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## Asymmetric alkylation of diarylmethane derivatives. Improved results using methoxyethoxy substituent

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Abstract—Alkylation of 2-methoxyphenyl phenyl methane using *sec*-BuLi and (–)-sparteine has been carried out in excellent yields and up to 94% ee. The best results were obtained in allylation reactions but methylation, ethylation, benzylation and trimethylsilylation have all been carried out with acceptable ee. © 2004 Elsevier Ltd. All rights reserved.

In a previous paper we reported the asymmetric alkylation of prochiral diphenylmethane derivatives including **1** using *sec*-BuLi and (–)-sparteine.<sup>1</sup> The best result is shown (Scheme 1). When the 2-substituent was an unprotected hydroxyl group the selectivity was reversed giving a 46% ee of the S-product.

Here we report asymmetric alkylations of a similar substrate, compound **4**, substituted with a methoxyethoxy group. The rationale behind the choice of the methoxyethoxy group was to provide an extra oxygen to coordinate the lithium in the reactive species (Fig. 1). This coordination effect has been used to promote *ortho*-lithiation of phenol derivatives.<sup>2</sup>

The synthesis of **4** was carried out, trivially, by *O*-alkylation of the commercially available phenol **3** 



Scheme 1.



Figure 1.

(Scheme 2).<sup>3</sup> Initially, allylation of **4** was investigated since this had been a profitable area for reactions of 1. The results are shown in Table 1. Allylation under conditions A (entry 1, substrate, base and (-)-sparteine stirred together at -78 °C for 6 h before introduction of electrophile) gave 5 in a 44% ee, lower than that obtained in the methoxy series. However, use of a warmcool cycle according to the procedure of Beak (entry 2, conditions B: substrate, base and (-)-sparteine mixed at -78 °C, warmed to -20 °C for 1 h and recooled) resulted in a 50% ee.<sup>4</sup> When the electrophile was added in two batches of 0.5 equiv with a warm-cool cycle in between the additions the ee rose again (entry 3, conditions C).<sup>5</sup> Finally when the electrophile was allyl tosylate, under the same conditions (entry 4) the reaction gave a very pleasing 94% ee with no significant loss of yield.





Keywords: Asymmetric; Alkylation; Diarylmethane; Sparteine.

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Table 1. Asymmetric allylations of 4



Conditions: (A) Mixture of 4, (-)-sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether stirred at -78 °C for 6 h followed by addition of alkylating agent (1.2 equiv) and warming to rt. (B) Mixture of 4, (-)-sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether mixed at -78 °C, then warmed to -20 °C for 1 h and recooled to -78 °C before addition of electrophile (1.2 equiv) and warming to rt. (C) Mixture of 4, (-)-sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether mixed at -78 °C, then warmed to -20 °C for 1 h and recooled to -78 °C before addition of electrophile (1.2 equiv) and warming to rt. (C) Mixture of 4, (-)-sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether mixed at -78 °C, then warmed to -20 °C for 1 h and recooled to -78 °C before addition of electrophile (0.5 equiv). Mixture warmed to -20 °C for a further 1 h before recooling to -78 °C and addition of electrophile (0.5 equiv) and warming to rt. Ee values were calculated by conversion to 6.

These results are in accordance with those obtained by Beak for reactions of *N*-*o*-pivaloyl ethylaniline but disagree with our results for the methoxy compound **1** (Scheme 1), where the best ee was obtained using conditions A. Our assumption is that the pair of diastereomeric organolithium/sparteine complexes derived from **1** were interconverting rapidly at -78 °C. In the case of **4** it would seem that the organolithium species is less configurationally labile (as would be expected with extra stabilisation from the two oxygens) and needs to be warmed to allow equilibration.

The ee and predominant enantiomer (*R*) were confirmed by conversion of product **5** into the known lactone **6** and comparison of optical rotation (Scheme 3).<sup>6</sup> This was achieved in two steps and a 70% overall yield by oxidative cleavage of the double bond with potassium permanganate in the presence of a crown ether and treatment with boron tribromide to remove the methoxyethyl group with concomitant cyclisation.<sup>7</sup> This



Scheme 3.

Table	2.	Asymmetric	alkylations	/silylation	of <b>4</b>
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compound has been synthesised by Meyers who assigned the absolute configuration as shown. Enantiomeric excesses could also be determined by use of the chiral shift reagent 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE), which cleanly split the methoxy singlets of the two enantiomers in the <sup>1</sup>H NMR spectrum.<sup>8</sup> The results correlated well with those obtained by comparison of optical rotation.

We were then able to extend the methodology to a range of other electrophiles as shown in Table 2. Methylations (entries 1-3) were achieved with marked improvements over similar reactions performed on 1 (the best ee for methylation of 1 was 6%). Using a warm-cool cycle and batch addition of electrophile (conditions C from Table 1) the ee was still very modest for methyl iodide but could be increased considerably by using methyl triflate or methyl tosylate as the alkylating agent. This increase in enantioselectivity from halide to a tosylate is precedented in the work of Beak and has been rationalised as a consequence of slower reaction and possible coordination of the sulfonyl oxygen to lithium.<sup>9</sup> Ethylation, benzylation and reaction with trimethylsilyl chloride (entries 4-6) were also carried out in good yields and at least respectable ee. Enantiomeric excesses were determined using TFAE analysis on the methoxy singlet (compounds 7-9) or the trimethylsilyl singlet (compound 10).

		OCH <sub>2</sub> CH <sub>2</sub> OMe		OCH <sub>2</sub> CH <sub>2</sub> OMe			
			conditions C (Table 1)	l R			
		<u>```</u>	R-X	$\checkmark$ $\Upsilon$			
		4 Ph		7-10 Ph			
Entry	Product	R–X	Conditions	Yield	Config.	Ee	
1	7	MeI	С	86	R	12	
2	7	MeOTf	С	90	R	36	
3	7	MeOTs	С	95	R	58	
4	8	EtI	С	65	$R^*$	70	
5	9	BnBr	С	90	$R^*$	68	
6	10	TMSCl	С	91	$R^*$	82	

\* Indicates major enantiomer assigned by analogy with other reactions.



## Scheme 4.

Removal of the methoxyethyl group from compounds lacking the assistance of an internal carboxylic acid required rather vigorous conditions as exemplified by the conversion of 7 to the phenol 11 (Scheme 4).<sup>10</sup> The reaction proceeded in acceptable yield allowing us to assign the stereochemistry of the major product as R by comparison of optical rotation. Products 8–10 are assigned as having the same configuration as the methyl and allyl products.

To conclude, we have increased the stereoselectivity of diarylmethane alkylation considerably by employing an extra coordinating oxygen in the stabilising group. In addition to recording excellent yields and some high enantiomeric excesses we have demonstrated the versatility of the reaction with regard to different electrophiles and shown that the methoxyethyl group can be removed efficiently.

Future work will include investigations into the origin of the enantioselectivity, screening other potential coordinating groups and the application of the methodology in synthesis.

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