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Preliminary communication

Asymmetric synthesis of differentially protected α-alkyl succinates

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Abstract

The alkylation of the chiral iron acyls $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2R]$ (R = H, Me, n-Pr, n-Bu, i-Bu, n-C_5H_{11}) with t-butyl bromoacetate takes place highly stereoselectively to provide a series of novel iron succinoyl complexes, which on oxidative decomplexation lead directly to chiral α-alkyl succinates.

Chiral succinic acid derivatives are becoming increasingly important synthetic intermediates. Recently they have been utilised in the synthesis of several pseudopeptides, some of which have displayed antibiotic [1], anticancer [2], and enzyme-inhibitory properties [3], which may prove clinically useful. Nevertheless, there is still a paucity of methods for the asymmetric synthesis of succinic acids and derivatives. An attractive route to α-alkyl succinic acid derivatives is the alkylation of chiral ester enolate equivalents with bromoacetates, providing that the problem of differential protection of the product succinate can be solved. Two recent communications describe the use of Evans' oxazolidinone methodology for the asymmetric synthesis of α-alkyl succinates. However, removal of the chiral auxiliary produces in one case only similarly diprotected succinic esters [4] while in the second example [5] the stereochemical integrity of the differentially protected succinic ester produced is not rigorously established.

We report here one of our methods for the asymmetric synthesis of α-alkyl succinates containing two different acyl-protecting functionalities, which are capable of being removed selectively [6*]. In the present procedure, we make use of the high asymmetric induction imparted by the iron chiral auxiliary in $[(\eta^5\text{-}C_5H_5)Fe(CO)\text{-}(PPh_3)COCH_3]$ (1) to prepare a number of α-alkyl succinoyl complexes. From these complexes, either of the two masked acyl functions can be

* Reference number with asterisk indicates a note in the list of references.

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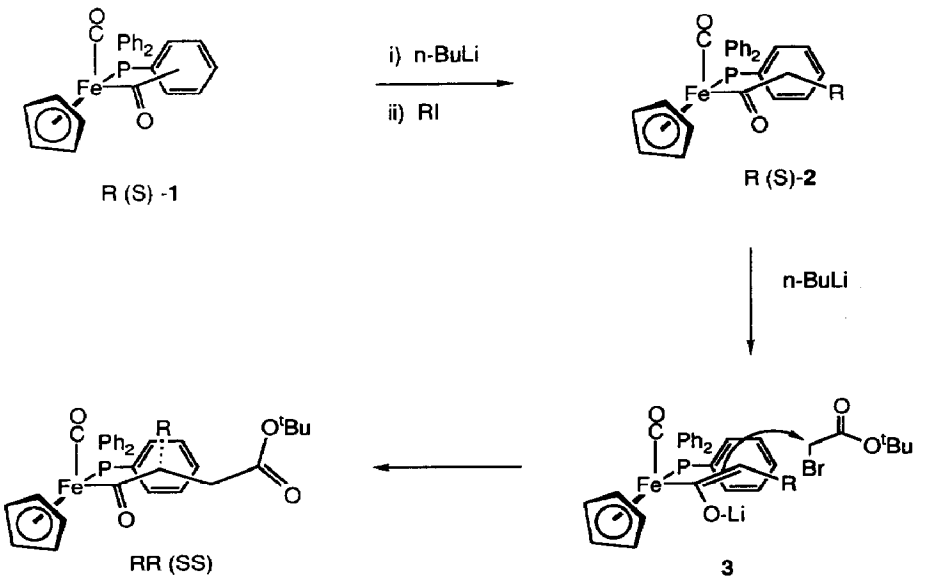
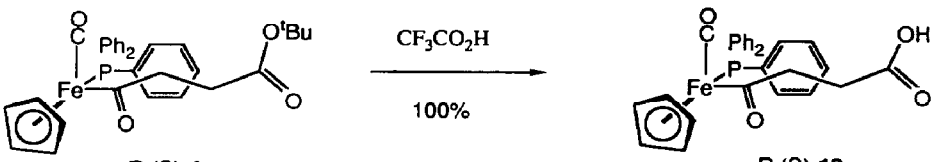
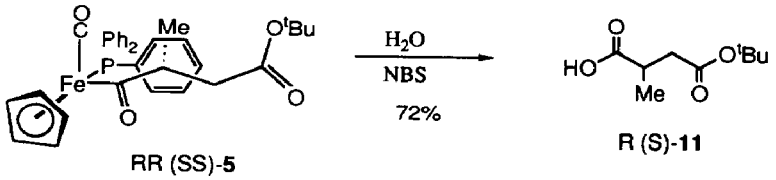


