition is highly *syn*-stereoselective giving excellent yields in adducts. It is worth noting that the solvent plays a significative role in the diastereoselection (compare entries 1 to 4), the best results being achieved with Et_2O (to the comparison THF:Et_2O see entries 2-4 and 5-6), whereas the mixture THF-HMPA gave the worst stereoselectivity (entry 3). Additionally the stereoselectivity increases with the size of R group. So, with unsaturated sulfones **8b**, **8c** and **8d** (R groups bigger than Me) only the *syn*-adduct **9** was detected by ^{1}H-NMR (entries 9 to 13).

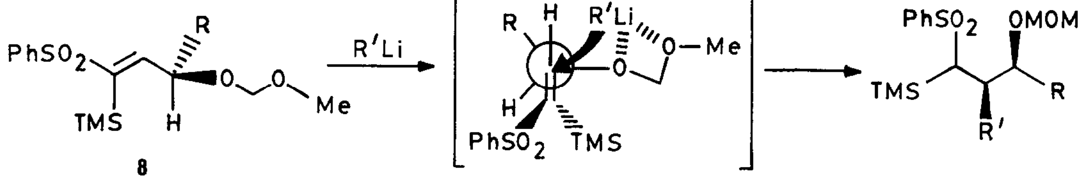
A chemical correlation with compounds of known configuration was made in one case in order to prove the *syn*-stereoselectivity of these conjugate additions (scheme 3). *Syn*-alcohol **11** was unequivocally prepared in 81% yield by stereospecific opening of epoxide of *trans*-2-butene with the α-sulfonylcarbanion of phenyl methyl sulfone (THF-HMPA 3:1, r.t., 16h.). In the same way the *anti*-alcohol **12** was prepared in 79% yield from epoxide of *cis*-2-butene. The acid hydrolysis (HCl 6M) of the acetal moiety of the adducts obtained in the reaction of **8a** with MeLi in THF (entry 5 in table 1) afforded a 93:7 mixture of alcohols **11**:**12** in 83% overall yield, showing inequivocally the *syn*-stereoselectivity of this conjugate addition.

Scheme 3



The observed *syn*-diastereoselection is consistent with a mechanistic model analogous to one proposed by Isobe and coworkers[4], for related (Z)-diastereomers, based on the chelation effect between the γ-oxygen atom of the α,β-unsaturated sulfone and the nucleophile anion through lithium cation (scheme 4). According to this hypothesis a significative decrease in the stereoselectivity was observed when HMPA was used as cosolvent (entry 3 in table 2).

Scheme 4



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9.- The (E) configuration of compounds 2-8 has been determined by ^{1}H-NMR as well as by comparation with reported NMR data of related trisubstituted α,β-unsaturated sulfones^{4,8c}. For instance, the olefinic proton chemical shift of compounds 8 is highly deshielded (δ= 7.2-7.3 ppm) compared with the chemical shift of related α-silyl-α,β-unsaturated sulfones of (Z)-configuration (δ= 6.3-6.5 ppm).

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