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APPLICATION OF THE IRON ACYL COMPLEX R-(-)-[(η^5-C_5H_5)Fe(CO)(PPh3)-$COCH_2O$({1R,2S,5R}menthyl)] AS A HOMOCHIRAL FORMYL ANION EQUIVALENT

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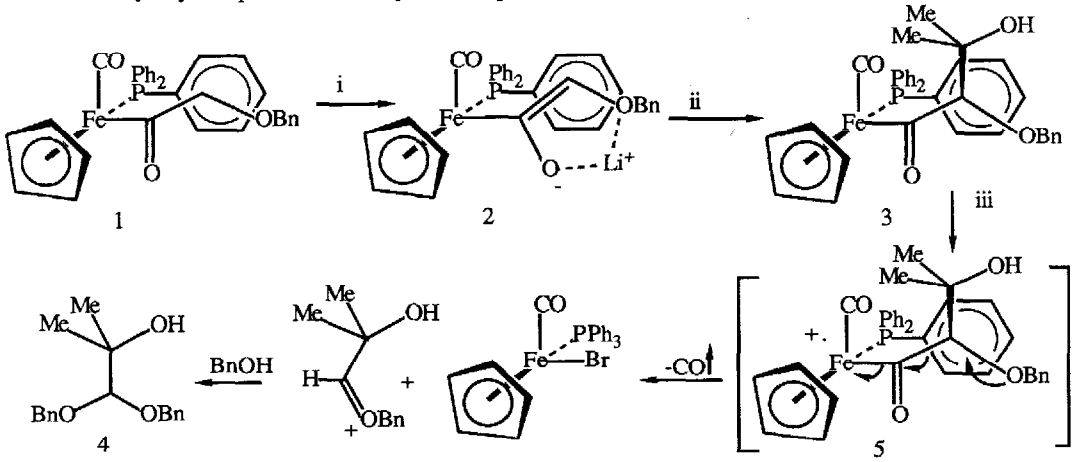
Summary: The enantiomerically pure iron acyl complex R-(-)-[(η^5-C_5H_5)Fe(CO)(PPh3)-$COCH_2O$({1R,2S,5R}menthyl)] represents a source of homochiral formyl anion equivalent applicable to the synthesis of enantiomerically pure α-hydroxy acetals from aldehydes.

The formyl anion or a synthetic equivalent thereof, has wide application in synthetic organic chemistry. Although a number of formyl anion synthons have been reported,[1] there are relatively few examples of reagents which are designed to add preferentially to only one prochiral face of a carbonyl group, such as an aldehyde, and thereby provide an asymmetric synthesis of α-hydroxy aldehydes.[2] Such a synthon would represent a source of homochiral formyl anion. In this paper we describe the development of a homochiral formyl anion equivalent based on a homochiral α-alkoxy iron acyl complex.

Deprotonation of racemic α-benzyloxy iron acyl complex **1**[3] gave a deep red solution of the E-enolate **2**. Addition of acetone to the enolate solution led, after workup, to the formation of the diastereoisomerically pure β-hydroxy complex **3** in 44% yield, along with 30% of starting material **1**, presumably formed *via* a competing deprotonation of the ketone. A single crystal X-ray structure analysis of **3** revealed it to be the RR(SS) diastereoisomer,[4] which results from addition of the electrophile onto the face of the enolate **2** away from the bulky triphenylphosphine ligand when it lies in the *anti* (O^- to CO) conformation.[5] Oxidative decomplexation of **3** using bromine in dichloromethane at -78°C gave the α-hydroxy dibenzyl acetal **4** (40%). This unexpected decomplexation product arises *via* cleavage of the C_{acyl}-Cα bond, assisted by electron donation from the ether oxygen in the radical cation intermediate **5**.[6] The above sequence of reactions therefore illustrates the application of the α-benzyloxy complex **1** as a formyl anion equivalent.



