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A STEREOSELECTIVE ROUTE TO *E*-3-HYDROXYALKENYL PHENYL SULFIDES

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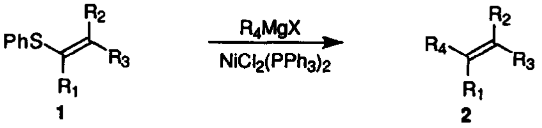
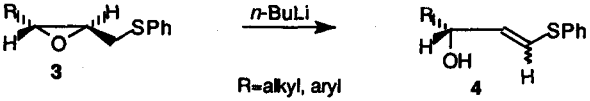
Summary: *E*-3-Hydroxyalkenyl phenyl sulfides are generated stereoselectively when 2,3-epoxyalkyl phenyl sulfides having 3-*syn*-substituent are exposed to an excess *n*-butyllithium in THF solution.

Phenyl sulfide on alkenyl sp^2 carbon is a good leaving group in the cross-coupling reaction with Grignard reagents in the presence of a nickel catalyst[1] (Scheme 1). Since the reaction proceeds with retention of the olefin configuration, stereoselective preparation of the alkenyl phenyl sulfide precursors is the most important. Herein we report a stereoselective method for the preparation of *E*-3-hydroxyalkenyl phenyl sulfides starting with 2,3-epoxyalkenyl phenyl sulfides having 3-*syn*-substituent.

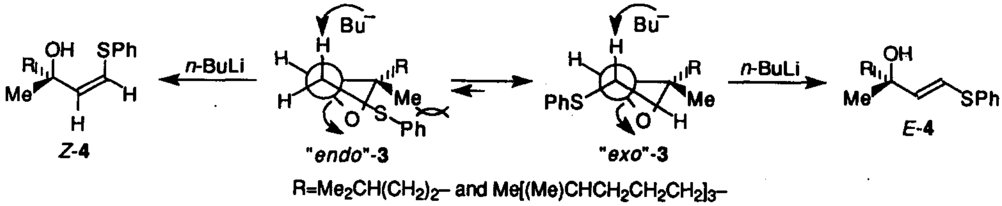


Scheme 1

Quite recently we found[2] an efficient formation of a *E*/*Z*-mixture of 3-hydroxyalkenyl phenyl sulfides (**4**) by treating 2,3-epoxyalkyl phenyl sulfides (**3**) with an excess *n*-butyllithium in THF (Scheme 2). In this transformation we observed that the trisubstituted epoxides generated from geraniol and phytol showed an exceptionally high stereoselectivity to furnish the corresponding alkenyl phenyl sulfides (**4**) having *E* configuration. Since we reasoned that this striking difference is due to the steric repulsion between the 3-*syn*-methyl group and the thiophenyl group forcing the substrates to take "*exo*" transition state (*exo*-**3**) to give rise to the *E* olefin products (*E*-**4**) (Scheme 3), we now choose the epoxy sulfides (**5**) having 3-*syn*-substituent as the substrates so as to obtain the alkenyl phenyl sulfides (**6**) having *E* configuration in a selective manner.

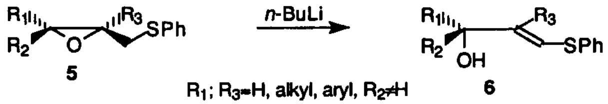


Scheme 2



R=Me$_2$CH(CH$_2$)$_2$– and Me[(Me)CHCH$_2$CH$_2$CH$_2$]$_3$–

Scheme 3



Scheme 4

Table 1 Reaction of the Epoxy Sulfides (5a~j) with *n*-Butyllithium

Entry	epoxy sulfide[1] (5)	R_1:R_2:R_3	alkenyl sulfide (6)	yield[2] (%)	ratio[3] (*E*:*Z*)
1	**5a**	H:$BnOCH_2$:H	**6a**	91.9	8.8 : 1
2	**5b**	H:*n*-C_5H_{11}:H	**6b**	83.3	10.8 : 1
3	**5c**	H:$BnOCH_2CH(OH)CH_2$:H[4]	**6c**	99.4	13.2 : 1
4	**5d**	H:$BnOCH_2CH(OH)CH_2$:H[5]	**6d**	84.9	6.3 : 1
5	**5e**	Me:Me:H	**6e**	75.4[6]	>99 : 1
6	**5f**	$-(CH_2)_5-$:H	**6f**	68.8[7]	>99 : 1
7	**5g**	Me:$Me_2CH(CH_2)_2$:H	**6g**	87.2	>99 : 1
8	**5h**	$-(CH_2)_5-$:Me	**6h**	86.2	8.7 : 1
9	**5i**	$Me_2CH(CH_2)_2$:Me:H[8]	**6i**	93.9	31 : 1
10	**5j**	$Me[(Me)CHCH_2CH_2CH_2]_3$:Me:H[8]	**6j**	88.9	>99 : 1

1. prepared by treating the alcohol precursor with diphenyl disulfide in the presence of tri-*n*-butylphosphine.[3] 2. isolated yield. 3. determined by ^{1}H-Nmr (500 MHz). 4. (2*R*,3*S*,5*S*). 5. (2*S*,3*R*,5*S*). 6. 15.2% of the starting material was recovered. 7. 9.1% of the starting material was recovered. 8. Ref. 2.

Three types of the 2,3-epoxyalkyl phenyl sulfides, 3-*syn*-disubstituted (**5a~d**), 3-*syn*-3-*anti*-trisubstituted (**5e~g**), 3-*syn*-3-*anti*-tetrasubstituted (**5h**), were subjected to the reaction conditions. Thus, treatment of **5** with 1.5 equiv. of *n*-butyllithium in THF at −78 °C for 30 min afforded the sulfides **6** in excellent yields (**Table 1**). Among these the trisubstituted substrates (**5e~g**) furnished 3-hydroxyalkenyl phenyl sulfides (**6e~g**) having *E* configuration exclusively in an excellent yield (entries 5~7). Both the disubstituted and the tetrasubstituted epoxides, on the other hand, furnished the corresponding *E*-olefins (**6**) in excellent yields in ratios of 6.3~13.2:1 though they did not exhibit complete stereoselectivity (entries 1~4 and 8) (**Table 1**). It seems that the stereoselectivity is mostly due to the 3-*syn*-substituent on the epoxides, but the secondary effect by the remote hydroxy group seems to be also significant (compare entries 3 and 4). Since the present procedure may be coupled with the Katsuki-Sharpless epoxidation reaction, it is particularly useful for the preparation of optically active *E*-3-hydroxyalkenyl phenyl sulfides.

References and Notes

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