Non-chelation-control in Nucleophilic Additions to Chiral α- and β-Alkoxy Aldehydes

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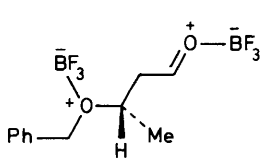
The addition of two equivalents of gaseous BF_3 to α- and β-alkoxy aldehydes having a centre of chirality at the α-position leads to doubly complexed species which react diastereoselectively with silyl enol ethers and allylsilanes to provide non-chelation-controlled adducts.

We recently reported high levels of 1,2- and 1,3-asymmetric induction in Grignard- and aldol-type additions to chiral α- and β-alkoxy aldehydes and ketones.[1,2] In the case of α-alkoxy aldehydes chelation-controlled products[3] dominate if Lewis acid reagents such as $MeTiCl_3$ or $TiCl_4$ in combination with R_2Zn, allylsilanes, or enol silanes are used. They react *via* 5-membered chelates in which titanium is 6-co-ordinate (octahedral). In contrast, non-co-ordinating analogues[1] $RTi(OCHMe_2)_3$ afford Felkin–Anh products.[4] Generally, such non-chelation-control is more difficult to attain.[5] The present communication describes new approaches to the latter problem.[3]

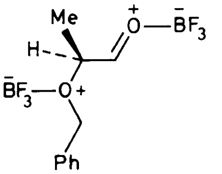
We speculated that double complexation of chiral α- and β-alkoxy aldehydes using Lewis acids *incapable* of bis-ligation (*e.g.*, BF_3) could result in adducts (**1**), (**2**), and (**3**), which might be expected to have a rigid conformation due to electrostatic repulsion. They should then react with nucleophiles from the less hindered diastereotopic π-face. Inspection of (**1**) and the $TiCl_4$-chelated form of the aldehyde (not shown here) shows that in both cases the *same* diastereotopic face is exposed. In fact, (**1**) has been shown to 'simulate' chelation.[1] However, (**2**) and (**3**) are different. The present operational model† predicts non-chelation-control (Felkin–Anh products) for both intermediates. Indeed, treating (**2**) (made by reacting the aldehyde with an excess of gaseous BF_3 in CH_2Cl_2 at −95 °C/5 min) with the silyl enol ether (**4**) (−95 °C/60 min) resulted in a 90 : 10 ratio of (**7a**) : (**8a**). This contrasts to the <5 : >95 distribution obtained in chelation-control *via* $TiCl_4$.[1] Similarly, (**5**) and (**6**) afforded 84 : 16 and 80 : 20 ratios of (**7b**) : (**8b**) and (**7c**) : (**8c**), respectively. Again, this is reversal of diastereoselectivity, the $TiCl_4$-promoted reaction affording almost exclusively (**8b,c**).[1] In all cases conversion is >85%.

The doubly complexed α-chiral β-alkoxy aldehyde (**3**) also shows significant levels of non-chelation-control in reactions with (**4**) and (**6**). The reason for stereorandomness in the case of (**5**) is unclear. We have also tested the use of BF_3–diethyl ether in CH_2Cl_2, but stereoselectivities are poor [*e.g.*, (**7b**):(**8b**) = 65:35; (**7c**):(**8c**) = 65:35; (**9a**):(**10a**) = 77:23]. As with α-alkoxy aldehydes, β-alkoxy derivatives show opposite stereoselectivity depending upon whether simple BF_3-addition or $TiCl_4$-chelation is used. Thus, chelation of β-benzyloxy-α-methylpropanal [the free aldehyde corresponding to (**3**)] with $TiCl_4$ at −78 °C followed by addition of (**4**), (**5**), or (**6**) at that temperature results in complete reversal of diastereoselectivity [(**9a**) : (**10a**) = 5 : 95; (**9b**) : (**10b**) = <3 : >97; (**9c**) : (**10c**)= 17 : 83]. In all cases conversion is >85%.