Reagents; i. n-BuLi, -78°C, THF, ii. Me_2CO, THF, -78°C, iii. Br_2, BnOH, -78°C, CH_2Cl_2.

Successful application of α-alkoxy acyl complexes as chiral formyl anion equivalents in reactions with aldehydes requires the ability to control the stereoselectivity at the β-centre in an aldol reaction with the prochiral carbonyl group. Unfortunately, addition of the lithium enolate **2** to acetaldehyde at -78°C led to the formation of all four of the possible diastereoisomeric products in a ratio of 3:2:1:1, suggesting that highly reactive and unhindered aldehydes react at a rate too fast for effective stereocontrol. It was therefore necessary to investigate alternative counterions which would reduce the reactivity of the enolate derived from **1** and also control the stereochemical outcome of the reaction *via* chelation or steric effects.

Treatment of a THF solution of enolate **2** with *ca.* one equivalent of cuprous cyanide for four hours at -40°C resulted in transmetallation to the copper enolate **6**, characterised by a significant lightening of the colour of the solution. Addition of a series of aldehydes to the copper enolate **6** resulted in the formation of aldol products **7-10** as mixtures of only two diastereoisomers out of a possible four in ratios of 3:1 to 4:1 (Table). Since it has been demonstrated[5] that addition of electrophiles to the enolate derived from **1** occurs preferentially from the face away from the bulky triphenylphosphine ligand when it lies in the *anti* (O^- to CO) conformation, the two diastereoisomeric products from the aldol reaction above were asigned as β-epimers. This assignment was substantiated by the upfield positions of the benzylic protons in the ^1H n.m.r. spectra, which were all in the region δ 3.6-2.9, suggestive of a close proximity of these protons to the triphenylphosphine phenyl rings and characteristic of the RR(SS) relative configuration of iron to C_α centres.[7] In each case the major diastereoisomer was assigned as RRS(SSR) and the minor diastereosiomer as RRR(SSS) relative configuration by relating the ^1H n.m.r. spectroscopic information to a conformational analysis of each of the possible diastereoisomeric products.[7]

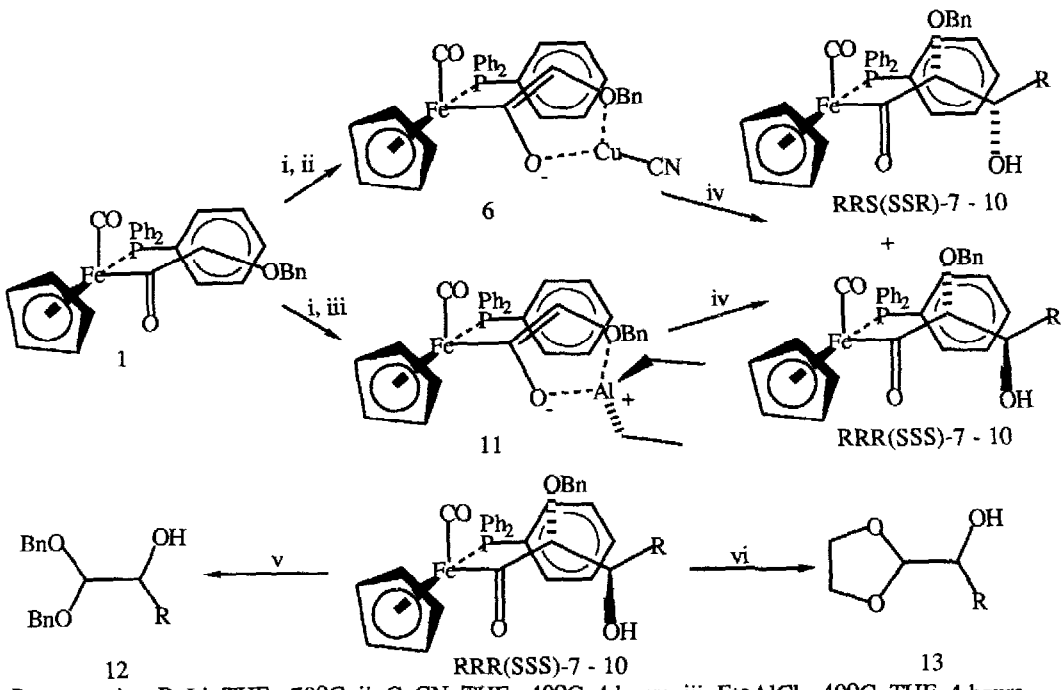
If the lithium enolate **2** was stirred with excess diethylaluminium chloride at -40°C for four hours, transmetallation to the diethylaluminium enolate **11** occurred, again characterised by a significant lightening of the colour of the solution. Addition of the same series of aldehydes as before to **11** led to the formation of aldol products **7-10** as mixtures of the same two diastereoisomers as were observed in the reactions of the copper enolate **6**, but in inverted ratios (Table).

