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Nucleophilic Substitution at the Acetalic Center of Mandelate 1,3-Dioxolan-4-ones using Magnesio-Copper Reagents: Application to the Synthesis of Chiral Secondary Alcohols.

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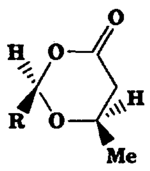
Summary : *Ethereal magnesio-copper reagents, in contrast to lithio-copper reagents, add stereoselectively to mandelic acid derived 1,3-dioxolan-4-ones to afford optically active secondary alcohols after removal of the chiral auxiliary.*

1,3-Dioxan-4-ones[1] and 1,3-dioxolan-4-ones[2], e.g., (1) and (2), respectively, have been used for the synthesis of chiral secondary alcohols via addition of silicon reagents. In the former case, it was possible to extend[3] this approach to lithium triorganocuprates (higher order cuprates); lithium diorganocuprates, however, tended to react at the carbonyl. Unfortunately, the chiral auxiliary required for (1) is expensive in its monomeric form (Aldrich Chem. Co.) and is only available commercially in its polymeric form as the (R)-antipode[4] (Fluka Chem. Co.). We report herein methodology for exploiting 1,3-dioxolan-4-ones (2) derived from mandelic acid which is inexpensive and commercially available in both enantiomeric forms.



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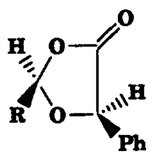
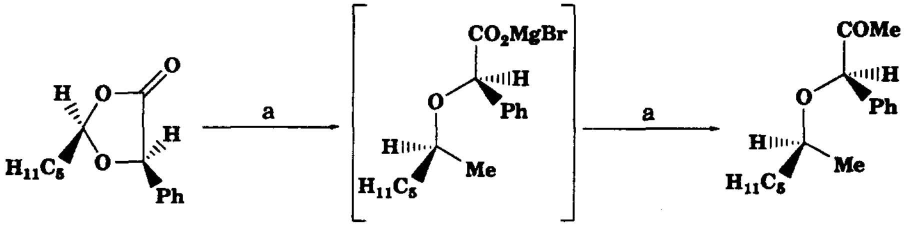


2

The condensation of mandelic acid with a variety of aldehydes in the presence of catalytic p-TsOH or $BF_3.Et_2O$ according to literature procedure[5] furnished 2-substituted-5-phenyl-1,3-dioxolan-4-ones (2) in yields of 70 % or better (90-98 % *cis*). The method[6] of Noyori gave (2) nearly quantitatively, but with poorer stereoselectivity in some cases, e.g., pivaldehyde gave rise to an 86:14 *cis/trans*-mixture. Since the mandelate acetals are generally solids, *cis*-(2) was typically obtained pure by recrystallization[7].

Contrary to Schreiber's experience[3] with (1), exposure of *cis*-(2) to lithium triorganocuprates (high order cuprates) resulted in exclusive attack at the carbonyl. Other carbon nucleophiles, *inter alia*, RMgBr, RLi, RCu(LiBr), and R_2CuLi behaved similarly. On the other hand, prompted by the report of Bolitt et al[8], we observed displacement at the acetal center in *cis*-(2) by diorganocuprates and organocopper reagents prepared from Grignards.

The results from addition of representative magnesio-copper reagents to *cis*-2-pentyl-5-phenyl-1,3-dioxolan-4-one (3) summarized in Table 1 are typical[9,10]. Yields and reaction times were comparable for both diorganocuprates and organocopper reagents. Ethereal primary and secondary alkyls added smoothly with exclusive cleavage of the lactonic acetal bond to give (4), conveniently isolated as its methyl ester. Chromatographic separation (SiO_2) of the resultant diastereomers and removal of the chiral auxiliary with $Pb(OAc)_4$[2] or preferrably by the method described in the following paper[11] furnished the corresponding optically pure alcohol. It should be noted that for methyl copper, 10-15% of a second product arising from double addition could be isolated (eq. 1).



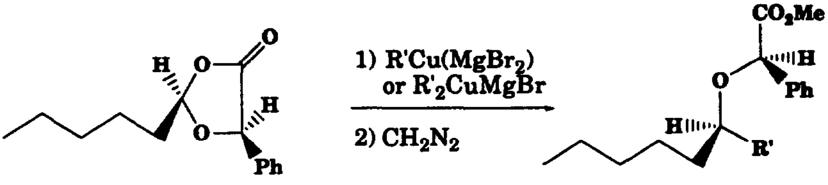
(eq. 1)

Reagent (a) MeCu

Phenyl copper reagents reacted more sluggishly. At ambient temperature, the yields improved, but were accompanied by a reciprocal decrease in d.e.. The presence of THF (as a 10 % mixture in Et_2O) had the opposite effect, i.e., improving the d.e. while significantly depressing the reaction rate and yield. Nucleophile addition was completely inhibited using THF as solvent and the starting material was recovered unchanged. This is undoubtedly the consequence of THF complexation with the magnesium salt, thus preventing activation of the acetal[12].

