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STEREOSELECTIVE ALDOL CONDENSATION REACTIONS OF IRON ACETYL ENOLATES

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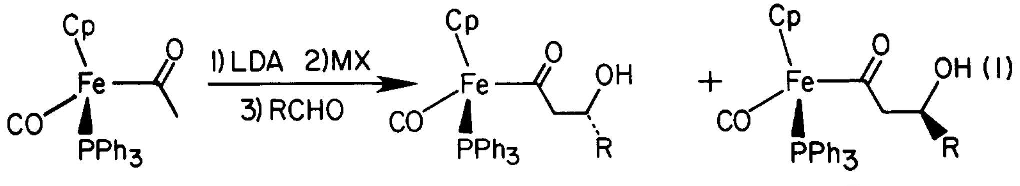
Abstract: By proper choice of counterion, the enolate of η^5-CpFe(CO)(PPh$_3$)COCH$_3$ will react with aldehydes to form the aldol products with high stereoselectivity.

Chiral iron acyls, η^5-CpFe(CO)(PPh$_3$)COCH$_2$R, can be deprotonated by strong base to the corresponding enolates that then react with organic electrophiles (RX, RCHO, RCH=NR') to produce new, elaborated iron acyls.[2-7] Mild oxidative cleavage of these iron acyls proceeds in high yield to organic acid derivatives thus making these iron complexes chiral enolate equivalents. Because traditional organic approaches to asymmetric induction from the enolates of acetic acid and methyl ketone systems usually show poor stereoselectivities,[8-11] our efforts, to date, have focused on exploring the potential of the parent iron acetyl, η^5-CpFe(CO)(PPh$_3$)COCH$_3$, 1, as a chiral acetate enolate equivalent. Although the original studies by ourselves[2] and the Davies group,[3] of the aldol condensation reaction of the lithium enolate of η^5-CpFe(CO)(PPh$_3$)COCH$_3$ with aldehydes showed little influence of the iron chirality on the formation of the new chiral center, our previous success using a diethylaluminum counterion to induce a highly diastereoselective condensation of the enolate of 1 with imines[6] suggested that a survey of enolate counterions in the aldol reaction might uncover significant asymmetric inductions. We now report that the enolate counterion has a dramatic influence on the stereoselectivity of the aldol reaction of η^5-CpFe(CO)(PPh$_3$)COCH$_3$, 1, and that either of the two possible product diastereomers 2 or 3 can be predominated by the proper choice of counterion (eq. 1).



1 2 3

Generation of the lithium enolate of 1 with LDA at -42°C followed by addition of the counterion, MX, and subsequent aldol reaction with RCHO at -78°C gave the product yields and ratios shown in Table 1.[12] Most counterion additives predominated diastereomer 2 with moderate selectivity [$MgBr_2$,$ClTi(OiPr)_3$, 9-BBN-OTf,$iBuAlCl_2$]; however, diisobutylaluminum chloride showed good selectivity with a variety of aldehydes. In general, α,β-unsaturated aldehydes gave lower ratios than saturated aldehydes. Significantly, when less electropositive counterion additives were used (Cp_2ZrCl_2, $Sn(OTf)_2$, $SnCl_2$) the stereoselectivity completely switched to favor the formation of diastereomer 3,with $SnCl_2$[13] giving good to excellent diastereomer ratios in all cases investigated (Table 1).

Table 1. Counterion Influence on Stereoselectivity[a,b]

RCHO	MX	Product Yield (%)	Ratio 2/3[c]
EtCHO	iBu_2AlCl	73	5.2:1
n-PrCHO	"	74	7.5:1
i-PrCHO	"	76	8.2:1
PhCHO	"	81	3.7:1
t-PhCH=CHCHO	"	68	1.7:1
t-PrCH=CHCHO	"	82	2.5:1
MeCHO	$SnCl_2$	60	1:5.4
EtCHO	"	66	1:11.6
n-PrCHO	"	52	1:11.4
i-PrCHO	"	74	1:11.0
PhCHO	"	72	1:12
t-PhCH=CHCHO	"	44	1:5.5
t-PrCH=CHCHO	"	56	1:3.9

a) All ratios reflect kinetic aldol conditions at -78°C. Quenching of the iBu_2AlCl reactions was performed at -78°C while the $SnCl_2$ reactions could be quenched after warming to room temperature without any significant loss in stereoselectivity.

b) All products were analyzed by IR and ^1H NMR (200 MHz or 270 MHz) and gave satisfactory elemental analyses.

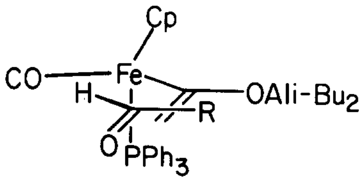
c) Ratios were determined by integration of the ^1H NMR spectra.

