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η^4 to η^5 : Stereocontrolled Reactivation of Exocyclic Triene Iron Complexes

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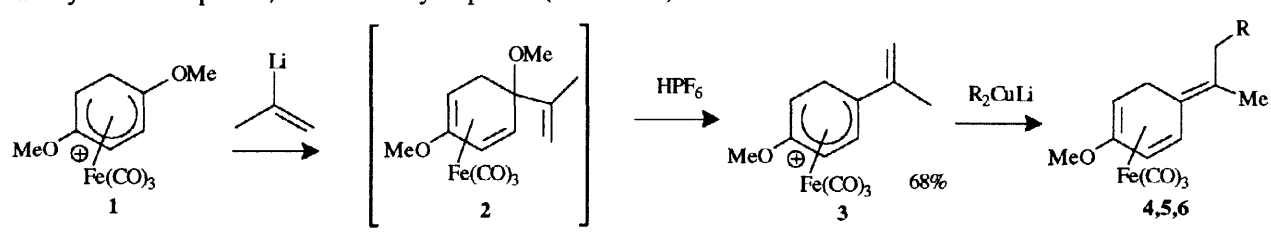
Abstract: The protonation of prochiral exocyclic double bonds in cyclohexa-2,4-dieneiron(0) complexes introduces a chiral centre adjacent to the emergent η^5-cyclohexadienyliron(1+) portion of the product. This reaction has been shown to be fully diastereoselective. The stereochemical course of the reaction has been elucidated by X-ray crystallography and correlated with a complementary procedure starting from dienol complexes.

Stereocontrolled carbon-carbon bond formation mediated by a cationic η^5-tricarbonyliron moiety is well precedented in the literature and many syntheses of natural products[1] have involved bond-forming steps directly influenced by the lateral attachment[2] of an iron control group to the working ligand.[3] Due to the stoichiometric nature of these complexes, to be of real synthetic value the metal must be directly involved in the control of more than one step, and this necessitates the inclusion of a reactivation procedure in the synthesis. There are a number of different strategies to achieve this, including hydride abstraction,[4] dealkoxylation,[5] acid-induced rearrangement of α-hydroxyalkyl complexes[6] and the protonation of exocyclic double bonds.[7] The first two methods, whilst being stereoselective,[8] do not in themselves produce new chiral centres. The diastereoselectivety of the acid-induced rearrangement strategy, which has been examined[9] within our research group, has been shown to be very dependent on conditions and substrate, exhibiting modest d.e. values in most cases and in only one example giving complete stereocontrol. It has also been demonstrated that the protonation of an adjacent alkene by strong acid reforms cationic dienyl systems. This has been performed on an exocyclic double bond in the cyclohexadienyl series but the stereochemical outcome of the transformation has not been addressed since the exocyclic substituent did not possess a prochiral centre.[7]

As part of our ongoing investigation into the synthesis and reactivity of alkenyl-substituted organoiron cations (such as **3**) we have demonstrated[10] that these complexes will undergo conjugate addition with a variety of nucleophiles, most notably cuprates (Scheme 1).



Scheme 1. **4**: R = Me, 78%; **5**: R = Bu, 70%; **6**: R = Ph, 67%.

The geometry of the exocyclic double bond formed during the addition of the cuprate reagent is fully controlled[11] and has been confirmed by n.O.e. experiments in this and other cases. Because the exocyclic

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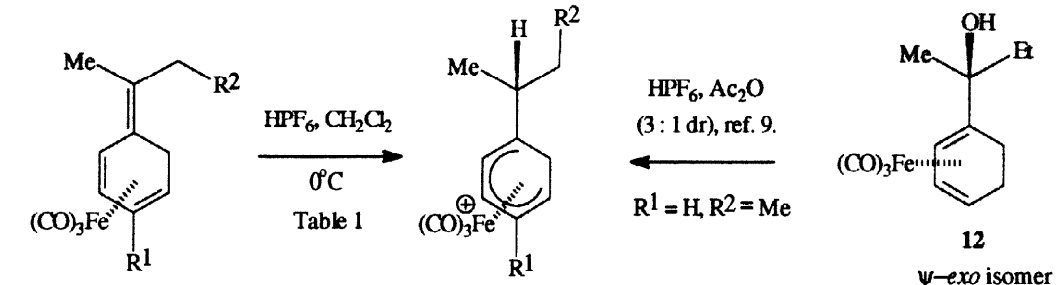
double bonds in **4-6** contain a prochiral centre, these now easily accessible compounds provide the opportunity to study the stereochemistry of protonation at the end of the double bond remote from the iron. The results are presented in this *Letter*. The protonation reactions[12] were performed at 0°C under an inert atmosphere with HPF_6 as the acid, and dichloromethane as the solvent (for details see Scheme 2 and Table 1). Entries 1, 2 and 3 show that the reaction is completely stereoselective, as demonstrated by ^{13}C nmr spectra in which only one set of lines could be detected for each of the products **8**, **9** and **10**, indicating the presence of one diastereoisomer in each case.



