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STEREOSELECTIVE HOMOALLYLIC ALCOHOL SYNTHESIS via SULPHONE α-CARBANION-MEDIATED COUPLING REACTIONS

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Summary: A novel method is described for the synthesis of homoallylic alcohols based on one-pot coupling reactions of sulphone-stabilized carbanions with epoxides and aldehydes.

The diverse reactivity of the sulphonyl group is such that it may be utilized to effect a wide range of synthetic transformations.¹ Perhaps the most commonly exploited property of sulphones is the ease with which protons α - to the sulphur atom may be abstracted using strong bases such as *n*-butyllithium and lithium diisopropylamide. The resulting carbanions have successfully been reacted with electrophiles such as aldehydes,² ketones,³ haloalkanes⁴ and epoxides.⁵ In this Letter we report a novel procedure for the sequential three-component coupling of sulphone-stabilized carbanions with epoxides and aldehydes *in one pot*, and the stereoselective elaboration of the products into *E*-homoallylic alcohols.

The basis of the method is depicted in the Scheme. Deprotonation $(-78^{\circ}C)$ of benzenesulphonylmethane 1 in tetrahydrofuran (THF) solution (0.2M) using *n*-butyllithium (1.1 eq) yields a carbanion which is treated sequentially with hexamethylphosphoramide (HMPA) and the epoxide component 2 (1.05 eq) in THF at room temperature, and *tert*-butyldimethylsilyl trifluoromethanesulphonate (1.1 eq) at 0°C. Addition to the recooled $(-78^{\circ}C)$ reaction mixture of a further portion (1.1 eq) of *n*-butyllithium, and the aldehyde component 3 (1.1 eq) in THF, followed by low-temperature proton quench gives the monoprotected diols 4 upon extractive work-up and column chromatography on silica gel. Exposure of 4 to 6% sodium amalgam in 3:1 THF-methanol⁶ and treatment of the resultant crude alkenes 5 with tetra-*n*-butylammonium fluoride in THF⁷ gives homoallylic alcohols 6 after chromatography. The yields and *E:Z* ratios for 6 are listed in the Table.



R ¹	R ²	Yield ^e of 4 (%)	Yield of 6 (%) ^{8,}	E:Z Ratio of 6 ¹⁰
Ph	Me	63	95	2:1
Ph	Ph	62	75	2:1
Ph	ⁿ C ₆ H ₁₃	64	76	2:1
Ph	ⁱ Pr	70	87	7.5:1
Ме	ⁱ Pr	60	71	6.5:1
CH ₂ OCH ₂ Ph	ⁱ Pr	64	75	7:1
(CH ₂) ₂ C(Me)OCH ₂ CH ₂ O	ⁱ Pr	51	81	8.5:1

Table

Extensive experimentation indicated the optimum quantity of HMPA to be one equivalent with respect to *n*butyllithium added overall: the use of smaller ratios resulted in incomplete consumption of epoxide in the first step, whilst larger quantities reduced the yield of the reaction with the aldehyde. Silylation of the alkoxide intermediates from the epoxide step was essential to ensure clean reaction with aldehydes: attempted reaction of the alkoxide-derived dianions¹¹ with aldehydes gave poorer yields of diols corresponding to 4, which were more difficult to separate than the monosilylated analogues.

The method presented herein is efficient and easy to carry out, and in principle allows the synthesis of almost any disubstituted homoallylic alcohol by virtue of its three-component nature. Replacement of the aldehyde component with a carboxylating agent should yield lactones,¹² and use of an aziridine would give protected aminoalcohols as potential intermediates in piperidine synthesis.¹³ Optically active products are accessible *via* homochiral epoxides. The results of these investigations will be reported in due course.

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References and notes

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