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Chiral Recognition in the S_N2 Reaction of t-Butyl 2-Bromopropionate with the Enolate Derived from [(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$]

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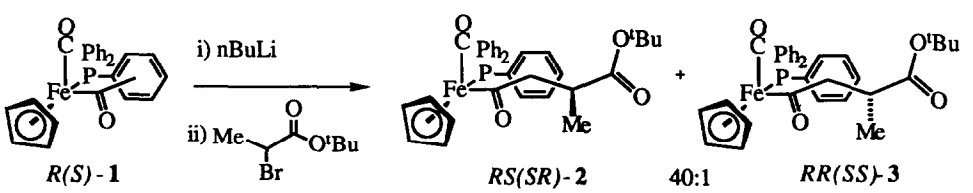
Abstract: The lithium enolate derived from the homochiral iron acetyl complex S-[(η^5-C_5H_5)-Fe(CO)(PPh_3)$COCH_3$] reacts preferentially (40:1) with the R-enantiomer of racemic t-butyl 2-bromopropionate.

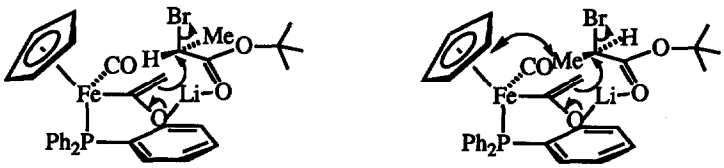
Homochiral α-alkyl succinic acid derivatives are key building blocks of many pharmacologically active molecules. Recent reports have described pseudopeptides displaying antibiotic,[1] anticancer[2] and enzyme inhibitory properties.[3] We recently communicated two methods for the asymmetric synthesis of differentially protected homochiral α-alkyl succinic acid derivatives using the iron chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)]: the reaction of chiral ester enolate equivalents with bromoacetates[4] and the alkylation of a chiral succinate enolate equivalent.[5,6] We now report that the enolate of the iron acetyl complex (η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$ (**1**) exhibits remarkable chiral discrimination in its S_N2 reaction with t-butyl 2-bromopropionate to give an iron 3-methylsuccinoyl complex of high diastereoisomeric purity.

Deprotonation of the racemic iron acetyl complex R,S-**1** with butyllithium at -78°C in tetrahydrofuran followed by treatment with racemic t-butyl 2-bromopropionate gave a 40:1 mixture (>95% d.e.) of the succinoyl complexes RS,SR-**2** and RR,SS-**3**. The yield was only moderate (29%) owing to decomposition *via* competitive debromination of the α-bromoester. The selectivity represents the degree of chiral discrimination between the enantiomers of the iron acetyl enolate and those of the α-bromoester, and is an order of magnitude superior to that previously obtained by methylation of the unsubstituted succinoyl complex.[6] The major diastereoisomer was isolated pure by crystallisation and a single crystal X-ray structure analysis established the relative configuration between the iron and β-carbon centres as RS,SR.[7]



R(S)-**1** *RS(SR)*-**2** 40:1 *RR(SS)*-**3**

The proposed origin of the above chiral discrimination phenomenon is shown in the Figure. Lithium chelation between the enolate oxygen and the ester carbonyl delivers the α-carbon of the ester over the enolate in the correct orientation for the S_N2 displacement. For the mismatched R-enolate and R-bromoester this delivery involves a significant steric interaction of the α-methyl group and the cyclopentadienyl ligand. Such a destabilising interaction is absent in the R-enolate, S-bromoester matched combination. Consistent with the proposed importance of lithium chelation, repetition of the alkylation in the presence of HMPA resulted in a diminution of the diastereoselectivity to 6:1.



R-iron + *S*-bromo ester *R*-iron + *R*-bromo ester

Figure : Matched and unmatched transition states

Homochiral SR-2 was obtained in 95% d.e. from the reaction of the enolate of homochiral S-1 with ten equivalents of racemic t-butyl 2-bromopropionate. The complex could be obtained diastereoisomerically and enantiomerically pure by column chromatography {$[\alpha]_D^{20}$ -49.4 (c 0.235, C_6H_6)}. Reaction of the enolate of homochiral R-1 with homochiral S-t-butyl 2-bromopropionate gave homochiral RS-2 as a single diastereoisomer whereas reaction of the enolate of S-1 with S-t-butyl 2-bromopropionate gave a 50:50 mixture of SR-2 and SS-3. These results demonstrate that the reaction is S_N2 in character. Furthermore the latter result implies that S-t-butyl 2-bromopropionate is racemised by liberated bromide ion faster than it reacts with the S-iron enolate under the reaction conditions employed.

The use of complexes such as 2 as homochiral differentially protected succinic acid derivatives has been previously established.[4-6] Furthermore the chiral discrimination appears to be general, for example, d.e.s of >50:1 were observed for $RCH(Br)CO_2{}^tBu$, R = Et (37%), ^iBu(30%) and the yield could be improved by utilisation of the triflate as leaving group, e.g. R = ^iBu(46%) without compromising the selectivity.

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