Tetrahedron Letters Vol. 21, pp 1035 - 1038
©Pergamon Press Ltd. 1980. Printed in Great Britain

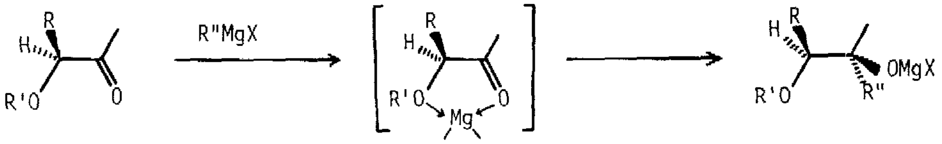
0040-4039/80/0308-1035$02.00/0

CHELATION-CONTROLLED NUCLEOPHILIC ADDITIONS.
2. A HIGHLY EFFECTIVE SYSTEM FOR ASYMMETRIC INDUCTION IN THE REACTION OF ORGANOMETALLICS WITH β-ALKOXYALDEHYDES.

W. Clark Still* and Josef A. Schneider
Department of Chemistry, Columbia University, New York, New York 10027

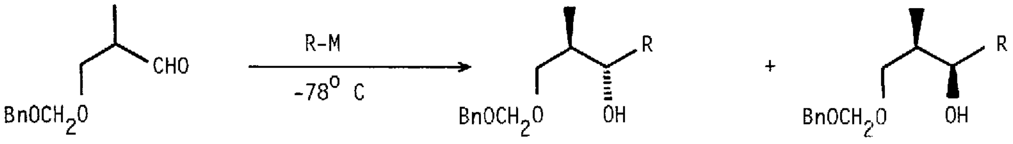
SUMMARY: Organocuprates have been found to be highly stereoselective reagents for the addition of carbanionic nucleophiles to α-asymmetric aldehydes bearing β-oxygen substituents. The major products are those predicted by a chelation-controlled transition state and have diastereomeric purities ranging from ~15-30:1.

In the accompanying paper,[1] we demonstrated that chiral α-alkoxyketones underwent reaction with Grignard reagents in tetrahydrofuran with extremely high stereoselectivity for the product predicted by the chelation-controlled addition mechanism shown below:



Since the effect of an α-asymmetric center substituted by oxygen is an exceedingly powerful one with important applications to natural product synthesis, we wished to evaluate this form of stereocontrol in other systems. We have therefore examined the reaction of organometallics with various oxygen-substituted aldehydes having α-asymmetric centers in a search for new systems showing high asymmetric induction.

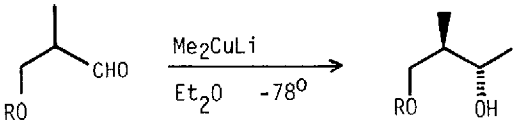
Some of the most synthetically interesting substrates for stereoselective nucleophilic additions are derivatives of β-alkoxyisobutyraldehydes since they are potential precursors of 1,3-diol substructures occurring in numerous polyether and macrolide antibiotics. Although β-dialkylaminoisobutyl ketones appear to be reasonably stereoselective in their reaction with Grignard reagents,[2] we are not aware of reports of high asymmetric induction in the addition reactions of related β-alkoxyaldehydes. Thus we were not surprised to find that the addition of either methyllithium or methylmagnesium bromide to aldehyde 1 (Table, next page) proceeded at low temperature without significant α-induction. As shown in the following table, however, the situation is dramatically improved through the use of lithium dimethylcuprate (Et_2O, -78° C) as the source of methyl nucleophile.[3] Although the addition is not totally stereospecific, it does proceed in high chemical yield to give the product of chelation-control (threo) with 97% diastereomeric purity.[4] High stereoselectivity for the threo product is also found in other organocuprate additions so long as the organic nucleophile is saturated. In contrast, relatively stable, sp^2 organic anions such as vinyl seem to give poor asymmetric induction.[5]



1 Threo Erythro

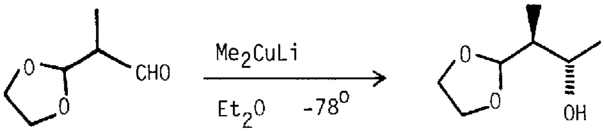
		Threo/Erythro	Isolated Yield
R = CH_3	R-M = CH_3Li	0.7 (PMR)[7]	90%
	= CH_3MgBr	1.0 (PMR)[7]	>95%
	= $(CH_3)_2CuLi$	30.0 (PMR)[7]	92%
R = n-C_4H_9	R-M = C_4H_9Li	1.7 (CMR)[7]	83%
	= $(C_4H_9)_2CuLi$	17.0 (CMR)[7]	82%
R = $CH{=}CH_2$	R-M = $CH_2{=}CHLi$[6]	<1.0 (PMR, HPLC)[8]	>95%
	= $(CH_2{=}CH)_2CuLi$	3.0 (PMR, HPLC)[8]	>95%
	= $CH_2{=}CHCu{\cdot}Bu_3P$	8.0 (PMR, HPLC)[8]	88% (50% conversion)

The stereoselective addition is not limited to oxygenated aldehydes bearing benzyloxymethyl protecting groups. As outlined in the diagrams below, other hydroxyl protecting groups also give high threo stereoselectivity. Interestingly, only a single oxygen is necessary for efficient



>20:1 threo:erythro[7]
(90% yield)

