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Grignard Additions to α,β-Unsaturated Dioxolanones: Preparation of Chiral Allylic Alcohols and Protected α-Hydroxy Aldehydes

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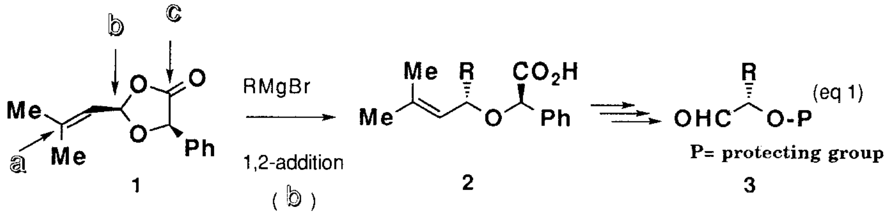
Summary: *α,β-Unsaturated dioxolanones derived from mandelic acid smoothly add most Grignard reagents with good to excellent regio- and diastereoselectivities. The adducts are converted to chiral secondary alcohols by peroxidation at low temperature or to protected α-hydroxy aldehydes via ozonolysis.*

Much attention has been given to the controlled addition of organometallics to dioxolanones and related heterocyclic templates for the asymmetric synthesis of heteroatom-substituted intermediates.[1] Recently, we described the stereospecific addition of organocopper reagents to the acetalic center of 1,3-dioxolan-4-ones and the utilization of the adducts for the preparation of chiral secondary alcohols.[2] In contrast, nucleophilic additions to α,β-unsaturated dioxolanones are rare; furthermore, their synthetic potential is complicated by the presence of three electrophilic centers at positions a, b, and c (eq 1). Mackenzie,[3] for instance, observed mainly 1,4-addition when using Pd or Ni π-allyl complexes derived from α,β-unsaturated 1,3-dioxolan-4-ones. Ester enolates also add, but only in the presence of TMSOTf.[3] Herein, we report that Grignard reagents add regio- and stereospecifically to the acetalic "b" center of α,β-unsaturated mandelate dioxolanones **1** and that the adducts **2** are readily transformed to chiral allylic alcohols or protected α-hydroxy aldehydes.



P= protecting group

Improved yields of **1** were obtained by modifying Farines' protocol[4] with pyridinium *p*-toluenesulfonate (PPTS) to give **1** nearly quantitatively as a *ca.* 70:30 *cis*/*trans*-mixture. Similar results were obtained using the diethyl acetal of 3-methyl-2-butanal and mandelic acid in refluxing benzene with azeotropic removal of EtOH. Preferential crystallization from EtOAc/hexane at -78°C[5] in the presence of a trace of acid afforded pure *cis*-**1** (80%).[6]

Contrary to saturated 1,3-dioxolan-4-ones, *cis*-**1** demonstrated similar regio- and diastereoselectivities with both Grignard and organocopper reagents. As a matter of convenience, all subsequent reactions were conducted with the more readily available Grignard reagents. Somewhat better selectivities were obtained in Et_2O as compared with toluene. Notably, there was no reaction in THF. Addition of nBuMgBr to *cis*-**1** in Et_2O at 25°C generated an 85:15 mixture of 1,2- and 1,4-adducts in 95% total yield. The major regioisomer consisted of an 85:15 combination of chromatographically separable diastereomers. At -78°C, the regio- and diastereoselectivities both slightly improved to 92:8. These values were 87:13 and 80:20, respectively, in toluene at -78°C.

Table 1.

