Chiral Acetate Enolate Equivalent for the Synthesis of β-Hydroxy Acids

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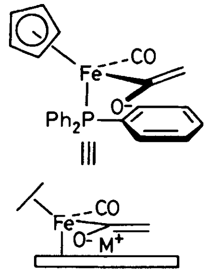
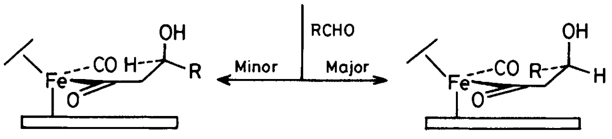
The aluminium enolate derived from (η^5-C_5H_5)Fe(CO)(PPh_3)(COMe) undergoes stereoselective aldol condensations with aldehydes to generate β-hydroxy acyl complexes which yield β-hydroxy acids on decomplexation.

The use of chiral enolates to achieve extremely high stereoselectivities in aldol condensations with aldehydes is now well established.[1] A critical feature of all of the methods reported to date is the presence of an α-substituent on the enolate. Little or no stereoselectivity has been observed for chiral enolate equivalents of acetate or methyl ketones where no α-substituent is present. In common with these observations we have previously reported that the lithium enolate derived from the iron acetyl complex (η^5-C_5H_5)Fe(CO)(PPh_3)(COMe) (**1**) shows little stereoselectivity in its reactions with aldehydes.[2] Recently this problem has been circumvented by the introduction of an α-sulphur substituent (*e.g.* SMe,[3]



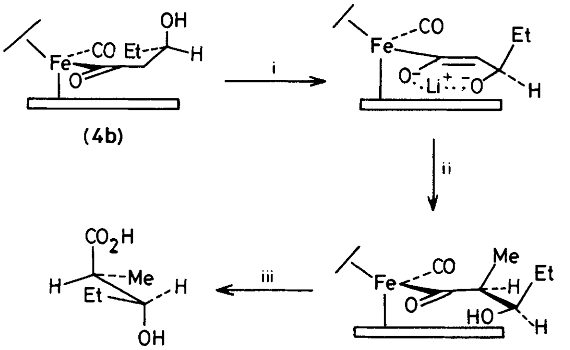
(2) M = Li
(3) M = Et$_2$Al



(5)

(4)

a; R = Me
b; R = Et
c; R = Pr^i
d; R = Bu^t
e; R = Ph



(4b)

(7) *erythro*

(6)

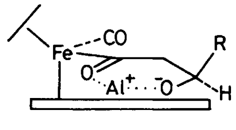
Reagents: i 2 BuLi; ii MeI then H$_2$O; iii Br$_2$, H$_2$O.

p-tolyl-SO[4]) which can be subsequently removed by reduction. We report here that the aluminium enolate derived from (**1**) undergoes very stereoselective aldol condensations with aldehydes to give β-hydroxy acyl complexes, which yield β-hydroxy acids on decomplexation.

Treatment of the iron acetyl complex (**1**) with Bu^{n}Li at −78 °C in tetrahydrofuran generates the corresponding lithium enolate (**2**).[2] Transmetallation is achieved on addition of Et$_2$AlCl and warming to −40 °C for 45 min. Cooling the solution of the aluminium enolate (**3**) to −100 °C followed by addition of propanal generates, after work-up, the diastereoisomeric β-hydroxy acyl complexes (**4b**) and (**5b**) in a ratio of >100 : 1 as determined by ^{1}H and ^{13}C n.m.r. spectroscopy.

Table 1. Ratio of diastereoisomers (**4**) : (**5**) obtained from the reaction of enolates (**2**) and (**3**) with aldehydes.

Aldehyde	Li-enolate (2)	Al-enolate (3)
MeCHO	1.4 : 1	24 : 1
EtCHO	1.2 : 1	>100 : 1
Pr^{i}CHO	1.2 : 1	>100 : 1
Bu^{t}CHO	1.7 : 1	>100 : 1
PhCHO	1.3 : 1	20 : 1



(8)

(η^5-C$_5$H$_5$)Fe(CO)(PPh$_3$)(COMe)
(1)

The relative configurations of (**4b**) were determined by stereoselective α-methylation to give (**6**) whose ^{1}H n.m.r. spectrum contained a doublet for the α-methyl group at δ 1.03, thus establishing the relative configurations of Fe to C_α as *RS,SR*.[5] Decomplexation of (**6**) gave the known[6] *erythro* β-hydroxy acid (**7**), which established the relative configurations of C_α to C_β as *SR,RS* and hence the Fe to C_β configurations for (**4**) are *RR,SS*.

Table 1 lists the results obtained for a range of aldehydes reacting with both the lithium (**2**), and aluminium (**3**), enolates. Isolated product yields for these aldol reactions were in the range 85—90%.

The relative configuration of the new chiral centre is consistent with the β-alkyl group taking up the least sterically-hindered position in both the transition-state and in the initial aluminium-chelated product (**8**) *i.e.* away from the phenyl group of the PPh$_3$.[7]

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