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Preliminary communication

An approach to the stereoselective synthesis of α-hydroxycarboxylic acids

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Abstract

The complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2OCH_2Ph]$ undergoes, via the corresponding enolate, highly stereoselective alkylation, deuteration and aldol reactions, can be hydrogenated to the corresponding hydroxyacetyl complex, and gives the ester $PhCH_2OOCCH_2OCH_2Ph$ on oxidative decomplexation in the presence of benzyl alcohol.

Carbonyl compounds containing an α-hydroxyl or α-alkoxyl function represent an important class of natural products and synthetic intermediates. However, to date there are few asymmetric synthetic routes available for these compounds in high yield and optical purity [1]. We outline here the potential of the chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ for the stereoselective synthesis of α-hydroxycarboxylic acid derivatives.

Reduction of the iron dimer complex **1** gave the nucleophilic iron anion **2**. Treatment of **2** with methoxyacetyl chloride afforded the α-methoxyacyl complex **3** whereas addition of chloromethyl benzyl ether to **2** gave complex **4**. Treatment of complex **4** with triphenylphosphine in refluxing acetonitrile in the presence of calcium hydroxide gave the chiral α-benzyloxyacyl complex **5** *. The use of calcium hydroxide to promote the formation of **5** can be rationalised in terms of chelation of the calcium ions to both the alkoxy and acyl oxygens in the product **5**, driving the iron alkyl–acyl equilibrium.

The complex **3** undergoes smooth deprotonation with lithium hexamethyldisilazide [2] to give the corresponding enolate **6**. Methylation of enolate **6** gave complex **7**, which on oxidative decomplexation in the presence of benzyl alcohol afforded the α-methoxy ester **8**.

Deprotonation of **5** with n-butyllithium in THF at $-78°C$ gave the incarnidine enolate **9**, whose geometry was assigned as *E* on the assumption that the conforma-

* All complexes are racemic, but for clarity only those with the *R* configuration at iron are shown.

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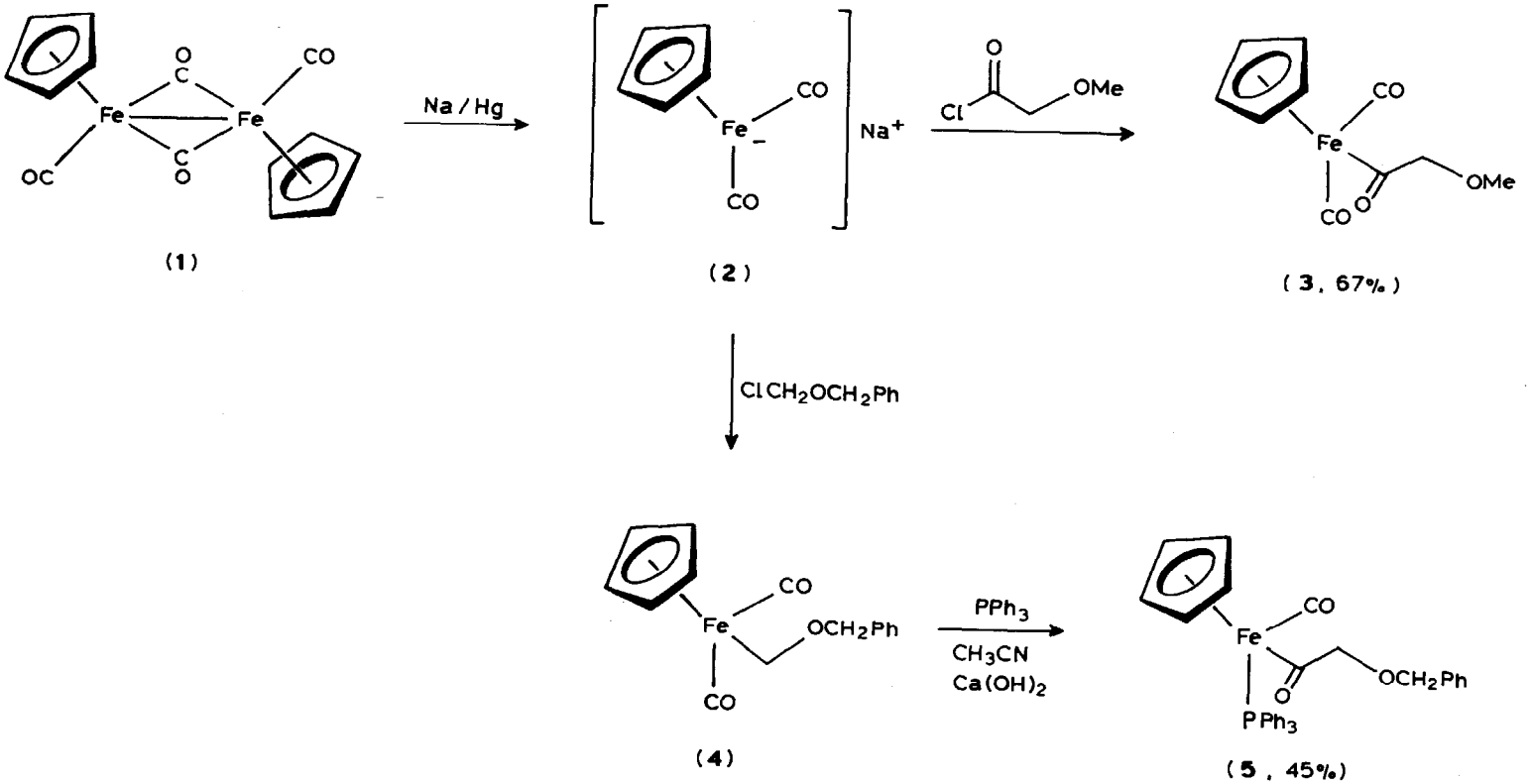

