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More Efficient Iterative Uses of Tricarbonyliron Complexes are Possible by Diastereoselective Formation of η^5-Cyclohexadienyl Complexes.

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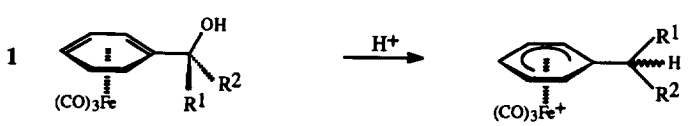
Abstract: Diastereoselective addition of nucleophiles to 1-(RCO)-substituted tricarbonyl(η^4-cyclohexadiene)iron(0) complexes, and a diastereoselective acid-induced rearrangement to form 1-(branched alkyl)-substituted tricarbonyl(η^5-cyclohexadienyl)iron(1+) salts, are described. Stereocontrol in the rearrangement has been studied, and HPF_6, Ac_2O has been shown to be the most suitable acid to promote diastereoselectivity. The product was reacted with $LiCH(SO_2Ph)_2$, completing one turn of an iterative cycle which formed a chiral centre at each step.

The stereocontrolled reactions of stoichiometric transition metal π-complexes are attractive as a bond-forming methodology in organic synthesis, provided that the metal can be used to control a series of chiral centres.[1] There are two distinct strategies by which this may be achieved.[2] In a linear approach, the hapticity of the π-system is progressively reduced as each bond is formed. An iterative approach, on the other hand, alternates between η^n and η^{n+1} π-systems. The use of both approaches is well established in target molecule synthesis,[3,4] but an iterative sequence typically needs two steps to build each chiral centre, an activation step to convert a neutral η^n complex into a cationic electrophilic η^{n+1} species, and a nucleophile addition step which builds a chiral centre and returns the bonding to η^n. By inducing chirality in both activation and nucleophile addition steps, progress towards a series of chiral centres in a target structure will be twice as rapid. This approach is fundamentally more efficient. In this *Letter*, we report the first example of an iterative cycle which achieves this. The key feature of this investigation has been the examination of asymmetric induction during the salt formation step (Scheme 1). The cyclohexadienyl complexes **2-6** have been obtained in yields of 70-80% and diastereoselectivities ranging between 50 and 100% by the use of HPF_6 with the *exo* isomer of **1**.



ψ - *exo* R^1 larger than R^2

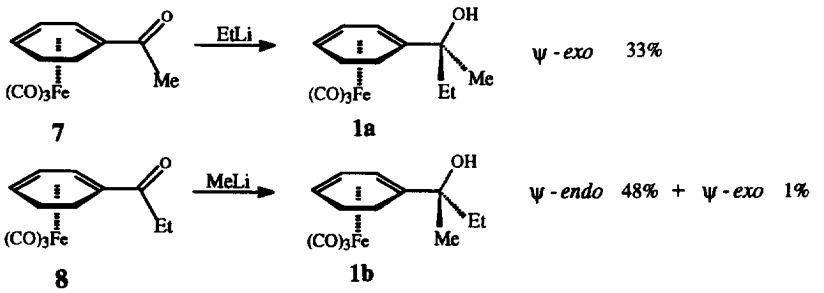
ψ - *endo* R^1 smaller than R^2

2 R^1 = Et, R^2 = Me
3 R^1 = Me, R^2 = Et
4 R^1 = Bu, R^2 = Me
5 R^1 = Me, R^2 = Bu
6 R^1 = Ph, R^2 = Me

Scheme 1: relative stereochemistry of products not determined.

Organoiron complexes are among the most widely used stoichiometric metal/ligand systems, and there are now many methods available for the activation step, which forms stable but highly electrophilic η^5 dienyl complexes. Pearson employed hydride abstraction with Ph_3C^+ in his synthesis of C1-C11 fragment of tylosin,[4a] while syntheses performed in Norwich[4b,c] have exploited leaving groups, as illustrated by our construction[4c] of the two chiral centres of the BC ring junction in hippeastrine. Several other methods[5-7] are

