

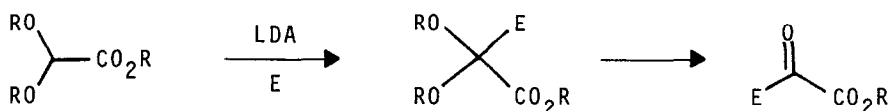
2-ARYL ACETALS AS ACYL ANION EQUIVALENTS

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Summary: Metallation of 2-H in aryl acetals produces a stable anion when the oxazoline moiety is present in the para position. Selective hydrolysis and metallation allow the formation of a variety of substituted aromatics.

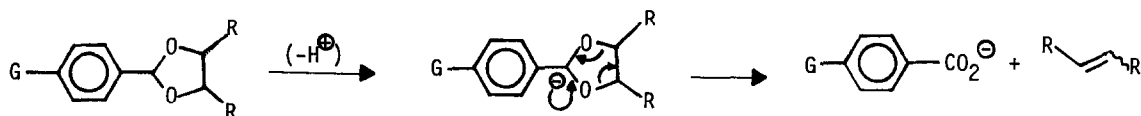
The advent of reagents which exhibit reverse polarity (umpolung) in their chemical behavior has been a major force in modern synthetic methodology. Prominent among the most useful umpolung reagents is the acyl anion equivalent which arises from a variety of ingenious routes.¹ Recently the use of fully oxygenated acyl anion equivalents were reported² using esters of α,α -dialkoxyacetic acids

SCHEME 1



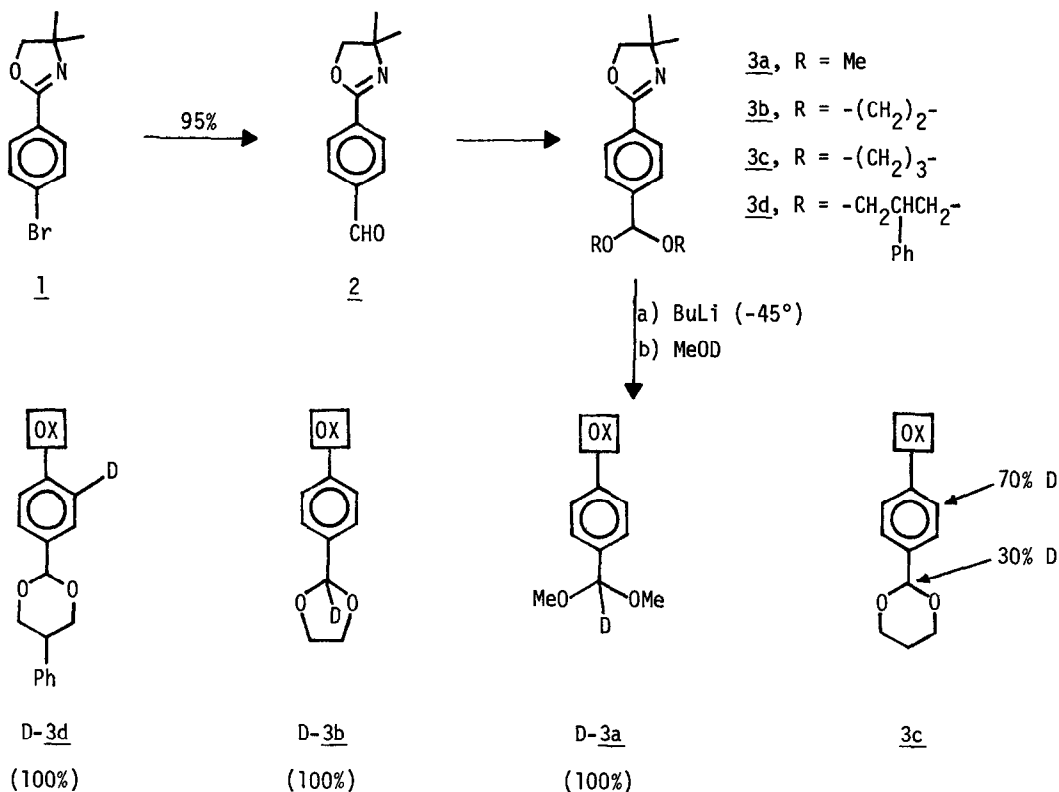
in the sequence shown in Scheme 1. However, there are no reports of successful implementation of this concept in 2-aryl acetals mainly because of the unstable nature of the α,α -alkoxy aryl anion and its tendency to rearrange and/or fragment (Scheme 2).