Fe
Fe
CO
OC
Na / Hg
Na+
Cl
OMe
OMe
ClCH2OCH2Ph
OCH2Ph
PPh3
CH3CN
Ca(OH)2
PPh3

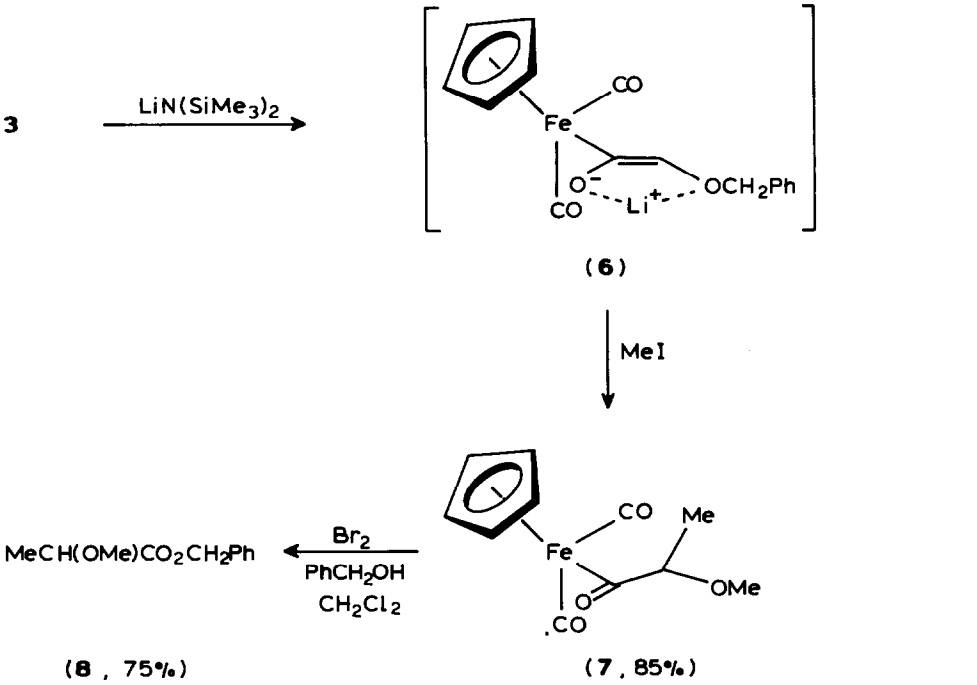
(1)

(2)

(3, 67%)

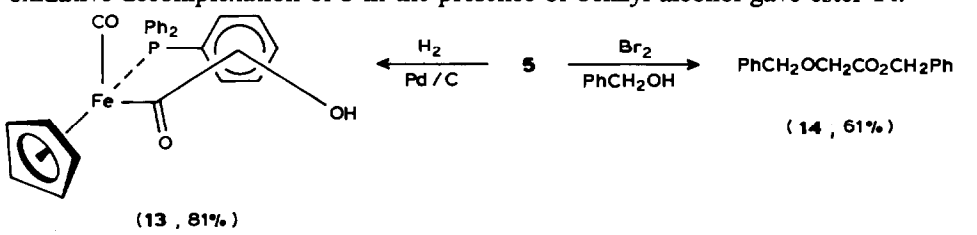
(4)

