# DIASTEREOSELECTIVE ORGANOCUPRATE ADDITION TO HOMOCHIRAL KETALS OF 3-ACETYLCYCLOPENT-2-EN-1-ONE

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Abstract: Addition of lower or higher order cuprates to the enone homoketals **4a-d** give the alkylated products with de's ranging from 12% to 34%.

The efficient production of optically active materials from prochiral precursors by asymmetric induction is one of the goals in synthetic organic chemistry today.[1] Of the several diverse methods for accomplishing this aim, one that has received significant attention recently is the use of homochiral ketals or acetals in diastereoselective processes. Notable in this regard is the work of Mash,[2] who has published extensively on the cyclopropanation (via Simmons-Smith reaction) of homochiral ketals of enones using chiral 1,2-diols, and that of Oku,[3] who has reported selective formation and reactions of diastereomeric spiroketals from meso 1,2- and 1,3-diols and l-menthone. We have been interested in the potential diastereoselective addition of nucleophiles to homochiral ketals of more highly
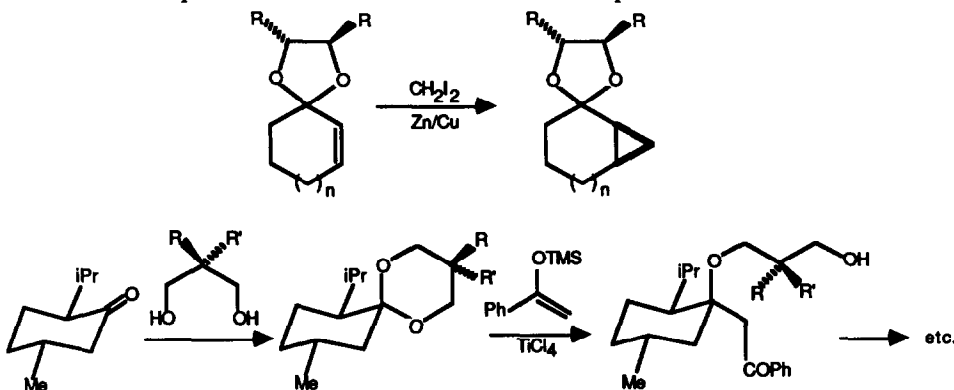
functionalized enones, especially those with electron-withdrawing groups in the 3-position. We now report our results on the addition of organocuprates to 1-acetylcyclopentenes bearing various homochiral ketals at the 3-position.

We hoped that addition of an organocuprate (Scheme 1) to the ketal **C** (prepared from the readily available precursors cyclohexenone **A** and various optically active 1,2-diols **B**) would proceed with high diastereoselectivity from the less hindered top face of the ketal in order to avoid interaction with the alkyl group on the ketal on the bottom face (as shown in **D**). The resultant stabilized lithium anion **E** could then be trapped with various electrophiles trans to the alkyl group to give predominately **F**. Hydrolysis would then afford the optically active ketone **G** and regenerate the optically active diol **B**. Alternatively protonation of **E** followed by base-catalyzed epimerization should give the trans 1,2-disubstituted cyclopentane **H** and after hydrolysis **I**. Compounds such as **G** or **I** might be of value in the synthesis of cyclopentenone natural products such as prostaglandin A and didemnenone
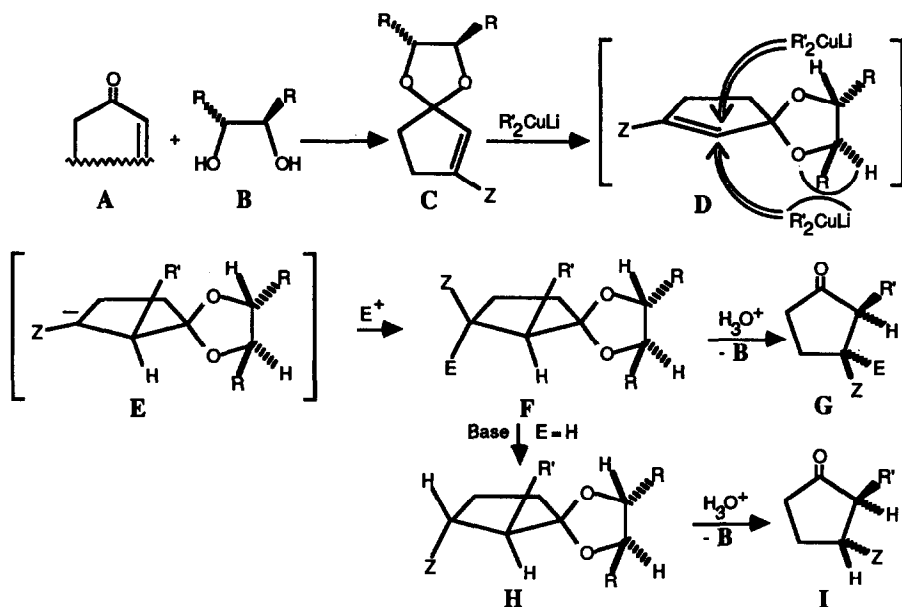
Scheme 1

