

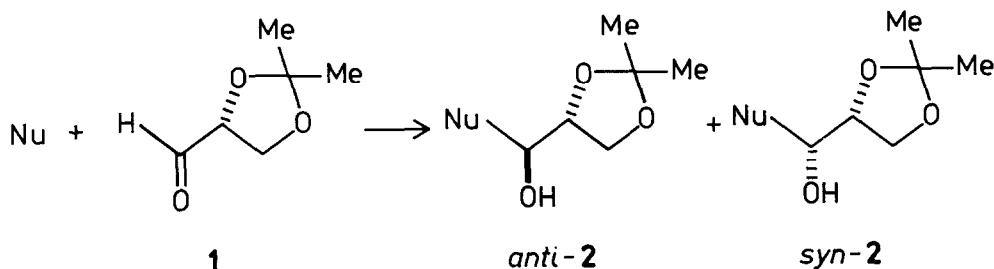
STEREOCHEMICAL CONSEQUENCES OF NUCLEOPHILIC ADDITIONS TO
2,3-O-ISOPROPYLIDENEGLYCERALDEHYDE. HIGH-PRESSURE APPROACH
versus THE USE OF ORGANOMETALLIC REAGENT

STANISŁAW PIKUL AND JANUSZ JURCZAK*

Institute of Organic Chemistry, Polish Academy of Sciences,
01-224 Warszawa, Poland

Abstract: Reactions of (R)-2,3-O-isopropylidenglyceraldehyde with 2-methylfuran under high pressure and with lithium derivative of 2-methylfuran under atmospheric pressure are studied and the stereochemical models involving coordinating interactions between the metal cation and oxygen atoms of the aldehyde are discussed.

(R)-2,3-O-Isopropylidenglyceraldehyde (**1**)¹ has attracted attention of many synthetic chemists during the past years. Its wide utility in stereocontrolled synthesis of various natural polyhydroxylated compounds has recently been thoroughly surveyed.² Most of its applications involve nucleophilic addition to the carbonyl group, affording a mixture of diastereoisomeric alcohols *anti*-**2** and *syn*-**2**, the former generally being the predominant product (Scheme 1).



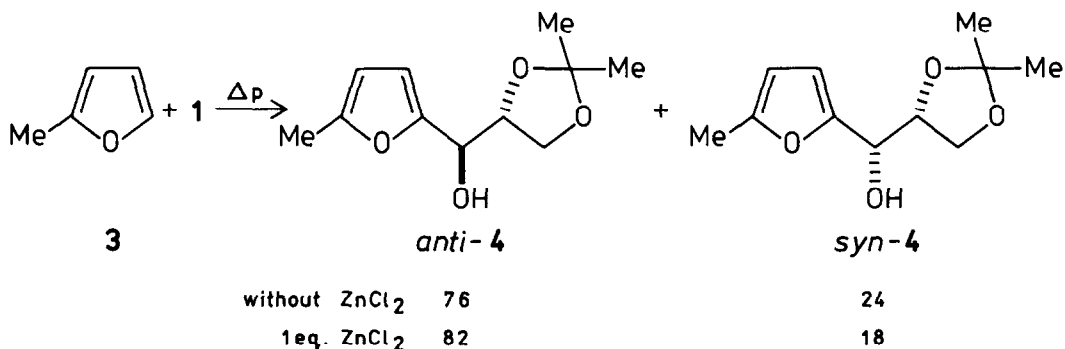
Scheme 1

The degree of selectivity of these reactions is usually limited, and thus very high asymmetric inductions (>9:1) are not frequently reported. Distribution of products is usually explained in terms of Felkin's model,³ while chelating interactions are taken into account less often.^{4,5} However, the results obtained by Still and al.⁶ for addition of Grignard reagent to α -alkoxyketones emphasizes the significance of the complexing processes which seem to play an important part also in the reactions of **1**. In case of **1**, chelation may involve oxygen atoms either at the α - or β -position,⁷ this leading to predominant formation of the *syn*- or *anti*-isomer, respectively. From the Felkin's model, the *anti*-isomer can be predicted as the major product. Thus it is difficult to distinguish the reaction-controlling mechanism, particularly because the organometallic reagent addition is associated with the presence of a metal cation.