4 - 6 R^1 = OMe, **7** R^1 = H

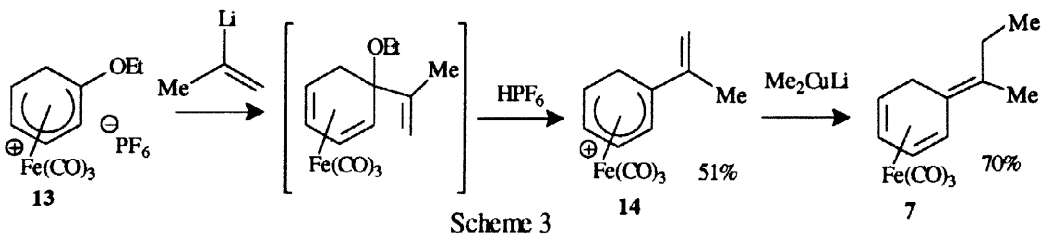
8 - 10 R^1 = OMe, **11** R^1 = H

Scheme 2

	Starting material			Product		
Entry	No.	R^1	R^2	No.	Yield %	d.e. %
1	**4**	OMe	Me	**8**	72	>99
2	**5**	OMe	Bu	**9**	66	>99
3	**6**	OMe	Ph	**10**	65	>99
4	**7**	H	Me	**11**	77	>99

Table 1. Results for the protonation of exocyclic trienes.

The chiral centres introduced in this reaction are at the same position relative to the cyclohexadienyliron complex as those formed by the protonation of the α-hydroxyalkyl starting materials (eg. **12**),[9] but in the latter examples the diene complexes lacked the OMe substituent present in substrates **4-6**. In order to relate the relative stereochemistry of the two reactions, the substrate **7** was prepared by the same conjugate addition route starting from the 1-ethoxy salt **13** (Scheme 3).



Scheme 3

The conjugate addition reaction with **14** proceeded in the normal stereocontrolled manner to afford **7** with a single geometry about the exocyclic double bond. This was characterised by an n.O.e. enhancement of 5% between the methyl group and the hydrogen at C-2. Protonation afforded a single diastereoisomer of the cyclohexadienyliron complex (Table 1, entry 4) and the product **11** had nmr spectral characteristics identical to the major diastereoisomer obtained in a 3 : 1 ratio by the use of HPF_6 with the alcohol **12**.[9]

The complete stereoselectivity may be accounted for in two ways. Either the metal mediates the reaction pathway by initial protonation at the iron centre followed by the delivery of the proton in an *M-endo*

sense across the same face of the molecule (Figure 1: pathway 1), or the protonation may proceed directly in an *anti*periplanar fashion leading to addition at the *M-exo* face of the working ligand (Figure1: pathway 2).

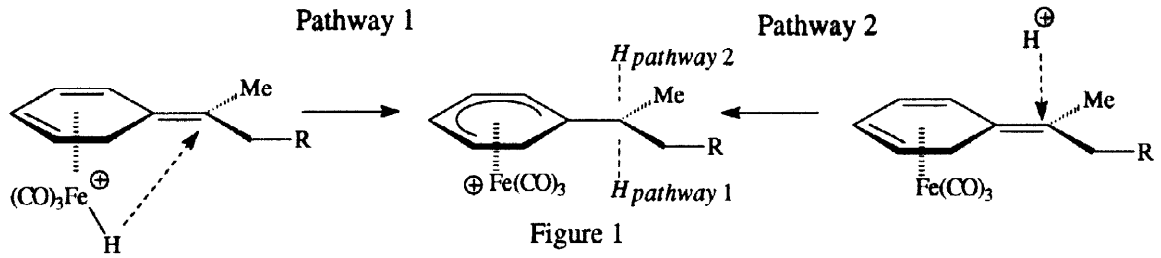
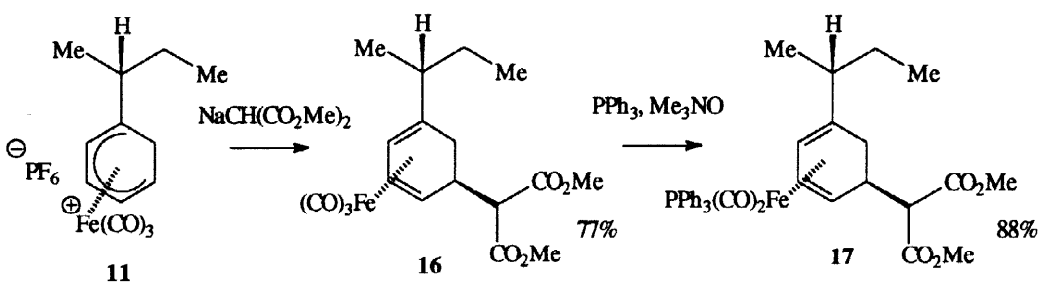