Assignment of relative stereochemistry to the diastereomers 2 and 3 was achieved by a combination of X-ray crystallography and ^1H NMR spectroscopy. Rigorous structure proof of 3, R=Ph, was obtained through a crystal structure determination. In addition to establishing the relative stereochemistry for 3, R=Ph, this structure determination and our earlier structure of the PhCH=NPh adduct of the enolate of 1,[6] provide two more examples of the tendency of η^5-CpFe(CO)(PR_3)COR acyl complexes to orient the acyl oxygen anti to the ligated carbon monoxide oxygen.[14]

With the structure of the major diastereomer formed from PhCHO and the Sn(II) enolate confirmed as 3, the minor diastereomer of the tin reaction, which was the major diastereomer when the aluminum enolate was used, must have structure 2. The two isomers were easily distinguished by ^{1}H NMR because the methylene hydrogens adjacent to the acyl of 2, R=Ph, appeared as a multiplet resonating between the well separated and distinct methylene hydrogen absorptions of 3, R=Ph [270 MHz ^{1}H NMR in C_6D_6; 2: 3.40-3.31 (m,2H); 3: 3.60 (dd,J = 18 Hz, 2 Hz, 1 H; with overlapping OH absorption at 3.63δ); 3.09 (dd,J = 18 Hz, 9 Hz, 1 H)]. In fact, all major isomers formed with the aluminum enolate showed their methylene absorptions between the chemical shifts of methylene absorptions of the corresponding major isomer from the tin enolate. We used this conformity of the high-field ^{1}H NMR spectra to justify assignment of structure 2 to the major isomer of all the aluminum reactions and structure 3 to the major isomer of all the tin reactions. Diastereomer ratios, 2:3, were determined by integrating the cyclopentadienyl absorption or the methylene absorptions of each isomer.

The significant dependence of product stereochemistry on enolate counterion provides some clues to how the aldol transition states are influenced by the various counterions. Before rationalizing product stereochemistry with transition state arguments, it was important to confirm that the diastereomer ratios were, in fact, kinetic in origin and not influenced by any equilibration of the aldol products. For all cases reported we have confirmed the kinetic origin of the stereoselectivity by comparing diastereomer ratios of reaction mixtures quenched after varying times and at different temperatures (-100°, -78°, rt) and found no effective equilibration of the tin system at low or moderate temperature and no equilibration of the aluminum system at low temperature within 6 hrs.

As first pointed out by Davies, the general observation of near 180° dihedral angles between the acyl oxygen and carbon monoxide oxygen in crystal structures of η^5-CpFe(CO)(PR$_3$)COR complexes might be a manifestation of an electronic effect which could also control the solution structures of the corresponding enolates.[14] Our observed diastereoselectivities can then be rationalized by selective addition of one face of the aldehyde to the less hindered face of the iron acyl enolate opposite the large, bulky PPh$_3$ ligand. To accommodate the selectivity change from diastereomer 2 to 3 on switching from the aluminum counterion to the tin counterion, we propose that the aluminum system reacts through an extended transition state, 4, which directs the aldehyde R group away from the bulk around the iron. The much less reactive stannous enolate, in order to activate the aldehyde for attack, might require a cyclic, coordinated transition state, 5, that directs the aldehyde R group away from the iron bulk. It is also possible that the tin system could react through the C-bonded enolate 6.[15] The transition state rationalizations of the observed aldol stereoselectivities are fully compatible with our previously described condensation of imines with the aluminum enolate which required prior coordination of the imine nitrogen, via a cyclic transition state, to induce the sluggishly electrophilic imines to condense.[6]



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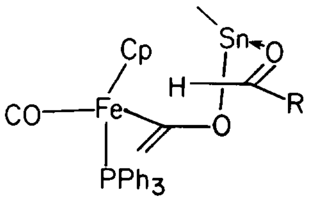

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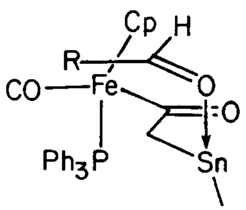

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High yield transformation of the iron acyl aldol products to carboxylic acid derivatives was also possible. Treatment of the benzaldehyde aldol product with 1.1 eq of NBS in 1:1 CH_2Cl_2/EtOH for 1 hr at 0°C gave ethyl 3-hydroxydihydrocinnamate in 79% yield.

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References and Notes

1. Fellow of the Alfred P. Sloan Foundation, 1983-1985. After January 1, 1985 address correspondence to this author at Department of Chemistry, Emory University, Atlanta, GA 30322.
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11. For an exception to this statement see N. Iwasawa and T. Mukaiyama, Chem. Lett. 1983, 297.
12. For the experimental details of the generation of the lithium enolate of 1, see reference 2. The lithium enolate was generated at -42°C. Anhydrous stannous chloride (Hershberg and Cason, Org. Syn. Col. Vol. III, page 627) was added as a freshly prepared 0.25 M THF solution. If stored for >2 days these solutions of $SnCl_2$ gave poor yields.
13. The use of tin(II) enolates in organic chemistry was originated by Mukaiyama. For a recent example of his chemistry see the literature citation in reference 11.
14. For a discussion of the importance of this phenomenon see S. G. Davies and J. I. Seeman, Tet. Lett. 1984, 1845.
15. Because of possible equilibration between 5 and 6 (see K. Kobayashi, M. Kawanisi, T. Hitomi, and S. Kozima, Chem. Lett. 1983, 851 for equilibration of a Sn(IV) system), a distinction between the two enolates may be irrelevant. However, it is interesting that the proposal of a C-bonded Sn(II) enolate is supported by the high C-bonded enolate content of Sn(IV) enolates (A. G. Davies and P. J. Smith in "Comprehensive Organometallic Chemistry"; G. Wilkinson, F. G. A. Stone, and E. W. Abel, Eds., Vol. 2, pg. 581) and by our observation of a significant acyl absorption band at 1611 cm^{-1} in an infrared spectrum of the lithium enolate of 1 treated with 1 eq of $SnCl_2$. No acyl absorption band was evident in an analogous sample of the aluminum enolate.

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