C.[4] Our results now show that such diastereoselectivity is indeed possible, although only modest de's have been obtained thus far.

The ring ketals of 3-acetylcyclopentenone **4a-d** were prepared by a modification of the method of Truesdale.[5] Ketalization of cyclohexenone with the commercially available optically active R,R-diols **1ab** and with the R,R-diol **1c** readily prepared from D-tartaric acid[6] afforded the ketals **2abc** in excellent yield.[7] The ketal **2d** was prepared in two steps by the method of Mash[2g] from the S,S-diol **1d** and 3-bromo-2-methoxycyclohexene. Ozonolysis of **2a-d** with a reductive workup produced the dialdehydes which were directly cyclized to the enals **3a-d** with piperidinium acetate.[8] Final conversion to **4a-d** was affected in yields of 44-76% by reaction of **3a-d** with
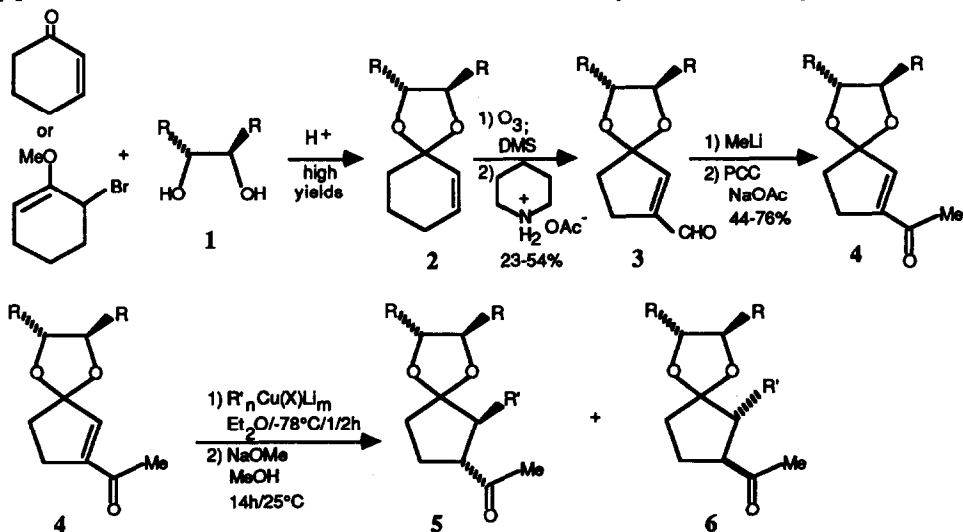
a R=Me b R=Ph c R=CH$_2$OBn d R=MeOC(Me)$_2$

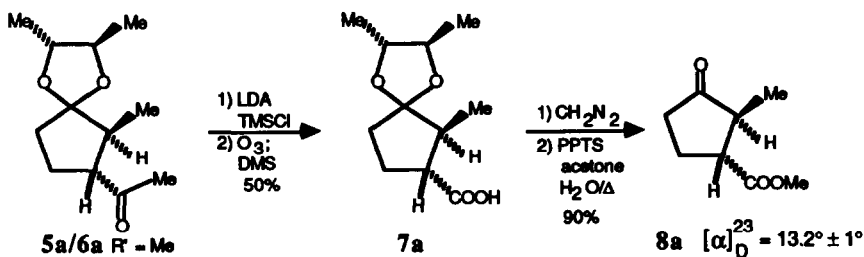**Table: Ratio of Diastereomers 5/6 from Organocuprate Addition to 4a-d**
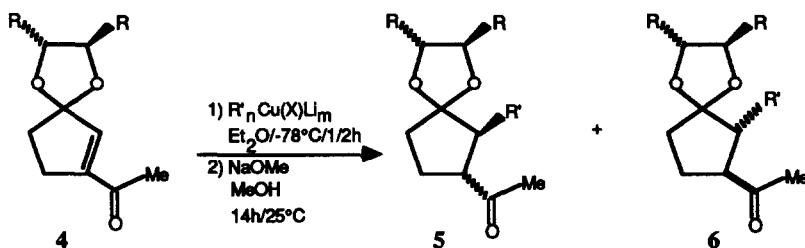
Cuprate	4a R=Me	4b R=Ph	4c R=CH₂OBn	4d R=MeOC(Me)₂
Me₂CuLi	64/36[b]	61/39	58/42	67/33
Me₂Cu(CN)Li₂	63/37	59/41	60/40	66/34
(Bu₃P)MeCuLi[c]			60/40	56/44
(Th)MeCu(CN)Li₂[d]			67/33	
PhCH₂(CN)ZnBr	63/38			