available, and of these, the acid-induced rearrangement of tricarbonyl(η^4-1-(α-hydroxyalkyl(cyclohexadiene)iron(0) complexes (Scheme 1), first reported (for $R_1 = R_2 = H$) by Birch and Williamson[7] in 1973, is particularly suited for modification to form a chiral centre adjacent to the metal-complexed ring. Until now, this possibility has not been examined. Our first objective was the stereoselective preparation of a pair of diastereomeric η^4 complexes **1a** and **1b** to determine the effect of conformational preferences in the side chain on the diastereoselectivity of the rearrangement. Nucleophile addition to C-1 acyl substituents on (1-4-η)-1,3-diene complexes is well known to be efficiently controlled,[8] and is applicable[9] to η^4-cyclohexa-1,3-diene complexes. In view of this, the two ketones **7** and **8** were chosen as starting materials, and reaction with EtLi and MeLi, respectively, afforded selectively in each case the expected stereoisomer (Scheme 2).[10,11]



Scheme 2

Sulfuric acid at 5 °C was used first (Table 1, entries 1 and 2) to induce the rearrangement as a ^1H nmr study[9] suggested that in this medium the cationic intermediate was conformationally locked around the *exo*-cyclic double bond. The η^5 salts were precipitated by addition to saturated ammonium hexafluorophosphate. The ψ-*exo* starting material **1a** afforded a pair of diastereomeric cyclohexadienyl complexes (**2** and **3**) in a 2:1 ratio. The ψ-*endo* counterpart **1b** gave the same products, but in a 3:4 ratio favouring the opposite diastereoisomer. A selection of acids were examined in search of better stereocontrol. Use of FSO_3H at -37 °C (entries 3 and 4) and -70 °C (entries 5 and 6), and $HBF_4.OEt_2$ at -10 °C (entries 7 and 8), gave similar results, and, in the case of the ψ-*exo* starting material **1a**, showed no diastereoselectivity at all, giving a 1:1 mixture of products. With HPF_6, Ac_2O (entries 9 and 10), however, an improvement was observed with a 3:1 diastereoisomer ratio in 85% yield, starting from the ψ-*exo* isomer. This initial series of experiments shows that steric effects from substituents at the α-position can influence the course of the rearrangement reaction. It is also clear that equilibration via the η^4 complex of an exocyclic triene intermediate (a possibility anticipated from the conclusions of the original mechanistic investigation[9] of the rearrangement) did not dominate the stereochemical course of the reaction, since, had this been so, the same (thermodynamic) ratios of diastereoisomeric products would be obtained in each case. However, since different acids gave different stereochemical results, the possibility of slow partial equilibration of kinetic products in some cases, could not be ruled out.

The HPF_6, Ac_2O procedure gave the greatest de values for *both* starting materials (*exo*: 50%; *endo* 20%). It seemed likely that this gave the closest approximation to the kinetic selectivity for the two diastereomers. Two further starting materials were prepared, and examined with HPF_6. Addition of butyllithium to **7** afforded a 47% yield of the ψ-*exo* isomer, together with a small amount (7%) of the ψ-*endo* complex. Phenyllithium was also used, and in this case, only the ψ-*exo* isomer **1e** was obtained in 79% yield (Scheme 3). The relative stereochemistry was proved by X-ray crystallography. Introducing the more bulky butyl substituent in place of the ethyl groups had no effect on the diastereoselectivities of the rearrangement (Table 1, entries 11 and 12), but the large and far more strongly charge-stabilising phenyl substituent allowed a totally diastereoselective rearrangement (e.g. entry 16). The 1-substituted η^5-cyclohexadienyl complex **6** was

obtained as a single diastereoisomer in 80% yield. The product reacted with $LiCH(SO_2Ph)_2$ (generated using lithium *bis*(trimethylsilyl)amide) in THF to afford the neutral diene complex **9** in 87% yield. As expected, this nucleophile addition step also proceeded with complete control of relative stereochemistry.