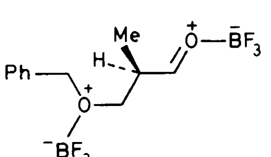
In a second approach to non-chelation-control, we performed a fluoride ion induced aldol addition[6] of (**11**) and (**12**). Remarkably, of the four possible diastereoisomers, only two are formed [(**13**) : (**14**) = 82 : 18]. Compound (**13**)‡ is the Felkin–Anh product (non-chelation-controlled) in which the relative stereochemistry at the two new chiral centres is *syn* (simple diastereoselectivity[7]). The minor isomer (**14**)‡ represents formal chelation-control, simple diastereoselectivity being *syn*. Apparently, the intermediate ammonium enolates, whatever their precise structure may be,[6] are incapable of



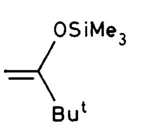
(**1**)



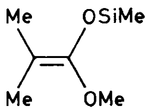
(**2**)



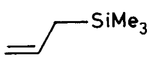
(**3**)



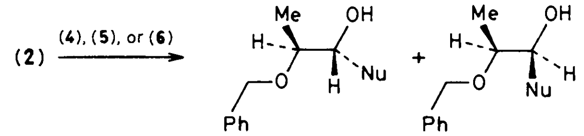
(**4**)



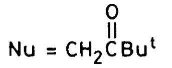
(**5**)



(**6**)



(**7**) (**8**)



a; Nu = $CH_2\overset{O}{\overset{\|}{C}}Bu^t$ (**7a**) : (**8a**) 90 : 10

b; Nu = $C(Me)_2CO_2Me$ (**7b**) : (**8b**) 84 : 16

c; Nu = $CH_2CH{=}CH_2$ (**7c**) : (**8c**) 80 : 20

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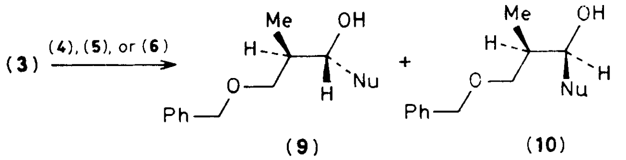
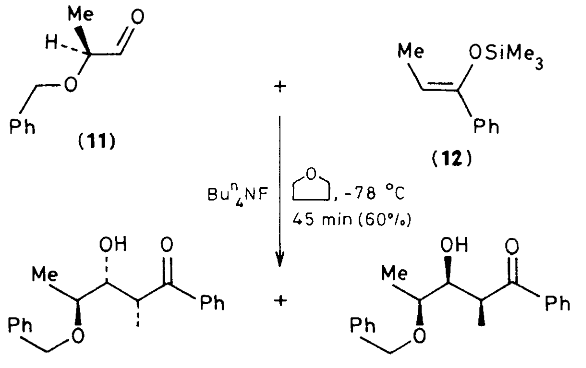
† Other models also explain the results, *e.g.* Felkin–Anh conformations in which $\pi^*_{C=O}$–σ^*_{C-OR} conjugation is important. On the basis of molecular models, folded conformations in which Coulombic *attraction* (ref. 1) is dominant, appear less likely.

‡ Non-chelation-control is also observed by using the tri-isopropoxytitanium enolate corresponding to (**12**) as previously reported, although a definitive assignment regarding simple diastereoselectivity (ref. 7) was not made (ref. 1). We now report that it is not *anti* as arbitrarily assumed (ref. 1), but *syn* as shown in (**13**). One of Heathcock's aldol adducts [prepared by adding the lithium enolate of 2-methyl-2-(trimethylsiloxy)pentan-3-one to (**11**) according to C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. Van Derveer, *J. Org. Chem.*, 1980, **45**, 3846] was correlated chemically with (**13**) by the following sequence: protection of the HO-group by tetrahydropyran-H^+, addition of two equivalents of phenyl-lithium, and oxidative cleavage and deprotection using H_5IO_6–MeOH. The structure of (**14**) was assigned by an analoguous sequence as well as by *X*-ray crystallography.



(9) (10)

a; Nu = $CH_2C(=O)Bu^t$	(9a) : (10a)	88 : 12
b; Nu = $C(Me)_2CO_2Me$	(9b) : (10b)	45 : 55
c; Nu = $CH_2CH{=}CH_2$	(9c) : (10c)	70 : 30



(11) (12) (13) (14)

chelation, so that the Felkin–Anh model applies. § Adding (**12**) to (**11**)/$TiCl_4$ results in opposite stereoselectivity [3 : 97 ratio of (**13**) : (**14**)].[1] It is interesting to note that the corresponding lithium enolate at −78 °C delivers a mixture of 60% (**13**), 10% (**14**), and 30% of another diastereoisomer, whereas the zinc enolate affords all four isomers.

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§ We emphasize that such explanations are simply working hypotheses. Low temperatures and short reaction times are necessary, otherwise equilibration due to the reversibility of such reactions (ref. 6) occurs. Commercial tetra-n-butylammonium fluoride in tetrahydrofuran was dried using CaH_2; the precise nature of the fluoride is not known, formation of HF_2^- being possible (R. K. Sharma and J. L. Fry, *J. Org. Chem.*, 1983, **48**, 2112).