2, R = -THP, $-CH_2Ph$

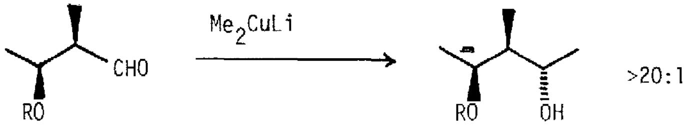


12:1 threo:erythro[7]
(93% yield)

control of the addition and if that oxygen is sufficiently hindered, then chelation-directed stereoselectivity is lost. Thus the trityl derivative of β-hydroxyisobutyraldehyde (2, R = CPh_3) reacts at -78° C with either methylmagnesium bromide or lithium dimethylcuprate to give roughly the same mixture of products in which the erythro (Cram steric) diastereomer predominates 2:1. It should also be pointed out that the observed results do not appear to derive from the presumably bulky nature of organocuprates since 2-phenylpropanal gives almost the same product distribution with either organocuprates or Grignard reagents.

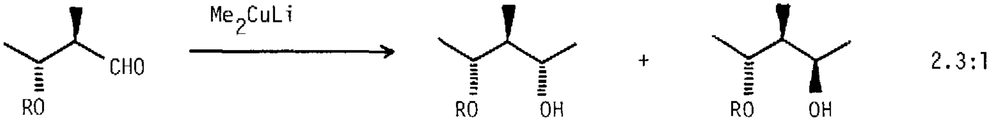
To assess the reaction on more highly substituted β-alkoxyaldehydes, dimethylcuprate was added to compounds 3 - 5. As shown below β-substitution can have significant effects on stereoselectivity when α-substitution is also present. Stereochemistry was assigned by PMR of the

3

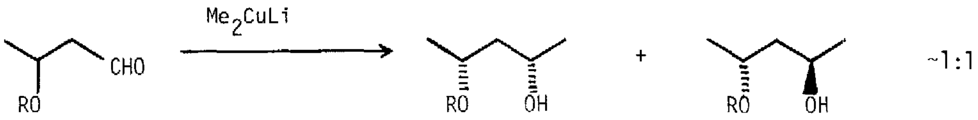


* R = CH_2OCH_2Ph

4

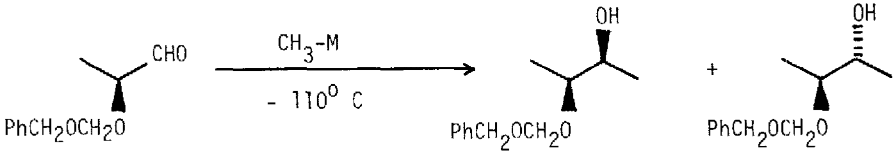


5



derived bis(benzyloxymethyl) ethers. Thus 3 gave a product showing three methyl doublets ($CDCl_3$, δ 0.84, 1.18, 1.19) whereas the isolated major diastereomer from 4 gave a diether displaying only two different methyl signals (δ 0.89 (3H) and 1.30 (6H)).

The high stereoselectivity observed with the cuprate additions to β-alkoxyaldehydes does not appear to extend to the corresponding α-alkoxyaldehydes. Thus substrates like 6 prepared from (-)-ethyl lactate reacted much more stereoselectively with the methyl Grignard reagent than with the corresponding cuprate. Although these Grignard additions are significantly less selective



6

CH_3-M = CH_3MgBr 10 : 1[9]

= $(CH_3)_2CuLi$ 2 : 1[9]

than are additions to related α-alkoxyketones, they do give synthetically useful diastereomeric product distributions.[10]

In conclusion, it has been shown that the addition of organometallics to alkoxyaldehydes can be a highly stereoselective and thus synthetically useful operation. However, the mechanistic origin of some of the observed effects remains obscure. The marked preference of Grignard reagents for α-chelation (5-membered chelate ring) and of organocuprates for β-chelation (6-membered chelate ring) provides some information but further work is required.[11]

References and Notes:

1. W. C. Still and J. H. McDonald, Tetrahedron Lett., preceding paper in this issue.
2. L. Angiolini, P.C. Bizzarri and M. Tramontini, Tetrahedron, 25, 4211 (1969); ibid., 26, 3959 (1970).
3. Although dialkylcuprates are relatively unreactive with saturated ketones, they are known to add rapidly to aldehydes: G.H. Posner, C.E. Whitten, and P.E. McFarland, J. Am. Chem. Soc., 94, 5106 (1972).
4. Stereochemistry was assigned by comparison with authentic material (threo) prepared from tiglic acid via hydroboration of the corresponding protected alcohol.
5. This loss of stereochemistry may not be related to an inherent property of divinylcuprate but could be due to competitive, nonselective addition of free vinyllithium.
6. Vinyllithium was prepared from tetravinyltin via butyllithium exchange.
7. Stereochemistry was assigned by comparison with authentic material.
8. Stereochemistry was tentatively assigned by analogy with the results using methyl and butyl cuprates.
9. Stereochemistry was assigned by conversion to the crystalline bis(p-bromobenzoate) after deprotection, mp = 60.5-61.5° C (lit. 64.0-64.5° C for optically active threo; 139-140° C for meso: F.M. Robertson and A.C. Neish, Can. J. Res., 26B, 737 (1948)).
10. Several other reports of highly selective Grignard additions to α-alkoxyaldehydes have appeared: M.L. Wolfrom and S. Hanessian, J. Org. Chem., 27, 1800 (1962); T. Nakati and Y. Kishi, Tetrahedron Lett., 2745 (1978).
11. This work was supported by NSF grant CHE78-01769.

(Received in USA 18 December 1979)