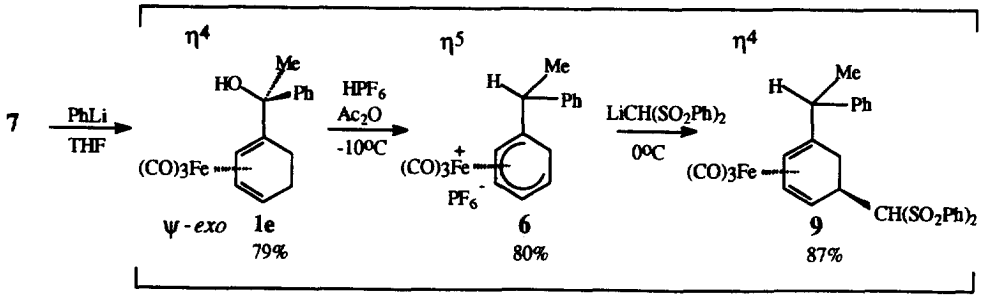
Table 1. Variation in diastereoselectivity of the acid-induced rearrangement.

Entry	Conditions		Substrates				Products[a]		
	acid	Temp	R_1	R_2	ψ-	N°.	yield (%)	ratio[b] of diastereoselectivity	de (%)
1	H_2SO_4	+5°C	Et	Me	*exo*	1a	76	2:1	33
2	H_2SO_4	+5°C	Me	Et	*endo*	1b	83	3:4	14
3	FSO_3H	-37°C	Et	Me	*exo*	1a	84	1:1	0
4	FSO_3H	-37°C	Me	Et	*endo*	1b	89	3:4	14
5	FSO_3H	-70°C	Et	Me	*exo*	1a	77	1:1	0
6	FSO_3H	-70°C	Me	Et	*endo*	1b	64	3:4	14
7	$HBF_4.OEt_2$	-10°C	Et	Me	*exo*	1a	79	1:1	0
8	$HBF_4.OEt_2$	-10°C	Me	Et	*endo*	1b	70	3:4	14
9	HPF_6,Ac_2O	-10°C	Et	Me	*exo*	1a	85	3:1	50
10	HPF_6,Ac_2O	-10°C	Me	Et	*endo*	1b	70	2:3	20
11	HPF_6,Ac_2O	-10°C	Bu	Me	*exo*	1c	80	3:1	50
12	HPF_6,Ac_2O	-10°C	Me	Bu	*endo*	1d	72	2:3	20
13	H_2SO_4	+5°C	Ph	Me	*exo*	1e	75	3:1	50
14	$HBF_4.OEt_2$	-10°C	Ph	Me	*exo*	1e	70	5:1	66
15	FSO_3H	-70°C	Ph	Me	*exo*	1e	95	35:1	94
16	HPF_6,Ac_2O	-10°C	Ph	Me	*exo*	1e	80	c	100

a) the products were precipitated by the addition of the reaction mixture to saturated NH_4PF_6(aq.) at room temperature

b) the ratios of diastereomeric salts were determined by ^1H NMR (400 MHz, CD_3CN)

c) a single diastereomer was observed (^1H NMR, 400 MHz)



One turn of an iterative cycle: [$\eta^n \longrightarrow \eta^{n+1} \longrightarrow \eta^n$] with n = 4

Scheme 3

Other acidic conditions have been tested with this substrate (Table 1, entries 13-15). In each case, diastereoselectivity was better with the phenyl substituent than with the ethyl substituent, and FSO_3H showed

considerable stereocontrol, but only in the case of HPF_6 could none of the minor diastereomer be detected.

Conclusions. We have demonstrated for the first time, the principle that it is possible to employ an iterative procedure in which chirality is relayed at both salt formation and nucleophile addition steps, and have illustrated this in one 'turn' of the iterative cycle by the reaction sequence shown in Scheme 3. The product **9** was formed with complete control of relative stereochemistry at chiral centres four atoms apart.[11] This was possible through the stereodirecting influence of the *same* carbonylmetal control group, operating in each step. To achieve high diastereoselectivity, a charge-stabilising substituent is required at the migration terminus. Since stereocontrol in the reaction requires hydrogen migration before loss of stereochemical homogeneity occurs, the use of an organometallic starting material with greater capacity to stabilise positive charge [e.g. $Fe(CO)_2PPh_3$] might offer a more generally applicable version of the reaction. This will be a target of future work in this area in Norwich.

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11. Relative stereochemistry has not been determined. The product **9** was recrystallised from dichloromethane / hexane but the crystals (m.pt. 83-86 °C) proved unsuitable for X-ray diffraction.

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