a) Diastereomeric ratios (after base equilibration to predominately the trans isomers) for all except those from ketal enone **4c** were determined by integration of the peaks on HP model 5790A capillary gas chromatograph using an HP-1 (fused methyl silicone) column. In all cases, the major isomer was the faster eluting off the column. For those from **4c**, the ratios were determined by integration of the methyl ketone peaks in the ¹H NMR spectra. b) Reaction at -105°C afforded approximately the same ratio. c) This reaction produced the trans isomers as the major products even before equilibrium. d) Th = thiophen-2-yl methyllithium followed by oxidation with PCC in the presence of sodium acetate.

Addition of various organocuprate reagents to **4a-d** in diethyl ether at -78°C for 1/2 h proceeded well to give the expected 3-acetyl-2-alkylcyclopentanone ketals in high yield as a mixture of the cis (major) and trans (minor) isomers. Treatment of the purified reaction product with sodium methoxide in methanol at 20°C for 14h afforded cleanly the trans isomers with only about 5% of the cis isomers remaining. The diastereomeric ratios were determined by either capillary gas chromatography or, for the benzyloxymethyl ketals, by integration of the pertinent peaks in the ¹H NMR spectrum. As the Table shows, the diastereoselectivity of organocuprate additions ranged from a minimum of 12% to a maximum of 34%, always favoring the isomer eluting faster on the GC. We have assigned structures **5** to the major and **6** to the minor isomer based on conversion of the **5a/6a** diastereomeric mixture (R'=Me) to the known ketoester **8** as follows. Treatment of **5a/6a** with LDA and TMSCl followed by ozonolysis of the resultant kinetic enol silyl ether and reductive hydrolytic workup gave the corresponding acid **7a** in 50% yield. Diazomethane esterification of **7a** and mild acidic hydrolysis afforded in 90% yield the keto ester **8a**, which had a specific rotation of $[\alpha]_D^{23} = +13.2° \pm 1°$. Since the optically pure (1R,2S) methyl 2-methyl-3-oxo-

cyclopentanecarboxylate has a specific rotation of $[\alpha]_D^{23} = + 70°$,[9] this implies that our ester **8** is mainly the (1R,2S) enantiomer as shown.[10] We have assigned the S configuration at the alkyl center to the other adducts by analogy to that proven for **5a/6a** (R'=Me). This is the configuration predicted by our model **D**, in which the top face of the molecule (as drawn in **D**) is more accessible sterically.

As the Table also shows, there is not a great difference between the various ketals in their diastereoselectivity, although **4d** gives somewhat better results than the others. An addition carried out at the lower temperature (-105°C) gave essentially the same ratio. Finally other non-cuprate nucleophiles were briefly examined. Thiophenolate ion added to **4a** to give an 80% yield of an approximately 1:1 mixture (by NMR) of the 1,4-addition product while dimethylsulfoxonium methylide, when reacted with **4a**, gave only the allylic epoxide in poor yield rather than the expected cyclopropyl ketone.

In conclusion, diastereoselective addition of organocuprates to homochiral ketals of 3-acetylcyclopentenone can be carried out in good yield with low to moderate de's.

References and Notes

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6. N. Ando, Y. Yamamoto, and Y. Inouye, *Synthesis*, 688 (1978).

7. The general procedure of Mash for the formation of these homochiral ketals was followed. See references 2hi.

8. Our yields of 3bcd from 2bcd were 25%, 23%, and 54% respectively, while Truesdale reports an overall 90% yield of 3a from 1a via three steps. Our own yields of 3a from 2a were about 50%.

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10. The optical rotation was done on a very small sample and therefore the enantiomer excess (18.9%) derived from this value is less reliable than that calculated by GC peak integration of the **5a/6a** mixture.