In all of the examples contained in the above description, the diastereoisomeric aldol products were readily separable by chromatography on active alumina, therefore the methodology provides access to aldol products of either desired configuration at the β-centre relative to the configuration at the iron atom.

Treatment of diastereoisomerically pure RRR(SSS)-**8** with bromine in dichloromethane solution at -78°C in the presence of benzyl alcohol gave the dibenzyl acetal **12** (70%) *via* the cleavage described above for **3**. Alternatively, decomplexation with bromine in the presence of ethanediol gave the cyclic acetal **13** (62%), the identity of which was confirmed by its independent preparation from **12** (84%) using a suspension of ethanediol in dichloromethane in the presence of a catalytic amount of trifluoromethanesulphonic acid.

Table: Diastereoselectivities of aldol reactions using enolates **6** and **11**

Product	Enolate	R	% yield	RRS(SSR) : RRR(SSS)
7	**6**	Me	70	3:1
8	**6**	n-Pr	88	3:1
9	**6**	i-Pr	90	4:1
10	**6**	Ph	72	3:1
7	**11**	Me	77	1:4
8	**11**	n-Pr	65	1:8
9	**11**	i-Pr	71	1:9
10	**11**	Ph	76	1:8

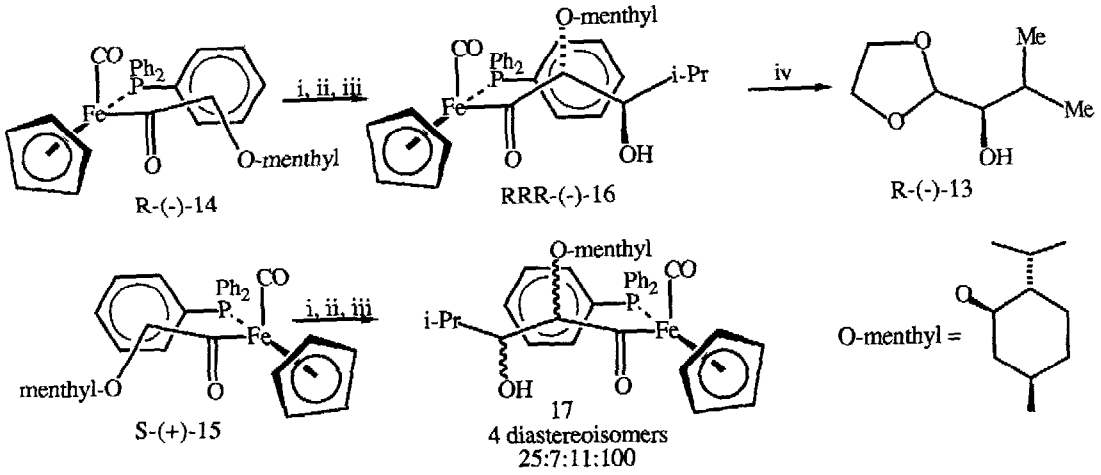


Reagents; i. n-BuLi, THF, -78°C, ii. CuCN, THF, -40°C, 4 hours, iii. Et_2AlCl, -40°C, THF, 4 hours, iv. RCHO, THF, -100°C, 1 hour v. Br_2,BnOH, CH_2Cl_2, -78°C, vi. Br_2, excess $(CH_2OH)_2$, CH_2Cl_2, -78°C