Addition of *i*PrCu to *trans*-dioxolanone (5) in Et_2O at - 20 °C led to the same major diastereomer of (4) (90 % yield, 76% d.e.) as produced by (3). This observation is most consistent with a rapid equilibrium between the *cis*-and *trans*-isomer (eq. 2) wherein the former suffers preferential SN2 displacement. An acyclic oxonium intermediate is unlikely to be a major contributor to product formation since approach of a nucleophile would not be highly diastereoselective.

TABLE 1 - Addition of magnesio-copper reagents to (3)

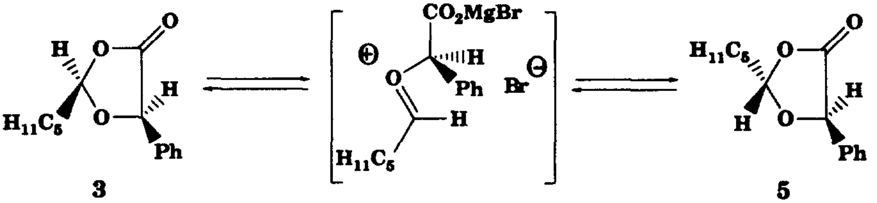


3 4

R '	Solvent	Temp (°C)	Time (h)	d.e.[a] (%)	Yield [b] (%)
Me[d]	Et_2O	- 20	2	90 - 92	65 - 70
Bu[e]	Et_2O	- 20	3	N.D[c]	82 - 85
iPr[e]	Et_2O	- 15	3	94	88 - 90
Ph[f]	Et_2O	- 15	14	72 - 74	72 - 78
Ph[f]	Et_2O	20	1,5	54 - 60	87 - 92
Ph[f]	Et_2O/THF (9:1)	20	36	90 - 92	17 - 22
Ph[f]	THF	20	36	-	0

[a] Determined by ^1H NMR or GLC. [b] Based on isolated, chromatographically homogeneous material.
[c] N.D. = not determined. [d] 2 eq. of reagent. [e] 3 eq. of reagent. [f] 4 eq. of reagent.

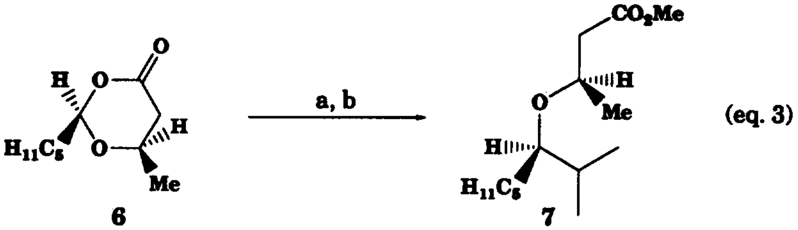
Corroboration of this hypothesis was provided by NMR analysis. In the presence of catalytic $BF_3.Et_2O$, (3) was rapidly equilibrated to a temperature dependent mixture of (3) or (5) : 70/30 at ambiant and 90/10 at - 20 °C.



3 5

(eq. 2)

For comparison, we also evaluated the reactivity of the 1,3-dioxanone (6) with *i*PrCu under condition identical to those used for (3). The addition product (7) was obtained in 85 % yield with a 60 % d.e. (eq. 3), considerably less than the 94 % d.e. achieved using the mandelate derived dioxolanone (Table 1).



Reagents: (a) *i*PrCu, Et_2O / -15°C; (b) CH_2N_2.

In conclusion, we have shown that dioxanones and dioxolanones display dramatically different reactivities toward lithium and magnesio-copper reagents. Mandelate dioxanones are usefull intermediates for the synthesis of chiral secondary alcohols by reaction with magnesio copper reagents in ether and removal of the chiral auxiliary under smooth conditions as decribed in the folowing paper[11]. Initial studies indicate that synthetically useful levels of diastereoselectivity for nucleophilic additions can also be obtained using chiral dioxalanones prepared from ketones[13].

Acknowledgments

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References and notes

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