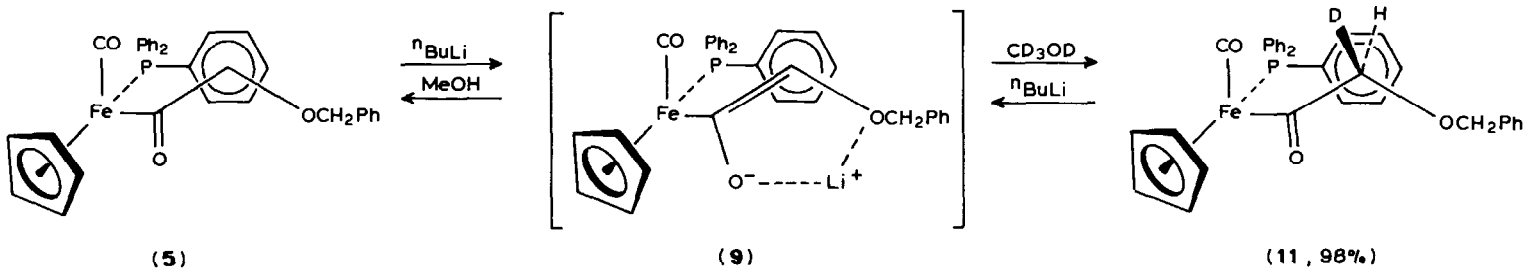
(5, 45%)



tion of **5** would be fixed by coordination of the two oxygen atoms to the lithium cation prior to deprotonation. Consistent with this, quenching enolate **9** with acetone gave complex **10** as a single diastereoisomer (> 100/1) whose structure was established by X-ray diffraction [3]. The stereoselective formation of **10** can be understood in terms of addition to the unhindered face of the *E*-enolate **9** in the *anti* O^- to CO conformation [4]. Deuteration of enolate **9** also occurred stereoselectively (> 20/1) to give **11**. Subsequent regeneration of enolate **9** from **11**, reformed, on addition of methanol, complex **5** essentially deuterium free. Removal of deuterium from **11** demonstrates that the initial deprotonation of **5** is also stereoselective as predicted above. Alkylation of enolate **9** at −78 °C with a series of alkyl halides (MeI, EtI, i-PrI, allyl bromide, benzyl bromide) afforded products **12** stereoselectively. As with the alkylation of other enolates, only for the small electrophile methyl iodide was the minor diastereoisomer detectable by 300 MHz ^{1}H NMR spectroscopy [4].

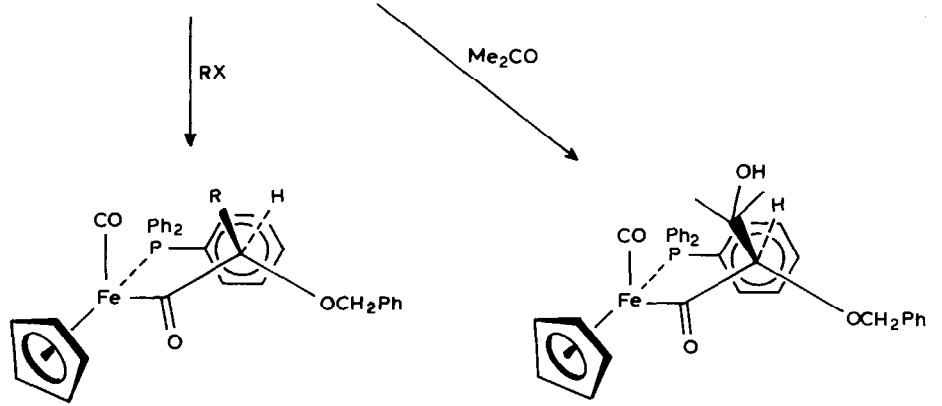
Hydroxyacetyl complexes are believed to be important intermediates in the reductive polymerisation of carbon monoxide [5], but to date few reports of the synthesis of hydroxyacetyl complexes have appeared [6]. Debenzylation of complex **5** was achieved by hydrogenation, to give the hydroxyacetyl complex **13**. Finally, oxidative decomplexation of **5** in the presence of benzyl alcohol gave ester **14**.





(5) (9) (11, 98%)

R	Yield (%)	Selectivity
Me	77	> 60/1
Et	67	>100/1
^{i}Pr	58	>100/1
Allyl	80	>100/1
CH_2Ph	72	>100/1



(12) (10, 40%)

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