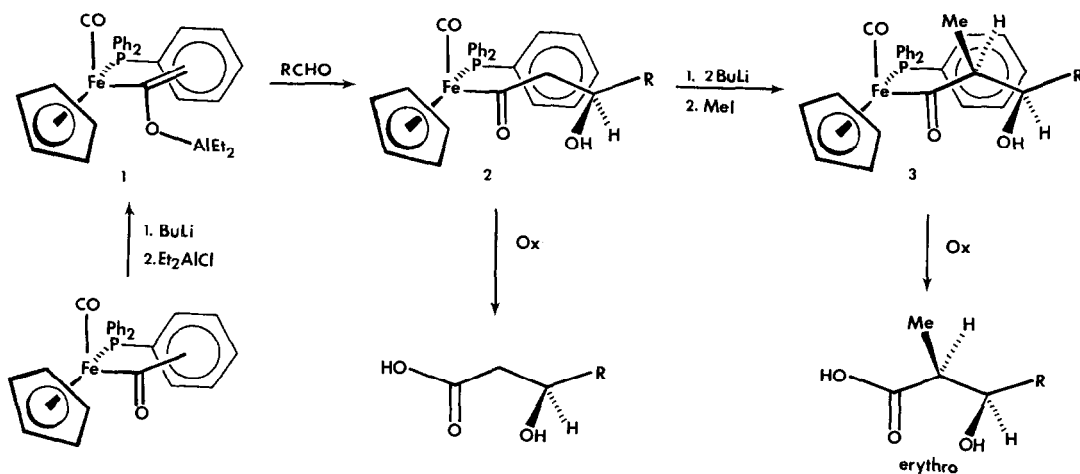


CHIRAL PROPIONATE ENOLATE EQUIVALENTS FOR THE STEREOSELECTIVE SYNTHESIS
 OF *THREO*- OR *ERYTHRO*- α -METHYL- β -HYDROXY ACIDS

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Summary: The aluminium and copper enolates derived from $(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})(\text{PPh}_3)\text{COCH}_2\text{CH}_3$ are chiral propionate enolate equivalents which on reaction with aldehydes (RCHO, R=Me, Et, ⁱPr, ^tBu) provide stereoselective syntheses of *threo*- and *erythro*- α -methyl- β -hydroxy acids respectively.

The use of chiral enolates to achieve extremely high stereoselectivities in aldol condensations with aldehydes is now well established.¹ We have demonstrated recently that the aluminium enolate **1** derived from $(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})(\text{PPh}_3)\text{COCH}_3$ is an efficient chiral acetate enolate equivalent for the synthesis of β -hydroxy acids.^{2,3} Furthermore α -methylation of the initially formed β -hydroxy acyl complexes **2** also proceeded with high diastereoselectivity to give, after decomplexation, *erythro*- α -methyl- β -hydroxy acids.^{2,4} The relative configurations of the α and β centres were determined by ¹H n.m.r. spectroscopy and confirmed by an X-ray crystal structure determination of **2** (R=Et).³ Subsequently Liebeskind *et al.* reported, in his independent study of this aldol reaction, that changing the enolate counterion from aluminium to tin reversed the stereoselectivity.⁵ We report here that enolates derived from $(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})(\text{PPh}_3)\text{COCH}_2\text{CH}_3$ undergo highly stereoselective aldol reactions with aldehydes to yield in the case of the aluminium enolate *threo*- α -methyl- β -hydroxy acids while for the copper enolate the corresponding *erythro*-acids predominate.



Deprotonation of $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})(\text{PPh}_3)\text{COCH}_2\text{CH}_3]$ with *n*-butyllithium (1.1 equiv., THF, -78°C) generates the E-enolate 4a.⁶ Reaction of the lithium enolate 4a with aldehydes at -100°C shows little stereoselectivity producing all four possible diastereoisomers 5, 6, 3 and 7 in approximately equal proportions, i.e. both the *anti* and *syn* enolates are reacting non-stereoselectively. Aldehyde addition to the unhindered face of the *anti* (OLi to CO) enolate would produce 5 and 6 while similar addition to the *syn* enolate would give 3 and 7.^{6,7} Addition of diethylaluminium chloride (3 equiv.) to 4a and warming to -40°C for 1.5 hrs gives the aluminium enolate 4b.^{2,3} Addition of solutions of aldehydes (RCHO) in THF to the aluminium enolate 4b at -100°C gives predominantly diastereoisomer 5 together with small amounts of 3 but with no 6 and little if any of 7 being observed (Table I). In the case of the aluminium enolate both the *anti* and *syn* enolate conformations are reacting stereoselectively. Addition to the *anti*-enolate 4b is preferred and is highly stereoselective giving only 5 with none of 6 being observed. Complexes 5 are isolable pure by chromatography and give the known *threo*-acids on decomplexation.

Table I: Addition of RCHO to the aluminium enolate 4b at -100°C .

RCHO	5	6	3	7
MeCHO	100	--*	7	3
EtCHO	100	--	14	--
ⁱ PrCHO	100	--	10	<1
^t BuCHO	100	--	--	--

* -- indicates diastereoisomer could not be detected.

Addition of the lithium enolate 4a at -78°C to cuprous cyanide (1 equiv.) and stirring at -40°C for 2 hrs gives the copper enolate 4c. Addition of solution of aldehydes (RCHO) in THF to 4c at -78°C gives predominantly diastereoisomer 6 together with small amounts of 5 but with no 7 and very little if any of 3 being observed (Table II). For the copper enolate 4c addition to the *anti* enolate is essentially completely preferred over addition to the *syn*. The stereoselectivity of the aldehyde (RCHO) addition to the *anti* enolate 4c to give 6 increases with the bulk of R. Complexes 6 could be isolated pure by chromatography and on decomplexation gave the known *erythro*-acids.

Table II: Addition of RCHO to the copper enolate 4c at -78°C

RCHO	5	6	3	7
MeCHO	14	100	<1	--*
EtCHO	10	100	<1	--
ⁱ PrCHO	7	100	<1	--
^t BuCHO	4	100	--	--
PhCHO	4	100	<1	--

* -- indicates diastereoisomer could not be detected.

The results described above show that for the aluminium enolate 4b essentially complete control is being exerted by the iron centre over the newly formed β -centre together with moderate to complete control over the α -centre. For the copper enolate, however, essentially complete control over the α -centre is observed with the β -stereoselectivities increasing with the size of the aldehyde. Of most importance however is that the observed very high stereoselectivities between 5 and 7 and also between 3 and 6 (Tables I and II) correspond to the enantioselectivities that will be achievable with the resolved iron acyl complex $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})(\text{PPh}_3)\text{COCH}_2\text{CH}_3]$ in asymmetric syntheses of *threo*- and *erythro*- α -methyl- β -hydroxy acids. Such asymmetric syntheses are currently under investigation as is the further optimisation of the reported stereoselectivities

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