

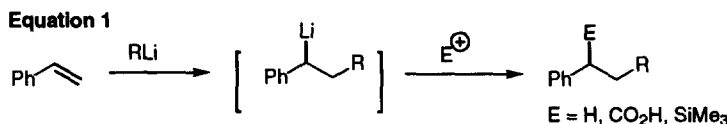
Organolithium Additions to Styrene Derivatives: Intramolecular Alkylation Processes

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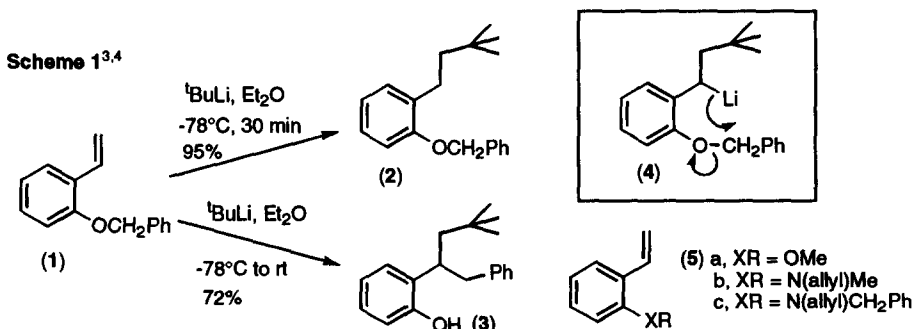
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Abstract: 2-Benzyloxystyrene undergoes efficient carbolithiation-protonation at -78°C. At higher temperatures, however, carbolithiation is followed by intramolecular alkylation to generate the corresponding 2-alkylphenol. 2-Alloxystyrenes are shown to undergo similar reactions.
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We recently reported that styrene undergoes efficient addition and addition-trapping reactions with a range of organolithium reagents (Equation 1).¹ The expected anionic oligomerisation processes² were not observed providing diethyl ether was employed as solvent. In this *Letter* we describe some related transformations in which the intermediate benzyl lithium species is alkylated intramolecularly.

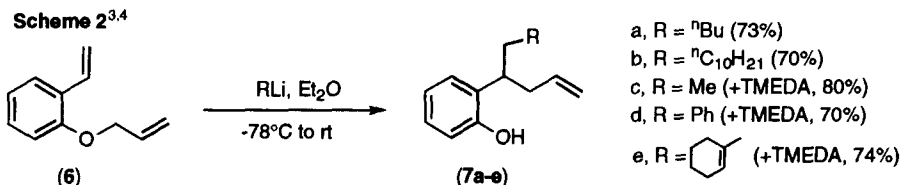


The styrene addition reactions are normally carried out and quenched at -78°C.¹ The reaction of 2-benzyloxystyrene (1) was originally investigated using this protocol (Scheme 1) and the expected product (2) was isolated in almost quantitative yield. When the reaction was allowed to warm to room temperature before work-up, however, a new product (3) was obtained in 72% yield.^{3,4} It seems likely that intermediate (4) undergoes an intramolecular alkylation, as shown, on warming the reaction mixture prior to work-up.

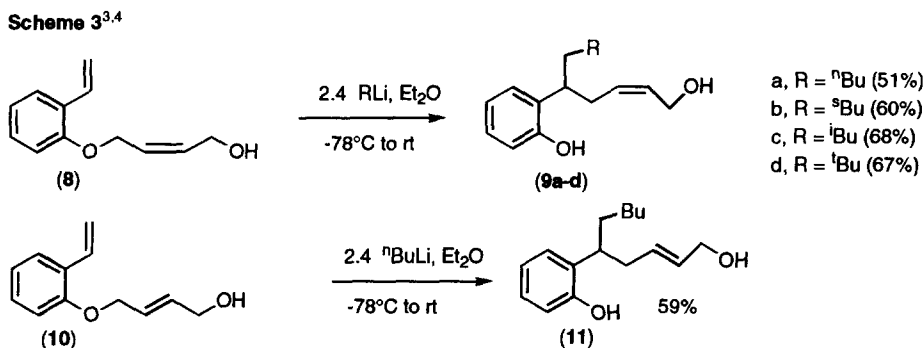


Other substrates capable of internal alkylation were therefore examined under similar reaction conditions. The *O*-methyl analogue (5a) did not undergo methyl transfer on warming, and with the *ortho*-amino compounds (5b) and (5c), transfer of the *N*-methyl, *N*-benzyl or *N*-allyl groups was not observed. We therefore investigated *O*-allyloxy compounds on the assumption that an "activated" internal alkylating agent

was required. 2-Allyloxystyrene (**6**) underwent efficient carbolithiation-intramolecular alkylation with a range of organolithium reagents (Scheme 2). The efficient addition of butyllithium and decyllithium using ether as solvent was expected from the reactions using styrene.¹ With styrene in ether, however, no reactions were observed with the relatively unreactive MeLi, PhLi and cyclohexenyllithium but in ether-TMEDA or THF styrene polymerisation occurred.¹ The fact that the methyl, phenyl and cyclohexenyl adducts (**7c-e**) were formed using ether-TMEDA in this study is noteworthy, therefore. We presume that the initial organolithium adducts leading to (**7c-e**) undergo alkylation at a faster rate than polymerisation. This observation supports the proposal that the alkylation is intramolecular (*c.f.* **4**).



This process also takes place with substituted allyloxy derivatives (Scheme 3). Thus, with several alkylolithium reagents in ether, *Z*-butenol (**8**) was converted into the rearranged adducts (**9a-d**), the allyloxy transfer occurring with retention of alkene configuration. In a similar manner the isomeric *E*-butenol (**10**) was converted into (**11**) with the *E*-stereochemistry of the migrating group intact.



We are currently exploring further the synthetic potential of these processes with particular emphasis on asymmetric variants and applications in medicinal chemistry.

Acknowledgement: We are grateful to the Royal Society for the award of a Royal Fellowship (X.W.).

References and Notes

- # On leave from the Chemistry Department, Nanjing University, China
- Wei, X.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.*, 1996, 187.
- Merton, M. *Anionic Polymerisation: Principles and Practice*, Academic Press, New York, 1983; Waach, R.; Doran, M. A. *J. Org. Chem.*, 1967, 32, 3395, and references therein.
- The starting alkenes were prepared *via* Wittig homologation of the corresponding aldehyde [(**1**) and (**6**)], or by alkylation of 2-vinylphenol under Mitsunobu conditions [(**8**) and (**10**)].
- All new compounds were fully characterised by high field ¹H and ¹³C NMR spectroscopy and by elemental analysis or high resolution mass spectrometry.

(Received in UK 26 February 1996; revised 22 April 1996; accepted 26 April 1996)