SCHEME 2

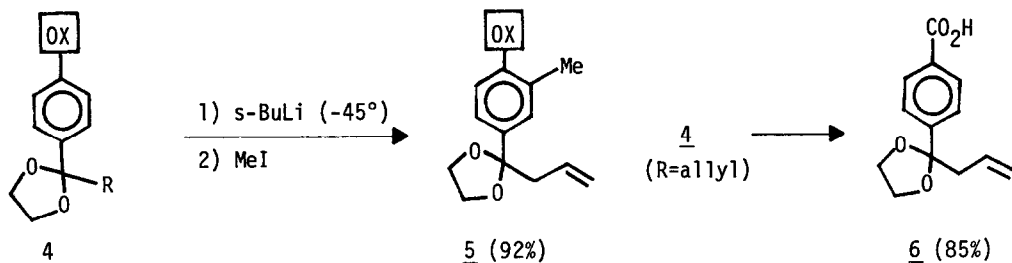


G = alkyl, alkoxy

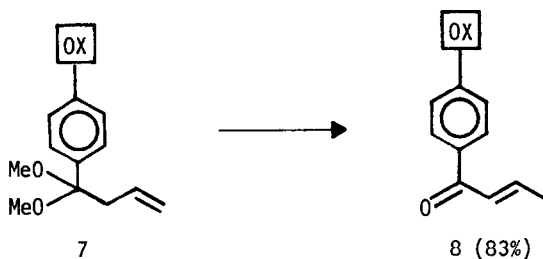
We wish to describe herein the successful utilization of an aryl acetal as an acyl anion equivalent and the regioselective metallations which cause this to be a rather efficient route to substituted aromatics. The presence of a *p*-oxazolinyll substituent (but not *ortho* or *meta*) is undoubtedly responsible for this useful behavior.



The aryl acetals $\underline{3(a-d)}$ were readily prepared in high yield using 2-(*p*-bromophenyl) oxazoline⁴ and transforming it to the formyl derivative $\underline{2}$ (*n*-BuLi, -78° , DMF) in 94% yield. Treatment with 2.0 equiv of the appropriate alcohol (*p*-TsOH, toluene) and heating with azeotropic water removal gave the acetals $\underline{3a-3d}$ in 75-95% yield.⁵ When the various acetals were treated with 1.0 equiv *n*-butyllithium (-45° , THF) and quenched after 4 h with CH_3OD at -45° , a surprising array of deuteriated products was isolated. Thus, the dimethoxy acetal and the 1,3-dioxolane gave 100% D-incorporation at the acetal carbon and assured the success of $\underline{3a}$, $\underline{3b}$ as an acyl anion equivalent. However, $\underline{3c}$ gave a mixture of *ortho*-D and acetal D incorporation while $\underline{3d}$ gave exclusively *ortho*-D product.⁶ This unusual metallation pattern for $\underline{3a-3d}$ will be discussed in the accompanying paper.

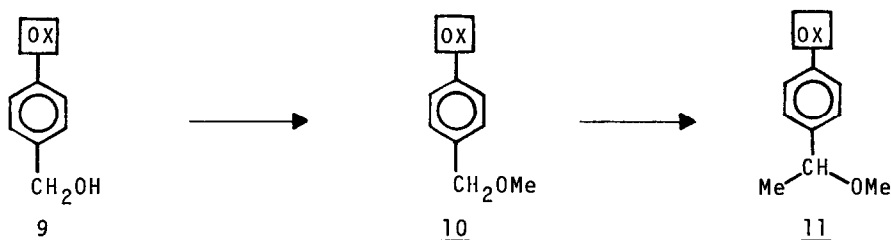


R (in 4)	%	Mp ($^\circ\text{C}$)
Me	93	65-66
Et	95	88-89
Allyl	85	48-49
PhCO	74	128-129
	88	115-116



The aryl dioxolane 3b was metallated using LDA (-78°) or *n*-BuLi (-45°) in THF and treated with a variety of electrophiles which, upon aqueous workup, gave 4 with various substituents in high purity and high yield. Now that the more acidic acetal proton had been removed in going to 4, subsequent treatment with base (*sec*-BuLi, 1.1 equiv, ether, -45° , 4h) gave the ortho-lithio derivative which was treated with methyl iodide to furnish the methylated derivative 5 (H^1 nmr in CDCl_3 , δ 2.58 singlet, 3H). In order to demonstrate the further utility of this regioselective elaboration of aromatics, either of the protecting groups could be selectively removed. The carboxylic acid was unmasked under basic conditions ($\text{Et}_3\text{O}^+ \text{BF}_4^-$, 1.0 equiv; CH_2Cl_2 , 25° , 6 h; then 20% NaOH, DMSO- H_2O , reflux, 12 h) to give 6. Due to acidic conditions required to free the carbonyl group and the oxazoline sensitivity to acid, the dioxolanes were not a suitable protecting group. Therefore, the dimethoxy acetal 7 was used as the acyl anion equivalent. Treatment of 7 with Me_3SiI ⁷ gave the ketone 8 smoothly.

In an effort to determine the scope of metallation on the side chain, the benzyl alcohol 9 (derived from 2 and NaBH_4 , EtOH) was transformed into the methyl



ether 10 (NaH, DMF, HMPA, 25°, followed by Me₂SO₄, 91%). Treatment of the latter with LDA (-78°, THF) and addition of methyl iodide gave the α-methyl derivative 11 [94%, bp 135-145°/0.01 mm; H¹-nmr (CDCl₃) δ 4.31 (q, 1H, J=7 Hz), 3.20 (s, 3H), 1.38 (d, 3H, J=7.0 Hz)]. It is important to note that no ring metallation was ever observed using LDA as the base. The conversion of 10 to 11 without any evidence of elimination or rearrangement (Wittig rearrangement⁸) is unique in metallated benzyl ethers.⁹

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