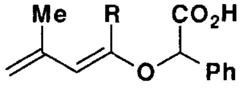
Grignard Addition to Mandelate Dioxolanones*

RMgBr	Time(h)	1,2-Add./ 1,4-Add.	Diastereomer Ratio	Yield(%)**
Bu	2	92/8	92/8	75
iPr	3	70/30	97/3	60
Ph	3	>95/5	91/9	63
Hexynyl	3	95/5	92/8	77
Allyl	3	-	-	0

* in Et_2O at -78°C

** isolated yield of the major isomer of 1,2-Add. product

The results observed with several representative Grignard reagents in Et_2O at -78°C are summarized in Table 1. Generally, the yields and diastereomeric ratio were preparatively useful with the exception of allyl Grignards with which the elimination product **4** was the major isolated product (30%). In all cases, the major diastereomer was isolated by SiO_2 chromatography.[6]



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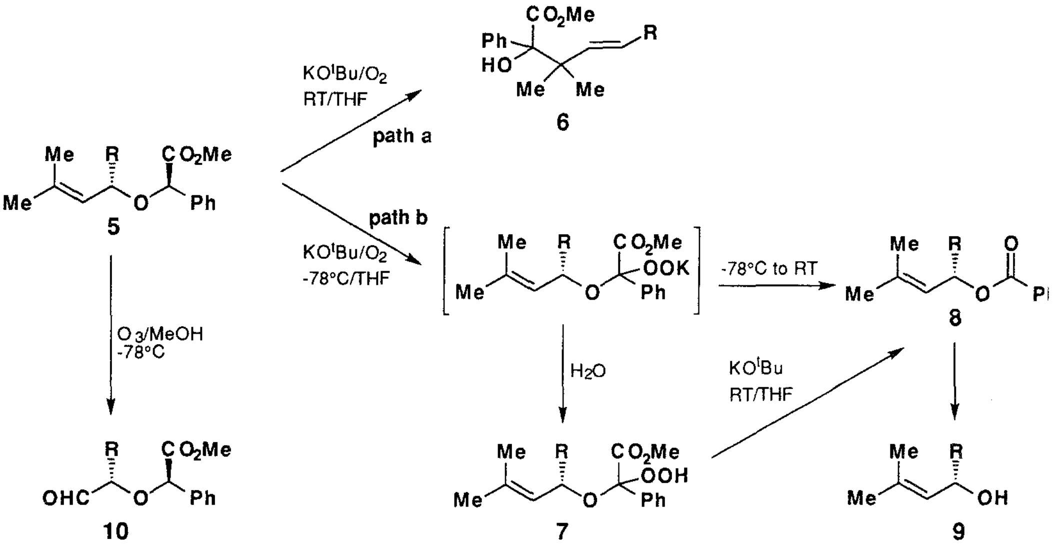
Stereochemical analysis of the major diastereomer of **2** (R = nBu) via catalytic hydrogenation (H_2, Pd/C, EtOAc) and spectral comparisons with saturated standards revealed inversion of configuration at the acetalic center as previously seen with the corresponding saturated dioxolanones.[2]

However, oxidative deprotection of the corresponding methyl ester **5** using KO^tBu/O_2 at room temperature, in stark contrast with saturated dioxolanones,[7] mainly induced a homologous Wittig rearrangement through the initially formed α-anion (Scheme 1, path a).

Scheme 1.



This could be overcome by a modification in which the intermediate α-hydroperoxide was generated at -78°C/KO^tBu/O_2, and subsequently warmed up to room temperature, thus inducing decarboxylation to form benzoate **8** (Scheme 1, path b). Alternatively, by quenching the reaction mixture at -78°C, hydroperoxide **7** could be isolated in 85 % yield. Subsequent exposure of **7** to KO^tBu at room temperature provided quantitatively ester **8** by the same reaction mecanism.[7] Saponification gave optically pure allylic alcohol **9** in 80% overall yield.[8]

Alternatively, ozonolysis of **5** at -78°C in MeOH led to protected α-hydroxy aldehyde **10**, also in 80% or better yield. The synthetic potential of **9** and **10** is illustrated in the accompanying total syntheses.

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6. All new compounds were fully characterized by ^{1}H, ^{13}C, and mass spectroscopy using chromatographically homogeneous samples.
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8. Mosher esters of allylic alcohols **9** (R= Bu, iPr, Ph and hexynyl) schowed one single isomer.

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