In the light of the above considerations it was important to develop reaction conditions preventing complexation, because the product composition ought to inform about the reaction

course resulting from the "pure" Felkin's model. We felt that the reactions carried out under high pressure, with no metal salt added, can help in solving of this problem. Consequently, we compared the stereochemical course of both - the high-pressure reaction between 2-methylfuran (3) and 1, and nucleophilic addition of lithium derivative of 3 to 1.⁸

High-pressure reactions were carried out in an earlier described⁹ piston-cylinder type apparatus, in CH₂Cl₂ as a solvent, at room temperature under 10 kbar for 12 h¹⁰ (Scheme 2). It can be seen that the high-pressure reaction exhibited relatively high *anti*-selectivity. We think that this result approximately illustrates the efficiency of differentiation between both faces of the C=O double bond of 1 in a process described by the Felkin's model.¹¹ A similar reaction involving an addition of ZnCl₂ improved the *anti*-selectivity from 52% to 64% d.e., this pointing to interactions preferring the formation of *anti*-4.



Scheme 2

Organometallic additions were carried out using the lithium derivative of 3, with two different modes of ZnCl₂ addition. In mode A, ZnCl₂ was first stirred with 1 in tetrahydrofuran at room temperature, followed by addition of the lithium derivative of 3; in mode B, ZnCl₂ was mixed with the lithium derivative of 3 and the resulting solution was added to 1.¹⁰ The results of these experiments are presented in Table 1.

Table 1. Stereochemical Results of Nucleophilic Addition of Lithium Derivative of 3 to 1

Mode of ZnCl ₂ addition	Temperature °C	<i>anti</i> - <u>4</u> : <i>syn</i> - <u>4</u>
-	0	47 : 53
A	0	79 : 21
B	0	80 : 20
-	-78	46 : 54
A	-78	57 : 43
B	-78	91 : 9

The reactions carried out without ZnCl₂ either at 0°C or at -78°C showed a similar degree of stereoselectivity and product *syn*-4 slightly predominated. The reactions performed at 0°C with an addition of ZnCl₂, in both, mode A and B, exhibited a reversed direction of asymmetric induction, and afforded *anti*-4 with 8:2 selectivity. These results were in great contrast to

those obtained at -78°C ; namely, in case of mode B, the *anti*-selectivity was considerably enhanced, while mode A resulted in an only limited predominance of *anti*-4. In our opinion, the differences between these reactions in the behaviour of 1 can be rationalized upon the assumption that chelation plays an important part, controlling the conformation of 1. Various possibilities of coordinating interactions between the metal cation and oxygen atoms of the aldehyde are presented in Figure 1; they involve coordination of M^+ to oxygen at the α -position (I), to oxygen at the β -position (III or IV) and to both oxygens (II). For projections III and IV, other views (IIIa and IVa) are shown to emphasize their difference.