liberated selectively, facilitating further synthetic transformations. Acid (trifluoroacetic acid, TFA) treatment deprotects the t-butyl ester, providing the free acid, while oxidative decomplexation, employing any of a variety of oxidants including bromine or *N*-bromosuccinimide, in the presence of a nucleophile removes the iron auxiliary and effects coupling in a one-pot, two-step reaction to form, for example, pseudopeptide bonds.

A series of racemic iron acyls $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2R]$ (R = Me, n-Pr, n-Bu, i-Bu, n-C_5H_{11}) *R*(*S*)-**2** was obtained in practically quantitative yields by sequential deprotonation of complex *R*(*S*)-**1** with n-butyllithium and alkylation with the appropriate alkyl iodide. These acyls *R*(*S*)-**2** undergo deprotonation by n-butyllithium at −78°C, to form the *E*-enolate **3**, in which the acyl ligand lies approximately parallel to the plane of one of the phenyl groups of the triphenylphosphine ligand. Alkylation with t-butyl bromoacetate is then constrained to occur from one face of the enolate [7] in the *anti* (O^- to CO) conformation, resulting in the highly diastereoselective formation of *RR*(*SS*) iron succinoyl complexes **5–9** (diastereomeric excess (d.e.) > 96%). The minor diastereoisomers of complexes **6–9** were undetectable by 300 MHz proton NMR spectroscopy, whereas the minor diastereoisomer of complex **5** was apparent at a level of less than 2%. The yield of the parent iron succinoyl complex **4** is practically quantitative; however, the yields of the alkyl substituted iron succinoyl complexes **5–9** were somewhat lower, owing to decomposition via competitive debromination of t-butyl bromoacetate.

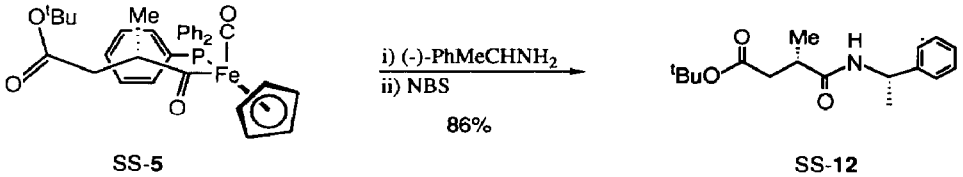
Either of the masked carboxyl groups of these iron succinoyl complexes may be easily revealed. For instance treatment of complex *R*(*S*)-**4** with neat trifluoroacetic acid for 2 h at room temperature produced iron succinoyl complex *R*(*S*)-**10** in quantitative yield. Alternatively, oxidative decomplexation of complex *RR*(*SS*)-**5**





with *N*-bromosuccinimide (NBS) in aqueous tetrahydrofuran provided the succinic acid half ester **11** in 72% yield.

The above set of reactions is equally applicable in the homochiral series. Sequential treatment of (*S*)-iron succinoyl complex *S*-**1** with n-butyllithium, methyl iodide, n-butyllithium, and t-butyl bromoacetate gave (*SS*)-iron succinoyl complex *SS*-**5** in 47% overall yield. Reaction of *SS*-**5** with NBS in the presence of (*S*)-α-methylbenzylamine [8] furnished the differentially-substituted succinic acid derivative *SS*-**12** in 86% yield. Analysis of the proton NMR spectrum of amide **12** confirmed the original diastereoselectivity of alkylation and the absence of epimerisation during decomplexation.



We have described a highly stereoselective synthesis of iron α-alkylsuccinoyl complexes. Further simple manipulation allows the preparation of succinic acid derivatives via concomitant deprotection and coupling whilst maintaining the stereochemical integrity of the newly formed chiral centre.

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