Having demonstrated that the α-alkoxy iron acyl complex **1** *represented a formyl anion equivalent and* could be stereoselectively elaborated in a predictable manner, it was necessary to extend the methodology to homochiral materials. Although the complex **1** is available in enantiomerically pure form,[8] the low selectivities observed in its aldol reactions precluded its use as an effective homochiral formyl anion equivalent. We therefore chose to exploit the expendability of the alkoxy group by replacing it with a homochiral moiety to create a reagent in which the resultant double asymmetric induction[9] provided by a group matched in selectivity to that of the iron centre would boost the overall diastereoselectivity of the aldol reaction. In practice, the readily available α-menthoxy complex R-(-)-[$(\eta^5$-$C_5H_5)Fe(CO)(PPh_3)COCH_2O$({1R,2S,5R}menthyl)] **14** proved to be such a reagent.

R-(-)-**14** and its epimer at the iron centre S-(+)-**15** may be prepared as a 1:1 mixture in three steps from the readily available iron dimer $[(\eta^5$-$C_5H_5)Fe(CO)_2]_2$,[8] and are readily separable by chromatography on active alumina or flash chromatography on silica gel. In each case, S-(+)-**15** is the first to elute. Treatment of a THF solution of R-(-)-**14** with BuLi at -78°C, followed by transmetallation with diethylaluminium chloride (4 hours, -40°C) and addition of i-butyraldehyde (1 hour, -100°C) gave the aldol product **16** as a mixture of two diastereoisomers in a ratio of 15:1. The major product, which could be isolated diastereoisomerically pure (>100:1) *via* a single recrystallisation from dichloromethane/hexane, was assigned the RRR configuration by analogy with the reactivity of complex **1** described above. Conversely, the same reaction repeated on the epimeric compound S-(+)-**15** gave a mixture of the four possible diastereoisomers of **17** in a ratio of 25:7:11:100. These results indicate that in the case of R-(-)-**14**, the influence of the menthyl and the iron configurations are matched and reinforce each other to give products in high diastereoisomeric purity whereas in the case of S-(+)-**15**, the two groups oppose each other and are mismatched in their stereochemical influence.

Treatment of RRR-(-)-16 with bromine in the presence of excess ethanediol (dichloromethane, -78°C) led to decomplexation to the homochiral acetal R-(-)-**13** (46%). The enantiomeric purity of the acetal **13** was confirmed using the chiral ^1H n.m.r. shift reagent R-(-)-2,2,2-(trifluoromethyl)anthryl ethanol **18**.[10] Addition of *ca.* five molar equivalents of **18** to a racemic solution of the acetal **13** resulted in clean separation of the two pairs of diastereotopic methyl doublets in the ^1H n.m.r. spectrum. Addition of five equivalents of **18** to R-(-)-**13** resulted in the observation of only one pair of methyl doublets.



Reagents; i. n-BuLi, THF, -78°C, ii. Et_2AlCl, THF, -40°C, 4 hours, iii. i-PrCHO, THF, -100°C, 1hour, iv. Br_2, excess $(CH_2OH)_2$, CH_2Cl_2, -78°C.

The application of the readily available iron complex R-(-)-[$(\eta^5$-$C_5H_5)Fe(CO)(PPh_3)$-$COCH_2O$({1R,2S,5R}menthyl)] as a homochiral formyl anion equivalent applicable to the synthesis of enantiomerically pure α-hydroxy acetals has therefore been demonstrated.

We wish to thank Glaxo Group Research (Ware) for a studentship (to M.W.).

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3. Satisfactory spectroscopic data and elemental analyses were obtained for all new compounds.

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