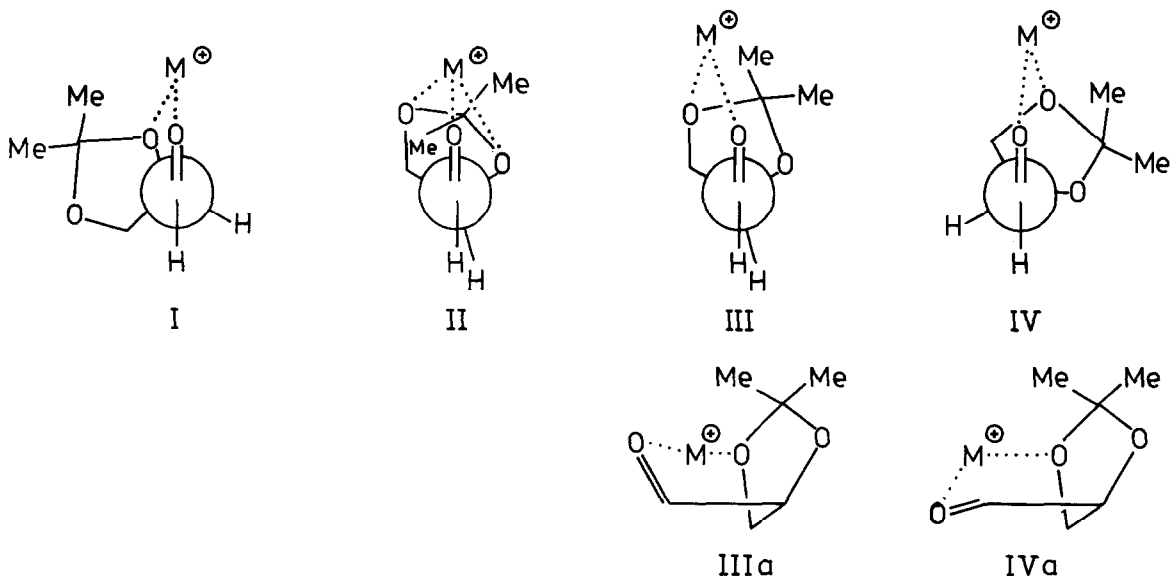


Figure 1. Coordinating interactions between the metal cation and oxygen atoms of 2,3-O-isopropylidene-glyceraldehyde (1)

There is an evident possibility of continuous transition of the chelating cation from interaction with α -oxygen to that with β -oxygen; considerable changes in conformation of 1 follow this shift. Moreover, the conformational changes seem to be reflected in the stereochemical course of the reaction, since the transition from I to IV should result in predominance of the *syn*- and *anti*-isomer, respectively. In turn, the most favoured conformation depends on the kind of metal. Thus, for the small lithium cation, conformations I and II seem to be predominant, this explaining the very low *syn*-selectivity, if any. In case of more bulky metals (e.g. Zn), conformations III and IV could be expected to be energetically preferred, this well explaining the *anti*-selectivity.

The basic assumption of these considerations requires the occurrence of sufficiently strong chelating interactions between the metal cation and oxygen atoms of 1. It seems that the active organometallic reagent, as compared with the metal salt alone, has a much stronger coordination ability, as shown by the results of the reaction carried out at -78°C in mode A; the very low *anti*-selectivity indicates that the organolithium reagent interacts with 1 much stronger than ZnCl_2 . The greater predominance of the *anti*-isomer is probably due to the action of the organozinc species formed *in situ*. The latter process proves to be much more rapid at 0°C than at -78°C , since there is virtually no difference between the results of this reaction and

that run in mode B at the same temperature.

This interpretation seems to rationalize the major part of the experimental results obtained not only for 1 but also for its imine derivatives.¹² The results of nucleophilic additions to 1, recently published by Mead and Macdonald,⁷ are also consistent with our explanation, although the authors rationalized their experiments in term of non-chelating approach. We feel that chelating interactions in case of 1 are modified by some additional factors (e.g. steric repulsion between the methyl groups of the dioxolane ring and ligands of metal). Thus, much more work is necessary to gain insight into all factors responsible for the stereochemistry of various reactions of 2,3-O-isopropylidene-glyceraldehyde.

REFERENCES AND NOTES

1. (R)-1 was the model compound in our work; obviously, all considerations presented here apply also to its (S)-enantiomer.
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7. Chelation versus non-chelation control in addition reactions of 1 in comparison to 2,3-O-dibenzylglyceraldehyde was studied very recently: K.Mead and T.L.Macdonald, J.Org.Chem., 50, 422(1985).
8. Reaction of furyllithium with 1 was studied by Mukaiyama et al.,⁴ we were however unable to perform this reaction under high pressure due to polymerization of furan.
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10. After aqueous work-up, the crude product was silylated under high-pressure conditions according to W.G.Dauben, R.A.Bunce, J.M.Gerdes, K.E.Henegar, A.F.Cunningham and T.B.Ottobani, Tetrahedron Lett., 24,5709(1983). The mixture of protected diastereoisomeric alcohols was directly analysed by HPLC (heptane - ethyl ether 97.5 : 2.5 v/v, Lichrosorb 10 μ m).
11. A similar degree of selectivity (*anti:syn* 8:2) was obtained in the high-pressure reaction of 2,5-dimethylfuran with 1 (J.Jurczak and S.Pikul, Tetrahedron Lett., 25,3107(1984)) as well as in the high-pressure Diels-Alder reaction of 1 with 1-methoxybuta-1,3-diene (J.Jurczak, T.Bauer, S.Filipek, M.Tkacz and K.Zygo, J.Chem.Soc.,Chem.Commun., 1983,540).
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