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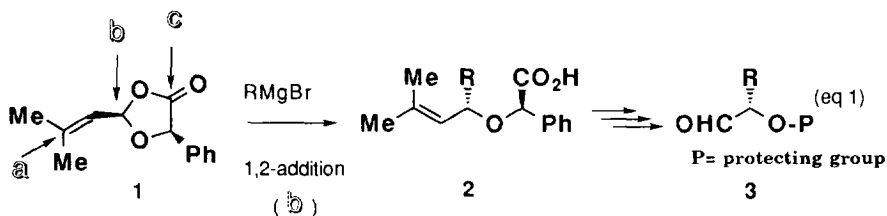
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Summary: α,β -Unsaturated dioxolanones derived from mandelic acid smoothly add most Grignard reagents with good to excellent regio- and diastereoselectivities. The adducts are converted to chiral secondary alcohols by peroxidation at low temperature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



Improved yields of **1** were obtained by modifying Farines' protocol⁴ 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°C⁵ 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 Et₂O as compared with toluene. Notably, there was no reaction in THF. Addition of *n*BuMgBr to *cis*-**1** in Et₂O 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.

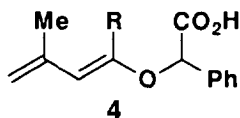
Grignard Addition to Mandelate Dioxolanones*

RMgBr	Time(h)	1,2-Add./ 1,4-Add.	Diastereo- mer 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 Et₂O at -78°C

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

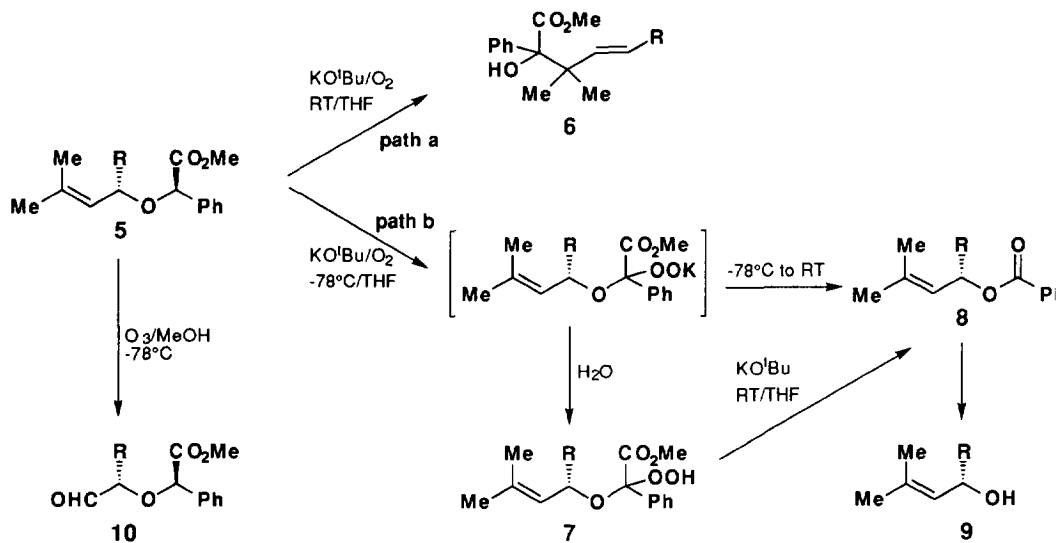
The results observed with several representative Grignard reagents in Et₂O at -78°C are summarized in Table 1. Generally, the yields and diastereomeric ratio were preparatively useful with the exception of allyl Grignards with which the elimination product **4** was the major isolated product (30%). In all cases, the major diastereomer was isolated by SiO₂ chromatography.⁶



Stereochemical analysis of the major diastereomer of **2** (R = nBu) via catalytic hydrogenation (H₂, 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/O₂ 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/O₂, 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 mechanism.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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References and notes

1. Seebach, D.; Imwinkelried, R.; Stucky, G. *Angew. Chem. Int. Ed.* **1986**, 25, 178-180.
Mashraqui, S.H.; Kellogg, R.M. *J. Org. Chem.* **1984**, 49, 2513-2516.
Schreiber, S.L.; Reagan, J. *Tetrahedron Lett.* **1986**, 27, 2945-2948.
2. Heckmann, B.; Mioskowski, C.; Yu, J.; Falck, J.R. *Tetrahedron Lett.* **1992**, 33, 5201-5204.
3. Faunce, J.A.; Friebe, T.L.; Grisso, B.A.; Losey, E.N.; Sabat, M.; Mackenzie, P.B. *J. Am. Chem. Soc.* **1989**, 111, 4508-4510.
Krysan, D.J.; Mackenzie, P.B. *ibid.* **1988**, 110, 6273-6274.
4. Farines, M.; Soulier, J. *Bull. Soc. Chim. Fr.* **1970**, 332-340.
5. ¹H NMR analysis in the presence of catalytic BF₃·Et₂O showed a dynamic equilibrium in which *cis*-**1** was favored, e.g., *cis/trans* 64:36 at 18°C and 79:21 at -40°C.
6. All new compounds were fully characterized by ¹H, ¹³C, and mass spectroscopy using chromatographically homogeneous samples.
7. Heckmann, B.; Alayrac, C.; Mioskowski, C.; Chandrasekhar, S.; Falck, J.R. *Tetrahedron Lett.* **1992**, 33, 5205-5208.
8. Mosher esters of allylic alcohols **9** (R= Bu, iPr, Ph and hexynyl) showed one single isomer.

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