Figure 1

This issue can be addressed by X-ray crystallography as the pathways predict opposite diastereoisomers. We attempted to grow X-ray quality crystals of all the salts (**8** - **11**) but with no success, so it was decided to further functionalise one of the salts by the addition of dimethyl malonate (Scheme 4). To compare the two reactions shown in Scheme 2, compound **11** was chosen for elaboration by reaction with the sodium salt of the enolate of the malonate diester. The expected product **16** corresponding to alkylation at the unsubstituted terminus of the dienyl system was obtained and this was converted into its dicarbonyltriphenylphosphine analogue **17**, since within our experience these compounds tend to be more crystalline. Good quality crystals were successfully grown and a structure was obtained[13] (Figure 2) which showed that protonation to form the salt **11** had taken place from the *M-exo* face of the molecule, supporting pathway 2 (Figure 1).



Scheme 4

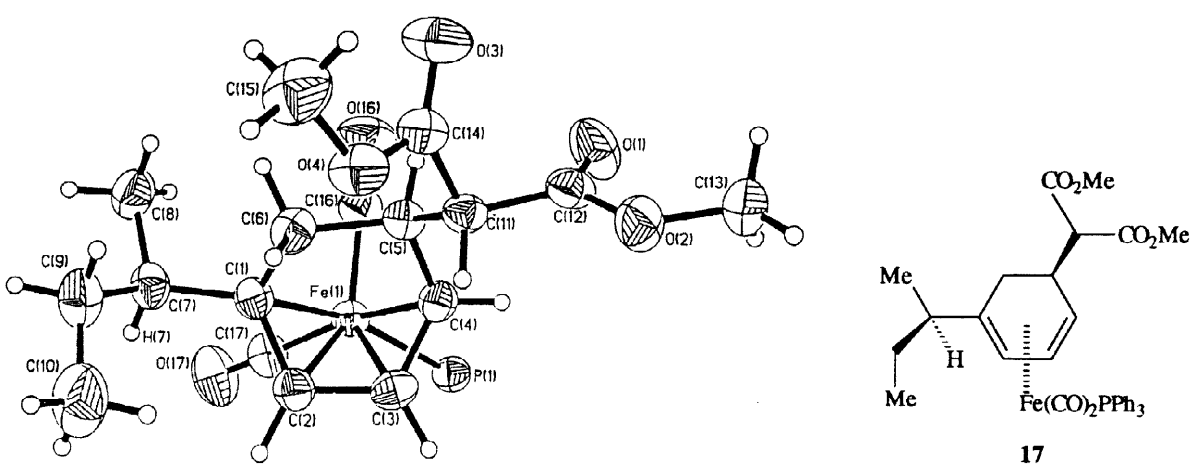


Figure 2. X-ray structure of **17** (phenyl rings have been omitted for clarity).

Similarly it is now possible to define the relative stereochemistry in the reaction that forms **11** from **12** since the structure of **12** has been inferred from the known stereochemical course of the addition of nucleophiles to acyl substituents at C-1 of cyclohexadieneiron complexes, which has itself been proved by X-ray crystallography for one example.[9]

Nucleophile additions to cyclohexadienyliron complexes (eg. **11** → **16**) have been exploited in organic synthesis and are versatile and typically 100% diastereoselective. In this *Letter* we have shown that protonation next to the cyclohexadiene ring is also fully stereocontrolled, even with substituents as similar as Me and Et. Furthermore our work on conjugate addition[10] has demonstrated that even two atoms out from the metal-bound portion, substantial (up to 8:1) diastereoselectivity is possible. With the reactivation strategy described here in which the iron completely controls the chirality of the emergent centre, this hitherto necessary but stereochemically unproductive step becomes much more synthetically useful providing a sequence of at least three consecutive stereoselective bond-forming steps.

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12. *General procedure for the protonation of the exocyclic double bonds in 4 - 7.* The neutral complex (1 eq.) was dissolved in dichloromethane (5 ml) at 0°C and HPF_6 (75% soln. in water) was added dropwise until the IR spectrum of the mixture showed only cationic bands in the region of 2120 - 2050 cm^{-1}. The solution was poured into diethyl ether and a dense yellow precipitate formed. This was collected by filtration and redissolved in a minimum of acetone. Reprecipitation by addition to diethyl ether afforded the cyclohexadienyliron compound as a yellow solid.
13. $P\bar{1}$; $Z = 2$; $a = 11.736(2)$, $b = 12.181(3)$, $c = 12.840(2)$Å, $\alpha = 86.29(2)$ $\beta = 86.48(1)$, $\gamma = 66.33(2)°$ Refinement on F^2: $wR_2 = 0.1247$, $S = 0.974$, R_1 ($F > 4\sigma(F)$) = 0.0426.