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Reaction of Achiral Titanium Z-Enolates with Chiral α-Silyloxy Aldehydes

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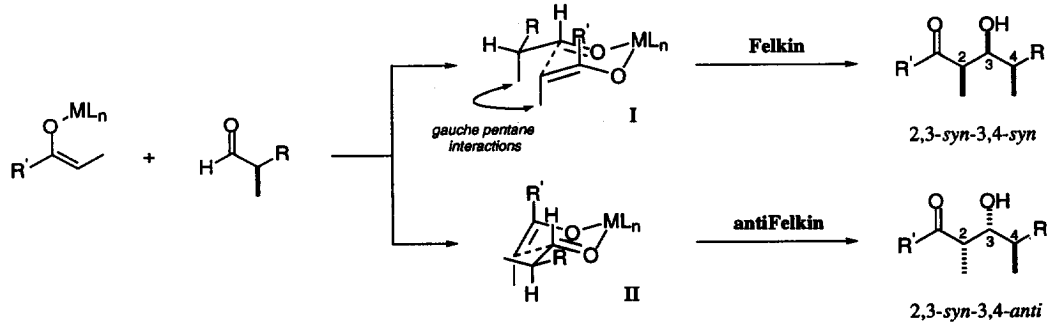
Abstract

Aldol reactions between the putative Z-enolate derived from 2-methyl-3-pentanone and several chiral α-*tert*-butyldiphenylsilyloxy aldehydes have been studied. The stereochemical outcome suggests that stereoelectronic effects play a dominant role in these reactions and the results can be accommodated by the Felkin model, with gauche pentane interactions being less important.

Keywords: Aldol reactions; Diastereoselection; Stereoelectronic effects.

The stereochemical outcome of the aldol addition of an achiral Z-enolate to a chiral α-methyl aldehyde has been rationalised by Roush assuming that *"the dominant stereocontrol element that determines aldehyde diastereofacial selectivity is the minimisation of gauche pentane interactions in the competing cyclic chairlike transition states"*.[1] Roush's statement is rooted on steric grounds and requires, for instance, that the Me group is considered larger than Ph or vinyl groups. The groups of Gennari and Paterson[2] have quantitatively analysed several transition structures that might be involved in the addition of achiral boron Z-enolates to chiral α-methyl aldehydes, concluding that gauche pentane interactions in the Felkin-like approach (see **I**, Scheme 1) can be alleviated by opening the CH···C(O)-C*-Me dihedral angle; if the R group is bulky, this alleviation is not satisfactory and the antiFelkin approach (see **II**, Scheme 1) becomes the lowest in energy because it avoids gauche pentane interactions that destabilize **I**. According to these studies, gauche pentane interactions and Felkin bias have to be



Scheme 1

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considered in order to rationalise the outcome of the addition of achiral *Z*-enolates to chiral aldehydes, the former being the most important in the case of chiral α-methyl aldehydes.

In spite of their importance, α-hydroxy and α-amino aldehydes have received less attention. Nevertheless, Heathcock *et al.* have established that the addition of lithium enolates to chiral α-alkoxy aldehydes mainly affords the Felkin aldol stereoisomer.[3] Other examples[4] confirm this trend and show that, occasionally, the Felkin bias can even override the π-face selectivity of an enolate[4a] or the *Z-syn* relationship of an internal auxiliary.[4b] Therefore, gauche pentane interactions do not seem to play a dominant role on the stereochemical outcome of the addition of *Z*-achiral enolates to chiral α-OR or α-NR_2 aldehydes.

We have recently reported a highly stereocontrolled aldol reaction of titanium enolates derived from α-silyloxy ketones.[5] We planned to expand the scope of this reaction using chiral α-hydroxy aldehydes and it was of paramount importance to work out the balance between Felkin and gauche pentane interactions in this kind of system.[6] We would like to disclose our preliminary results on the aldol reaction between the putative titanium *Z*-enolate derived from 2-methyl-3-pentanone and chiral α-*tert*-butyldiphenylsilyloxy aldehydes **1–3**.

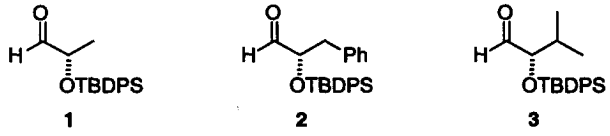
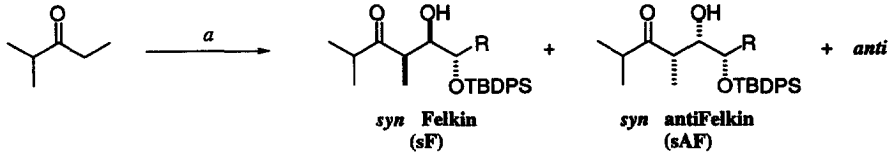


Figure 1

Aldehydes **1–3** were prepared by protection of the corresponding (*S*)-α-hydroxy methyl esters followed by reduction with DIBALH.[7] They were allowed to react with the titanium enolate derived from 2-methyl-3-pentanone (see Scheme 2) and the crude mixtures were analysed by HPLC and ^1H NMR and purified by chromatography. The results are summarised in Table 1.[8]



a) i. $TiCl_4$, DIPEA, CH_2Cl_2, –78 °C, 1.5 h. ii. **1–3** (1.5 equiv.), 1–2 h.

Scheme 2

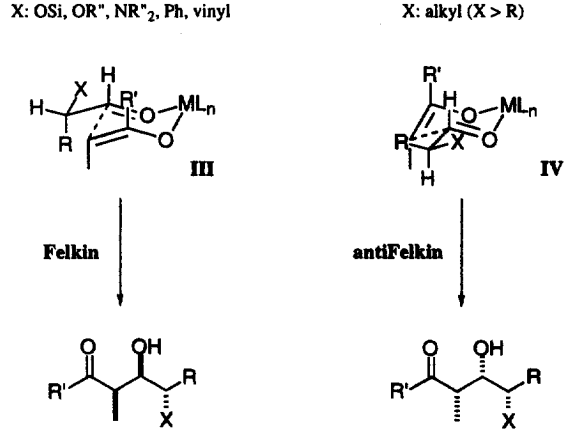
Table 1. Diastereoselective aldol reactions of aldehydes 1–3

entry	aldehyde, R	yield[a], %	ratio[b] *syn / anti*	ratio[b] sF / sAF
1	**1** Me	78	14 : 1	4 : 1
2	**2** Bn	81	6.1 : 1	16.2 : 1
3	**3** Pr^i	68	4.5 : 1	> 99 : 1

a. Isolated overall yield of aldols. *b*. Determined by HPLC.

The major aldol diastereomer turned out to be the *syn*-Felkin one. This result suggests that the stereoelectronic behaviour of the OTBDPS group strongly favours a Felkin approach (**III**, X = OTBDPS in Scheme 3); gauche pentane interactions might be then minimised by relaxing mechanisms previously proposed.[2] Contrary to what was previously thought, an increase in the steric bulk of group R (Me, Bn, Pr^i) does not favour the *syn*-antiFelkin approach (**IV**, X = OTBDPS in Scheme 3); unexpectedly, the more important the gauche pentane interactions the higher the proportion of *anti* aldols and the *syn*-antiFelkin structure is less important. These results suggest that boat or twist boat transition states leading to *anti* aldols should be taken into account if gauche pentane interactions cannot be properly alleviated.

In summary, stereoelectronic effects play, in some cases, a dominant role in the aldol addition of *Z*-enolates to α-chiral aldehydes, RCHXCHO, and the stereochemical outcome can be accommodated by the Felkin model; it can be stated that α-silyloxy aldehydes (X = OSi) and other α-chiral aldehydes (where the X group is OR", $NR"_2$, Ph or vinyl) having a lower σ* orbital than those containing simple alkyl groups, R,[3d] yield the Felkin aldol as the major stereoisomer through **III** (see Scheme 3). Steric effects related to gauche pentane interactions, which can be minimised by the invoked relaxing mechanisms, may only affect the diastereoselectivity. Otherwise, if the features of X and R are similar (two alkyl groups for instance) gauche pentane interactions play a dominant role in predicting the major aldol stereoisomer through antiFelkin approach **IV** (see Scheme 3). Then, if the steric bulk of R increases, other transition states should be considered in order to rationalise the trend observed (see Table 1) and other anomalous results previously reported.[4b] Further studies in order to confirm and expand these conclusions are underway in our laboratory.



Scheme 3

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[6] To the best of our knowledge no systematic study addressing the Felkin *vs* gauche pentane issue in the reaction of achiral *Z*-enolates with α-hydroxy aldehydes has been reported. Heathcock *et al.* (see ref. 3d) have reported addition of the lithium enolate of pinacolone to several α-methoxy aldehydes, RCH(OMe)CHO; the Felkin aldol is always the major stereoisomer and the diastereoselectivity increases as the size of R increases. Reetz (see ref. 4c) has reported a systematic study related to the addition of a 9-BBN enolate derived from a *S*-phenyl thioester to several *N,N*-dibenzyl-α-amino aldehydes, $RCH(NBn_2)CHO$; the *syn* Felkin compound was identified as the major aldol, but a loss of diastereoselectivity is observed as the size of R increases; however, the other stereoisomers have not been characterized and no further explanations have been provided.

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[8] All new compounds show spectroscopic and analytical data consistent with the assigned structures.